Heroin Overdose: Prevalence, Correlates, Consequences and Interventions

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Key Points

- There are approximately 74,000 dependent heroin users in Australia. Opioid overdose was responsible for 737 deaths in Australia in 1998. The death rate from opioid overdose more than doubled from 38.3 to 87.1 per 1,000,000 adults between 1989 and 1998. It is estimated that there are between 12,000 and 21,000 non-fatal overdoses in Australia annually.
- Victims of overdose are predominately single, unemployed men aged in their late 20s and early 30s, with a long history of heroin dependence.
- Concomitant alcohol or benzodiazepine use, and recently depleted tolerance, are significant risk factors for overdose.
- Death from overdose is rarely instantaneous. Overdose most commonly occurs in a private home, with or near other people. Witnesses of overdose are reluctant to seek help.
- Overdose fatality is not a simple function of heroin dose or purity. There is no evidence of toxicity from contaminants of street heroin in Australia.
- Non-fatal opioid overdose has the potential to cause significant persisting morbidity. Research is required to quantify overdose related morbidity. Health care costs associated with overdose are significant. Ambulance call-outs to overdoses in Australia cost approximately $7.7 million annually. Adverse effects associated with the narcotic antagonist naloxone appear to be rare events.
- Opioid overdose fatalities are preventable. Treatment services, such as methadone, protect against fatality from overdose and should be expanded where possible. Alternative pharmacotherapies should be trialled to attract high-risk untreated heroin users into treatment.
- Education based interventions for both heroin users and police have the potential to reduce overdose fatality. The distribution of naloxone to heroin users may prevent fatality from overdose.

Executive Summary

Introduction

Over the past decade fatal opioid overdose has emerged as a major public health issue in Australia.

This report has been prepared in order to provide a comprehensive overview of the epidemiology and circumstances of heroin overdose and interventions that may potentially reduce mortality from overdose.

Heroin Use and Dependence

The Prevalence of Heroin Use in Australia

In household surveys of alcohol and illicit drug use in Australia between 1985 and 1995, 1 to 2% of the adult Australian population report that they have used heroin at some time in their lives. These figures are likely to underestimate heroin use for a number of reasons. Nevertheless, even if we assume that surveys underestimate the number of heroin users by half, the proportion of the Australian population that has ever used heroin would still be less than 5%.

The Prevalence of Heroin Dependence in Australia

A variety of estimation methods have been used to estimate the number of heroin users in Australia, based on ABS overdose mortality data, methadone client database and arrest data. A convergence of estimates from these sources gives a best estimate of 74,000 dependent users (range from 67,000 to 92,000). This estimate (for 1997) represents a doubling of the 34,000 estimated in 1984-87 and 25% increase on the estimate of 59,000 in the period 1988-1993, and gives a population prevalence of opioid dependence in Australia of 6.9 per 1000 adults aged 15 to 54 years (range from 4.6 to 8.2).

The Australian prevalence rate is within the range of recent European estimates of the population prevalence of "problem drug use" in the 15 to 54 year age group, namely 3 to 8 per 1000. The Australian data are not significantly different from the estimated rate of heroin dependence in the United Kingdom of 7 per 1000 (with a range of 3 to 11 per 1000). The Australian rate is only marginally higher than the estimated prevalence of opioid dependence in the USA from household surveys, namely, between 4 and 7 per 1000.

Opioid Overdose Mortality

Deaths from opioid overdose among young Australian adults increased dramatically between 1964 and 1998. The number of deaths attributed to opioid overdose among

Australian adults aged 15-44 years increased from 6 in 1964 to 737 in 1998. This increase is not explained by the increase in population size over this period, as the rate (per million adults aged 15 to 44 years) increased 67-fold from approximately 1.3 in 1964 to 87.1 in 1998, while the proportion of all deaths among adults aged 15 to 44 years attributed to opioid overdose increased 110-fold from 0.08% in 1964 to 8.78% in 1998.

The highest rate of fatal overdose occurs in New South Wales. In 1998, overdose fatalities in NSW accounted for 48.6% of all fatal overdoses nationally. Victoria has the second highest rate and the standardised mortality rate among the remaining States and Territories fluctuates quite markedly. While the rate of overdose has increased across all States and Territories, the rate of increase has varied between jurisdictions. In particular over the last decade the rate of opioid overdose has increased more markedly in South Australia, Western Australia, Tasmania, Northern Territory and Australian Capital Territory than it has in New South Wales, Victoria or Queensland.

International Experience

Crude inter-country differences in reported drug-related mortality need to be interpreted with caution. Even within the European Union, for example, differences exist in registering procedures and classifications of cause of death.

In recognition of the difficulties inherent in comparing drug related mortality between countries, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Eurostat and the World Health Organisation are collaborating to produce standard guidelines for reporting results from mortality and forensic registers. In addition the EMCDDA has developed a standardised protocol for the conducting of mortality cohort studies of drug users recruited in treatment centres. These protocols may lead to better comparisons of overdose mortality between member countries of the European Union.

While crude differences in drug-related mortality must be interpreted with caution, time trends in drug-related deaths between countries may provide a more robust basis for comparison, assuming that classification of cause of death within a particular registration system are relatively constant over time.

Based on the data that is currently available, the recent marked increases in fatal opioid overdose reported earlier do not appear to be peculiar to Australia. The EMCCDA reports that drug related deaths in Ireland, Greece, Austria and Sweden in particular appear to have been increasing steadily over the last decade, but cautions that previous under-reporting may be contributing to these trends. There have been similar rises in the rate of fatal opioid overdose reported in the Nordic countries, Spain, Italy, Austria, the United States and the United Kingdom.

A small number of countries have observed decreases in overdose deaths over the last decade. The EMCDDA reports that drug related deaths appear to have been decreasing in France, Belgium, and Germany since 1991, and that drug related deaths in The Netherlands, Portugal, Finland, Italy, Luxembourg and Spain appear to have stabilised or declined since 1995. Over the last decade reductions of between 18% and 80% in total

numbers of overdose deaths have been reported in France, Switzerland, the Netherlands and at least some parts of Germany.

Non-Fatal Opioid Overdose in Australia

Non-fatal opiate overdoses are common among heroin users. Non-fatal overdoses may be defined as instances where loss of consciousness and depression of respiration occurs but is not fatal. While trends in fatal overdose have been well documented, data on non-fatal overdose is sparse. Studies that have investigated non-fatal overdose report that a large proportion of regular heroin users have experienced non-fatal overdose.

Estimating the Number of Non-Fatal Overdoses

We estimate that the 737 overdose deaths in Australia in 1998 represent a total of 14,750 overdoses in that year, based on reports of the ratio of fatal to non-fatal overdoses witnessed by heroin users.

An estimate of the prevalence of non-fatal overdose calculated by multiplying the prevalence of dependent heroin use by the proportion of users who report having overdosed in the last 12 months gives a prevalence of approximately 10,500 to 15,000 fatal and non-fatal overdoses nationally per year.

Estimates of the prevalence of non-fatal overdose based on NSW ambulance data give an estimate of 16,500 and 20,500 non-fatal overdoses nationally in 1997-8.

These three methods suggest that the current total prevalence of fatal and non-fatal overdose in Australia lies in the range of 10,500 to 20,500 annually, with a best estimate of 15,000.

Characteristics of Victims and Circumstances of Overdose

Characteristics

Age

It is commonly believed that many overdose deaths occur among young, relatively inexperienced heroin users. However, the average age of those dying from overdose ranges from 29.4 years to 31.0 years, having increased from 24.2 in 1979.

Gender

Males and females are equally likely to have experienced a non-fatal overdose, however males are typically over-represented in fatalities attributed to overdose, accounting for over 80% of recorded fatalities in some studies.

The over-representation of males in overdose fatalities is explained in part by the higher prevalence of heroin use among males. It has been well documented that males constitute a majority of heroin users, with studies typically reporting two thirds of current users as being male. However, it would appear that, even when this is taken into account, males are still over-represented among fatal cases.

Length of heroin using career

Contrary to popular belief, the `typical' overdose victim is not a young novice or inexperienced user. Mortality from overdose has been linked with longer heroin using careers. Given that the mean age of death reported in most studies is approximately 30 years, and that heroin using careers typically start in the late teens most fatal cases have been using heroin for a considerable amount of time prior to death. This also holds true for non-fatal overdose.

Marital and Employment Status

The majority of fatal overdose victims have been found to be single at the time of death, although there is a significant gender difference. While males are more likely to be single, the reverse is true for females.

Unemployment may also be a risk factor for overdose. However, further research is required to establish whether unemployment rates are higher in among victims of fatal overdose relative to living heroin users, as this population is typically underemployed.

Treatment

Overdoses among heroin users receiving treatment (such as maintenance pharmacotherapies and drug-free therapeutic communities) appear to be relatively rare. For example, only 2% of heroin-related deaths in New South Wales in 1992 were in methadone maintenance (the dominant treatment modality) at the time of death, while seventy-five percent of fatalities had never been in methadone treatment. Enrolment in methadone maintenance has been found to be protective against overdose in spite of continued use of heroin, probably reflecting a combination of reduced heroin use while in treatment and/or a higher tolerance to opioids while being maintained on methadone.

Reduced Recent Use

A number of overdose fatalities appear to occur after periods of reduced use, such as immediately after prison.

The recent development of drug detection techniques for hair samples has enabled detailed analysis of recent drug use among heroin users. Studies using these techniques found that fatal heroin overdose cases were using considerably less heroin in the two months preceding death than were active street users.

Polydrug Use

Concomitant use of opioids with other CNS depressant drugs is an important risk factor for opioid overdose death. In particular, significant proportions of overdose fatalities are found to be positive for alcohol and/or benzodiazepines at autopsy. It has been suggested that alcohol and benzodiazapines may have synergistic interactions with opioids, potentiating their respiratory depressant effects and thereby increasing overdose risk.

The association between fatal heroin overdose and concomitant alcohol use may provide a possible reason for the over-representation of males among overdose fatalities, since males are three times more likely to have alcohol detected at autopsy.

The evidence of polydrug use in fatal overdose is consistent with the experience of non-fatal overdose victims, particularly in terms of alcohol and benzodiazepine use. Overall, overdoses involving heroin use alone are in the minority. Alcohol appears to be especially implicated, with the frequency of alcohol consumption being a significant predictor of overdose.

Route of Administration

One behavioural factor that may become of increasing relevance in relation to overdose is route of administration. Smoking heroin may be a less dangerous route of administration.

Time between Administration and Death

The interval of time between the final injection of heroin and death has been estimated in several studies. Instant death following administration is relatively rare, having been found to occur in approximately 20% of cases. In the majority of cases death occurs two or more hours after administration.

Circumstances

Location

The majority of deaths occur in a private home. Studies typically report that approximately half of all overdose fatalities occur in the own home of the victim, while a quarter occur in the home of a friend or relative. This pattern also holds true for non-fatal overdose, with only 10% of users reporting that their last overdose occurred on the street.

Some distinct regional differences have been noted in relation to location of death. Geographic clustering of deaths in public may related to the pronounced presence of heroin markets.

Time

Few studies have investigated the time, day, or season of death. Overdose most commonly occurs in the hours between 6pm and midnight, and is more common on Thursdays and Fridays.

Suicide?

A common belief in the general population is that overdose deaths are often intentional, and are therefore misclassified suicides. However, a significant body of evidence is inconsistent with this belief. While drug dependent people are over-represented among suicide mortalities, suicide only accounts for a small proportion of mortality in this group.

Survivors of non-fatal opioid overdoses rarely report that their overdose had been a suicide attempt and witnesses of overdose rarely report that the overdose had been deliberate.

Witnesses

The majority of deaths attributed to overdose occur in the company of others and there is evidence suggesting that the majority of non-fatal overdoses also occur in the company of others. Witnesses to overdose are most commonly a friend, with only a minority being a regular sexual partner.

The limited data available suggest that users that inject alone are over-represented in overdose fatalities. It thus appears that overdosing in the presence of others decreases the lethality of overdose.

While overdose frequently occurs in the company of others, witnesses to fatal overdose (commonly other heroin users), appear reluctant to seek assistance. Fear of police involvement is overwhelmingly the main reason for not seeking, or delaying seeking, help.

Causes & Mechanisms

The pharmacology of heroin

Heroin (diacetylmorphine) is rapidly hydrolysed to 6-monoacetylmorphine which in turn is hydrolysed to morphine. The blood concentration of morphine depends on the route of administration, drug dose, body weight, time elapsed since the last dose, and individual pharmacokinetics.

Mechanisms of heroin-caused deaths

Cardinal signs of heroin toxicity include a reduced level of consciousness, from drowsiness or a stuporous state to coma, pinpoint pupils and a depressed respiratory rate. Death is usually due to respiratory failure.

Dose

The most long-standing and widely accepted explanation for death due to heroin is that a fatal `overdose' is the result of using a quantity or quality (purity) of heroin in excess of the person's current tolerance to the drug. There is little evidence to suggest that this is actually the case. If this were the case, one might expect to find relatively high blood levels of morphine at autopsy in persons whose tolerance had not diminished. Despite the predominance of experienced, long-term heroin users among fatalities, a large proportion have low blood morphine concentrations. In many cases these concentrations are below accepted toxic levels.

Tolerance

A recent decrease in tolerance to opioids has been proposed as a possible explanation for the low blood morphine levels typically seen in overdose victims. The possible effect of the depletion of tolerance due to reduced recent use may be compounded by variations in the development of tolerance across different effects. Tolerance to the respiratory depressive effects of opiates increases at a slower rate than tolerance to the euphoric and analgesic effects. This fact partially explains why long term users are potentially at greater risk of overdose than novices and why most users report not experiencing their first overdose until a number of years after commencing regular heroin use.

Tolerance to opioids has been found to be affected by conditioning, suggesting that consumption in an unusual setting may increase the risk of overdose.

Purity

Two popular misconceptions, among both heroin users and the wider community, are that the major causes of opioid overdose are either unexpectedly high potency of heroin or the presence of toxic contaminants in heroin. The evidence supporting these notions is, at best, sparse.

If overdose were a simple function of purity one would expect the blood morphine concentrations of fatal overdose victims to be significantly higher than living intoxicated heroin users. As described above, it has been found that many individuals who die of an opioid overdose have blood morphine concentrations at autopsy which are below the commonly accepted toxic dose.

Studies that have investigated the relationship between the purity of street heroin seizures and fatality from overdose report a weak correlation, or no correlation, between heroin purity and fatality from overdose.

Contaminants

It is highly unlikely that toxic contaminants in heroin are responsible for fatalities associated with heroin use in Australia. If it were the case that contaminants were associated with fatalities one would expect decreases in rates of fatal overdose as heroin purity increased. While seizures of street heroin in Australia between 1996 and 1999 have shown an increase in purity over this period, no corresponding decrease in fatalities has been observed.

In general, studies outside the eastern United States do not report the detection of impurities in seized heroin. Adulterants found in Australian heroin samples are largely pharmacologically inactive dilutants (used to add bulk) or caffeine (believed to increase the bioavailability of heroin when smoked).

Drug Interactions

Concomitant use of other drugs (polydrug use), particularly CNS depressants such as alcohol and benzodiazepines, appears to be a common practice among heroin users. Co-administration of other depressant drugs can substantially increase the likelihood of a fatal outcome following injection of heroin, due to the potentiation of the respiratory depressant effects of heroin. Thus, in the presence of other CNS depressant drugs a usual dose of heroin may prove fatal.

Liver dysfunction

A number of physiological and epidemiological factors suggest that there may be an association between liver disease and mortality from heroin overdose. Further research is required to establish whether such an association exists and, if so, the nature and extent of this association.

Pulmonary dysfunction

A number of factors suggest that mortality from opioid overdose may be associated with pulmonary dysfunction, however, little epidemiological research into this potential association exists in the literature. Further research is required to confirm or refute the existence of any such association.

Consequences

Fatal

Approximately one in ten overdoses ends fatally. While heroin overdose deaths are grossly outnumbered by deaths from licit drug abuse, they represent a significant number of potential years of life lost.

Non-fatal

There is a dearth of epidemiological literature on medical morbidity associated with heroin overdose. The literature describing complications of heroin overdose has generally been in the form of case reports, and thus provides little insight into the incidence and prevalence of overdose related morbidity.

Sequellae of acute heroin intoxication described in the literature include various pulmonary, cardiac, muscular and neurological complications. Pulmonary conditions and rhabdomyolysis (the disintegration or dissolution of muscle cells) appear to be the most common complications of overdose. It is highly likely that a significant burden of morbidity is associated with these complications, particularly the later.

It is often difficult to separate medical morbidity arising from heroin use per se from morbidity related to overdose. A number of conditions have been attributed to both chronic and acute heroin use.

The literature describing or quantifying overdose related morbidity is sparse, suggesting a need for further research in this area. This research needs to confirm the existence of specific types of morbidity and to quantify the degree of morbidity and the risk of morbidity arising from heroin overdose.

Health care costs

While the dearth of epidemiological data on heroin related morbidity makes it very difficult to quantify the health care costs associated with treating heroin overdose, it has been established that drug users are high cost consumers of health care. Estimates from ambulance data suggest that ambulance attendance at overdoses in Australia in 1998-1999 cost approximately $7.7 million.

Interventions

Given the significant and increasing incidence of fatal opioid overdose, there is a need to develop, implement and evaluate effective strategies to prevent overdose or reduce the lethality of overdose. There are a number of promising strategies that may be successful in achieving this aim.

Increasing Access to Treatment

The risk of overdose death is substantially reduced in individuals who are enrolled in treatment. Since older, long-term users are at greatest risk of fatal overdose, one strategy for reducing fatalities would be to increase the number of older heroin users who are enrolled in methadone maintenance (the principle treatment modality in Australia) and other treatment. While an increase in the number of people enrolled in methadone maintenance treatment has occurred over the past decade, more effort may need to be made to enrol older users who have not been attracted to methadone treatment. This may

require the trial and evaluation of alternative maintenance pharmacotherapies including injectable heroin, levo-alpha acetyl methadyl (LAAM), buprenorphine and slow-release oral morphine. There is insufficient evidence to determine whether increasing access to non-pharmacological treatment would reduce the incidence of overdose. While relatively few overdoses occur among persons in treatment (either pharmacological or non-pharmacological) the relatively poor retention rates typically seen in non-pharmacological treatments (therapeutic communities and out-patient counselling) limit their effectiveness. In addition, losses of tolerance while in non-pharmacological treatment may increase patients risk of overdose after leaving treatment.

Educating Drug Users

A striking degree of cognitive dissonance has been observed in the risk perceptions of heroin users. Users have been found to be unrealistically optimistic about their own risk of overdosing, even though they are remarkably accurate in estimating the risk of others overdosing. Risk perceptions are not found to be associated with users' own experience of overdose, or with having witnessed an overdose.

Given that a number of highly significant behavioural risk factors for overdose have been identified, and that overdose can be relatively easily treated, educating heroin users to change their behaviour may have the potential to reduce the incidence of overdose and reduce fatality from overdose. This requires interventions that directly target risk behaviours and perceptions for overdose.

It should be noted that it is remarkably difficult to change behaviour through education programs, particularly complex behaviours such as those associated with drug dependence. In spite of this the results of the only Australian intervention of this kind published thus far suggest that such approaches may be feasible. A trial of a peer-based intervention to educate heroin users in order to reduce their risk of overdose was recently conducted in South Australia. Two of the three key components of this intervention were the development and implementation of a peer education process and the development and dissemination of information materials. This intervention was found to be successful in reaching and educating heroin users. Evaluation of the intervention found almost half of the post-intervention sample surveyed reported exposure to the intervention, the majority of whom reported that they were more aware of overdose signs and how to avoid overdose as a result of the intervention.

