

**PROCEEDINGS OF AN INTERNATIONAL
OPIOID OVERDOSE SYMPOSIUM, SYDNEY,
AUSTRALIA, 14-15 AUGUST 1997**

Edited by Wayne Hall

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**PROCEEDINGS OF AN INTERNATIONAL OPIOID OVERDOSE
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National Drug and Alcohol Research Centre
University of New South Wales

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An Overview of International Opioid Overdose Symposium

by

Wayne Hall, Director, NDARC¹

Introduction

The aim of the International Opioid Overdose Symposium was to review trends in illicit opioid overdose deaths in a number of countries in order to identify strategies for preventing such deaths. Australia was prompted to host this meeting because it has experienced a sustained increase in illicit opioid overdose deaths over the past decade. One response to this increase has been an expansion in methadone maintenance treatment places. An apparent increase in methadone-related deaths among persons in treatment and from diverted methadone has produced community concern about the methadone program.

It therefore was timely to meet to discuss trends in heroin and methadone-related deaths in Australia and to invite international speakers to help place recent Australian experience in an international context. A Symposium was jointly convened by the Central Sydney Area Drug and Alcohol Services and the National Drug and Alcohol Research Centre in its role as a WHO Collaborating Centre in the Treatment and Prevention of Drug and Alcohol. Funding for the meeting was provided by the Commonwealth Department of Health and Family Services and the Drug and Alcohol Directorate of the New South Wales Department of Health. This paper summarises the issues discussed at the Symposium.

International Trends in Heroin Use

In his introduction to the Symposium, Dr Alan Lopez (Programme on Substance Abuse, World Health Organization) reviewed evidence on international trends in opioid use around the world. While acknowledging the difficulties in obtaining accurate information on an illegal and socially stigmatised form of behaviour as heroin injecting, he noted that there has been a global increase in the production and in the illicit consumption of opioids, especially heroin by injection. New sources of opium production in Colombia and Mexico, and new trafficking routes in Western and Southern Africa and in Eastern Europe, have exposed new populations to opiate and heroin use. In recent years opiate use appears to have increased in North America, Eastern Europe and Australia.

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Increases in heroin use appear to be cyclical and epidemic. A major epidemic occurred in the UK in the mid 1980s (Strang and Gossop, 1994). This followed a decade or more during which heroin use had decreased, as indicated by the steady aging of heroin users in treatment who had initiated use in the 1970s. The mid 1980s epidemic was fuelled by the availability of cheap and high purity heroin from SW Asia, principally from Pakistan. There was a similar epidemic in the USA in the late 1960s and early 1970s. There is recent evidence of a new epidemic of heroin use among young drug users in Australia who have initiated by snorting with a substantial minority moving to injecting as their opioid tolerance increases (Maher, 1996).

Different regions of the world show variations in patterns of opiate use. Synthetic opiates (e.g. methadone, buprenorphine, and fentanyl) are increasingly used in developed countries. In some countries, drug users are resorting to crude forms of manufactured opiates, such as, "homebake" in Australia and New Zealand, and "kompot" in Poland. There has also been a trend in Pakistan, China, India, Vietnam Thailand for opiate users to make a transition from more traditional opium smoking to injecting heroin. There is now evidence of an injecting drug use problem in 122 countries. A small number of mainly developed countries, such as the Netherlands and the UK, have shown a move away from injecting to "chasing" and snorting heroin.

Despite its substantial public health impact, the prevalence of heroin use is typically below 1% of population in USA (Anthony and Helzer, 1991; Anthony et al, 1994) and Australia (Hall, 1995). Among those who become dependent on heroin, there is a high rate of premature mortality, approximately 1-3% per annum, a rate that is 13 times higher than that among non-heroin using peers (English et al, 1995). Users are also at higher risk of infectious disease transmission. Opioid overdose remains the major cause of death among heroin users despite the advent of HIV and HCV (English et al, 1995).

Definition of an Opioid Overdose

The WHO defines a drug overdose (from WHO lexicon of alcohol and drug terms) as: "the use of any drug in such an amount that acute adverse physical or mental effects are produced". The ICD-10 allows for the classification of opioid overdose as acute intoxication (for those with a substance use disorder) and "poisoning by narcotics and psychodysleptics" for those who do not have a substance use disorder.

Dr Jason White, (Department of Pharmacology, University of Adelaide) outlined the pharmacology of opioid overdose. He described the distribution of mu receptors in the brain stem regions and explained their role in controlling respiration. He also discussed the possible interactive effects between GABA, glutamate and opioid receptors in the respiratory centres.

Sandra Sunjic (South Western Sydney Drug and Alcohol Services), described the pathway to a diagnosis of opioid related death in New South Wales, Australia. This illustrated how uninformative are the diagnoses that are often made by coroners and pathologists in opioid-related deaths. The most frequent diagnoses in such cases were "acute narcotism", "opiate dependence", and "accidental opiate poisoning".

The difficulties with diagnosing a cause of death in "opioid overdoses" were outlined in a paper by a forensic pathologist, Dr Johan Duflou (New South Wales Institute of Forensic Medicine). He reported a small study in which pathologists were asked to judge the cause of death in several hypothetical cases of presumed overdose. The analyses of blood samples in these cases showed either a high or low blood morphine level, in the presence or absence of high blood alcohol levels and benzodiazepines. The results showed substantial lack of agreement on the contribution that opioid and other depressant drug use made to these hypothetical deaths.

The problems in understanding opioid overdose deaths are compounded in developing countries which do not have sophisticated systems for the collection of mortality and other health data. Even when reasonable mortality data exist, there are problems in calculating rates of overdose mortality and morbidity because of our ignorance of the number of heroin and other drug users in the population. Differences in the definition of an overdose between countries also make it difficult to compare incidence and prevalence rates across countries. It is still nonetheless useful to examine trends in opioid overdose deaths within particular countries.

Trends in Opioid Overdose deaths

Wayne Hall (National Drug and Alcohol Research Centre) described trends in opioid overdose deaths in Australia between 1979 and 1995. Opioid overdose deaths in 1992 comprised 76% of all illicit drug deaths in the 15-34 age group in Australia. This was a third of all drug related deaths in that age group, second to alcohol which accounted for 52% of drug-related deaths in this age group. It also comprised 9% of all deaths in the age group. The most frequent "causes" of opioid overdose deaths were "opiate dependence" and "accidental poisoning".

The number of opioid overdose deaths attributed to dependence and accidental poisoning increased sixfold from 70 in 1979 to 550 in 1995. Males accounted for 79% of overdose deaths over the period. The increase was more marked among males. Half of all male deaths occurred in New South Wales which had an overdose mortality rate almost twice that in Victoria, and three times that in the remaining states (Hall and Darke, 1997).