The Distribution of Naloxone

The use of opiate antagonists is virtually universally indicated for the acute treatment of heroin overdose. These antagonists, most commonly naloxone (Narcan®), are generally regarded as very safe. Naloxone has few contraindications and in the absence of opioids has essentially no pharmacological effect.

The distribution of naloxone may be effective in reducing the rate of fatal opioid overdose. However, some complications have been reported in association with its use in

the presence of opioids. It is difficult to establish whether complications are caused by naloxone or by drugs ingested prior to treatment.

Also of concern in the use of naloxone to reverse acute intoxication is the short duration of its effect, relative to many opiates. It has been argued that the effects of naloxone may wear off while there are still significant amounts of opioids in the blood, resulting in recurrent intoxication. While recurrent intoxication may be a theoretical risk following naloxone-induced reversal of intoxication, this risk appears negligible in practice.

As there are both benefits and potential liabilities to the distribution of naloxone, the net benefits of naloxone distribution should be assessed by a carefully planned trial and evaluation.

Establishing Medically Supervised Injecting Centres

Medically supervised injecting centres are places in which injecting drug users are able to inject drugs in a clean environment, with sterile equipment and with medically trained persons on hand in the event of an overdose. There is evidence to suggest that supervised injecting centres hold benefits for both users and the community. A trial of a medically supervised injecting centre in Kings Cross, Sydney, is currently being developed. While it is recognised that it is unlikely that this trial will have a significant impact on heroin overdose rates the evaluation of this trial will provide valuable insight into the effectiveness of supervised injecting centres at reducing high-risk behaviours for overdose, such as injecting on the street or alone. It may also reduce other harms associated with injecting drug use, such as the transmission of blood borne viruses, and may reduce public nuisance from heroin use. This trial will provide a sound body of evidence on which to base policy decisions regarding the role of injecting centres in a multifactorial public health strategy for reducing the harms associated with injecting drug use.

1.0 Introduction

Over the past decade fatal opioid overdose has emerged as a major public health issue in Australia. The number of deaths attributed to opioid overdose among Australian adults aged 15-44 years increased from 6 in 1964 to 737 in 1998. Mortality from overdose now represents a significant cause of death in the 15 to 44 year age group and is now the third greatest cause of death in the 25-35 year age group, after mortality from motor vehicle accidents and suicide.

The precise causes and mechanisms of heroin overdose are still unclear, as discussed in Chapter 5, making definition difficult. For the purposes of this introduction however overdose can be simplistically defined as fatality from respiratory arrest following heroin consumption.

Opioid overdose discussed in this report refers to unintentional overdose only. While drug dependence is a significant risk factor for suicide, methods other than overdose are usually employed. Suicide by deliberate overdose is relatively easily differentiated from unintentional overdose and is reported separately in mortality statistics.

This report has been prepared in order to provide a comprehensive overview of the epidemiology and circumstances of heroin overdose and interventions that may potentially reduce the incidence of, and mortality from, overdose.

2.0 Heroin Use and Dependence

2.1 The Prevalence of Heroin Use in Australia

Before considering the prevalence of overdose it is useful to examine the epidemiology of heroin use and dependence. In household surveys of alcohol and illicit drug use in Australia between 1985 and 1995, 1 to 2% of the adult Australian population report that they have used heroin at some time in their lives (Makkai and McAllister 1998). In the 1998 National Household Survey, 2.2% of the population over the age of 14 (2.9% of males and 1.5% of females) reported that they had ever used heroin (Australian Institute of Health and Welfare (AIHW), 1999). The prevalence of heroin use was higher among young adults aged 20 to 29 years. In this age group, 6.2% of males and 3.2% of females reported lifetime heroin use and 2.2% and 0.5% respectively reported that they had used heroin in the past year (AIHW 1999).

These figures are likely to underestimate heroin use for a number of reasons. First, heroin users are probably under-represented in household survey samples. Their lifestyle makes them less likely to live in conventional households and the distribution of heroin use tends to be concentrated in particular localities, making it likely that household surveys will underestimate use. Second, if heroin users are interviewed, their heroin use may be under-reported because it is an illegal and socially stigmatised behaviour. Nevertheless, even if we assume that surveys underestimate the number of heroin users by half, the

proportion of the Australian population that has ever used heroin would still be less than 5%.

2.2 The Prevalence of Heroin Dependence in Australia

Heroin dependence is differentiated from heroin use by a number of behavioural characteristics. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV 1994) defines opioid dependence as opioid use accompanied by signs and symptoms of compulsive prolonged self-administration without legitimate medical purpose. These signs include: tolerance; withdrawal; taking larger amounts or for a longer time than was intended; a persistant desire or unsucessful efforts to control use; spending a great deal of time obtaining, using or recovering from opiates; forgoing important social, occupational or recreational activities to use opiates, and; continued use despite recognition of adverse effects.

A variety of estimation methods have been used to estimate the number of dependent heroin users in Australia, based on ABS overdose mortality data, methadone client database and arrest data (Hall, Lynskey et al. 2000). A convergence of estimates from these sources gives a best estimate of 74,000 dependent users (range from 67,000 to 92,000). This estimate for 1997 (74,000) represents a doubling of the 34,000 estimated in 1984-87 (NDADS 1988) and 25% increase on the estimate of 59,000 in the period 1988-1993 (Hall 1995), and gives a population prevalence of opioid dependence in Australia of 6.9 per 1000 adults aged 15 to 54 years (range from 4.6 to 8.2).

The Australian prevalence rate is within the range of recent European estimates of the population prevalence of "problem drug use" in the 15 to 54 year age group, namely 2.8 (Austria, Finland, Sweden) to 8.4 (Luxembourg) per 1000 (EMCDDA 1999). The majority of these European "problem drug users" are opioid dependent polydrug users (EMCDDA 1999). The Australian data are not significantly different from the estimated rate of heroin dependence in the United Kingdom of 7 per 1000 (with a range of 3 to 11 per 1000). The Australian rate is only marginally higher than the estimated prevalence of opioid dependence in the USA from household surveys, namely, between 4 (Kessler, McGonagh et al. 1994) and 7 per 1000 (Anthony and Helzer 1991).

Summary

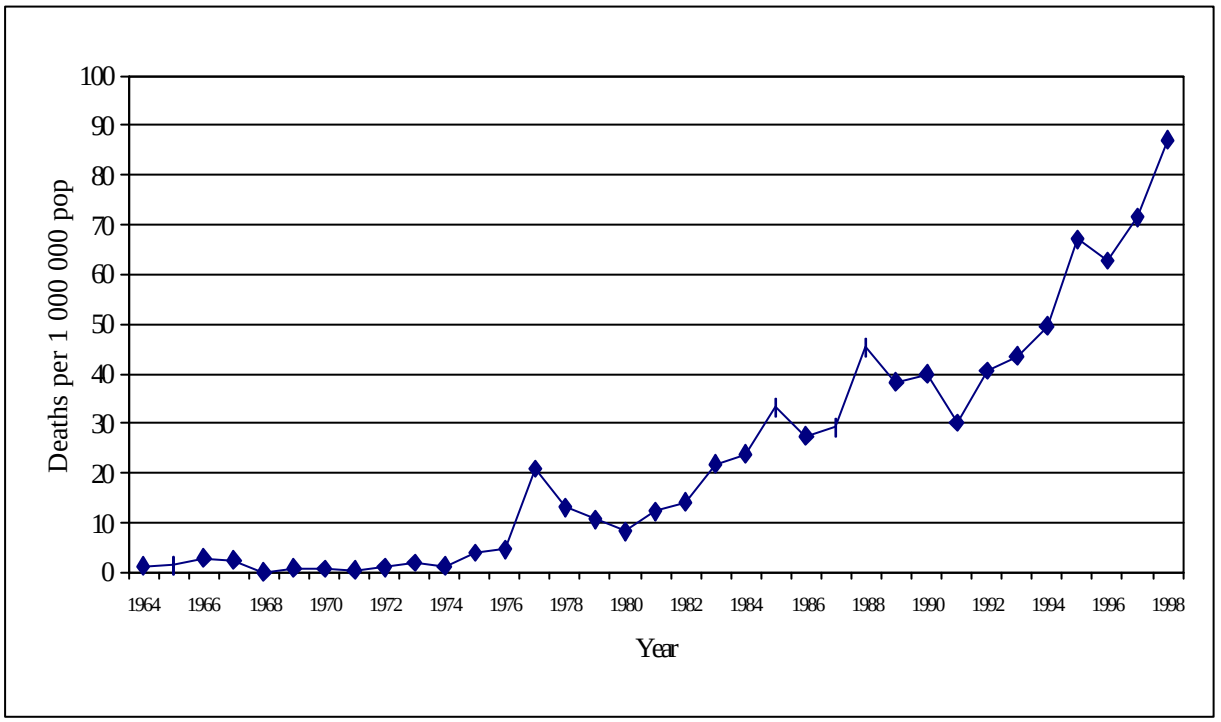
- There are approximately 74,000 dependent heroin users in Australia.
- The estimated prevalence of heroin use in Australia is similar to that in other developed countries.

3.0 Opioid Overdose Mortality

3.1 Australian Experience

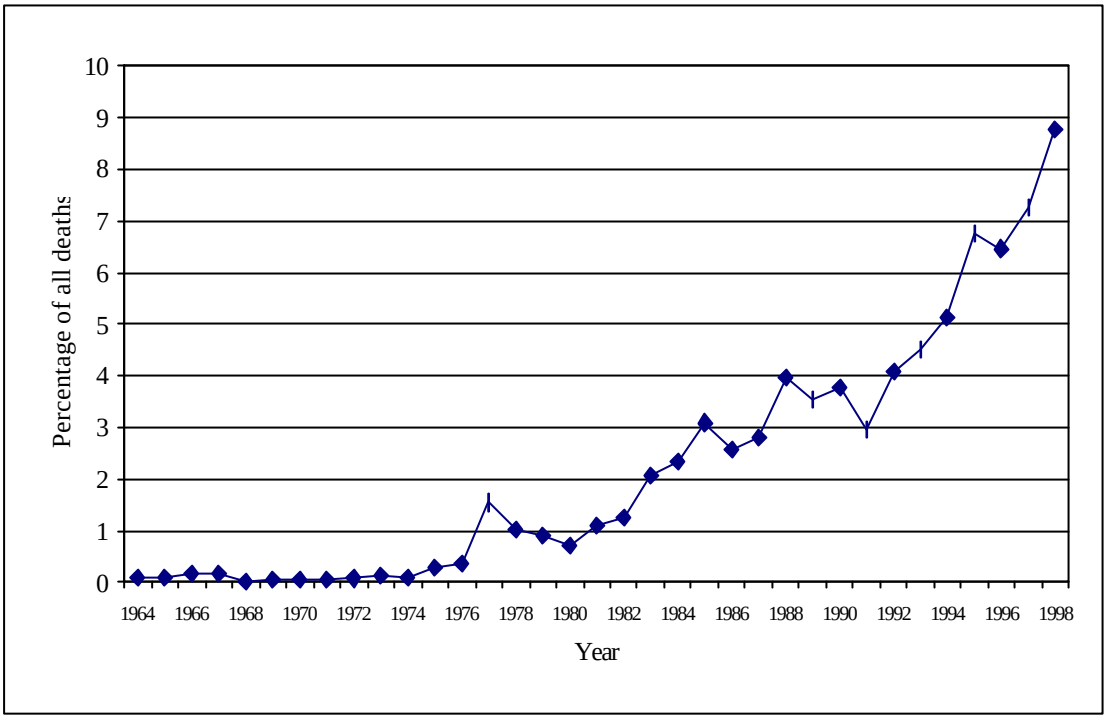
Deaths from opioid overdose among young Australian adults increased dramatically between 1964 and 1998. The number of deaths attributed to opioid overdose among Australian adults aged 15-44 years increased from 6 in 1964 to 737 in 1998. This increase is not explained by the increase in population size over this period, as the rate (per million adults aged 15 to 44 years) increased 67-fold from approximately 1.3 in 1964 to 87.1 in 1998 (Figure 1), while the proportion of all deaths among adults aged 15 to 44 years attributed to opioid overdose increased from 0.08% in 1964 to 8.78% in 1997 (Figure 2) (Hall, Lynskey et al. 2000; McKetin, Darke et al. 2000; ABS 1999).

Figure 1: Overdose death rate per million adults aged 15 to 44 years from 1964 to 1998 (Hall, Lynskey et al. 2000; McKetin, Darke et al. 2000).



Data describing mortality from opiate overdose is collected by the Australian Bureau of Statistics (ABS) based on cause of deaths classified by the coroner. All cases of suspected opiate overdose undergo post-mortem examination. Cause of death is classified according to ICD-10 codes, which allow the coroner to specify whether the cause of death was intentional poisoning (suicide), unintentional poisoning or a result of dependence. Overdose deaths recorded by the ABS exclude deliberate overdoses (suicide).

Figure 2: Proportion of all deaths due to overdose among adults aged 15 to 44 years from 1964 to 1998 (Hall, Lynskey et al. 2000; ABS 1999).



Data presented in Figures 3 and 4 suggests that 1969 was the year in which illicit opioid overdose deaths began to overtake overdose deaths from iatrogenic opioid dependence. Although the number of deaths was small, in this year there was an abrupt change in the proportion of deaths that were male (Figure 3) and in the average age at death (Figure 4). Iatrogenic opioid dependence has primarily been found among middle-aged and older females who become dependent on opioids as a result of their use for chronic pain (Ball and Chambers 1970; Courtwright 1982). Illicit opioid dependence, by contrast, has primarily been found among younger, anti-social males who initiate use in the late teens and begin to die of overdoses in their 20s (Courtwright 1982).

Figure 3: Proportion of opioid overdose deaths in 15-44 year olds occurring among males, 1964-1998 (Hall, Lynskey et al. 2000; McKetin, Darke et al. 2000).

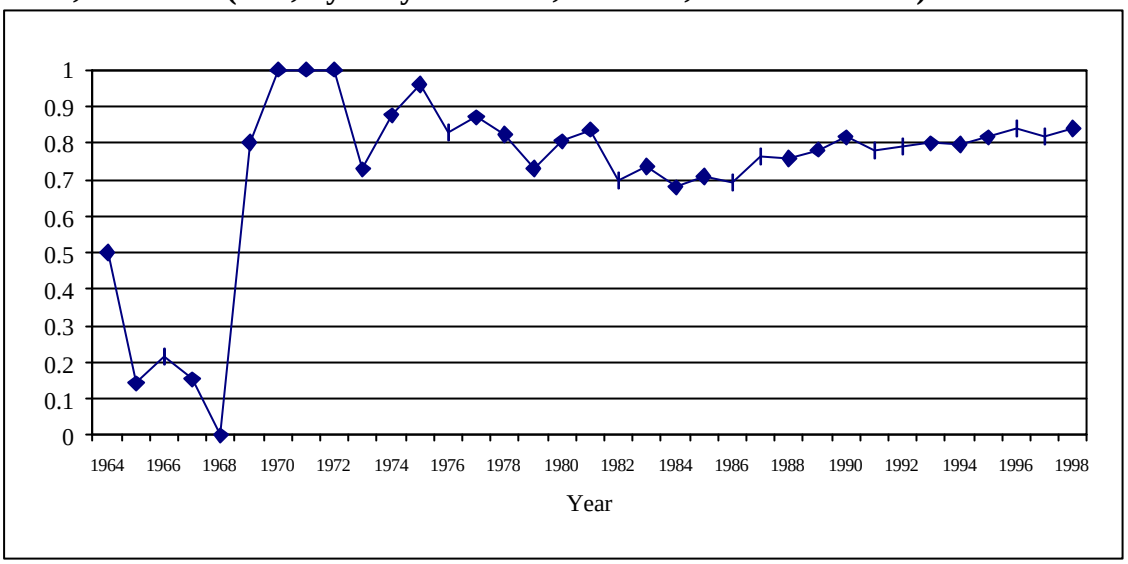
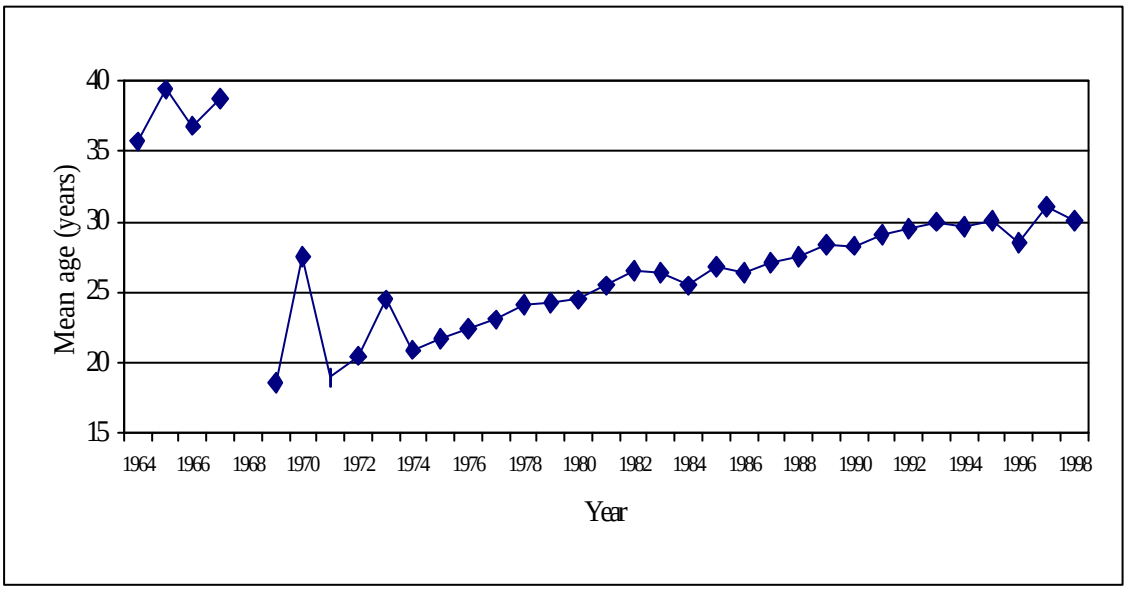


Figure 4: Average age of opioid overdose deaths among persons 15-44 years, 1964 to 1998 (Hall, Lynskey et al. 2000; McKetin, Darke et al. 2000).



The highest rate of fatal overdose occurs in New South Wales. In 1998, overdose fatalities in NSW accounted for 48.6% of all fatal overdoses nationally. Victoria has the second highest rate and the standardised mortality rate among the remaining States and Territories fluctuates quite markedly. While the rate of overdose has increased across all States and Territories, the rate of increase has varied between jurisdictions. In particular over the last decade the rate of opioid overdose has increased more markedly in South Australia, Western Australia, Tasmania, the Northern Territory and the Australian Capital Territory than it has in New South Wales, Victoria or Queensland.

The increase in the rate of fatal opioid overdose in Australia between 1964 and 1998 is unlikely to be an artefact of changes in the way in which deaths among young adults have been classified. Any such change in diagnostic practice would have to be very marked to explain the large increase in mortality rate from these causes between 1964 and 1998. These changes would also need to vary markedly with age and sex to explain the observed trends.