The mean age at death for males increased from 24.5 years in 1979 to 30.1 years in 1995. This reflected large increases in overdose mortality among men and women aged 35 to 44 years, and 25 and 34 years. The rate of increase was lowest among those aged between 15 and 24 years. Analysis by decade of birth showed that 46% of male and 50% of female overdose deaths in the period occurred among those born between 1960 and 1969. Deaths among persons born between 1950 and 1959 accounted for 38% of male and 33% of female deaths. These figures indicate that most overdose deaths occurred among persons who initiated their heroin use in the late 1970s and early 1980s (Hall and Darke, 1997).

A number of possible explanations of the increase in opioid overdose mortality were briefly considered. It was unlikely that the increase reflected a change in the diagnostic

practices of pathologists and coroners since any such changes would have to be large and to have varied strongly with the age and sex of the deceased.

It was also unlikely that the increase was due to an increase in the number of heroin users. The increase in the age at death throughout the period for men and women, and the marked differences in mortality for the different age cohorts, suggest that most of the increase in mortality has not been due to increase in deaths among new recruits to heroin use.

The popular explanation for the rise in opioid overdose deaths is an increase in heroin purity. There is reasonable evidence that purity increased between 1992 and 1995 but this is unlikely to be the reasons for the increase. If increased heroin purity was the explanation one would reasonably expect that most of the increase would be among newer recruits who would have the lowest tolerance for opioid drugs and be the least experienced in using street drugs. But deaths among young, inexperienced users in the 15-24 age group were outnumbered by deaths among older users.

Data were also presented on opioid overdose deaths in the United Kingdom and Europe by Dr Michael Farrell (National Addiction Centre, London). His data indicated that there has been an increase in opioid overdose deaths in UK (Neeleman and Farrell, 1997) and parts of Europe over the past decade. Britain has also had an increase in methadone-related deaths among drug users who were not enrolled in methadone treatment. Dr Farrell stressed that it was difficult to compare rates between different European countries and between Europe and Australia because of differences in diagnosis and classification of causes of death between countries.

Data on opioid deaths in New Zealand were presented by Dr Doug Sellman (National Treatment Development Centre, Christchurch School of Medicine). New Zealand has no dependable illicit heroin supply so illicit opioid users either use diverted pharmaceutical drugs, such as slow release morphine and temgesic, or they extract opiates from over-the-counter analgesic medications ("homebake"). There are a small number of opioid overdose deaths in New Zealand each year, most of which occur among older drug users and show polydrug involvement in a substantial proportion of cases.

Trends in Methadone-related deaths

Methadone-related deaths are a concern in countries which methadone maintenance treatment is used to treat opiate dependence. Dr Deborah Zador (Central Sydney Area Drug and Alcohol Services), described trends in methadone-related deaths and causes of deaths among persons in the NSW methadone maintenance program between 1990 and 1995. During this period the number enrolled in methadone treatment increased from 7,419 in 1990 to 12,924 in 1995.

There was a total of 211 deaths among program participants between 1990 and 1995. Most of these were among males (72%) and the average age at death was 34 years. The number of deaths per annum increased but the rate of deaths from all causes did not. That is, the increase in the number of deaths was proportional to the increase in the number of persons who were enrolled in methadone treatment. The overall mortality rate

among methadone participants was 3.4 times that of age peers in New South Wales who did not use heroin. But this was only 26% of the rate reported in studies of untreated heroin users, a finding that was consistent with the literature (Caplehorn et al, 1994).

Drug overdose accounted for 40% of deaths among MMT patients. Medical illnesses accounted for 29% of all deaths, 14% were attributable to trauma (e.g. motor vehicle accidents) and the remainder were due to suicide or a combination of two or more of these causes (8%). Only 24 deaths occurred within the first seven days of treatment and in two of these the persons may have presented a false history of opioid dependence.

Ms Sandra Sunjic (South Western Sydney Area Drug and Alcohol Service), reported on 242 methadone-related deaths in NSW between 1990 and 1995. These accounted for 10% of all opioid-related deaths during this period. Of these 134 deaths involved methadone syrup, the form of the drug exclusively prescribed for opioid dependence in New South Wales. Among these deaths, 72 were enrolled in a methadone program at the time of their death. In 89% of these cases polydrug use a contributory factor.

Professor A.T. McLellan, (Department of Psychiatry, University of Pennsylvania) described American research on methadone diversion. He noted the media preoccupation with methadone diversion despite the fact that there were low rates of street methadone use, low rates of methadone mentions in the Drug Abuse early Warning Network, and no evidence of primary methadone dependence among illicit drug users who were not in methadone treatment. Professor McLellan concluded that methadone diversion was an indication of unmet demand for methadone treatment since it was largely used to avert withdrawal symptoms.

Risk Factors for Heroin Overdose

Variations in individual tolerance are likely to be an important factor in opioid overdose deaths. Such deaths appear to be more common after release from prison or after detoxification when the user's opioid tolerance has been substantially reduced (Darke et al, 1996a,b). Variations in purity are also a contributory factor but they are unlikely to be the sole explanation. Dr Shane Darke (National Drug and Alcohol Research Centre), summarised the findings of a recently published review of risk factors of fatal opioid overdose (Darke and Zador, 1996). He reported that there is substantial variation in blood morphine levels among persons who die of apparent "heroin overdoses". There is also a marked overlap in the blood morphine levels in those who have died of an "overdose" and heroin users who have died of other causes. Most persons who die of heroin overdoses are also older and experienced users rather than neophytes (Darke and Zador, 1996).

A major risk factor for heroin overdose appears to be the concurrent use of heroin with alcohol and other drugs. Polydrug use is increasingly common among drug users, and especially heroin users (Darke and Hall, 1995). Such combinations increase the overdose risk and make it more difficult to attribute the cause of overdose to specific drugs.

Dr Wendy Loxley (National Centre for Research into the Prevention of Drug Abuse) reported findings from the Australia Study of HIV and Injecting Drug Use on the prevalence and correlates of self-reported nonfatal overdose (Loxley et al, 1995). These confirmed earlier studies in showing that heroin users had a high lifetime risk of personal overdose and most had been present at someone else's nonfatal or fatal overdose (e.g. Bammer and Stengoz, 1993; Darke et al, 1996a,b). The risk of a nonfatal overdose increased with the duration of opioid use, as did the risks of contracting infectious diseases, such as hepatitis C. The users' preferred explanation of nonfatal overdoses was increased heroin purity.

Preventing Heroin-related Deaths

A workshop on preventing heroin related deaths was convened by Professor Tim Stockwell and Mr Simon Lenton (National Centre for Research into the Prevention of Drug Abuse) and Dr Robert Ali (Drug and Alcohol Services Council of South Australia) on the second day of the Conference. The consensus among participants was that opioid overdose needed urgent attention. Such deaths have increased and they are responsible for substantial monetary and human costs. An appropriate response requires collaboration between different sectors and an adaptation of responses to specific local circumstances.

There was agreement that health professionals, drug users and their friends and families needed to be educated about the risk factors for overdose and how best to respond to an overdose. Education of users may best be done by using outreach peer educators, as has been done in India and Nepal where overdose education is combined with needle and syringe distribution and HIV education. An intervention program conducted by the Drug and Alcohol Services Council in South Australia is another good example of peer education. Other approaches that have been used include disseminating information through users' group newsletters (e.g. in New Zealand) and targeting dealer injectors in Vietnam.

The role of opioid antagonists in resuscitating persons who overdose remains controversial. Some have recommended that naloxone should be distributed to opioid users at high risks of overdose (e.g. Strang et al, 1996). Its cost, however, probably means that it is not an option in many developing countries. Ms Annie O'Loughlin (Kirketon Road Centre, Darlinghurst) described an outreach program in the inner city area of Sydney that successfully used intramuscular naloxone to resuscitate a high risk population of street injectors.

Drug maintenance treatment programs such as methadone maintenance are effective in reducing opiate overdoses. There have been arguments about the net benefits of methadone treatment, given the overdose risks of methadone. The data presented the previous day by Dr Deborah Zador and colleagues suggest that this concern is overstated. If overdose is a major concern, alternative maintenance agents which have a lower risk of overdose, such as, buprenorphine, can be used.

Preventing Methadone-related Deaths

A workshop on the prevention of methadone-related deaths in treatment was convened by Dr Deborah Zador and Dr James Bell. Workshop participants agreed that good clinical guidelines were needed to assess applicants' suitability for MMT. This needed to include: a more rigorous assessment of the applicants' opioid dependence, the extent of their polydrug use, and the amount and type of psychological morbidity.

Structured induction protocols were also required for the first seven days of treatment, when new entrants to methadone maintenance treatment are at increased risk of drug overdose. These protocols needed to be supplemented by regular clinical reviews of patients and the education of patients about the risks of polydrug use and the symptoms of methadone overdose. Amendments were suggested to national policy guidelines on induction doses during the first week of treatment, and assessments of liver function.

There was agreement on the desirability of achieving consensus among coroners and forensic pathologists on the definition of and criteria for a "methadone related death", especially when other drug use was involved. There was no consensus on a methadone take-away policy that balanced the goal of maximising participants' reintegration into the community while minimising diversion of methadone.

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Opioid Overdose: An International Perspective

by

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Introduction

Australia is a fitting country in which to debate the complex issues of opioid overdose. The World Health Organization is impressed by the pragmatism, innovation and commitment which may be observed in Australian drug policy and programming. The International Opioid Overdose Symposium demonstrates how sensible and open the Australian approach is. WHO is aware of some of those local factors which provided the impetus for holding this meeting and some of the current issues which are fuelling the debate.

As with other critical drug policy issues, such as HIV infection and hepatitis C, the Australian response to increasing numbers of opioid overdose fatalities in the past few years appears to be one of careful analysis of the situation, drawing on overseas experiences and encouraging public debate, development of pragmatic interventions and ensuring effectiveness through thorough evaluation and practical research. Such an approach has been facilitated by the Australian National Drug Strategy, a coordinated and comprehensive national initiative which provides a model for many other countries.

Although it is apparent that many of the important issues that need to be addressed with regard to opioid overdoses in Australia are locally specific, many share commonalities with situations in other countries. This paper comments on some of these issues and places them within an international context. It concludes with some suggestions about how WHO might assist in responding to opioid overdose and other drug related deaths.

Nature and extent of opioid use

The methodological challenges presented by drug use epidemiology, particularly when the drugs concerned are opioids such as heroin, are well known and will not be repeated here. It is acknowledged that accurate information on the nature and extent of heroin and other opioid use is difficult to obtain and interpret. The available evidence does suggest that there has been a global increase in the production, transportation and consumption of opioids, mainly heroin (Childress, 1994; Gossop and Grant, 1990; UNDCP, 1997).

Heroin use has become increasingly common in some developed countries in North-

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America, Europe and Australia since the 1960s. More recently, traditional patterns of opium use in some developing countries of south-east Asia have been replaced by more wide-spread use of opium solution, heroin and buprenorphine (Stimson and Choopanya, in press). Opioid use and injection are being reported from countries where traditionally opioid drugs and injection have not been reported in the past, for example Mexico and Nigeria (Adelekan and Stimson, 1997; International Narcotics Control Board, 1996).

While the current global trend in opioid use is generally upward, historical patterns of heroin use in some countries have been cyclical, with increases in use following periods of relative stability or even decline. In Australia, an epidemic of heroin use which occurred in the late 1960s and early 1970s led to the establishment of methadone maintenance treatment for dependent heroin users (Manderson, 1993; Ward et al., 1992). A second Australian epidemic began in the early and mid-1980s. In the United Kingdom there was also a well reported heroin epidemic in the mid 1980s, following a period in the 1970s when the heroin using population was generally stable and ageing (Power, 1994). The UK epidemic in the 1980s was in part the result of the availability of cheap, high purity heroin from South-west Asia, notably Pakistan. This form of heroin could be smoked and became attractive to young non-injecting users, fuelling an epidemic of young heroin smokers (Pearson, 1987).

There is some recent evidence to suggest a new interest in heroin among the young in the UK. In contrast, in other European countries, for example the Netherlands, the number of young heroin users has been reported as falling, whilst the number of older users has remained stable (WHO, 1997). Recent evidence suggests that the use of heroin has once again become increasingly common in the United States. Unlike an earlier epidemic of heroin injecting in the US from 1964 to 1972 (Boyle and Brunswick, 1980), these increases in heroin use are associated with new, younger users taking the drug intra-nasally (snorting) rather than injecting (National Institutes of Health, 1997). This new "epidemic" of heroin use in the United States is in part associated with the availability of cheap, high purity heroin from South America (National Institutes of Health, 1997).

In Europe and the United States the role of the media has come under some scrutiny for glamorising heroin use and creating a climate in which heroin use is more socially acceptable, although there is no scientific evidence to prove this association. Availability, price and purity are important factors influencing the extent and nature of opioid use. Increased tolerance or declining purity of the drug may eventually lead opioid smokers or snorters to injection as a favoured route of administration.

Heroin is not the only opioid of concern. Never before has there been such a diverse range of opioids being used for non-medical purposes. The "traditional" opiates, such as opium and heroin, are increasingly sharing the scene with synthetic opioids (such as methadone, buprenorphine and fentanyl) often diverted from medical sources. A range of locally produced opioids are also used in different countries. In Western Australia and New Zealand "home-bake" is manufactured from pharmaceutical preparations containing codeine (Black and Caswell, 1993). In Poland "kompot" and "soup" prepared from poppy straw are injected. In Ukraine "himier", an opium solution, is injected.