3.2 International Experience

While death rates from opioid overdose among European countries were reported above for comparative purposes, it should be noted that crude differences in reported drug-related mortality need to be interpreted with caution. Even within the European Union, for example, differences exist in registering procedures and classifications of cause of death (DNBH 1997; WHO 1998). For example, if a person known to be heroin dependent dies from pneumonia arising as a complication of what would otherwise have been a non-fatal overdose, should this death be classified as an overdose death, a drug-related death, or a death by infectious disease? Similarly, should accidental poisoning by an illicit drug in a person with no other record of drug involvement, such as a small child, be classified as an overdose, a drug-related death, or as an accidental poisoning? Different countries may classify these deaths in different ways. An extreme example is that of Portugal, where, according to a 1997 Danish Board of Health Report,

"…it is well known that about 90% of drug related deaths are coded with the code for unknown cause of death" (p51).

A recent report by the Home Office has been critical of the system for recording drug related death data in the UK (ACMD, 2000). It notes that deaths may not be classified as drug deaths if they are not referred to the coroner, as can happen when a certifying doctor is unaware of the deceased drug use, or if the death is attributed to an indirect effect of drug use, such as viral infection. There also appears to be a great deal of variation between the propensity of individual coroners to record deaths as drug-related. The report identifies the:

"immediate and evident problem that there are coroners working in areas of known high drug prevalence who never certify a death as related to drug misuse" (AMCD 2000, p80).

Other sources for variation within the UK drug recording framework include the fact that neither post-mortem nor toxicological analysis are formally required for suspected drug related deaths; that the verdicts available to the coroner are not mutually exclusive; that coroners do not have the necessary skills to distinguish between the verdicts available to them, most notably "dependence on drugs" and "non-dependent abuse of drugs"; and that there is no requirement of the coroner to identify the drugs involved (AMCD 2000).

Inter-country variation also exists as to how much information is gathered about the circumstances or cause of death (DNBH 1997; WHO 1998). In Australia, for example,

autopsy is routinely conducted on all suspected overdose deaths, making forensic and toxicological data available on which to base the classification of cause of death. This, however, is a far from universal practise. In the United States, for example, only approximately 20% of drug-related deaths are subject to autopsy (WHO 1998). Similarly, while the immediate cause of death is recorded in death registers, contributing factors may or may not be recorded (DNBH 1997; WHO 1998). Whether or not contributing factors are recorded can cause large differences in analyses of drug-related deaths based on death registers.

In recognition of the difficulties inherent in comparing drug related mortality between countries, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Eurostat, and the World Health Organisation are collaborating to produce standard guidelines for reporting results from mortality and forensic registers. In addition the EMCDDA has developed a standardised protocol for the conducting of mortality cohort studies of drug users recruited in treatment centres (EMCDDA 1999). These protocols may lead to better comparisons of overdose mortality between member countries of the European Union.

While crude differences in drug-related mortality must be interpreted with caution, it can be argued that time trends in drug-related deaths between countries may provide a more robust basis for comparison, assuming that classification of cause of death within a particular registration system are relatively constant over time. Thus while it is difficult to say with any certainty whether gross differences in reported drug mortality rates between countries truly reflect actual differences, consistent differences in *rates of change* in reported drug-related deaths between countries are likely to be more reliable indicators of differences in mortality between countries (DNBH 1997).

Based on the data that is currently available, the recent marked increases in fatal opioid overdose reported earlier do not appear to be peculiar to Australia. The EMCDDA (1999) reports that drug related deaths in Ireland, Greece, Austria and Sweden in particular appear to have been increasing steadily over the last decade, but cautions that previous under-reporting may be contributing to these trends. There have been similar rises in the rate of fatal opioid overdose reported in the Nordic countries (Steentoft, Teige et al. 1996); Spain (Fuente, Barrio et al. 1995; Sanchez, Rodriguez et al. 1995); Italy (Davoli, Perucci et al. 1997); Austria (Risser and Schneider 1994); the United States (USDHHS 1997; Drucker 1999); and England and Wales (Neeleman and Farrell 1997; Hall, Lynskey et al. 1999).

The rate of opioid overdose deaths in the UK, for example, dramatically increased between 1985 and 1995. ICD-9 coded opioid deaths notified to the Office of National Statistics in the United Kingdom between the years 1985 and 1995 indicate that the proportion of all deaths attributed to opioid overdose increased from .02% of all deaths in the UK in 1985 to .12% in 1995. This represented a six-fold increase in the proportion of all deaths attributed to opioid overdose (Hall, Lynskey et al. 2000).

While the observed increases in Australian overdose rates are reflected in many English

speaking countries, such as the United Kingdom, a small number of countries have observed decreases in overdose deaths over the last decade. The EMCDDA (1999) reports that drug-related deaths appear to have been decreasing in France, Belgium, and Germany since 1991, and that drug related deaths in The Netherlands, Portugal, Finland, Italy, Luxembourg and Spain appear to have stabilised or declined since 1995. Over the last decade reductions of between 18% and 80% in total numbers of overdose deaths have been reported in France; Switzerland; the Netherlands and at least some parts of Germany.

3.3 Non-Fatal Opioid Overdose in Australia

Non-fatal opiate overdoses are common among heroin users (Darke, Ross et al. 1996a). Non-fatal overdoses may be defined as instances where loss of consciousness and depression of respiration occurs but is not fatal. While trends in fatal overdose have been well documented, data on non-fatal overdose is sparse. Studies that have investigated non-fatal overdose report that a large proportion of regular heroin users have experienced non-fatal overdose.

The Illicit Drug Reporting System (IDRS) found that in 1999 51% of a sample of 396 IDUs reported having experienced a non-fatal overdose at some time in their lives. Of this sample 29% reported overdosing in the previous 12 months. Regional differences were noted in the proportion of users that reported experiencing an overdose in the previous 12 months. In Adelaide 20% of users reported overdosing in the previous year, compared to 28% of Sydney users and 36% of Melbourne users (McKetin, Darke et al. 2000). The geographic variation in non-fatal overdose rates reported by the IDRS is also evident from other studies (Darke, Ross et al. 1996; McGregor et al. 1998). The proportion of Sydney users in this study that reported having experienced non-fatal overdose in the preceding year is supported by a previous study of non-fatal overdose among Sydney heroin users (Darke, Ross et al 1996a).

Darke, Ross et al. (1996a) found that 68% of a sample of 329 Sydney users reported having experienced an overdose at least once, with 20% of the sample overdosing in the last year. In a similar study McGregor (1998) found that 11% of a sample of 218 Adelaide heroin users reported experiencing an overdose in the previous six months. The limited data on Australian non-fatal overdose is in broad concurrence with overseas experience.

A recent British study, for example, found that 58% of 212 heroin users reported having ever overdosed, while 30% had overdosed in the preceding 12 months (Bennett and Higgins 1999). These findings were higher than an earlier British study that found that 22% of 432 users reported having ever overdosed, 9% in the preceding 12 months (Gossop, Griffiths et al. 1996). While it is possible that this difference reflects a true increase in non-fatal overdose rates in the UK, it is more likely to be attributable differences between the two studies. Of particular note is the fact that a substantially greater proportion of subjects in the second study nominated smoking as their preferred route of administration, as opposed to injecting.

Given the high prevalence of overdose, it is not surprising that the vast majority of heroin users have witnessed an overdose. Darke, Ross et al. (1996b) found that 86% of users reported having been present at at least one overdose, with a median number of 6 overdoses witnessed. Half reported having been present at an overdose in the last 12 months. Of the last overdoses witnessed 5% had been fatal (Darke, Ross et al. 1996b). Similarly, McGregor (1998) found that 70% of Adelaide users had witnessed another's overdose. Bennett and Higgins (1999) report similar proportions of heroin users having witnessed overdoses, with 70% ever having witnessed an overdose and 58% having witnessed an overdose in the preceding 12 months.

3.3.1 Non-fatal overdoses attended by ambulance officers

Ambulance calls to suspected drug overdoses are an important source of information regarding trends in heroin use and overdose. The first reported study of this kind occurred in Hamburg, Germany in 1990/91 (Schulz-Schaeffer, Peters et al. 1993). The authors were able to use this data to describe the demographic characteristics of overdose victims and the circumstances of overdose. They noted a 34% increase in the number of overdoses attended over the two years studied.

The first Australian study of this kind occurred in Canberra between 1990 and 1993 (Bammer, Ostini et al. 1995). Thirty-six heroin overdose cases were reported, with another 35 cases suspected as involving heroin, but without definitive evidence (e.g. victim responded to naloxone, but denied heroin use). While a time-series was not conducted as part of this study, the authors noted a general increase in the number of overdoses occurring over the three-year study period.

Degenhardt et al (2000) examined NSW ambulance call out records for suspected overdoses from July 1997 to June 1999. They reported that the number of call outs for suspected overdose increased from 4,335 in 1997-1998 to 5,989 in 1998-1999. Deitze et al (2000) recently presented data from a newly developed database of ambulance attendance at non-fatal overdose in Melbourne. They identified 388 non-fatal overdoses over a three-month period in 1997-1998 and again were able to identify demographic characteristics of victims and the circumstances of overdose. The authors concluded that the database has the potential to provide clear indicators of trends in heroin use and overdose and as such may be an excellent monitoring mechanism. Further examination of this database, and of other ambulance records, is required to ascertain whether observed increases in non-fatal overdose rates reflect a true trend of increasing ambulance call outs for suspected overdose, and to establish whether any such trend is indicative of an increase in overdose rates or an increase in the proportion of overdoses attended by ambulance services.

3.3.2 Estimating the total number of non-fatal overdoses in Australia

The number of ambulance call outs to suspected overdoses also provides a method for estimating the *number* of non-fatal overdoses, for which no other records are available. Darke (1996b) reported that an ambulance was called to 56% of overdoses witnessed by

other heroin users. Similarly, Thackaway and Poder (2000) reported that an ambulance was called to 44% of witnessed overdoses. Using these figures to extrapolate from the number of Ambulance attendances reported by Degenhardt et al (2000) we can estimate that for 1997-1998 there were between 7,700 and 9,850 overdoses in NSW. Assuming that the proportion of fatal to non-fatal overdoses in NSW is the same as the proportion of fatal to non-fatal overdoses in other jurisdictions we can use the proportion of national overdose fatalities that occurred in NSW, 48.6% (McKetin, Darke et al 2000), to calculate that there were between 16,000 and 20,500 non-fatal overdoses nationally in 1997.

An alternate method for estimating the prevalence of non-fatal overdose is to multiply the prevalence of dependent heroin use by the proportion of users who report having overdosed in the last 12 months. Using the estimate of 74,000 dependent users, as described above, and the prevalence of overdose reported by Sydney users gives a prevalence of approximately 10,500 to 15,000 fatal and non-fatal overdoses nationally per year.

A third method of estimating the prevalence of non-fatal overdose is by extrapolating from the number of fatalities from overdose. If the ratio of fatal to non-fatal overdoses among those witnessed (1 in 20) reflects the true ratio of fatal to non-fatal overdoses we can estimate that the 737 overdose deaths in Australia in 1998 represent approximately 14,750 overdoses in that year.

The three estimates of non-fatal overdose prevalence extrapolated from Darke (1996b), Thackaway and Poder (2000), Degenhardt (2000), overdose fatality data, and estimates of the prevalence of heroin dependence are in broad agreement. These three methods suggest that the current total prevalence of fatal and non-fatal overdose in Australia lies in the range of 10,500 to 20,500 annually, with a best estimate of 15,000.

Summary

- Opioid overdose was responsible for 737 deaths in Australia in 1998.
- The death rate from opioid overdose more than doubled from 38.3 to 87.1 per 1,000,000 between 1989 and 1998.
- It is estimated that there are between 10,500 and 20,500 non-fatal overdoses in Australia annually.

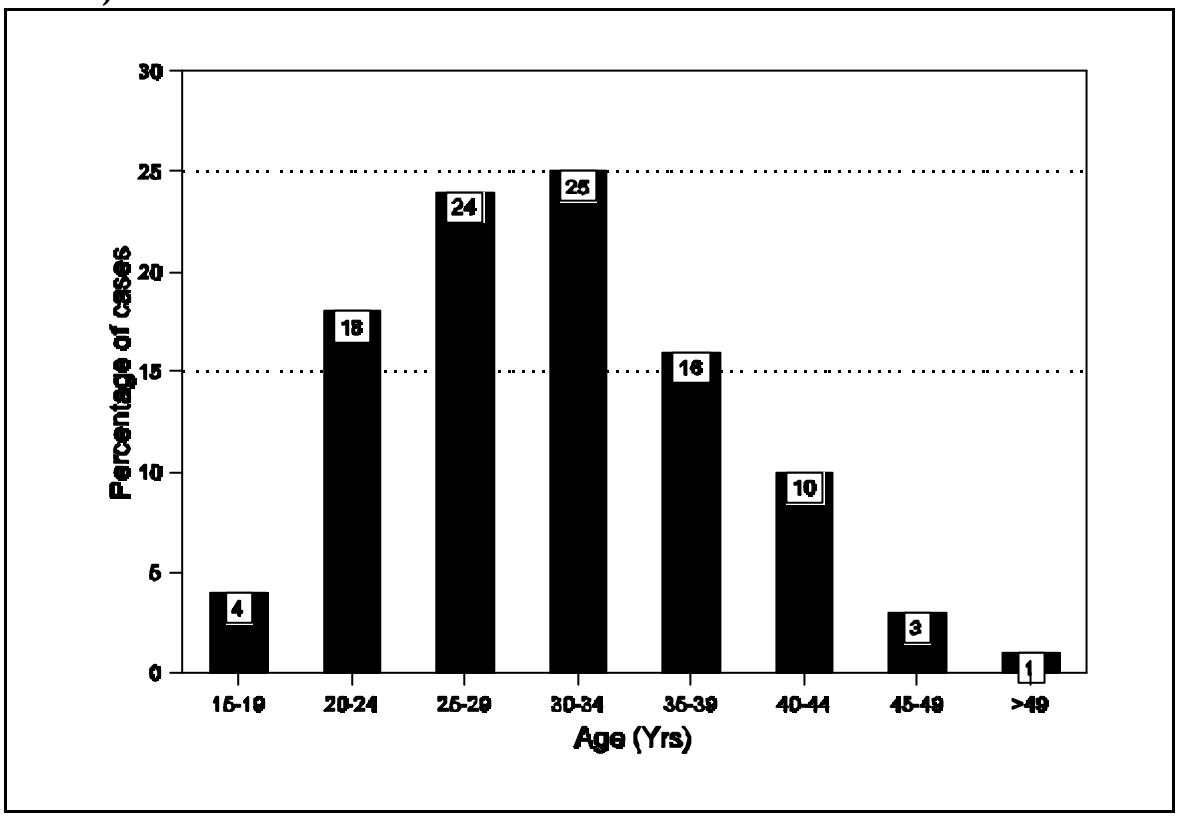
4. Characteristics of victims and circumstances of overdose

4.1 Characteristics

4.1.1 Age

It is commonly believed that many overdose deaths occur among young, relatively inexperienced heroin users. However, Hall and Darke (1997) found that the average age of those dying from overdose in 1995 was 30.6 years having increased from 24.2 in 1979. This is supported by a South Australian study that found the average age of fatal overdose victims from 1994 to 1997 to be 29.4 years (McGregor, Hall et al. 1999). Similarly, Darke, Ross et al (2000) reported that the average age among males dying from opioid overdose in New South Wales between 1992 and 1996 was 31.0 years, and that males were on average three years older than females at death (Figure 5). Only 4% of cases were below the age of twenty at the time of death.

Figure 5: Age distribution of NSW heroin-related fatalities, 1992-1996 (Darke, Ross et al. 2000).



4.1.2 Gender

While males and female heroin users are equally likely to have experienced a non-fatal overdose (Gossop, Griffiths et al. 1996; Darke, Ross et al. 1996a; Darke, Ross et al. 1999; McGregor, Hall et al. 1999), males are consistently over-represented in fatalities attributed to overdose (see Figure 4) (Cherubin, McCusker et al. 1972; Harlow 1990; Frischer, Bloor et al. 1993; Zador, Sunjic et al. 1996), accounting for over 80% of recorded fatalities in some studies (Cherubin, McCusker et al. 1972; Zador, Sunjic et al. 1996). In South Australia between 1994 and 1997, for example, males accounted for 72% of overdose fatalities (McGregor, Hall et al. 1999), while in NSW between 1992 and 1996 males formed the overwhelming majority of cases (85%) and never comprised less than 82% of cases over all years (Darke, Ross et al. 2000).

The over-representation of males in overdose fatalities is explained in part by the higher prevalence of heroin use among males. It has been well documented that males constitute a majority of heroin users, with studies typically reporting two thirds of current users as being male (McGregor, Hall et al. 1999). However, even when this is taken into account males are still consistently over-represented among fatal cases. A possible explanation for this over-representation of males among overdose fatalities may be increased use of alcohol among males, as described in section 4.1.6.

4.1.3 Length of heroin using career

Contrary to popular belief, the `typical' overdose victim is not a young novice or inexperienced user. Consistent with this have been studies linking mortality with longer heroin using careers (Davoli, Perucci et al. 1993; Eskild 1993). Darke, Ross et al. (2000) found that of 953 heroin-related deaths 88% were known heroin users, the overwhelming majority of which were dependent (85% of all cases). Less than one percent of cases (7 individuals) were believed to be novice users. In a study by Zador et al. (1996) eighty per cent of overdose deaths were found to be dependent, regular users, while only two were identified as novice heroin users. Both of those cases were classified by the coroner as suicides. Given that the mean age of death reported in most studies is approximately 30 years, and that heroin using careers typically start in the late teens (Lynskey and Hall 1998), most fatal cases have been using heroin for a considerable amount of time prior to death. This also holds true for non-fatal overdose.

In their study of the non-fatal overdose experience of Sydney heroin users, Darke, Ross et al. (1996a) found that a median of 30 months had elapsed between commencing regular heroin use and first overdose. Less than a quarter reported that their first overdose occurred within the first twelve months of heroin use. They also found that length of heroin using career and higher levels of dependence were associated with an increased risk of overdose. It appears, therefore, that overdose (both fatal and non-fatal) seems to occur later in the heroin using career, probably as drug involvement increases.

4.1.4 Marital and Employment Status

The majority of fatal overdose victims have been found to be single at the time of death, although there is a significant gender difference. While males are more likely to be single, the reverse is true for females (Darke, Ross et al. 2000). McGregor, Hall et al. (1999) found that 75% of South Australian fatalities were single. A longitudinal study conducted among Italian heroin users found that being single was a risk factor for overdose (Davoli, Perucci et al. 1993). It is possible that being single contributes to fatalities, as the person is more likely to be alone at the time of the overdose, and therefore less likely to be resuscitated.

Unemployment may also be a risk factor for overdose. McGregor, Hall et al. (1999) found that 87% of fatalities were unemployed at the time of death. In their investigation of NSW heroin related deaths between 1992 and 1996 Darke, Ross et al. (2000) found that 69% of victims were unemployed at the time of death. However, further research is required to establish whether unemployment rates are higher in among victims of fatal overdose relative to living heroin users, as this population is typically underemployed. McKetin (2000), for example, reported an unemployment rate of 69% in a sample of living injecting drug users. Marital status and employment status of all NSW heroin fatalities between 1992 and 1996 are presented in Table 1 (Darke, Ross et al. 2000).

Table 1: Marital status and employment status of NSW heroin-related fatalities, 1992-1996 (Darke, Ross et al. 2000).

Variable	Males (N=812)	Females (N=141)	Total (N=953)
Marital status (%):			
Single	76	32	74
Married/defacto	24	67	25
Unknown	<1	<1	<1
Employment status (%):			
Unemployed	67	79	69
Employed	33	21	31
Unknown	<1	<1	<1

4.1.5 Treatment

Overdose fatalities are less likely to have been in treatment at the time of death than living heroin users (Joe, Lehman et al. 1982; Gronbladh 1990; Segest, Mygind et al. 1990; Perucci, Davoli et al. 1991; Davoli, Perucci et al. 1993; Caplehorn, Dalton et al. 1994; Fugelstad, Rajs et al. 1995). Only 2% of heroin-related deaths in 1992 in New South Wales, Australia, were in methadone maintenance at the time of death, and 75% had never been in methadone treatment (Zador, Sunjic et al. 1996).

Current users enrolled in methadone maintenance were half as likely to report an overdose in the preceding six months as current users who were not in methadone maintenance treatment (Caplehorn, Dalton et al. 1994). Subjects who were enrolled in methadone maintenance over the preceding six months were significantly less likely to report an overdose in that period.

4.1.6 Polydrug Use

Concomitant use of opioids with other CNS depressant drugs appears to be common among opioid overdose fatalities (Ruttenber and Luke 1984; Ruttenber, Kalter et al. 1990; Walsh 1991; Goldberger, Cone et al. 1994; Zador, Sunjic et al. 1996). Concurrent use of alcohol and the benzodiazepines (Richards, Reed et al. 1976; Monforte 1977; Chan, Prolov et al. 1988; Fugelstad 1994; Zador, Sunjic et al. 1996; Darke and Zador 1996c) are especially prominent in opioid overdose fatalities. For example, Zador (1996) reported that alcohol was detected in 45% of heroin related deaths. The mean blood alcohol concentrations among these cases was 0.14g/ 100 ml and there was a negative correlation between blood morphine and alcohol concentrations, indicating that those individuals who had been drinking alcohol had lower mean blood morphine levels when they died. Table 2 summarises the results of 11 separate investigations into the toxicology of heroin-related deaths. From this it can be seen that morphine is rarely the sole drug detected at autopsy. Alcohol is frequently found at autopsy, often in a majority of cases. Benzodiazapines are also commonly reported. Considering the polydrug using patterns of heroin users, this is not surprising (Clayton 1986; Darke and Hall 1995).

Table 2. Presence of other drugs at autopsy of heroin related deaths.

Study	Morphine only	Alcohol present	Mean BAC (g/100ml)	Benzodiazapines present	N
Darke et al. 2000	24%	46%	0.13 (median)	27%	953
Monforte 1977	23%	68%	0.14	12%	100
Zador et al. 1996	27%	45%	0.14	27%	152
Richards et al. 1976	35%	34%	0.13	22%	114
Manning & Ingram 1983a	26%	68%	0.10	NA	81
Golberger et al. 1994	13%	74%	0.16	9%	23
Risser & Schnieder 1994	NA	29%	NA	13%	355
Ruttenber & Luke 1984	NA	74%	0.09	NA	260
Walsh 1991	NA	48%	0.14	24%	21
Steentoft et al. 1988	40%	32%	NA	NA	245
Fugelstad 1994	NA	75%	NA	55%	265

NA- not reported

The association between fatal heroin overdose and concomitant alcohol use may provide a possible reason for the over-representation of males among overdose fatalities, since males are three times more likely to have alcohol detected at autopsy. The combination of these two CNS depressants may well increase the probability of males experiencing a fatal overdose. While a higher proportion of females had benzodiazepines detected, there was no obvious relation between blood morphine concentrations and benzodiazepine use.

The evidence of polydrug use in fatal overdose is consistent with the experience of non-fatal overdose victims, particularly in terms of alcohol and benzodiazepine use. Darke, Ross et al (1996a) found that two thirds of most recent overdoses among a sample of Sydney heroin users involved the presence of another central nervous system depressant. Overall, overdoses involving heroin use alone are in the minority.

4.2 Circumstances

Most studies to date have focussed on the toxicology and epidemiology of fatalities attributed to overdose. A few, however, have examined some of the surrounding circumstances (Garriot and Sturner 1973; Monforte 1977; Drew 1982; Manning and Ingraham 1983; Walsh 1991; Zador, Sunjic et al. 1996).

4.2.1 Route of Administration

One behavioural factor that may become of increasing relevance in relation to overdose is route of administration. In the last decade, the smoking of heroin appears to have become more widespread as the preferred route of administration (Grund 1993; Griffiths 1994), particularly in the United States and the European countries. This is also true in Australia, most notably among Indo-Chinese users in the Sydney region (Darke and Ross 2000). In a Dutch study of non-fatal overdoses, only 6% of Surinamese heroin users reported having overdosed, compared to 29% of Dutch born users (Grund 1993). The relative levels of injecting for these groups were 4% and 37% respectively, suggesting a link with route of administration and overdose. Darke and Ross (2000) report that only 1% of a sample of 953 overdose fatalities in NSW resulted from non-injecting routes of administration. Smoking heroin may be a less dangerous route of administration because the drug effect is achieved by repeated small doses rather than a single injection.

4.2.2 Time between Administration and Death

Another variable of interest, the interval of time between the final injection of heroin and death, has been estimated in several studies (Garriot and Sturner 1973; Monforte 1977; Nakamura 1978; Manning and Ingraham 1983; Zador, Sunjic et al. 1996). Instant death following heroin administration does not appear to be the norm. Manning and Ingraham (1983) reported that only 23% of cases collapsed immediately after injection. Only 14% of cases in the study by Zador, Sunjic et al. (1996) were classified as instant, with 22% estimated to have died over a period of time longer than three hours. An interval of more than three hours was reported in over half (52%) of cases studied by Garriot and Sturner (1973), while Nakamura (1978) reported that in 44% of cases the interval was greater than 2 hours. Darke, Ross et al. (2000) found that an estimate of the elapsed time between heroin use and death was able to be made in 84% of cases and that in 26% of cases death was estimated to have occurred more than an hour after the final ingestion of heroin.

4.2.3 Location

In Australia, autopsy is routinely conducted on suspected opiate overdose cases, and coronial records identify the location of death. Studies that have examined coronial files have found that the majority of deaths occur in a private home. McGregor, Hall et al. (1999) in their study of South Australian fatalities, for example, reported that 71% of deaths occurred in a private home, while Darke, Ross et al. (2000) in their study of NSW fatalities found that nearly a half of cases (46%) died in their own home, with a further

15% dying in the home of friends or family. The location of death for all heroin fatalities in NSW between 1992 and 1996 is shown in Table 3 (Darke, Ross et al. 2000).

Table 3: Physical location of deaths in NSW, 1992-1996 (Darke, Ross et al. 2000)

Location of death	Males (N=812) %	Females (N=141) %	Total (N=953) %
Own home	45	51	46
Home of friend or family	15	14	15
Street/Park/Bushland	13	6	12
Hotel room	8	9	8
Public toilet	5	3	4
Hospital	4	8	5
Car	4	4	4
Prison	2	1	2
Railway station/Train	2	2	2
Hotel/club	2	2	2

This pattern also holds true for non-fatal overdose. Eighty-one percent of non-fatal overdoses among Adelaide heroin users occurred in a private home (McGregor, Hall et al. 1999), while two thirds (66%) of Sydney heroin users reported that their last overdose occurred in a home environment, with only 10% reporting that they had last overdosed on the street (Darke, Ross et al. 1996a).

However, some distinct regional differences have been noted in relation to location of death. Darke, Ross et al. (1999) noted that among the 191 fatalities in Kings Cross and immediate surrounds 47% died in home environments, 25% in hotel rooms and 19% in public places. Among the 144 cases in Cabramatta and surrounds, 65% occurred in a public place, 27% in homes and 4% in hotel rooms. It is probable that this geographic clustering of deaths in public is related to the pronounced presence of the heroin market in these two areas. The high rate of death in a public place in the Cabramatta region is likely to reflect the nature of heroin transactions in the area, in that many heroin users resident outside the area travel to the region specifically to purchase heroin, and hence consume it in public rather than waiting until they return home. By contrast, Kings Cross appears to have a resident population of heroin users, as is reflected in the proportion of overdoses that occur in private homes. A number of cheap hotels also exist in Kings Cross which offer users a private place to consume heroin purchased in the area.

Geographic clusters have also been noted in the distribution of heroin deaths across NSW. Of the fatalities between 1992 and 1996, twenty percent occurred outside the Sydney metropolitan region. In order to examine the impact of the major NSW drug markets (Kings Cross and Cabramatta) on overdose fatalities, Darke, Ross et al. (1999) investigated the number of overdoses that occurred in these localities and their immediate surrounds. Twenty percent of all NSW overdose deaths occurred in the 2km radius surrounding inner city Kings Cross, while 15% of all cases occurred in the 4km radius around Cabramatta in South-Western suburban Sydney. Overall, these two distribution points accounted for 35% of all heroin-related fatalities in NSW between 1992 and 1996.

4.2.4 Time

Few studies have investigated the time, day, or season of death. While it is commonly believed that temporal patterns in overdose fatalities exist, there is little evidence for this. McGregor, Hall et al. (1999), for example, in their study of the circumstances of overdose death in South Australia between 1994 and 1997, found no significant differences in the numbers of deaths across seasons of the year. Overdose deaths were more likely to occur on Thursdays and Saturdays, and between 6pm and 6am, with fewest deaths occurring early in the week and during daylight hours. However, this is contradicted by Darke, Ross et al. (1996a), who found no weekend over-representation of non-fatal overdoses among a sample of Sydney heroin users. Similarly, among overdose fatalities Darke, Ross et al (1999) found no weekend clustering of deaths nor any monthly variation, but did report that deaths more frequently occurred on Thursdays and Fridays.

4.2.5 Suicide?

A common belief in the general population is that overdose deaths are often intentional, and are therefore misclassified suicides. However a significant body of evidence is inconsistent with this belief (Kjelsberg, Winther et al. 1995; Vingoe, Welch et al 1999). Deliberate opioid overdoses (suicides) and accidental overdoses are classified and recorded differently in mortality statistics. Separate International Classification of Disease (ICD) codes are used for suicide and accidental overdose, and it is relatively easily to distinguish between them. Suicide by overdose generally involves large doses, indicated by high blood morphine concentrations (Darke, Ross et al. 2000). By contrast, accidental overdose victims generally have relatively low blood morphine concentrations, as discussed earlier. Moreover, when heroin users do commit suicide they prefer methods other than heroin overdose (Oyefeso, Ghodse et al. 1999; Vingoe, Welch et al. 1999).

While drug dependent people are over-represented among suicide mortalities (Farrell, Neeleman et al. 1996; Vingoe, Welch et al. 1999), suicide only accounts for a small proportion of mortality in this group. In the UK in 1992, for example, 6% of mortality among registered addicts was attributable to suicide, whereas 55% was attributable to accidental overdose (Farrell, Neeleman et al. 1996). Darke, Ross et al. (2000) reported that only 5% of heroin related fatalities in NSW between 1992 and 1996 were suicides.

Survivors of non-fatal opioid overdoses rarely report that their overdose had been a suicide attempt. Only one percent of subjects in Darke, Ross et al.'s 1996(a) study, for example, reported that their last overdose had been deliberate, and less than 2% of subjects in McGregor et al.'s 1999 study reported that their last overdose had been a suicide attempt. Similarly, at fatal overdoses where others were present, witnesses rarely report that the overdose had been deliberate. McGregor et al. (1999), for example, report that less than 1% of witnessed overdoses were believed to be suicide attempts.

4.2.6 Witnesses

There is evidence that the majority of deaths attributed to overdose occur in the company of others (Drew 1982; Manning and Ingraham 1983; Walsh 1991; Zador, Sunjic et al. 1996). Others were present at the time of death in 58% of cases reported by Zador (1996). Similar studies have reported the presence of others in 61% (Walsh 1991), 79% (Drew 1982) and "more than half" (Manning and Ingraham 1983) of fatal overdoses. In 61% of NSW fatalities between 1992 and 1996 others were present or in close proximity to the victim (Table 4) (Darke, Ross et al. 2000).

Table 4: Presence of other persons at time of death of NSW heroin-related fatalities, 1992-1996 (Darke, Ross et al. 2000).

Presence	Males (N=808) %	Females (N=137) %	Total (N=945) %
Died alone	40	35	39
Died in presence of others	32	42	34
Died segregated from others	28	23	27

The majority of non-fatal overdoses also occur in the company of others. Darke, Ross et al. (1996a) found that 85% of non-fatal overdoses experienced by Sydney heroin users occurred in the company of others, while McGregor et al. (1998) reported that 88% of non-fatal overdoses experienced by a sample of Adelaide heroin users had occurred in the company of others.

It appears that overdosing in the presence of others decreases the lethality of overdose. Darke, Ross et al. (1996a) found that only 10% of Sydney heroin users interviewed reported always injecting alone, yet in 40% of overdose fatalities in NSW between 1992 and 1996 the victim died alone. While these data are limited they suggest that users who inject alone are over-represented in overdose fatalities.

While overdose frequently occurs in the company of others, witnesses to fatal overdose (commonly other heroin users), appear reluctant to seek assistance (Louria, Hensle et al. 1967; Drew 1982; Manning and Ingraham 1983; Zador, Sunjic et al. 1996). In a study investigating the experience of others' overdose among Adelaide heroin users, McGregor, Darke et al. (1998) found that an ambulance was called in 45% of cases, while in a Sydney study Darke, Ross et al. (1996b) found that an ambulance was called in just over half of the incidents (56%). In the later study females were found to call ambulances sooner than males and were twice as likely to state that their first action at the last overdose was to call an ambulance. Manning (1983a) reported that in 42% of cases, help was only sought three hours after the final injection and that other remedies, such as cold showers and injections of home-made saline, were attempted prior to seeking help. In only 10% of fatal cases in Zador, Sunjic et al.'s (1995) study was medical assistance sought prior to death: there was no intervention before death in 79% of cases. Darke, Ross et al. (2000) found that in 56% of cases in which others were present, no intervention occurred prior to death.

Nearly half (44%) of the 284 subjects in Darke, Ross et al.'s (1996b) study of Sydney heroin users reported that something had ever stopped or delayed them seeking help for a person who had overdosed. A fifth (19%) reported that this had happened the last time that they were present at an overdose. Fear of police involvement was overwhelmingly the main reason for stopping or delaying seeking help (54%). In their study of Adelaide users, McGregor, Darke et al. (1998) reported that 40% of users who had witnessed an overdose reported that they had, on at least one occasion, delayed or not called an ambulance. The major perceived impediment to calling for medical assistance in this study was also a fear of police involvement (80%). The fear of police involvement following an overdose is not entirely an unrealistic one, as users are sometimes charged with manslaughter for administration of the drug to the person who overdosed.

Summary

- Victims of overdose are predominately single, unemployed men aged in their late 20s. and early 30s, with a long history of heroin dependence.
- Enrollment in treatment protects against overdose.
- Concomitant alcohol or benzodiazepine use, and recently depleted tolerance, are significant risk factors for overdose.
- Death from overdose is rarely instantaneous.
- Overdose most commonly occurs in a private home, with or near other people.
- Witnesses of overdose are reluctant to seek help.

5.0 Causes & Mechanisms

5.1 The pharmacology of heroin

Heroin (diacetylmorphine) is rapidly hydrolysed to 6-monoacetylmorphine which in turn is hydrolysed to morphine following intravenous administration in humans (Goodman and Gilman 1991). Heroin is mainly excreted in the urine as free and conjugated morphine. The blood concentration of morphine, the metabolite of heroin, depends on route of administration, drug dose, body weight, time elapsed since the last dose, and individual pharmacokinetics (Aderjan, Hoemann et al. 1995). The significant individual differences that exist in metabolic rates, and therefore rates of drug metabolism, and the genetic variation that exists in the expression of enzymes which metabolise drugs mean that "there are likely to be slow and rapid converters of heroin" (White and Irvine 1999, p965).

5.2 Mechanisms of heroin-caused deaths

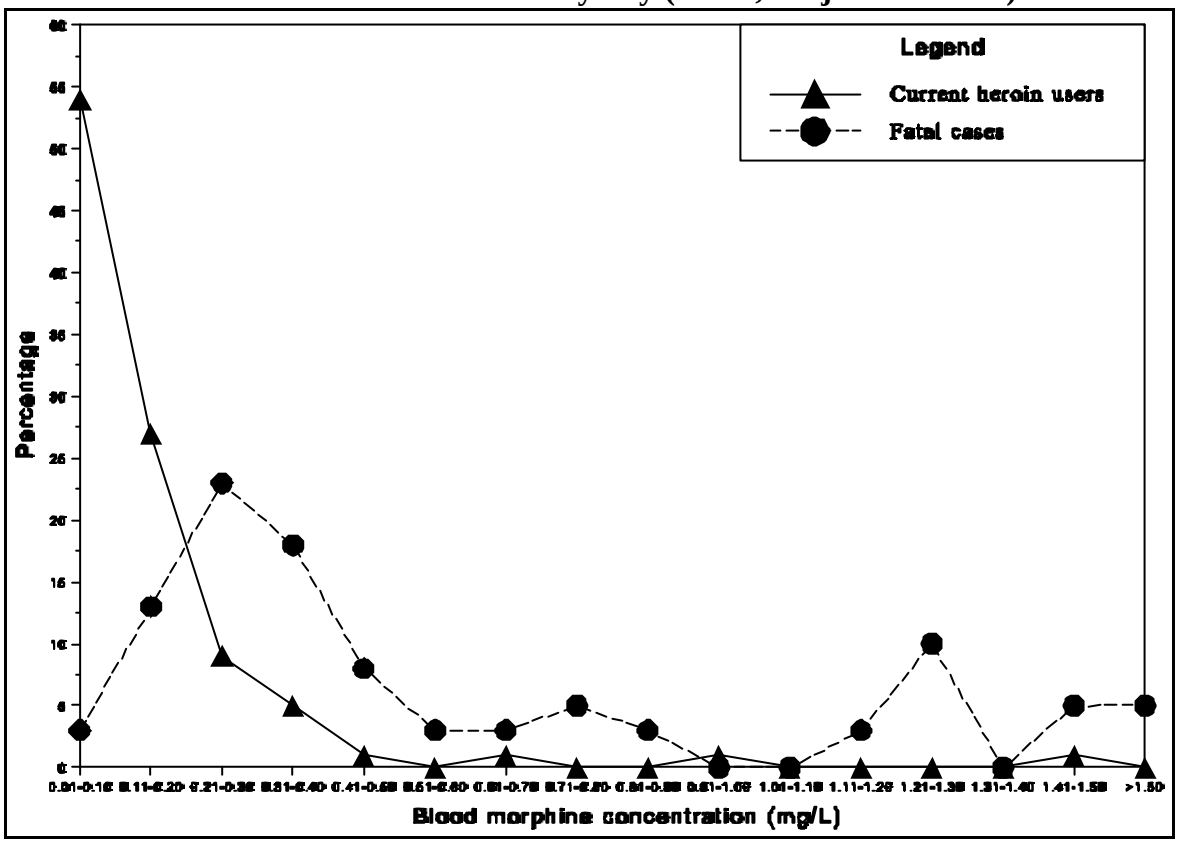
Cardinal signs of heroin toxicity include a reduced level of consciousness from drowsiness or a stuporous state to coma, pinpoint pupils and a depressed respiratory rate. Cyanosis, hypotension, bradycardia and hypothermia may also be present. Death is usually due to respiratory failure (Goodman and Gilman 1991). A number of papers have speculated on the clinical and etiological significance of pulmonary oedema (Cherubin, McCusker et al. 1972; Force, Fisher et al. 1973; Byers, Soin et al. 1975). However, although congested lungs and histopathological evidence of pulmonary oedema are frequently reported at autopsy in cases of heroin-related deaths, these are non-specific findings commonly documented in many cases of death due to respiratory failure. High doses of opiates have an emetic effect and therefore carry a risk of aspiration of vomit while intoxicated. However this is a very rarely reported phenomenon and is unlikely to be of epidemiological significance (Henry 1999).