The mode of administration is also changing in many regions. The transition from opium smoking to heroin smoking and "chasing", then to heroin and buprenorphine injecting is a familiar scenario in many countries, particularly those countries where opium is produced or trafficking occurs, such as Pakistan, India, Thailand, Viet-Nam and China (Stimson et al., 1996). There are now at least 127 countries and territories where injecting drug use occurs (Ball, in press; Stimson and Choopanya, 1996). With this transition to injecting the risk for overdose increases dramatically, as does risk of HIV and hepatitis infection.

On the other hand, some countries are seeing a transition in routes of administration from opioid injecting to smoking, chasing and snorting, particularly as drug purity increases. Transitions from injecting to non-injecting use have also been observed in response to HIV. The transition from heroin injecting to non-injecting use has been observed in the United States and Europe (Des Jarlais et al., 1994; Griffiths et al., 1994). The United States Community Epidemiology Work Group (CEWG), which has a tradition of identifying new, emerging and re-emerging trends in drug use, reports increases in heroin use in many US cities. These increases, first noted in 1995, are associated with snorting and smoking the drug, increases in purity and younger heroin users. In some of these cities (including Newark and New York City) the majority of heroin users entering treatment are currently non-injectors (National Institutes of Health, 1997). The CEWG has also reported a new method of heroin use: dissolving heroin, putting it into a syringe, nasal spray or dropper and squirting it into the nostrils (National Institutes of Health, 1997). Opioid use is also being reported in regions and countries where opioids have not traditionally been used by drug users. This has resulted from areas of new production, such as Colombia and Mexico, and the establishment of new trafficking routes, such as through western and southern Africa and Eastern Europe (International Narcotics Control Board, 1996).

These changes in opioid availability; new and changing patterns of use; shifts in the modes of administration; and variations in levels of purity of opioids all influence transitions to injecting use, and increase risks of blood borne infection and overdose. The relationships are complex and there is ongoing debate about this reflected in other papers in this monograph.

Opioid related mortality

Whilst the estimated world-wide production of heroin is reported to have more than doubled since 1985 (Childress, 1994; UNDCP, 1997) the actual prevalence of heroin use in general populations is low, typically less than 1% of the adult population, even in identified "consumer" countries, such as the United States, Australia, and certain European countries (Childress, 1994; Hall and Darke, 1997; EMCDDA, 1996). In spite of the comparatively low prevalence of use, heroin and other opioids cause widespread health and social problems in many countries. In many countries they are the most commonly used drugs among those seeking treatment for illicit drug use.

Longitudinal and cross-sectional studies conducted in the United States and Europe indicate yearly all-cause mortality rates (including HIV) of between 1% and 3% among dependent opioid (mainly heroin) users (Darke and Zador, 1996; Danish Board of

Health, 1997; Frischer et al., 1997; Oppenheimer et al., 1994). There is also evidence from studies in some countries that mortality rates among opioid users are increasing, sometimes dramatically, over time. There are, however, variations over time and between locations, even in the same countries. In western Europe, heroin injectors who regularly consume large amounts of different drugs, face a risk of death which may be as much as 20 or even 30 times higher than non-drug users in the same age range (EMCDDA, 1996). In Glasgow, Scotland, drug injectors are 22 times more likely to die than their peers and mortality rates for drug injectors have been increasing since the early 1980s (Frischer et al., 1997). Mortality rates among opiate addicts in Catalonia, Spain increased from 13.8 to 34.8 per 100,000 between 1985 and 1991 (Orti et al., 1996). In Amsterdam, the Netherlands, a mortality rate of 32.3 was reported for drug injectors recruited through low-threshold methadone clinics and a sexually transmitted disease clinic (van Haastrecht et al., 1996). In Milan, Italy an overall mortality rate of 25.2 per 100,000 was reported for injectors attending treatment centres. These rates remained under 16 from 1981 to 1986 then increased rapidly to 63.8 in the first half of 1991, when the follow-up period was closed (Galli and Mussicco, 1994).

Since heroin and other opioids are commonly used by injection, health risks including that of HIV and viral hepatitis transmission, are substantial (Donoghoe and Wodak, in press). However, even prior to HIV, pooled estimates from twelve studies indicated that opioid injectors faced a relative risk of death 17 times greater than non-using peers (Holman et al., 1990). In Baltimore (United States) and Amsterdam (Netherlands) similarly high standardised mortality rates have been calculated for HIV-1 negative drug injectors (van Ameijden et al., 1996). In spite of the devastating epidemics of HIV among drug injectors in some countries, overdose remains a major cause of death, and in many countries it is the leading cause of death among drug injectors (Darke and Zador, 1996; Frischer et al., 1994; Perucci et al., 1991; Oppenheimer et al., 1994). In spite of the importance of overdose as a major cause of death for opioid users, it remains poorly understood because of the methodological difficulties and confounding factors discussed below.

Methodological difficulties in defining and recording "overdose"

An overdose is generally understood to be an excessive dose of a drug which results in coma and respiratory failure (Proudfoot, 1988). According to the WHO Lexicon of Alcohol and Drug Terms (WHO, 1994) overdose is defined as: "The use of any drug in such an amount that acute adverse physical or mental effects are produced". The current tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1992) allows for the classification of opioid overdose (under F11.0 Mental and behavioural disorders due to use of opioids) as: acute intoxication due to use of opioids (for those with a substance use disorder) or poisoning by narcotics and psychodysleptics (for those who do not have a substance use disorder). Previous editions of the International Statistical Classification of Diseases and Related Health Problems were not able to code drug related deaths in this way and changes in the tenth edition were made to enable a more adequate coding system. The inadequacies of earlier ICD classifications to capture opioid related deaths may in part explain the lack of reliable and comparable international data. The introduction of ICD-10 will greatly improve the classification and coding of drug-related deaths. This is a

long-term process, even in countries with relatively well developed reporting systems. In the countries of the European Union, for example, only five countries have begun using ICD-10, although most have plans to introduce it over the next three or four years (Danish National Board of Health, 1997).

Even countries which collect data on drug related deaths classified according to the ICD coding system experience other problems. These include the extent to which toxicological analysis and forensic examination are undertaken to determine whether opioid use is a factor; whether all toxicological and forensic data are considered when the final ICD code is registered; different attitudes and traditions regarding the application of codes; and the extent to which information from the original death certificates is coded and transferred to the death register (Danish National Board of Health, 1997). Some opioid overdose deaths may be missed because they are not recorded as such. For example a death may be coded under "respiratory illness" or "heart failure" and the fact that an opioid was involved goes unrecorded. Drug related deaths are often under reported in national registers (Lecomte et al., 1995; Rodrigues et al., 1993). In addition to misreporting and under-reporting national registers are often slow to report. Even in countries with sophisticated and well developed reporting systems, drug related deaths can take more than a year to be nationally registered (Danish National Board of Health, 1997). Registers with such slow response may be of limited use in detecting trends to allow a rapid and effective intervention.