5.2.1 Dose

The most long-standing and widely accepted explanation for death due to heroin is that a fatal `overdose' is the result of using a quantity or quality (purity) of heroin in excess of the person's current tolerance to the drug. If this were the case, one might expect to find relatively high blood levels of morphine at autopsy in persons whose tolerance had not diminished. Despite the predominance of experienced, long-term heroin users among fatalities, a large proportion have low blood morphine concentrations (heroin is rapidly metabolised into morphine once administered) (Darke, Hall et al. 2000). In many cases this concentration is below accepted toxic levels. Studies have demonstrated that in many cases blood morphine concentrations are below, or similar to, those of living intoxicated heroin users, or of heroin users who died of causes other than overdose (Brecher 1972; Monforte 1977; Chan, Prolov et al. 1988; Kintz and Magin 1993; Fugelstad 1994; Zador, Sunjic et al. 1996).

Figure 6, for example, shows the blood morphine concentrations of overdose fatalities in 1995, relative to the blood morphine concentrations of living heroin users, taken from a study by Darke, Sunjic et al. (1997). It shows a substantial overlap between the blood morphine concentrations of the two groups, covering 90% of heroin-related deaths. A third of current users in this study had morphine concentrations more than twice the toxic morphine blood level employed by the analytical laboratories, while only 4 of the 39 heroin-related fatalities had blood morphine concentrations exceeding the highest recording for the current user group.

Figure 6: Blood morphine concentrations in 1995 accidental heroin-related fatalities and current heroin users in South Western Sydney (Darke, Sunjic et al. 1997a).



This is puzzling, as high blood levels of morphine at autopsy would be expected in long-term users who would presumably have a high tolerance to opioids. In a 1977 study, 74% of fatal heroin overdose cases were found to have blood levels no higher than those detected in a similar group of heroin users who died of other causes leading the researcher to comment that:

"...one must conclude that in the great majority of cases death was not a result of a toxic quantity of morphine in the blood" (Monforte 1977, p720).

A number of possible explanations for the apparently low blood morphine concentrations found in overdose fatalities have been postulated. In a review of the pharmacology of

opiate overdose White and Irvine (1999) state that the possibility exists for post-mortem metabolism or breakdown of drugs, and that as such studies of blood morphine concentrations of overdose victims may have underestimated morphine concentrations. In this review they argue that it is also possible that studies investigating opioid concentrations have underestimated total active opioids through failure to investigate all opioid metabolites (specifically morphine-3-glucuronide and morphine-6-glucuronide) (White and Irvine 1999).

5.2.2 Tolerance

A number of overdose fatalities appear to occur after periods of reduced use, such as immediately after prison. Of the NSW overdose deaths between 1992 and 1996, Darke, Ross et al (2000) found that five percent of cases died shortly after release from prison and that many who died shortly after release did so within 24 hours. A similar finding was reported in a longitudinal study by Seaman (1998) among British heroin users. The odds of a fatal overdose occurring in the two weeks after release were 34 times those of other times spent outside custody. Similar results have been reported for non-fatal overdose, with 13% of subjects in a Sydney study reporting that their most recent overdose occurred immediately after prison release (Darke, Ross et al. 1996a). It is clear that release from prison constitutes a high-risk period for overdose among heroin users. This increased risk is likely to be related to abstinence or infrequent use in prison.

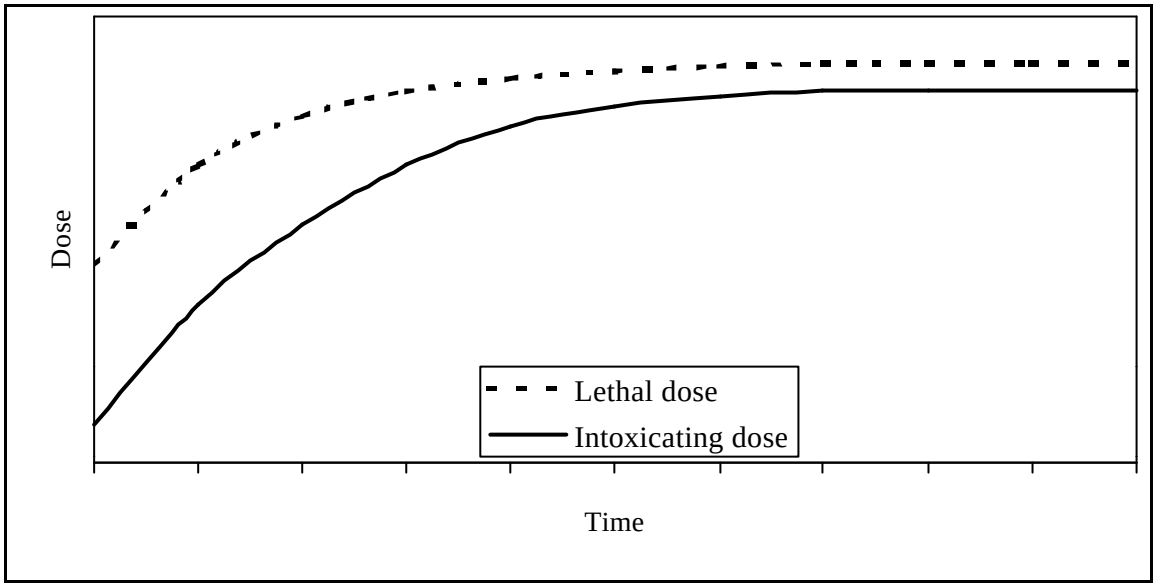
The recent development of drug detection techniques for hair samples has enabled detailed analysis of recent drug use among heroin users (Magura, Freeman et al. 1992; Kintz and Magin 1993). While blood morphine concentrations provide a record of opiate use in the preceding 24 to 72 hours, head hair provides a record of opioid use during the preceding months (Magura, Freeman et al. 1992). A recent Italian study (Tagliaro and De Battesti 1999) found that morphine concentrations in the hair samples of fatal overdose cases were significantly lower than those of current users. This finding has been supported by Darke, Ross et al (2000) in a replication of this study among Sydney heroin overdose fatalities. The conclusion of both these research groups was that fatal heroin overdose cases were using considerably less heroin in the two months preceding death than were active street users.

A recent decrease in tolerance to opioids has also been proposed as a possible explanation for the above phenomena. In the aforementioned studies of hair morphine concentrations in Italy and Australia, current heroin users were found to have median hair morphine concentrations as much as four times that of fatal overdose cases, indicating substantially heavier recent use (Tagliaro, Battisti et al. 1998; Darke, Hall et al. 2000). In one of these studies the researchers concluded that fatal cases were not abstinent in the period prior to death, as the median hair morphine concentration of this group was found to be six times that of abstinent users in treatment (Figure 9) (Darke, Hall et al. 2000).

Of relevance here is evidence that variation has been found to exist in the acquisition of tolerance to the various effects of opiates. It has been found that tolerance to the respiratory depressant effects of opioids may be incomplete and may develop more

slowly than tolerance to the euphoric effects. Thus long-term users may be at higher risk of overdose as the result of a reduction in the difference between the dose required to achieve the desired effects (euphoria) and the dose sufficient for lethal respiratory depression, as a result of differences in tolerance across effects (White and Irvine 1999). That is, as tolerance develops the dose required to produce euphoria may approach the lethal dose (Figure 7).

Figure 7: Hypothetical model of accrual of tolerance to the intoxicating and lethal effects of opioids (adapted from White and Irvine 1999).



The rates of loss of tolerance may also vary across the various effects. Thus long term users who have recently reduced their consumption may be at greater risk of overdose as their tolerance to the respiratory depressant effects may have diminished more rapidly than their tolerance to the desired psychotropic effects (White and Irvine 1999).

Loss of tolerance may also be mediated by opioid antagonists. Chronic administration of the antagonist naltrexone has been found to increase the density of various opioid receptors, increasing sensitivity to opioids. Thus after naltrexone maintenance users may be at greater risk of overdose due to a pronounced loss of tolerance as a result of both decreased recent use and increased sensitivity (White and Irvine 1999).

5.2.3 Purity

A popular misconception, among both heroin users and the wider community, is that the major cause of opioid overdose is unexpectedly high potency of heroin (Louria, Hensle et al. 1967; Ruttenber and Luke 1984). The evidence supporting this notion is, at best, sparse.

The notion that overdose is a simple function of a higher than expected dose (resulting from unexpectedly high purity or a larger than usual volume injected) cannot account for

the strong patterns of age and gender observed among overdose victims. If this were the case the age and gender distributions of overdose victims would reflect the age and gender distributions of the heroin-using population, or inexperienced users might be over-represented among overdose fatalities. Instead, as described previously, older, experienced, male users are dramatically over-represented in overdose fatalities.

Similarly, if overdose were a simple function of purity, and hence a greater than expected dose, one would expect the blood morphine concentrations of fatal overdose victims to be significantly higher than living intoxicated heroin users. As described above, it has been found that many individuals who die of an opioid overdose have blood morphine concentrations at autopsy which are below the commonly accepted toxic dose.

A number of studies have investigated the relationship between the purity of street heroin seizures and fatality from overdose. In 1978, for example, Desmond, Maddux et al (1978) found a small, non-significant correlation between the purity of heroin seized by police and mortality from heroin overdose in San Antonio, Texas. In a replication of that study over 20 years later, Risser, Schnieder et al (2000) reported no correlation between heroin purity and fatality from overdose in Vienna, Austria. However, a recent time series analysis found a moderate association between purity of street heroin seizures and fatality from overdose in South-Western Sydney, suggesting that while heroin overdose is not a simple function of purity, purity may be one factor contributing to overdose deaths (Darke, Hall et al. 1999).

5.2.4 Contaminants

In general, studies outside the Eastern United States do not report the detection of impurities in seized heroin (Nakamura 1978; Chan, Prolov et al. 1988; Walsh 1991; Wahbah, Winek et al. 1993; Fugelstad 1994; Risser and Schneider 1994; Zador, Sunjic et al. 1996). Zador (1996) found no evidence of contaminants in injecting equipment or at autopsy of the 152 heroin-related deaths examined. These findings have recently been replicated in a study of heroin-related deaths occurring in New South Wales between 1992 and 1996 (Darke, Ross et al. 2000). A recent analysis of street heroin seized in South Western Sydney similarly found no evidence of harmful adulterants (Swift, Maher et al. 1999). Adulterants found in this study were largely pharmacologically inactive dilutants (sugars) used to add bulk, or caffeine, believed to increase the bioavailability of heroin when smoked.

A number of studies from the Eastern United States in the late 1970s and early 1980s reported that the presence of contaminants, usually quinine, was detected in toxicological analyses of either heroin samples or at autopsy (Cherubin, McCusker et al. 1972; Monforte 1977; Ruttenber and Luke 1984). For example, Cherubin, McCusker et al. (1972) reported the presence of quinine in 19% of fatal New York City cases; Ruttenber and Luke (1984) reported a relationship between heroin deaths and the amount of quinine in street packages of heroin and Monforte (1977) reported the presence of quinine in 57% of cases in Michigan. However, in almost all cases, quinine levels at autopsy were well within therapeutic levels. It therefore appears that while it is theoretically possible that

impurities play a role in a proportion of heroin-related deaths, very little evidence supports such a theory.

5.2.5 Drug Interactions

As noted previously, concomitant use of other drugs (polydrug use), particularly CNS depressants such as alcohol and benzodiazepines, appears to be a common practice among heroin users. Co-administration of other depressant drugs can substantially increase the likelihood of a fatal outcome following injection of heroin, due to the potentiation of the respiratory depressant effects of heroin. Thus, in the presence of other CNS depressant drugs a `normal' or usual dose of heroin may prove fatal. Alcohol appears to be especially implicated, with the frequency of alcohol consumption being a significant predictor of overdose (Darke, Ross et al. 1996a)

In support of the hypothesis that fatality may result from an interaction between CNS depressant drugs is the frequently documented finding that cases where morphine only has been detected at autopsy appear to represent a minority of heroin fatalities (Richards, Reed et al. 1976; Monforte 1977; Nakamura 1978; Manning and Ingraham 1983; Chan, Prolov et al. 1988; Steentoft, Worm et al. 1988; Wahbah, Winek et al. 1993; Oppenheimer, Tobutt et al. 1994; Risser and Schneider 1994; Zador, Sunjic et al. 1996).

Studies that have reported mean blood alcohol concentrations (BAC) indicate high levels of alcohol intoxication, ranging from 0.09 g/100mL to 0.16 g/100mL (Table 3). A fifth (22%) of cases in Zador, Sunjic et al. (1996) had BACs above 0.20 g/100mL. Furthermore, blood morphine levels have been reported to be substantially lower in cases where alcohol is detected than in cases where it is not (Richards, Reed et al. 1976; Chan, Prolov et al. 1988; Steentoft, Worm et al. 1988; Ruttenber, Kalter et al. 1990; Zador, Sunjic et al. 1996). Zador, Sunjic et al. (1996) found that the median blood morphine level of 0.17 mg/L in alcohol positive cases was significantly lower than the level of 0.34 mg/L for morphine only cases. Chan (1988) reported similar findings, with mean blood morphine levels of 0.43 mg/L and 0.52 mg/L respectively and observed that the mean blood morphine level declined with increased blood alcohol. Steentoft, Worm et al. (1988) reported median morphine concentrations in cases where alcohol was detected of 0.4 umol/kg compared to 0.7 umol/kg in cases where alcohol was not present, while Richards, Reed et al. (1976) reported median levels of 0.4 mg/L and 0.6 mg/L respectively. Ruttenber, Kalter et al. (1990) reported a significant inverse correlation between blood alcohol and blood morphine concentrations in a study of 505 heroin related deaths positive for alcohol at autopsy, as did Zador, Sunjic et al. (1996).

Of all NSW overdose fatalities between 1992 and 1996, Darke, Ross et al. (2000) found that antidepressants were detected in 7% of cases, as was cocaine, making these the most commonly detected drug classes after alcohol and benzodiazepines. It appears likely that this is a reflection of the prevalence of the use of these drugs in the heroin using population. Darke and Ross (2000), for example, found that 21% of a sample of Sydney IDU reported using an antidepressant in the preceding six months. However, of the antidepressants, tricyclics appear to be over-represented among overdose fatalities despite

the fact that IDU report using both tricyclics and the other major class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), with equal frequency. Among NSW fatalities from 1992 to 1995, of the 63 cases in which antidepressants were detected 73% were tricyclics, 20% were SSRIs and 6% were monoamine oxidase inhibitors (Darke, Ross et al. 2000), suggesting that tricyclic antidepressant use may be a risk factor for overdose. This is supported by a study by Darke and Ross (2000) who found that a reported history of tricyclic use was associated with a greater risk of having had a non-fatal overdose, while no association was found between the use of SSRIs and overdose.

Thus it appears that the combining heroin with other psychoactive drugs may produce a synergistic effect, increasing the lethality of the drugs and thus placing the user at greater risk of overdose. The association between polydrug use and risk of overdose appears so strong that, in their review of the factors associated with overdose, Darke and Zador (1996) suggested that the term "opioid overdose" be replaced by the term "multiple drug toxicity".

5.2.6 Liver dysfunction

A number of physiological and epidemiological factors suggest that there may be an association between liver disease and mortality from heroin overdose. Firstly, it is biologically plausible, as the opioids are metabolised in the liver (Torre and Cami 1999) and "oxidation of opioids is reduced in patients with hepatic cirrhosis, resulting in decreased drug clearance" (Tegeder, Lotsch et al. 1999 p17). Thus heroin or other opioid users with liver disease are likely to be at greater risk of overdose due a prolonging of the period in which significant levels of opioids are present in the blood.

Secondly, intravenous drug use is the most significant risk factor for hepatitis C, the epidemiology of which closely mirrors that of overdose. Specifically, males have been found to be at greater risk of HCV, with chronic prevalence greatest in males aged 20-39 and acute prevalence greatest in males aged 30-39 (CDC 2000). Infection by HCV strongly associated with the duration of IV drug use. Crofts, Batey et al. (1999), for example, state that approximately 65% of Australian IDUs are HCV positive. Similarly, Bell et al. (1990) found that two thirds of IV drug users were HCV positive within two years of commencing drug use, while 100% of patients using IV drugs for more than 8 years were HCV positive. The average time from infection with HCV to clinically significant hepatitis has been found to be ten years (Sharara, Hunt et al. 1996).

Simultaneous infection with multiple strains of hepatitis increases the risk of liver failure (Keifer, Honish et al. 2000) and the prevalence of HAV and HBV infection among those already infected with HCV is particularly high. Keifer, Honish et al. (2000), for example, found that 53% and 44% of a sample of 343 HCV positive subjects were HAV and HBV positive respectively.

Males are at greatest risk of infection with HCV. In a Canadian study, for example, 73% of 187 HCV positive people aged between 36 and 50 were male (Keifer, Honish et al. 2000). The majority of overdose mortality also occurs among men, usually in their late

20s and early 30s, despite the fact that non-fatal overdose occurs with approximately equal frequency between the sexes, and over a wider age range (Darke and Zador 1996c; McGregor, Hall et al. 1999). Overdose mortality is also correlated to length of heroin using career, with the majority of fatalities having a history of dependence of in the order of 10 to 12 years (Darke and Zador 1996c; Sporer 1999).

Thirdly, heroin overdose mortality has been found to be poorly correlated with heroin dose. Heroin overdose fatalities have typically been found to have blood morphine concentrations in the same range as living heroin users and heroin users dying from causes other than overdose (see section 5.2.1) (Darke, Sunjic et al. 1997), suggesting the role of factors other than heroin purity or dose. Research has established the role of polydrug use in overdose, as discussed earlier, however this does not account for the clear age and gender patterns observed in overdose fatalities.

Finally, it is possible that IDUs are at greater risk of hepatitis infection producing liver damage. In a study of liver disease in drug users, for example, May and Helmstaedt (1975) found evidence of acute liver damage or liver function abnormalities in approximately 50% of drug users infected with hepatitis, as did Tennant and Moll (1995). Among people with HCV who did not inject drugs, only 20 to 35% have been found to develop cirrhosis (Sharara, Hunt et al. 1996). Alcohol consumption, even at moderate levels, has been found to exacerbate liver damage from hepatitis (CDC 2000) and there is evidence that a proportion of IDUs consume significant amounts of alcohol (Reid, Crofts et al. 2000).

Given the association between heroin overdose and liver disease in IDUs it is reasonable to assume that there may be an association between liver dysfunction and fatality from heroin overdose. Key informant interviews have revealed inconsistencies in opinions as to the probability of liver disease increasing overdose risk. While some completely rule out the possibility that liver disease may contribute to fatality from overdose, others agree that it may have a role in a multifactorial cause of death from overdose.