Whereas there is clear, well documented, evidence in a few countries, including Australia (Hall and Darke 1997) and Scotland (Glasgow) (Frischer et al., 1997), of recent increases in the number of opioid overdose fatalities, there are recognised difficulties in obtaining reliable data in which the cause of death can be confidently attributed. This is a much greater problem when trying to assess the incidence of non-fatal overdoses where many cases do not come into contact with the health care system. These difficulties occur in countries such as Australia and Scotland which have comparatively sophisticated systems for collection of health data. In many developing countries, and even in some developed countries, the most basic data on opioid use, mortality and health service contact do not exist.

Defining what constitutes an opioid overdose or any drug related death is problematic because of the lack of a common terminology across or even within countries. Standard epidemiological techniques cannot easily be adapted to calculate overdose and drug related deaths because of the lack of reliable estimates of denominator populations of drug users in the general population. Even where mortality data are collected they are often not comparable across countries because of the lack of standardisation and categorisation. Defining exactly what constitutes an overdose is problematic. The term itself may be misleading, since in many cases it is not clearly established that an "overdose" is a direct consequence of an excessive dose of the drug in question (Darke and Zador, 1996; Frischer et al., 1994). There are many confounding factors, such as individual tolerance and the consumption of other drugs (such as benzodiazepines and alcohol). Some of these factors are explored below.

Confounding factors

Individual tolerance

Variable individual tolerance is likely to be an important and complicating factor associated with overdose. Evidence suggests that some overdose deaths are more common within days of release from prison (Frischer et al., 1997) or after detoxification when tolerance to opioids has been lowered (Zador et al., 1996). Variations in the market, for example sudden increases in purity, may also be associated with overdose. Increased heroin purity has been noted as a probable contributory factor in increases in opioid related mortality in Australia (Hall and Darke, 1997). There is however a wide variation in post mortem blood levels of morphine (the major metabolite of heroin), suggesting that factors other than increased purity and individual tolerance are involved. Furthermore, persons whose deaths are attributed to overdose in Australia and elsewhere are unlikely to have blood morphine levels higher than overdose survivors or heroin users who die from other causes (Darke and Zador, 1996; Zador et al., 1996; Fugelstad, 1994). In many cases of fatal overdose in Australia the blood morphine levels fall below the conventionally accepted fatal range (Hall and Darke, 1997). Evidence from Australia and other countries suggests that overdose is not associated with young, inexperienced or first time users (Darke and Zador, 1996). This evidence strongly suggests that factors other than the purity, dose of the drug and individual tolerance are involved in "overdoses". There is a paucity of research evidence regarding tolerance to opioids, particular for opioid users in developing countries. It is not unusual to find individuals with very high tolerance to opioids in regions where these drugs are produced and are readily available at high levels of purity.

Consumption of alcohol, benzodiazepines and other drugs

One of the factors most strongly associated with opioid overdose is the concurrent use of other drugs, particularly alcohol and benzodiazepines (Darke et al., 1997; Darke and Zador, 1996; Fugelstad, 1994; Oppenheimer et al., 1994; Hammersley et al., 1995; Zador et al., 1996). Poly-substance use is becoming the norm for many drug users in many communities around the world. For example, dramatic increases in the past few years of amphetamine production along the Thai-Myanmar border has seen the drug users in Thailand using both amphetamines and heroin. In Vietnam, morphine and a wide range of pharmaceuticals, including benzodiazepines and barbiturates, are mixed in the syringe with "black water opium" and injected (Power, 1993). Combinations of cocaine and heroin (called a "speed ball" in the United States) are increasingly used in countries in Latin America. "Himier", (an opium solution), and "vint", (an amphetamine-type stimulant produced from ephedrine), are used in combination in Ukraine. Combinations of alcohol, benzodiazepines and opioids are common in most regions of the world where opioids are used. In the United States for example, heroin users typically also use cocaine, marijuana, benzodiazepines and alcohol (National Institutes of Health, 1997). Such combinations increase overdose risk considerably and make it difficult to attribute causation to a specific substance used (Gutierrez-Cebollada et al., 1994).

A special case for consideration is that of individuals on opioid substitution programmes. Notable has been a number of incidents in Australia of methadone related deaths, both among people enrolled in methadone maintenance programmes, and among heroin

users who used methadone diverted from a legitimate source. In Australia cases of methadone overdose are often associated with concomitant use of other drugs, including alcohol, benzodiazepines and heroin (Sunjic and Zador, 1997). Some methadone overdose in Australia is associated with the injection of methadone syrup intended for oral consumption. On the other hand, evidence also shows that methadone maintenance has a substantial protective effect on mortality from overdose (Caplehorn et al., 1994; Sunjic and Zador, 1996). Research is necessary to further investigate both the protective effect of methadone and methadone's contribution to increased rates of opioid overdose mortality.

Contaminants and adulterants

Often contaminants and adulterants, which may have toxic effects, are present in illicit opioids. In the United States the presence of quinine in heroin has been associated with overdose deaths (Ruttenber and Luke, 1984). Crude preparation methods used for producing such opioid solutions as "kompot" and "himier" made from opium poppy straw in Central and Eastern Europe and "home-bake" in Western Australia and New Zealand, utilise various toxic substances including gasoline, sulfuric acid and sodium hydroxide. Lack of access to clean water for preparing injecting solutions is a major problem for drug injectors from most developing countries. The role of contaminants and adulterants in opioid related overdose deaths is unclear and subject to much regional variation (Darke and Zador, 1996).

General health status of opioid users

As compared with opioid users in developed countries such as Australia, it is reasonable to assume that the health status of opioid users in most developing countries is much poorer. A high prevalence of malnutrition, tuberculosis, HIV infection, diarrhoeal diseases and malaria are some of the health problems which make drug using populations in developing countries more vulnerable to overdose. The comparative health status of opioid and other drug users in different countries will be investigated in a series of longitudinal cohort studies on the health implications of substance use currently being developed by the World Health Organization Programme Substance Abuse.

Other factors

A range of other factors have been associated with opioid overdose. Some of these factors are important when considering interventions to reduce the number of overdose fatalities. For example some studies suggest that it is likely that other people will be present during a fatal overdose and that the elapsed time from injection to death is often measured in hours. A "typical" death by overdose is therefore neither solitary nor instant. This provides opportunities for intervention (Darke and Zador, 1996). Some injectors are more likely to overdose when injecting on the street (Klee and Morris, 1995; Darke et al 1997). Street overdoses provide another opportunity for intervention.

Interventions

Overdose interventions may be classified as overdose prevention and overdose management. Such interventions may target individual behaviour change or more broadly promote a supportive environment.

Risk Assessment and Management

A critical intervention, that has been identified as having universal application for both prevention and management of overdose, is the education of drug users and their friends or other peers, who may be present during an overdose (Darke and Zador, 1996). Such education should cover a broad range of issues such as: risk assessment; risk management; specific strategies for prevention of overdose; and management of overdose, including resuscitation techniques.

Individual risk assessment covers three domains: i) the drug user's health status and tolerance; ii) the substances being used; and iii) the context of use. Individual risk-assessment is based on the premise that drug users should be able to determine their health status and tolerance so that they can titrate the drug dose in order to avoid overdose. At times of significant illness, malnourishment or after a period of abstinence, tolerance may be lowered and subsequently doses reduced. Users should also be aware of the type, quantity and purity of the substance(s) being used, and the risks associated with using combinations of different substances. Finally, they should be aware of the specific environmental risks that might exist within the drug use setting, and how to access assistance if necessary. As these variables are constantly changing, risk needs to be assessed prior to each drug using event.

A wide range of methods may be used by drug users to undertake such an assessment, including: observational techniques; monitoring of media and other sources of information; exchange of information through informal and formal drug user networks; seeking medical advice; mapping of drug using venues and sympathetic health services; and using test doses of drugs. This information enables the user to analyse the situation and modify drug using behaviour to minimise health risks such as overdose or HIV infection.

Outreach and Peer Education

Risk assessment and management requires drug users to have access to accurate information and opportunities to gain appropriate knowledge. Interventions which aim to educate drug users need to reach those at risk and be acceptable and credible to those targeted. Outreach programmes are operating in various regions of the world, many using drug users as peer educators. For example, in India and Nepal, outreach interventions, such as needle and bleach distribution, and HIV prevention education provide opportunities for overdose prevention and management education (Peak et al., 1995; Kanga, 1996). The "Drop" overdose campaign, developed by the Drug and Alcohol Services Council of South Australia and SAVIVE is one example of a formal education campaign targeting heroin users (Drug and Alcohol Services Council, 1996). The Centre for Education and Information on Drugs and Alcohol (CEIDA) received funding from the New South Wales (Australia) Health Department to conduct and

evaluate a nine month pilot peer education project targeting injecting drug users at risk of heroin overdose (CEIDA, 1997). Overdose is addressed in newsletters of a range of drug user groups, such as the Spike Collective of New Zealand (The Spike Collective, 1995).

Strategies Targeting Individual Risk Reduction

It has been shown that drug users can adopt specific behaviours which may reduce the risk of overdose. Some of these behaviours require new skills development, but most are simple and can be implemented relatively easily. Examples of individual overdose risk reduction strategies promoted in Australia include: testing (using a small amount to gauge the purity of the substance) and splitting (administering the drug in two or more doses) of doses; injecting slowly; avoiding using combination of substances (such as alcohol and sedatives with heroin or methadone); and using in the company of others (CEIDA, 1997).

Training of drug users and their peers in overdose assessment, resuscitation techniques, first aid and accessing emergency and other health services are components of a range of overdose intervention strategies promoted in Australia (CEIDA, 1997; Drug and Alcohol Services Council 1996; The Spike Collective, 1995). Some opioid users may have little control over the administration of their drug and therefore may not be able to take precautionary measures. For example, in so called 'shooting galleries' in Hanoi, Vietnam, the dealer manages all aspects of the opioid administration, including the preparation, drawing up of doses and injecting the client. It has been suggested therefore that outreach education needs to target dealer-injectors (Power, 1993).

Increasing Access to Emergency and other Health Services

In most communities, particularly developing ones, it is likely that the majority of overdose incidents are managed at the drug use setting, without involvement of the formal emergency or health care sectors. Various reasons for this are suggested: that the overdose incident may be adequately managed by those witnessing the incident, without outside intervention; in many countries, access to even the most basic health care services are limited due to limited resources; drug users may be discriminated against and refused treatment or be treated unsympathetically (New South Wales Users and AIDS Association, 1996); and drug users and witnesses may be fearful of contacting services in the event of an overdose because of risk of detection and recrimination for being involved in an illegal activity. It is suggested that strategies need to be developed which aim to increase access and utilisation of such services. This may require training of health professional staff to increase their understanding of drug users and their preparedness to provide services to them; training of community health workers and volunteers in overdose interventions; a review of confidentiality issues and requirements for reporting illicit drug users to authorities; and educating drug users on how to access services, providing accurate information to health providers on their drug use and dispelling fears they may have in utilising such services.

In response to increases in drug-related deaths in Glasgow, Scotland, the Glasgow Drug Problem Service was established in 1994. This service provides methadone prescribing linked with counselling and support. The Glasgow Drug Crisis Centre also opened in

1994 provides low threshold twenty-four hour walk-in assessment and support service and a short stay residential unit (Frischer et al., 1997).

Creating "Safer" Drug Using Environments

It has been suggested that drug using environments can be made "safer" through the education of drug users and others present in such venues. "Injecting rooms" aim to reduce deaths from drug overdoses and needle sharing and to minimise public nuisance by providing a safe and supervised environment for drug users to inject. (Dolan, 1997). Such interventions are not acceptable in many countries, but have been implemented in Switzerland and the Netherlands and are currently being debated in Australia (Mundy, 1997).

Opioid Antagonists

The role of opioid antagonists, such as naloxone and naltrexone, in treating opioid overdoses remains controversial (Moss, 1997). These interventions are under consideration in countries such as Australia, but because of their cost and availability, they have a limited role in developing countries. Adequate training of health professionals and others using opioid antagonists for treating opioid overdose is important, particularly with regard to risks of inadequate dosing when treating overdose from long acting opioids.

Drug Treatment

Drug treatment, including opioid substitution programmes, have been demonstrated to be effective in reducing overdose fatalities. In particular, methadone maintenance has been shown to have a substantial protective effect on mortality from overdose (Sunjic and Zador, 1997; Caplehorn et al., 1994; Darke and Zador, 1996). In some countries, including Australia, government guidelines set out strict rules for substitution prescribing, such as methadone, which aim to reduce the risk of overdose (Swiss Federal Office of Public Health, 1996; Drug Advisory Committee, 1992). Training materials and prescriber accreditation courses have been established in some countries to ensure rational and safe prescribing (Drug and Alcohol Services Council, 1994). It has been noted that while retaining users in treatment would also reduce overdose, adequate doctor or prescriber education may be more important than strict regulation, which may compromise access to treatment. Reports from various community based opioid substitution programmes in India, Nepal and Thailand indicate that overdoses are uncommon, even though strict guidelines do not exist and medical supervision is quite limited (WHO, in press). The use of buprenorphine in opioid substitution programmes, with its partial opioid antagonist properties, has an advantage over pure agonist opioids, such as methadone, by reducing overdose risks (Walsh et al., 1994).