In key informant interviews medical specialists have suggested that it is unlikely that liver disease *per se* could precipitate fatality from overdose, since any liver induced effect that may alter peak plasma concentrations would be detected as elevated blood morphine levels at autopsy. However, they conclude that it is possible that reduced metabolism of opiates in liver damaged users may prolong the period in which they are at risk of overdose, thus increasing their probability of overdosing. Further research is required to establish whether such an association exists and, if so, the nature and extent of this association.

5.2.7 Pulmonary dysfunction

A number of factors suggest that mortality from opioid overdose may be associated with pulmonary dysfunction.

Firstly, the mechanism of death in opiate overdoses is respiratory arrest. Hence it is

plausible that opioid users with reduced pulmonary function may be at greater risk of mortality from a given overdose event through their increased vulnerability to fatal respiratory depression.

Secondly, heroin users are likely to suffer from impaired pulmonary function as a result of tobacco smoking; complications of overdose; and increased susceptibility to infection. According to one researcher:

"complications resulting from intravenous drug misuse affect the lung more than any other organ" (Hind 1990a, p891)

Very little epidemiological data on the levels of systemic morbidity in heroin users exists in the literature. While the prevalence of pulmonary dysfunction in the heroin using population is largely unknown, there is some evidence to suggest that it may be common.

Limited studies have investigated the prevalence and severity of lung dysfunction in heroin users. Overland, Nolan et al (1980), for example, conducted an ecological study into the lung function of 512 intravenous heroin users entering a methadone program. They found that 42% had impaired respiratory function, defined as carbon-monoxide (CO) diffusing capacities of less than 75% of predicted.

Stark and Campbell (1993) state that the prevalence of smoking among heroin users is almost three times that of the general population, while Burling and Ziff (1988) report a prevalence of smoking above 90% in participants of a substance dependence program. Heroin users in their late 20s and early 30s, the highest risk age group for overdose, are highly likely to have a history of chronic tobacco use dating back 10 to 15 years. There is an overwhelming body of evidence illustrating the dose-response relationship between smoking and pulmonary disease and dysfunction (US Surgeon General, 1988), and smoking related respiratory conditions, such as bronchitis, are reported to be widespread among IDUs (Reid, Crofts et al. 2000). It is therefore highly probable that there is a significant degree of tobacco induced pulmonary disease among heroin users.

There is also evidence to suggest that heroin users may suffer impairment of pulmonary function as a result of overdose (Karliner, Steinberg et al. 1969; Duberstein and Kaufman 1971; Schachter and Basta 1973). Of the 58 overdose survivors with pulmonary oedema in Duberstein and Kaufman's (1971) study, for example, five were found to have a persistent reduction in vital capacity and total lung capacity. It has been suggested that heroin overdose induced pulmonary oedema may lead to chronic lung disease (Schachter and Basta 1973; Cherubin, 1971). Pulmonary oedema may precipitate pneumonia (Cherubin 1971), which may also occur as a result of the aspiration of vomit following overdose (O'Donnell, Selig et al. 1995). Thus heroin users may suffer long term pulmonary impairment proportional to their overdose experience, even in the apparent absence of other causes of lung dysfunction.

It has been well documented that heroin users are at greater risk of infection due to their generally poor state of health (Reid, Crofts et al. 2000). Malnutrition, for example, is

common among heroin users (Santolaria-Fernandez, Gomez-Sirvent et al. 1995; Reid, Crofts et al. 2000), and is a significant risk factor for acute respiratory infection (as is smoking). As a result of this poor immunity heroin users may be more likely to suffer from both chronic and acute respiratory infections such as influenza and pneumonia. The rate of community acquired pneumonia, for example, is ten times higher among IDUs than in the general population (Hind 1990b). Susceptibility to pneumonia appears to be correlated to duration of heroin use (Louria, Hensle et al. 1967), and undiagnosed pneumonia is frequently seen at autopsy of Australian heroin overdose fatalities. Such infections cause varying degrees of chronic and acute pulmonary impairment.

While heroin use has been cited as a possible risk factor for a number of other respiratory conditions which impair pulmonary function, such as tuberculosis (O'Donnell, Selig et al. 1995) and asthma (Cygan, Trunsky et al. 2000), these conditions may not contribute significantly to respiratory impairment in Australia as they may be related to other, low prevalence, factors. Tuberculosis and asthma, for example, appear to be related to HIV infection and heroin smoking respectively, both of which are relatively uncommon in Australia.

Key informant interviews revealed disagreement as to the likelihood of pulmonary disease contributing to fatality from overdose. While all agreed that individuals with severely compromised respiratory function would be more at risk of fatal respiratory depression, there was little agreement as to the extent of disease that would be necessary to increase overdose risk. Some pointed out that even a ten year history of heavy smoking is unlikely to result in discernible emphysema, and that respiratory compromised patients are clearly identifiable. However, others noted that for users at the threshold of respiratory depression while heavily intoxicated even a small decrease in respiratory function may be sufficient to precipitate overdose.

The biological plausibility of an association between pulmonary dysfunction and overdose mortality; the inconclusiveness of expert opinion; and the potential for substantial rates of pulmonary dysfunction among heroin users, suggest that pulmonary morbidity may contribute to mortality from opioid overdose. Since little epidemiological research into this potential association exists in the literature further research is required to confirm or refute the existence of any such association.

Summary

- Overdose fatality is not a simple function of heroin dose or purity.
- There is no evidence of toxicity from contaminants of street heroin in Australia.
- Recent depletion of tolerance to opioids is a risk factor for overdose fatality.
- Polydrug use is a significant risk factor for fatality from overdose.
- Research is needed to establish the role of liver and pulmonary disease in overdose.

6.0 Consequences

6.1 Fatal

Approximately one in ten overdoses ends fatally (Duberstein and Kaufman 1971; Darke, Ross et al. 1996b), and the emphasis on fatal overdose in the literature reflects the justifiable importance placed on this outcome by researchers and practitioners. As described in the preceding chapters, those that do die from overdose are usually in their early thirties, unlike, for example, deaths arising from alcohol abuse or tobacco. As such, while heroin overdose deaths are grossly outnumbered by deaths from licit drug abuse, they represent a significant number of potential years of life lost. In England and Wales in 1995, for example, drug deaths accounted for 48,500 male years of life lost. By comparison road traffic accidents over the same period accounted for 58,000 male years of life lost (ACMD, 2000). In Australia it has been estimated (using 1992 data) that overdose deaths represent over 20,000 years of life lost (Hulse, English et al 1999)

6.2 Non-fatal

There is a dearth of epidemiological literature on medical morbidity associated with heroin overdose. The literature describing complications of heroin overdose has generally been in the form of case reports, and thus provides little insight into the incidence and prevalence of acute heroin intoxication related morbidity. In order to determine the burden of morbidity suffered as a result of heroin overdose therefore, one must extrapolate from the potential complications reported to arise from overdose.

Analysis of hospital records may provide a good starting point for an attempt to quantify heroin overdose related morbidity. However, while secondary data on non-fatal overdose is routinely collected through most Australian ambulance services and emergency departments, a number of problems have been identified with such datasets (Dietze, Cvetkovski et al. 2000). These are principally that they are rarely computerised or centralised and that they generally code overdose inadequately, limiting their amenability to analysis (Deitze, Cvetkovski et al. 2000). A dataset collected specifically on heroin related admissions has apparently been compiled by the Mater Misericordeae hospital in Newcastle, NSW. Analysis of this data set may provide valuable insight into the scope and severity of overdose related morbidity.

Sequellae of acute heroin intoxication described in the literature include various pulmonary, cardiac, muscular and neurological complications. Pulmonary conditions appear to be the most common complications of overdose (Duberstein and Kaufman 1971; Schachter and Basta 1973; Neaderthal and Calabro 1975), of which the most widely reported is oedema, a build up of fluid in the lung.

Unfortunately it is often difficult to separate medical morbidity arising from heroin use *per se* from morbidity related to overdose. A number of conditions have been attributed to both chronic and acute heroin use. It is difficult to determine, for example, whether seizure is primarily a product of acute intoxication; a result of a history of chronic

dependence (Brust and Richter 1976); or a result of benzodiazapine withdrawal (Mant, Wodak et al 1987). Similarly, rhabdomyolysis, the breakdown of muscle tissue, has been described as occurring both as a result of chronic use and as a result of a single episode of intoxication (Gans, Stam et al. 1985).

6.2.1 Cardio-pulmonary complications

There is conflicting evidence in the literature regarding the prevalence of pulmonary oedema precipitated by overdose. While there are a number of case reports describing the condition, its presentation, course and treatment, few provide insight into the epidemiology of pulmonary oedema in the heroin using population.

In an ecological study of a minor epidemic of overdose in New York, one of the few epidemiological investigations of overdose morbidity, pulmonary oedema was found in 48% of 149 cases, both fatal and non-fatal (Duberstein and Kaufman 1971). Levine, Grimes et al. (1973) found evidence of pulmonary oedema in 35 of 40 (86%) heroin overdose fatalities occurring among US service men in Vietnam. Lynch, Greenbaum et al. (1970) state that oedema may occur in up to 90% of overdoses. However, in another ecological study of overdose (defined as incidents in which naloxone was administered by paramedics) Sporer, Firestone et al. (1996) found only 4 cases of pulmonary oedema among 726 patients treated for overdose, prior to admission to a hospital or emergency room. The apparently contradictory nature of the evidence of the frequency of pulmonary oedema in heroin overdose in the literature suggests a need for further epidemiological research into this phenomenon using specific criteria to diagnose oedema.

Pulmonary oedema has a very good prognosis. After treatment with narcotic antagonists, intubation and mechanical ventilation the condition usually resolves within a matter of days (Lynch, Greenbaum et al. 1970; Paranthaman and Khan 1976), but may leave residual impairment (Karliner, Steinberg et al. 1969; Schachter and Basta 1973). Of the 58 overdose survivors with pulmonary oedema in Duberstein and Kaufman's (1971) study five were found to have a reduction in vital capacity and total lung capacity. It has also been suggested that heroin induced pulmonary oedema may lead to chronic lung disease (Schachter and Basta 1973).

In Duberstein and Kaufman's (1971) study, pneumonia developed in 75% of cases with pulmonary oedema. Pneumonia also occurs as a common complication of aspiration following overdose. Duberstein and Kaufman (1971) describe bacterial pneumonia as a "frequent, if not universal" sequel to aspiration of vomit following overdose. Pneumonia following aspiration of milk, administered orally as a home remedy for overdose, has also been reported (Drenick and Younger 1970; Duberstein and Kaufman 1971), although not recently.

Residual effects following aspiration pneumonia and other pulmonary complications of overdose are infrequently reported, presumably due to the difficulties inherent in following up this population (Schachter and Basta 1973). In a report of two cases, Schachter and Basta (1973) state that permanent pulmonary morbidity occurred as a

result of heroin overdose complicated by aspiration. In one of these cases the patient was only able to walk short distances unassisted and remained out of breath at rest eight months after the incident, while the second patient was discharged from military service two months after the incident for pulmonary disability. The authors of this study concluded that:

"a reservoir of chronic pulmonary disease might be forming in that segment of the addict population that has survived acute episodes of drug overdose" (Schachter and Basta 1973, p366).

The cardiac complications associated with overdose were recently reviewed by Ghuran and Nolan (2000). They include "profound cardiovascular collapse", arrhythmia (Neaderthal and Calabro 1975); acute cardiomyopathy (Paranthaman and Khan 1976); and hemoglobinemia (Smith and Glauser 1975). While these are potentially life threatening conditions in the acute phase, they is no evidence presented in the literature of ongoing morbidity as a result of these complications.

6.2.2 Muscular complications

The principal muscular complication associated with acute intoxication or overdose appears to be rhabdomyolysis, which, while apparently being substantially rarer than pulmonary oedema, may potentially be far more serious. Rhabdomyolysis is essentially the disintegration or dissolution of muscle cells (Taylor 1988) leading to myoglobinurea (the presence of muscle cell contents in the urine), muscular necrosis, severe neurological complications and potentially fatal renal failure (Smith and Glauser 1975; Gans, Stam et al. 1985; Gibb and Shaw 1985; Crowe, Howse et al. 2000). While it is a condition most commonly associated with "crush injuries" (when a limb is compressed as a result of trauma, as in motor vehicle accidents for example), it has been described in heroin users as occurring as a result of limb compression by another part of the body while comatose during acute intoxication (Schrieber, Leibowitz et al. 1971; Schrieber, Leibowitz et al. 1972; Gans, Stam et al. 1985; Yang, Yang et al. 1995).

In extreme cases rhabdomyolysis may lead to compartment syndrome (Vucak 1991), where oedema raises intracompartmental pressure to such a degree that circulation is cut off to the rest of the limb. Treatment indicated for such injuries is generally fasciotomy (the excision of the fibrous tissue dividing muscle compartments) to reduce pressure, and dialysis to compensate for impaired renal function. Prognosis following treatment is generally good (Koffler, Friedler et al. 1976), with most patients surviving and recovering renal function. However permanent muscular impairment is common (Schrieber, Leibowitz et al. 1972; Yang, Yang et al. 1995). For example, of the eight cases described by Schreiber et al. (1972) six developed permanent neurological or muscular damage.

Rhabdomyolysis has also been described in heroin users in the absence of trauma (Gans, Stam et al. 1985; Vucak 1991). Gans, Stam et al. (1985), for example, described seven cases of rhabdomyolysis in heroin users none of which were related to intoxication. Of

these seven cases two suffered a permanent loss of some limb function. Five of the seven patients were believed to be abstinent prior to the development of rhabdomyolysis, suggesting that non-traumatic rhabdomyolysis may be related to chronic, as well as acute, heroin use.

6.2.3 Neurological complications

While neither heroin nor any of the other opiates are directly neurotoxic, a number of neurological complications may result from heroin use, including toxic spongiform encephalopathy (Sempere, Posada et al. 1991; McCann and Ricaurte 2000); stroke (Brust and Richter 1976; Vila and Chamorro 1997); and seizure (Alldredge, Lowenstein et al. 1989). These conditions have the potential to cause significant cognitive and other neurological morbidity. In addition, overdose has the potential to cause significant neurological damage through prolonged hypoxia.

In a recent study by Darke, Ross et al. (2000), one of the few studies to investigate heroin overdose related morbidity, overdose was found to be related to cognitive impairment. In a battery of tests of cognitive function methadone maintenance patients were found to have significantly greater levels of cognitive impairment than a control group, despite no differences being found in pre-morbid functioning. The 30 methadone maintenance patients examined performed significantly poorer than 30 matched non-heroin using controls in all neuropsychological domains tested: information processing; attention; short-term and delayed visual memory; long and short-term verbal memory; and problem solving. The number of overdoses experienced by a patient was found to be a significant predictor of poorer cognitive performance. Thus long term heroin users are likely to suffer from a significant burden of cognitive morbidity, proportional to their overdose experience.

In addition to hypoxic brain damage, it has been speculated that heroin users are at greater risk of head injury, through accident and violence, as a result of the heroin using lifestyle (Darke, Sims et al. 2000; Reid, Crofts et al. 2000). It is unclear to what extent this is related to overdose.

6.2.4 Other conditions

A variety of other conditions have been reported as being related to overdose, including hyperacute reactions (Werner 1969); subcutaneous emphysema (Nolla-Salas, Dinares et al. 1985); and pneumocephalus (Nolla-Salas, Dinares et al. 1985). These are relatively rarely reported and thus may be assumed not to contribute significantly to the total burden of morbidity arising from heroin overdose.

The broad range of overdose sequelae coupled with the high incidence of non-fatal overdose suggest that there is likely to be a large burden of morbidity associated with overdose in the heroin using population. It is reasonable to assume that this burden of morbidity is a function of the number of overdoses experienced by a given user, and thus is likely to be greater among older, more experienced and more dependent users.

Unfortunately literature describing or quantifying overdose related morbidity is sparse, suggesting a need for further research in this area. This research needs to confirm the existence of specific types of morbidity and to quantify the degree of morbidity and the risk of morbidity arising from heroin overdose.

6.3 Health care costs

The dearth of epidemiological data on heroin related morbidity makes it very difficult to quantify the health care costs associated with treating heroin overdose. It has been established that drug users are high cost consumers of health care (Zook and Moore 1980), and that treatment for potential complications of overdose are likely to be relatively expensive (Baldwin, Rosenfeld et al. 1993). Renal failure resulting from rhabdomyolysis, for example, requires dialysis, a high cost procedure.

It may, however, be possible to quantify some health care costs attributable to overdose. In their analysis of ambulance call outs in NSW, Degenhardt, Hall et al. (2000) determined that in 1998-1999 5,989 call outs were to attend overdoses. Deitze, Cvetkovski et al. (2000) calculated that ambulance costs averaged $600 per overdose call out. Extrapolating from these figures we can estimate that ambulance attendance at overdoses in NSW in 1998-1999 cost approximately $3.6 million. Assuming that the ratio of fatal to non-fatal overdoses in NSW is the same as that in other jurisdictions we can use the proportion of fatal overdoses that occurred in NSW (46.7%) (Lynskey and Hall, 1998a) to extrapolate that ambulance attendance at overdoses in Australia in 1998-1999 cost $7.7 million.

Summary

- Fatal opioid overdose represents a significant number of potential life years lost.
- Non-fatal opioid overdose has the potential to cause significant, lasting morbidity.
- Research is required to quantify overdose related morbidity.
- Health care costs associated with overdose are significant. Ambulance call-outs to overdoses in Australia cost approximately $7.7 million.

7.0 Interventions

Given the significant prevalence of fatal opioid overdose, there is a need to develop, implement and evaluate effective strategies to prevent or reduce the occurrence of opioid overdose. There are a number of promising strategies that may be successful in achieving this aim.

7.1 Increasing Access To Treatment.

The risk of overdose death is substantially reduced in individuals who are enrolled in treatment (Gearing and Schweitzer 1974), of which methadone maintenance is the dominant modality in Australia.

Six randomised-controlled trials have been conducted on the effectiveness of methadone maintenance. All of these trials have involved small numbers of patients (Dole, Robinson et al. 1969) who have been followed up for short periods (rarely longer than one year). Nevertheless, all have produced positive results, despite small sample sizes that worked against finding differences. The positive findings of these trials have been corroborated by the results of controlled observational studies in which statistical forms of control have addressed the major alternative explanations of apparent effectiveness which are dealt with by randomisation in controlled trials (Cook and Campbell 1979).

In their evaluation of the first methadone maintenance programs run in New York, Gearing and Schweitzer (1974) found a death rate of 7.6 per 1,000 among 3,000 methadone maintenance patients, relative to a death rate of 5.6 among the general population of comparable age. By contrast, the death rates in comparison groups of patients that had left methadone and drug users in detoxification treatment was found to be 28.2 and 82.5 respectively. Of the deaths in the methadone group, 50% were due to overdose or infection, while in the comparison groups 80% of deaths among patients that had dropped out of methadone and 90% of patients in detoxification programs were the result of overdose or infection. Thus methadone treatment was found to protect against mortality largely by preventing overdose.

This finding was supported by Caplehorn, Stella et al. 1996 in their cohort study of 296 Australian methadone patients. They found that heroin users not in treatment were four times more likely to die than methadone maintenance patients, and that the reduction in mortality risk for methadone patients was entirely attributable to a reduction in the risk of fatality from overdose. Current users enrolled in methadone maintenance were half as likely to report an overdose in the preceding six months as current users who were not in methadone maintenance treatment. Similarly, Davoli, Perucci et al. (1993) found that patients who left methadone treatment were eight times more likely to die from overdose in the 12 months after treatment and three times more likely in the period 12 to 36 months after treatment, relative to patients who remained in treatment. Fugelstad, Rajs et al (1995) found a three times relative risk of death attributed to overdose for those who have never been in methadone maintenance, relative to those currently in methadone maintenance. The reduced risk of overdose observed in methadone patients probably

reflects a combination of reduced heroin use while in treatment and/or a higher tolerance to opioids while being maintained on methadone.

In support of the findings of these studies, only 2% of heroin-related deaths in 1992 in New South Wales, Australia, were on methadone maintenance at the time of death, while 75% had never been in methadone treatment (Zador, Sunjic et al. 1996).

Since older, long-term users are at greatest risk of fatal overdose, one strategy for reducing fatalities would be to increase the number of older heroin users who are enrolled in methadone maintenance and other treatment. An increase in the number of people enrolled in methadone maintenance treatment has occurred over the past decade (Hall 1996). However, more effort may need to be made to enrol older users who have not been attracted to methadone treatment. This may require the trial and evaluation of alternative maintenance pharmacotherapies (Mattick, Oliphant et al. 1998) including injectable heroin, levo-alpha acetyl methadyl (LAAM), buprenorphine and slow release oral morphine. These are discussed in more detail in Appendix A.

A number of trials of alternative pharmacotherapies for heroin dependence are currently being conducted in Australia. These are being evaluated by the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) Project co-ordinated by the National Drug and Alcohol Research Centre in Sydney. This project will evaluate the effectiveness of such pharmacotherapies in attracting and retaining heroin users in treatment and the outcomes of that treatment, including effects on overdose incidence, in an Australian context. An alternative pharmacotherapy not currently being trialled in Australia that has shown potential internationally is heroin maintenance.

While heroin maintenance is not currently being trialled in Australia for political reasons there is evidence from international experience that it may be beneficial, particularly for patients for whom other treatment options have failed (Bammer, Dobler-Mikola et al. 1999). Heroin maintenance has been found to be more effective that methadone maintenance in retaining patients in treatment (McCusker and Davies 1996). Since treatment reduces risk of overdose increases in patient retention will reduce incidence of overdose. In a large, uncontrolled study of heroin maintenance no overdoses were observed among over 1,000 subjects indicating that such a pharmacotherapy may be even more effective than current treatments in reducing the incidence of overdose (Hall 1997; Bammer, Dobler-Mikola et al. 1999). That heroin maintenance has the potential to be at least as effective as current treatments is not disputed, rather, debate about heroin maintenance largely centres around its cost-effectiveness (Farrell and Hall 1998; Wodak 1998). Clinical trials are clearly required to ascertain whether heroin maintenance may be an effective, cost-effective treatment modality for heroin dependence in the Australian context.

7.2 Educating Drug Users

A striking degree of cognitive dissonance has been observed in the risk perceptions of heroin users. McGregor, Darke et al. (1998), for example, found that users were

unrealistically optimistic about their own risk of overdosing, even though they were remarkably accurate in estimating the risk of others overdosing. Sixty-two percent of the 218 regular heroin users surveyed in this study considered it "likely" or "very likely" that a regular heroin user would overdose, yet only 20% thought that they were "likely" or "very likely" to do so. Darke and Ross (1997) explored the overdose risk perceptions of 312 Sydney heroin users. Of this sample 61% had experienced an overdose, on a median of two occasions. The study found that 80% of current users believed that they had a low risk of overdose, despite accurately estimating that other heroin users had a 60% chance of overdosing. Risk perceptions were not found to be associated with users' own experience of overdose, or with having witnessed an overdose. The authors concluded that:

"If the incidence of heroin overdose is to be reduced, interventions that directly target risk behaviours and perceptions for overdose are essential" (Darke and Ross 1997, p92)

It should be noted that it is remarkably difficult to change behaviour through education programs, particularly complex behaviours such as those associated with addiction. For example, interventions that changed behaviour to reduce the spread of infectious disease, principally through reduced needle sharing, involved the behaviourally relatively simple process of substituting dirty equipment with clean equipment. However, interventions attempting to reduce risk behaviours for overdose, such as polydrug use, must actually prevent the consumption of other drugs immediately before or concurrent to heroin consumption. This is obviously a far more difficult objective.

A trial of a peer-based intervention to educate heroin users in order to reduce their risk of overdose was recently conducted in South Australia (McGregor, Hall et al. 1999). Two of the three key components of this intervention were the development and implementation of a peer education process and the development and dissemination of information materials. Evaluation of the intervention found a small increase in the proportion of heroin users reporting "rarely or never" using alcohol or benzodiazapines with heroin, but these changes were not statistically significant. Among the 99 heroin users surveyed who reported exposure to the intervention, however, over 60% reported that they were less likely to drink alcohol while taking heroin and over 70% reported that they were less likely to take benzodiazapines while taking heroin

This intervention may be viewed as successful as it was found to effectively convey relatively complex messages to a hidden population, despite the fact that statistically significant differences were only noted for a few behaviours. The process evaluation measures of this intervention give a better indication of the worth of such projects than simple outcome measures. Almost half of the post-intervention sample surveyed reported exposure to the intervention. The majority of these reported that they were now more aware of overdose signs and how to avoid overdose than they had been prior to the intervention.

Needle and syringe programs (NSP) throughout Australia provide a broad range of overdose prevention materials and education programs. These range from the simple

inclusion of printed material in fitpacks to training in CPR by ambulance officers, with users being paid as an inducement to attend. There is likely to be a great deal of variability between services in both the quality of materials and the extent to which they are distributed.

The West Australian Drug Abuse Strategy Office in conjunction with the National Drug Research Institute has produced a register of opiate overdose prevention projects being conducted in Australia. This register highlights the extreme variability of the quality, nature, and extent of projects. For example, projects listed range from sex-worker outreach programs providing unspecified overdose prevention information, to users-group magazine articles, to research-based and evaluated multi-channel education programs, such as the South Australian Heroin Overdose Project (WADASO 2000).

The South Australian intervention, for example, developed a range of materials, in consultation with users, which were evaluated and found to be effective. By contrast, some NSPs report distributing overdose articles from users publications or other printed material which may be poorly researched and completely unevaluated.

There appears to be a need for an evaluation of the materials currently available and the establishment of a process for the effective dissemination to NSPs of materials found to be of high-quality. Similarly, there is a great need for the evaluation of the effectiveness of such interventions by NSP staff. Such evaluation would provide a means to identify the relative potential of various interventions to reduce overdose mortality and hence a foundation for the planning of effective public health programs for overdose prevention.

7.2.1 Key messages for user education interventions

7.2.1.1 Avoid polydrug use

A recurrent finding in the literature has been that risks of fatal opioid overdose are heightened by the concurrent use of other CNS depressant drugs, particularly benzodiazepines and alcohol. It is therefore important that heroin users are informed about the risks of combining heroin with alcohol and other depressant drugs.

7.2.1.2 Do not use alone

Heroin users also need to be discouraged from injecting in the streets or alone, thereby denying themselves assistance in the event of an overdose. The evaluation of the South Australian intervention previously mentioned, found that, of a sample of over 200 heroin users, significantly more did not use heroin alone after the intervention. Prior to the intervention 16% of the sample reported that they did not use heroin alone, while after the intervention 31% reported not using alone (McGregor, Hall et al. 1999).

7.2.1.3 Encouraging witnesses of overdose to seek medical assistance

An additional priority must be to improve users' responses to overdoses that occur among their peers. A number of studies have shown that in the majority of fatal and non-fatal overdoses other people who are present delay seeking assistance for fear of police involvement (Zador, Sunjic et al. 1996; Darke, Ross et al. 1996a; Darke, Ross et al. 1996b). Current initiatives throughout Australia to limit police attendance at overdoses may go some way to reducing these concerns, thereby encouraging earlier requests for medical assistance. The South Australian intervention described earlier, for example, found that the proportion of witnesses of overdose that called an ambulance increased by 10% over the study period, although this increase was not statistically significant. Among the post-intervention sample of users who had been exposed to the intervention however, significantly more had called an ambulance as their initial or subsequent response at the most recent overdose witnessed (McGregor, Hall et al. 1999).

A further strategy to reduce the overdose toll may be to teach injecting drug users simple but effective resuscitation techniques to revive peers who have overdosed or to keep them alive until help arrives. The South Australian intervention, for example, found significant increases in the recognition of overdose signs and in the proportion of witnesses to overdose that checked for consciousness of suspected overdose victims as their initial action (McGregor, Hall et al. 1999). One possible component of such education may be education in the use of naloxone, which is discussed below (6.4).

7.3 Police Protocols

Minimise police attendance at the scene of overdose may reduce mortality from overdose by removing a major barrier to witnesses seeking help. Fear of police involvement is overwhelmingly nominated by witnesses of overdose as the main reason for stopping or delaying seeking help (Darke, Ross et al. 1996b; McGregor, Darke et al. 1998). Given that witnesses are present at the majority of overdoses, that the effects of overdose are easily reversible and that immediate death from overdose is rare, any intervention that increases help-seeking behaviour has the potential to reduce overdose mortality.

McGregor, Darke et al's intervention included collaboration with South Australian police to limit their presence at overdoses. As a direct result of this police policy was formally changed to prevent attendance at overdose unless the ambulance officers were under threat or the overdose had been fatal (McGregor, Hall et al. 1999).

This policy change has been adopted nationwide. Police protocol now states that police activity at overdose is to ensure the provision of appropriate medical care and to protect the welfare of attending ambulance officers. Police no longer routinely attend overdose incidents unless the overdose is fatal or ambulance officers safety may be jeopardised.

7.4 The Distribution of Naloxone

The use of opiate antagonists, most commonly naloxone (Narcan®), is virtually

universally indicated for the acute treatment of heroin overdose (Osterwalder 1996). Naloxone is generally regarded as very safe. It has few contraindications (MIMS 1999), and in the absence of opioids has essentially no pharmacological effect (Osterwalder 1996). However, complications have been reported in association with its use in the presence of opioids. It has been hypothesised, for example, that the rapid reversal of intoxication produced by naloxone may precipitate pulmonary oedema (Ghuran and Nolan 2000). In a prospective clinical study, Osterwalder (1996) found six instances of complications in 453 cases of naloxone administration for acute heroin intoxication. Included in these were one case of cardiac arrest, one of oedema, one of violent behaviour and three of general convulsions. Of these six cases however, the author noted that "three patients had severe disorders before administration of naloxone". They concede that it is therefore difficult to establish whether complications were caused by naloxone or by drugs ingested prior to treatment. The case of cardiac arrest, for example, occurred following intoxication with a mixture of cocaine and heroin, and cocaine has been associated with both convulsion and violent behaviour. Thus it appears that, while naloxone may not be entirely without risk, its use for the reversal of opioid intoxication to prevent fatal respiratory arrest appears justified.

The distribution of naloxone to heroin users has been mooted as a possible intervention to reduce fatality from overdose (Darke and Hall 1997). There are a number of reasons why the distribution of naloxone may be effective in reducing the rate of fatal opioid overdose. Firstly, there are often witnesses to an overdose who would be in a position to administer naloxone, if it were available. Secondly, research has indicated that immediate death from overdose is rare, meaning that there is often an opportunity for bystanders to intervene. Thirdly, the majority of fatal overdoses occur in the home of a victim or that of another user (Zador, Sunjic et al. 1996) so if heroin users had a supply of naloxone in their own homes, it could be used in the majority of overdose instances. In a pre-launch study of the possible impact and acceptability of a trial of naloxone distribution in the UK, Strang, Powis et al. (1999) found that 70% of 454 injecting drug users supported such an intervention. In this study the authors estimated that approximately two-thirds of witnessed overdose fatalities could be prevented by the distribution of naloxone.

There are also, however, a number of potential problems with the distribution of naloxone. These include the fact that in Australia naloxone is only available on prescription and can only be administered by a medical practitioner or licensed paramedic. Thus it would need to be rescheduled for over-the-counter sale or distribution. Another concern which has been raised is the issue of recurrent intoxication.

Naloxone has a relatively short plasma half-life, ranging from 30 to 80 minutes (MIMS 1999). While the plasma half-life of heroin is also approximately half an hour, the active metabolite of heroin, morphine, has a plasma half-life of approximately two hours (Reisine and Pasternak 1996). Similarly, the plasma half-lives of the commonly abused synthetic opioids fentanyl and methadone are approximately 4 hours and 15 to 40 hours respectively (Reisine and Pasternak 1996). Thus it has been argued that the effects of naloxone may wear off while there are still significant amounts of opioids in the blood, resulting in recurrent intoxication.

Recurrence of opioid intoxication after the administration of naloxone has been reported in approximately one-third of cases (Watson, Steele et al. 1998). However, the lethality of recurrent intoxication appears to be substantially less than that of initial intoxication. In their examination of all heroin overdose fatalities in NSW between 1992 and 1996, for example, Darke, Ross et al. (2000) found that only 4 cases out of 953 fatalities were reported to have occurred after the administration of naloxone. Given that naloxone is administered in the order of 5,000 times per year by ambulance officers attending suspected drug overdoses in NSW (Degenhardt, Hall et al. 2000), this study suggests that fatalities from recurrent intoxication following naloxone administration occurs in less than 0.02% of cases. These results support a previous study by Vilke, Buchanan et al. (1999) who found that pre-hospital treatment of overdose with naloxone, without admittance to hospital, did not result in any fatalities in the 12 hours following treatment over the 12 month period studied. Similarly, Jacobs (2000) found no overdoses occurred with 24 hours of treatment in 156 cases of pre-hospital resuscitation with naloxone. Thus the risk of fatality from recurrent intoxication following naloxone-inducted reversal of intoxication appears to be negligible in practice. Despite this fact recurrent intoxication is a theoretical risk that would need to be addressed in any trial of naloxone distribution. This problem could be overcome by educating users about the risks of further overdoses and by providing them with multiple doses of naloxone.

A major consideration regarding the viability of the distribution of naloxone is its cost-effectiveness. Naloxone is relatively expensive, costing approximately $11 a vial (Darke and Hall 1997). To avoid possible recurrent overdose users would need to be provided with multiple doses. Thus each unit distributed would cost at least $20, excluding actual distribution costs. A rigorous evaluation would be required to ascertain whether such an intervention would be cost-effective relative to more conventional interventions, such as peer education.

Other criticisms of the concept of distributing naloxone to heroin users are that it may either increase risky behaviour or encourage drug use. It has been suggested that heroin users may increase their dose when naloxone is available, in the knowledge that an overdose could be reversed, thus placing themselves at greater risk of overdose. While their is little evidence to suggest that this might occur in practise, it is an issue that would need to be investigated in any trial of the distribution of naloxone. Similarly, it has been suggested that the presence of naloxone might remove a barrier to experimenting with heroin by non-users. Again this notion would need to be examined in a trial. A final criticism of this concept is that it may be "sending the wrong message" to non-heroin users, and may therefore encourage the uptake of heroin. This criticism has been made of most public health activities that aim to reduce the harms associated with drug dependence, such as the provision of methadone and needle exchange programs. There is no evidence to believe that this is actually the case. Such an argument greatly underestimates the intellectual processes that prevent non-users from experimenting with heroin and grossly over-simplifies the behavioural processes involved in the commencement of heroin use. Such an intervention would be exclusively aimed at

existing users, with the intention of saving lives. It would appear unlikely that this intervention would encourage use among non-users.

In summary, as there are both benefits and potential liabilities to the distribution of naloxone, the net benefits of naloxone distribution should be assessed by a carefully planned trial and evaluation.

7.5 Establishing Medically Supervised Injecting Centres

Medically supervised injecting centres are places in which injecting drug users are able to inject drugs in a clean environment, with sterile equipment and with medically trained persons on hand in the event of an overdose. They are designed to reduce the risks posed by injecting drug use to long term users and to the public, including deaths from overdoses, and the transmission of blood-borne viruses. They also provide a point of contact with services for injecting drug users who are not in treatment.

There is evidence to suggest that supervised injecting centres hold benefits for both users and the community. Injecting rooms were opened in 1991 in Frankfurt, Germany, as part of a program of harm minimisation that included needle exchange and methadone maintenance programs. In the following 5 years, the number of lethal overdoses in Frankfurt declined by 80%, compared to a 20% reduction in Germany as a whole, suggesting that the program, of which injecting rooms had formed a part, was effective in significantly reducing overdose deaths (Joint Select Committee into Safe Injecting Rooms, 1998). Given the well described effectiveness of methadone maintenance in reducing mortality from overdose it is probable that the majority of the overdose reduction observed in Frankfurt is attributable to the methadone component of the program. The effect of injecting centres on this reduction is unquantifiable, but is likely to be slight, for reasons described below. A joint select committee was convened in NSW in 1997 to investigate the value and the viability of the establishment of injecting rooms in NSW, with the recommendation that medically supervised injecting rooms be trialled.

A trial of a medically supervised injecting centre in Kings Cross, Sydney, is currently being developed. It is recognised that it is unlikely that this trial will have a significant impact on heroin overdose rates. There are a number of reasons for this. Firstly, the number of injecting events likely to occur in the facility, even while operating at full capacity, will represent only a very small proportion of all injecting events in the state. Secondly, it is known that the majority of overdoses occur in a private home or hotel and there is no reason to believe that heroin users will chose to inject in an injecting centre rather than in their own home. Finally, the injecting centre will have limited hours of operation and therefore cannot influence overdoses that occur outside these hours. Of particular relevance is the fact that most overdoses occur between the hours of 6pm and midnight, outside of the proposed operating hours of the centre. These factors suggest that it is unlikely that the trail of a safe injecting centre will have a detectable effect on heroin overdoses.

However, the evaluation of this trial will provide an insight in to the effectiveness of

supervised injecting centres at reducing high-risk behaviours for overdose, such as injecting on the street or alone. It may also reduce other harms associated with injecting drug use, such as the transmission of blood borne viruses, and may reduce public nuisance from heroin use. As such the trail is deemed valuable and the evaluation of the centre will provide a sound body of evidence on which to base policy decisions regarding the role of injecting centres in a multifactorial public health strategy for reducing the harms and public nuisance associated with injecting drug use.

Summary

- Opioid overdose fatalities are preventable.
- Treatment services, such as methadone, protect against fatality from overdose and should be expanded where possible.
- Alternative pharmacotherapies should be trialled to attract high-risk untreated heroin users into treatment.
- Education based interventions for both heroin users and police have the potential to reduce overdose fatality.
- The distribution of naloxone to heroin users may prevent fatality from overdose.

8.0 Recommendations

This review has identified a number of strategies that may reduce the incidence of heroin overdose in Australia.

7.1 Research

Case-reports suggest that overdose may be associated with a significant burden of morbidity. However the paucity of literature in this area precludes quantification of this morbidity. It is recommended therefore that research be conducted to identify and quantify overdose-related morbidity.

The clear patterns of age and gender observed among overdose fatalities, coupled with the unusually low blood morphine levels found in overdose fatalities suggests the role of unidentified factors that may predispose users to overdose. Epidemiological evidence suggests that one such factor may be systemic dysfunction. It is recommended therefore that research be conducted to identify the effect of systemic dysfunction on overdose risk.