Drug and Policing Policies

Variations in drug purity may play an important role in overdose, although the evidence for this is unclear (see above). It has been suggested however that the purity of street drugs is determined in part through policing and other enforcement activities. For example, the interruption of heroin supply networks may result in uncut heroin of high purity reaching the streets. Sudden increases in the purity of street drugs, such as heroin, can result in drug users using excessive doses unknowingly. On the other hand, reduction in drug availability and purity may increase transitions from non-injecting drug

use to injecting drug use which will, in turn, increase overdose risk. Those responsible for community policing and drug enforcement need to be aware of the potential consequences of drug interdiction and they have a role to play in responding to opioid overdose.

Conclusion

The World Health Organization's Programme on Substance Abuse advocates for a better coordinated response to reduce the risk of opioid and other drug related deaths. This response includes the improvement of the quality and comparability of opioid overdose and other drug-related death data; the design and development of effective overdose prevention and management interventions, and increasing the capacity of communities and countries to respond to these issues.

This may be achieved by: 1) a standardisation of definitions using a common classification which distinguishes between direct and indirect drug related causes of death; 2) a standardisation in reporting procedures; and 3) an accurate and uniform coding, certifying and registration practices. These aims may be assisted by the application of the ICD-10 classification in a uniform way using the full range of codes and wherever possible additional information on the drugs involved. In the longer term, these data could be further improved by the: 4) encouragement of toxicological analysis and forensic examination where drug use is thought to be a contributing factor; and 5) making full use of this information when registering and recording causes of death.

In the absence of reliable, uniform and comparable data from national registers of drug related death (and the lack of any registers in some countries), WHO encourages: 6) cross national retrospective and prospective cohort studies of health implications of opioid and other drug use using standardised methodologies and instruments (the results from these studies could also be used to validate national registers); and 7) in depth investigations using qualitative methods of circumstances relating to fatal and non fatal overdose.

A number of initiatives of the WHO Programme on Substance Abuse are attempting to address the issue of opioid overdose. The WHO Drug Injecting Project is collecting data on injecting drug use in 21 cities around the world through rapid assessment methods and a survey, which includes components on overdose. The project also aims to assist project sites develop comprehensive and integrated policies and programmes targeting health risks associated with injecting drug use, including overdose. The WHO Drug Substitution Project aims to evaluate existing opioid substitution programmes, particularly in developing countries, and prepare guidelines and training materials to ensure rational and safe substitution prescribing. The project will develop policy and programme guidelines, together with training materials for prescribers and others involved in opioid substitution which aim to reduce overdose risk. Work is beginning on longitudinal cohort studies on the health implications of substance use, which will examine the comparative health status of opioid and other drug users in different countries and which will also look at overdose. These projects will identify and inform the development of appropriate interventions to prevent health risks and other problems related to drug use, including overdose. Further work is necessary in a number of areas including the relationship between opioids, alcohol and other drugs in the aetiology of

deaths attribute to overdose.

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by

Introduction

Despite the pandemic of HIV among injecting drug users, deaths attributed to overdose remain the major cause of mortality among opioid users (Frischer et al, 1997; O'Doherty & Farrington, 1997; Oppenheimer et al, 1994; Perucci et al, 1991). Zador et al (1996) reported that 80% of heroin-related deaths in NSW during 1992 were classified as due to "dependence" (ICD-9 code 304.0). In an analysis of all heroin-related deaths in south western Sydney during 1995, pathologists and coroners attributed the cause of death to "narcotism" in 80% of cases (Darke et al, 1997).

Recent reports of opioid overdose deaths among young Australian adults, and the media attention they have received, have created an impression that the frequency of opioid overdose has dramatically increased in Australia in recent years among young adults. This paper critically examines the data on opioid overdose deaths over the period 1979 to 1995 with a view to answering the following questions:

1. Has there been a statistically significant increase in the rate of opioid overdose deaths over the period?
2. If there has been an increase: has it been similar for men and women, for persons in different age groups, and for persons in different jurisdictions?
3. What are the most plausible explanations of any such increase?
4. Do the data suggest any potentially effective ways of reducing opioid overdose fatalities in Australia?

Methods

Data were obtained from the Australian Bureau of Statistics (ABS) on the number of deaths attributed to opioid dependence and accidental opioid poisoning for the years 1979 to 1995 inclusive. The age at death was obtained for males and females in each jurisdiction and the whole of Australia. Data were also obtained from the ABS on the numbers of men and women of each age between birth and 85 who were resident in each state, and in the whole of Australia, at June 30 of each year between 1979 and 1995 inclusive. These data were used to calculate age and sex-specific mortality rates.

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Data on deaths from opioid dependence and accidental poisoning were combined to give the total number of opioid "overdose" deaths occurring in each year for males and females. Most analyses were performed on deaths among persons aged between 15 and 44, the age group within which the overwhelming majority of heroin use occurs in Australian adults (English et al, 1995). Analyses of mortality in different birth cohorts used an extended age range of 15 to 54 years.

Mortality rates were calculated for each year for males and females in three age groupings: 15 to 24 years, 25 to 34 years and 35 to 44 years. These rates were used to calculate a mortality rate for each year for male and females which was standardised to the 1979 Australian adult population aged 15 to 44 years. Overdose mortality rates over the study period were compared between New South Wales, Victoria and the remaining states and territories.

The statistical significance of changes in rates were assessed by multiple logistic regression analysis of the odds of an opioid overdose death occurring with sex, year of death and age group as predictors. Multiple linear regression analyses were performed to discover whether the average age at death had changed between 1979 and 1995.

Results

Overall Mortality

The numbers of deaths attributed to opioid dependence or accidental poisoning between 1979 and 1995 in Australia among young adults between 15 and 44 years rose from 70 in 1979 to 550 in 1995. The standardised mortality rate (per 1,000,000 of population) increased from 10.7 in 1979 to 67.0 in 1995. For males, the rate increased 6.8 times, from 15.3 in 1979 to 104.6 in 1995. For females, the rate increased 4.7 times, from 5.9 in 1979 to 27.9 in 1995 (see figure 1). This represented a total of 3313 male and 957 female deaths between 1979 and 1995 among persons aged between 15 and 44.