It has been established that fatalities from overdose are rarely instant and generally occur in private homes in the presence of witnesses, suggesting that there is commonly ample opportunity for intervention to prevent fatality from overdose. The opiate antagonist naloxone may provide witnesses of overdose with a means to intervene to prevent fatality. It is therefore recommended that a trial be conducted to evaluate the effectiveness, cost-effectiveness, and feasibility of reducing fatality from overdose by distributing naloxone to at risk heroin users.

There is a substantial body of evidence showing that the concomitant use of alcohol and benzodiazapines with heroin increases the risk of overdose, and that witnesses responses at overdose events are generally poor. Thus interventions which can either reduce these high-risk behaviours or increase help-seeking behaviour by witnesses have the potential to prevent overdose. However the complexity of addictive behaviours may mean that such behaviours are difficult or impossible to change through education. It is therefore recommended that further trials be conducted to evaluate the effectiveness and cost-effectiveness of heroin user education programs in reducing high-risk behaviour and improving responses to overdose.

7.2 Interventions

A significant body of evidence has shown that treatment for heroin dependence substantially reduces the risk of overdose. It is therefore recommended that the range and availability of treatment services be expanded.

It has been shown that long term untreated heroin users are at greatest risk of overdose. It is therefore recommended that efforts be made to recruit long term untreated heroin users into treatment.

It is apparent that needle and syringe programs provide an effective interface between heroin users and health services, particularly untreated users at highest risk of overdose, that may be used to educate heroin users to reduce high risk behaviours. It is therefore recommended that the effectiveness of overdose prevention interventions conducted by needle and syringe program workers be maximised through the use of standardised, evidence–based messages, methods and materials.

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Appendix A. Forms and Effectiveness of Treatment for Heroin Dependence

There are a number of treatments and treatment approaches available for people who are heroin dependent or experiencing problems as a result of heroin use. A brief description of the principal treatment modalities (detoxification, drug free treatments, and drug substitution) and evidence on the efficacy of these treatments is given below. The research indicates that not only are these treatments of benefit to those who receive them; they are also a sensible investment of public funds in that they produce substantial reductions in heroin mortality (Gerstein, Harwood et al. 1994).

Ideally, the effectiveness of all treatments for drug and alcohol dependence would be evaluated by randomised controlled trials in which representative samples of patients are randomly assigned to receive either a specified treatment or some ethically defensible minimum form of treatment (e.g. advice to stop drug use and referral to Narcotics Anonymous). Such studies have only been conducted on MMT, and there are very few of them. Assessments of the effectiveness of treatments for heroin dependence has had to depend upon the consistency of evidence from observational treatment outcome studies in which large groups of persons selecting different types of treatment are followed over time to evaluate its impact on drug use, crime and other outcomes. Statistical methods are used to assess the plausibility of alternative explanations of differences in outcome between different forms of treatment. Among these the leading hypothesis is that the different forms of treatment attracted heroin users who had very different prognoses.

It has also been common to evaluate the success of treatment for heroin dependence in terms of the proportion of heroin users who become abstinent during treatment and remain abstinent thereafter (Hall, Bell et al. 1993). When evaluated by this standard, all interventions for heroin dependence have poor results. Most attempts at heroin detoxification, for example, fail since many users do not complete detoxification, and few of those who do achieve enduring abstinence from opioid drugs (Mattick and Hall 1996). It is more realistic to judge the outcome of treatment or heroin dependence by comparing the effects of drug treatment on the frequency of heroin use and crime, and the health and well being of heroin dependent persons. When judged by these more realistic criteria, treatment for heroin dependence is a good investment of community resources (Gerstein and Harwood 1990; Hall, Bell et al. 1993).

1.0 Detoxification

Detoxification is the supervised withdrawal of a drug dependent person from their drug of dependence with the aim of minimising the severity of the withdrawal symptoms that are experienced in the process. Although not a specific treatment for heroin dependence (or indeed for any other form of drug dependence) (Mattick and Hall 1996), detoxification is one of the interventions most often sought by dependent heroin users (Marsh, Joe et al. 1990). From the heroin user's point of view, one of its attractions is that it reduces their opioid tolerance, and hence, the amount of street heroin that they need to achieve the desired pharmacological effect (Marsh, Joe et al. 1990). It should be regarded

as a palliative treatment for opioid withdrawal that provides heroin users a respite from drug use, and an occasion to reconsider the wisdom of continued heroin use. It also provides an opportunity for outreach and education of heroin users, and although not a treatment in itself, it can be a prelude to abstinence-oriented treatment.

In Australia in recent years entrepreneurs have promoted "Ultra-Rapid Opiate Detoxification" (UROD) as a treatment for heroin dependence. UROD involves two stages of treatment: rapid detoxification under a general anaesthetic, followed by up to a year's maintenance on the opioid antagonist naltrexone. "Rapid detoxification" is achieved within 24 hours by administering naltrexone under a general anaesthetic to displace heroin from opioid receptors in the brain. This is accomplished under general anaesthesia so that patients do not experience the distressing symptoms of accelerated opioid withdrawal.

The purported benefits of UROD are: the rapid completion of withdrawal by 100% of patients who start the process; immediate commencement of daily doses of naltrexone that blocks craving and prevents the euphoric effects of heroin or other opiate agonists that may be injected, producing high rates of enduring abstinence a year after treatment. There is good evidence that naltrexone accelerates opiate withdrawal. General anaesthesia does prevent patients from experiencing withdrawal symptoms, however it carries a risk of fatality, and deaths from this procedure have been reported. There is no evidence from controlled clinical trials that UROD and naltrexone maintenance produce the high abstinence rates claimed at 12 months (Kleber 1998; Hall and Wodak 1999).

2.0 Drug-free Treatment Approaches

Drug-free treatment approaches include: residential treatment in Therapeutic Communities (TCs); out-patient drug counselling (DC); and self-help groups like Narcotics Anonymous (NA). All these approaches share a commitment to achieving abstinence from all opioid and other illicit drugs; they all eschew the substitution of other opioid drugs for heroin; and they all use group and psychological interventions to assist dependent heroin users to achieve enduring abstinence from all drugs and to learn to address their problems in ways other than by using opioids and other drugs.

TCs typically involve residential programs of 3 to 12 months' duration during which users live and work within a community of other users, ex-users and professional staff. Group processes and individual counselling are used to change self-defeating behaviour and to support abstinence (Mattick and Hall 1993). Drug-free outpatient counselling is usually provided individually on an out-patient basis by drug counsellors (usually professionals but may include some former drug users). The aim is to address any underlying psychological problems and to assist drug users to become and remain abstinent. These programs often provide vocational rehabilitation and training.

NA runs self-help groups in the community which follow a program modelled on the 12-step program originally developed by Alcoholics Anonymous. The assumption is that addiction is a disease for which there is no cure. Recovery can only occur if the addict

remains abstinent from all mind-altering substances. The fellowship aims to assist its members to achieve and maintain abstinence by providing mutual help and support in working through the structured program of the 12 steps (Wells 1987).

There is little research evidence on the effectiveness of NA and other self-help approaches, and there have been no randomised-controlled trials for TCs or outpatient DC. Most of the evidence on the effectiveness of TC and DC programs comes from observational studies such as the Drug Abuse Reporting Program (DARP) (Simpson and Sells 1982) and the Treatment Outcome Prospective Study (TOPS) in the USA (Hubbard, Marsden et al. 1989). In general, TCs and DC are more demanding of drug users, and hence are less successful than MMT in attracting dependent heroin users into treatment and in retaining them in treatment. They do nonetheless substantially reduce heroin use and crime in the minority of entrants who remain in treatment for long enough to benefit (at least three months) (Hubbard, Marsden et al. 1989; Gerstein and Harwood 1990; Mattick and Hall 1993). There is some evidence that TCs may be more effective if they are used in combination with legal coercion or during imprisonment to ensure that heroin users are retained in treatment long enough to benefit from it (Gerstein and Harwood 1990).

Recently, there has also been renewed interest in the use of Naltrexone, an opiate antagonist, as an adjunct to drug free treatment. Naltrexone has been used as an opiate antagonist for a number of decades: it completely blocks the opiate receptor cells so that any opiates in a person's system will be displaced, meaning that if any opiates are taken, they have no effect. Opiate antagonists have been discussed as possibly extinguishing the conditioned withdrawal response occurring in response to environmental stimuli associated with the use of drugs (Wikler 1980). Naltrexone maintenance hence aims to ensure that the client remains opiate-free.

A requirement for the effectiveness of naltrexone maintenance is that naltrexone is taken daily: hence, one of the biggest determinants of the effectiveness of naltrexone's efficacy is the client's motivation to remain abstinent (and therefore take naltrexone). Such motivation may not characterise the majority of opiate dependent persons, many of whom enter treatment through coercion (either legal or social). Research has shown that 90% of individuals on naltrexone maintenance resume illicit opiate use within 12 months in the absence of outpatient treatment (Kosten 1990). Resumption of heroin use following naltrexone maintenance may constitute a high risk period for overdose, due to reduced tolerance.

The success of naltrexone maintenance, as for any treatment, depends ultimately upon the outpatient treatment program, the nature of the client group, and the appropriateness of the program to the client group (Stine and Kosten 1997). Research indicates that the majority of business executives and physicians who are opiate-dependent who are prescribed naltrexone in combination with outpatient treatment and therapy will significantly improve their social and professional functioning and most will remain opiate free (Ling and Wesson 1984; Washton, Pottash et al. 1984; Roth, Hogan et al. 1997). In comparison, a study conducted in a suburban health project clinic with opiate-

dependent persons with an average length of 10.5 years of dependence, found that after 90 days, only 17% of clients remained in treatment, despite the fact that they all expressed a desire for abstinence-based treatment (Tennant, Rawson et al. 1984).

In summary, it appears that naltrexone may be appropriate for less heavily dependent heroin users, who are motivated to cease use, and who have social and employment stability. Trials of naltrexone are in progress across Australia, reflecting a recent increase in public interest for naltrexone maintenance as an additional treatment for opiate dependence. However, no results have yet been published in a peer-reviewed journal, and the client group targeted in such trials has not been made explicit by the researchers.

3.0 Drug Substitution Treatments

Drug substitution treatment substitutes a longer-acting, usually orally administered, opioid drug for the shorter-acting heroin that is typically used by injection. It aims to stabilise the dependent heroin user so that they become more accessible and amenable to rehabilitation. They are among the most popular forms of treatment with heroin users (Marsh, Joe et al. 1990). Methadone maintenance treatment (MMT) is the most common form of drug substitution world-wide and it is the only type of opioid substitution treatment that is currently provided in Australia (Mattick and Hall 1993).

3.1 Methadone Maintenance Treatment

Dole and Nyswander (1965; 1967) introduced orally administered maintenance doses of the synthetic opioid drug methadone as a drug-substitution treatment for opioid dependence. Methadone provided a legal and controlled supply of an opioid drug which only had to be taken once a day because its long duration of action eliminated opiate withdrawal symptoms for 24 to 36 hours. When given in high or `blockade' doses, it blocked the euphoric effects of injected heroin, thereby providing an opportunity for the individual to improve his or her social functioning by taking advantage of the psychotherapeutic and rehabilitative services that were an integral part of the program.

Six randomised-controlled trials have been conducted on the effectiveness of MMT. All of these trials have involved small numbers of patients (Dole, Robinson et al. 1969) who have been followed up for short periods (rarely longer than one year). Nevertheless, all have produced positive results, despite small sample sizes that worked against finding differences. The positive findings of these trials have been corroborated by the results of controlled observational studies in which statistical forms of control have addressed the major alternative explanations of apparent effectiveness which are dealt with by randomisation in controlled trials (Cook and Campbell 1979). These controlled observational studies have generally shown that patients in MMT decreased their heroin use and criminal activity while they remained in treatment; they relapsed rapidly to heroin use after leaving treatment (Ward, Mattick et al. 1992; Hall, Teesson et al. 1998).

More recent evidence indicates that MMT also substantially reduces the transmission of HIV via needle-sharing (Ward, Mattick et al. 1992). Studies of self-reported rates of

injecting and needle-sharing among opioid injectors who were or were not in methadone treatment indicate that MMT markedly reduces the frequency of sharing needles (Ball, Lange et al. 1988; Darke, Hall et al. 1990; Ball and Ross 1991). Studies of HIV seroprevalence also show that MMT has protected patients from HIV infection in locations where HIV has spread rapidly among injecting drug users who have not been in treatment (Abdul-Quader, Friedman et al. 1987; Jarlais, Friedman et al. 1989; Schoenbaum, Hartel et al. 1989; Novick, Joseph et al. 1990).

3.2 Other Maintenance Pharmacotherapies

There are a number of pharmacotherapies available as alternatives to methadone maintenance: levo-alpha-acetylmethadol (LAAM), buprenorphine, slow release oral morphine, and injectible heroin. The characteristics of these are outlined below.

3.2.1 Levo-alpha-acetylmethadol (LAAM)

LAAM is a synthetic opiate agonist with an action that is similar to morphine, but which has a much longer half-life than that of other opiates. Its duration of action extends from between 48 to 72 hours which means that dosing is only necessary three times a week. The safety and efficacy of LAAM is similar to that of methadone.

Early studies comparing methadone and LAAM found no significant differences in rates of positive urine screens to opiates, treatment retention, or attendance to the clinic, as well as no differences in self-reported anxiety or opiate use (Jaffe and Senay 1971; Jaffe, Senay et al. 1972). Several large scale studies have also been conducted as part of the process of registering LAAM as an alternative drug treatment approved by the US Food and Drug Administration (FDA). The VA Co-operative study examined the comparative effectiveness of LAAM and methadone (Ling, Charuvastra et al. 1976). It found that the rate of early termination was higher in the LAAM group (80 mg three times a week) than the low dose (50mg daily) or high dose (100mg daily) methadone groups but this appeared to be due to slow induction. For those who stayed in the study, the efficacy of LAAM was similar to high dose methadone, and superior to low dose methadone.

Studies have also assessed the feasibility of moving patients from methadone to LAAM (Ling, Klett et al. 1978). A comparison of transfer to LAAM with those continuing in MMT found that more methadone patients dropped out than those who crossed over to LAAM, and more patients opted to continue LAAM than methadone maintenance.

The advantages of LAAM in comparison to methadone lie in the relatively slower onset of the effects, and in the longer duration of the action. This has two consequences: the risks of abuse by patients are reduced as the effects are not felt immediately, which results in a lower risk of LAAM being diverted for abuse by persons not enrolled in LAAM maintenance. Second, it also provides the benefit of fewer visits being required for dosing, making fewer demands on both the patients and on the service provider. This allows greater flexibility to the client and reductions in time taken by clinic staff to prepare doses and keep records.

3.2.2 Buprenorphine

Buprenorphine is a mixed agonist-antagonist: it has partial agonist effects similar to those of morphine, but blocks the effects of pure agonists such as heroin or morphine. When given in high doses, the effects of buprenorphine can last for up to 3 days (Johnson, Jaffe et al. 1992). An attractive feature of buprenorphine is the antagonist effect that is seen at higher doses, which has important implications in the risk of overdose and abuse potential (Oliveto and Kosten 1997). The optimal dosage of buprenorphine is yet to be determined, but research has found that doses of 8mg daily result in similar rates of opiate-free urine screens to methadone doses of 60mg daily (Johnson, Jaffe et al. 1992). Because of the long half-life of buprenorphine, dosing may be made on an alternate or thrice-daily basis, which results in increased flexibility for the client and reduced demands upon the clinic.

3.2.3 Slow Release Oral Morphine

Slow release oral morphine is given orally on a 12 hourly or daily basis because its duration of action is shorter than that of methadone. The term "slow-release" refers to the gradual and predictable manner in which morphine is released into the body by the preparation, ensuring that the level of morphine in the blood is more even (Lintzeris and Benporath 1997). An open study of slow-release morphine in heroin-dependent persons was conducted in Austria (Fischer, Presslich et al. 1996), with apparent success but no randomised controlled trials have been conducted to date.

Slow release morphine has been used successfully to treat heroin-dependent patients who were intolerant of methadone, with successful results (Fischer, Presslich et al. 1996; Sherman 1996). Fewer symptoms of subjective discomfort (e.g. fluid retention, insomnia, poor concentration) were reported by persons when on morphine compared to their symptoms whilst on methadone. Slow-release may be useful for patients who cannot tolerate the negative side effects of methadone. Recent research has revealed that slow release oral morphine is suitable for pregnant clients, with no apparent complications or health consequences for the child, and no significant differences from methadone maintenance during pregnancy (Fischer, Jagsch et al. 1999).

Because it has a longer period of action than heroin, the abuse potential of slow-release morphine has been estimated to be similar to that of methadone (Ternes and O'Brien 1990). However, there have been some reports of injuries resulting from the injection of morphine extracted fom tablets (Bloor and Smalldridge 1990) and the tablets can be chewed producing a quicker release of morphine.

3.2.4 Injectible Heroin Maintenance

One way of attracting more heroin users into drug treatment may be to offer injectible heroin maintenance treatment (HMT). Its principal attraction is that it may increase the number of heroin users who are attracted into and retained in treatment by providing them with their preferred drug, heroin, by their preferred route of administration,

injection. There are reports of successful clinical experience using this form of maintenance treatment (Marks 1987). The opportunity to prescribe injectible heroin has been part of the so-called "British system" since 1926, although it has only rarely been used (Strang and Gossop 1994). The feasibility, safety and impact of HMT has also been evaluated in a controlled observational trial in a number of sites in Switzerland (Rihs 1994; Uchtenhagen, Gutzwiller et al. 1998).

The major constraint upon the use of HMT has been societal concern about providing injectible heroin, even when it is restricted to dependent heroin users who receive it under medical supervision. These concerns take various forms (Bammer 1995). Some community members have strong moral objections to providing any drug of dependence, whether it be heroin or methadone, to dependent drug users; for them abstinence is the only acceptable treatment aim and outcome. Parents of adolescents worry about sending the "wrong" message to youth about heroin and other drug use. Residents of localities that provide HMT are concerned that there will be a "honey-pot" effect attracting even more heroin users into their communities. Treatment personnel may fear that HMT will create an incentive for heroin users to become heroin dependent, that prescribed heroin will be diverted from dependent to non-dependent heroin users, and that HMT will adversely affect recruitment of dependent heroin users into less attractive forms of drug treatment.

Even if there was stronger public support for HMT the costs of providing it mean that the scale of its provision is likely to be modest. The costs of HMT are of the order of two to three times those of providing MMT (Uchtenhagen, Gutzwiller et al. 1998). If we assume a rough equivalence between HMT and MMT in their impact on heroin use and crime (Hartnoll, Mitcheson et al. 1980), then on the grounds of cost-effectiveness MMT would be preferable to HMT. That is, we would attract more users into drug substitution by using MMT than by HMT, even if the latter were more attractive than the former, because we could treat many more by MMT than by HMT. HMT would have to produce substantially greater benefits for each participant than MMT to make it competitive.

All considered, there is a case for cautious trial and evaluation of HMT as an option for opioid dependent persons who have failed to respond to other forms of treatment. It may also have benefits for the community if it reduces the criminal activity of a small actively criminal group of dependent users, and if it reduces their risks of contracting or transmitting HIV and other infectious diseases. It will be much more expensive to provide HMT than MMT. Given the cost of its provision, it will not replace existing forms of treatment but it may provide a modest additional way of ameliorating the health and social problems caused by opioid use.