Overdose Mortality Rate 1979-1995

Rate per 1,000,000 1979 population

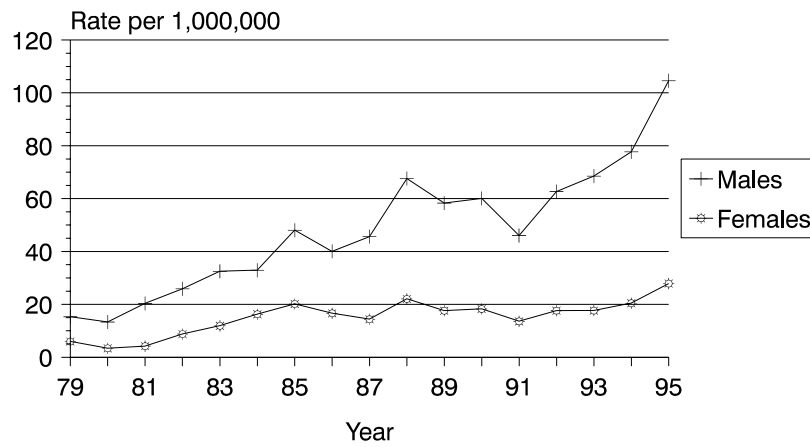


Figure 1

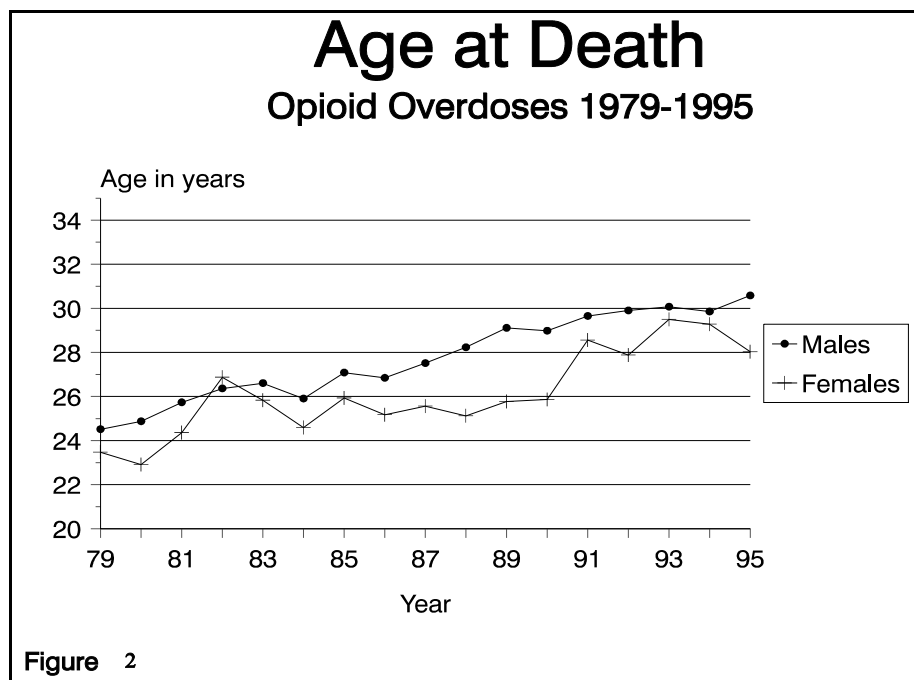
Overdose mortality rates also varied between the different jurisdictions, especially among males. For the purposes of description, the jurisdictions were divided into New South Wales, Victoria and the other states and territories. Among males, New South Wales accounted for around a half of all overdose fatalities, and its rate was almost twice that in Victoria, and three times the rate in the remaining states. There was a similar but less marked pattern among females. A logistic regression analysis confirmed that these differences were statistically significant. These differences in overall overdose

mortality closely parallel differences between the jurisdictions in rates of enrolment in methadone maintenance treatment (Hall, 1996), and probably reflect real differences in the prevalence of opioid dependence between different jurisdictions.

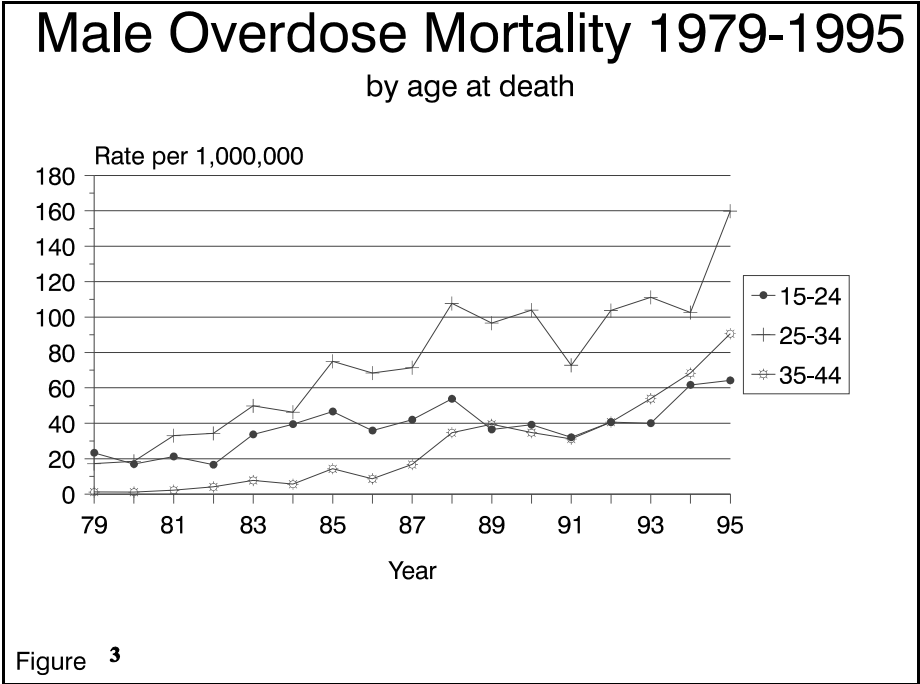
Mortality and age

The average age at death for males increased from 24.5 in 1979 to 30.6 years in 1995 while the average age for females increased from 23.5 years to 28.0 years over the same period (see figure 2). A multiple regression analysis confirmed that there was a significant linear relationship between age at death and year. Age at death increased by 4.2 months per calendar year and men were on average 21 months older at death than women.

A plot of age-specific mortality rates for males (see Figure 3) and females (see figure 4) between 1979 and 1995 confirms that the rate of increase in overdose mortality varied between the three age groups. For men and women the steepest rates of increase were among those aged between 35 and 44 years, and between 25 and 34 years at death.



A multiple logistic regression analysis indicated that there was a substantial increase in the odds of an opioid overdose death between 1979 and 1995. The model indicated that the rate of increase in the risk of opioid overdose death over the period 1979-1995 differed between men and women and the three age groups, and that the relationships between age group and year differed between men and women. The rate of increase in the odds of an overdose death was greatest among men and women who were 35 years or older at the time of their death.



Female Overdose Mortality 1979-1995

by age at death

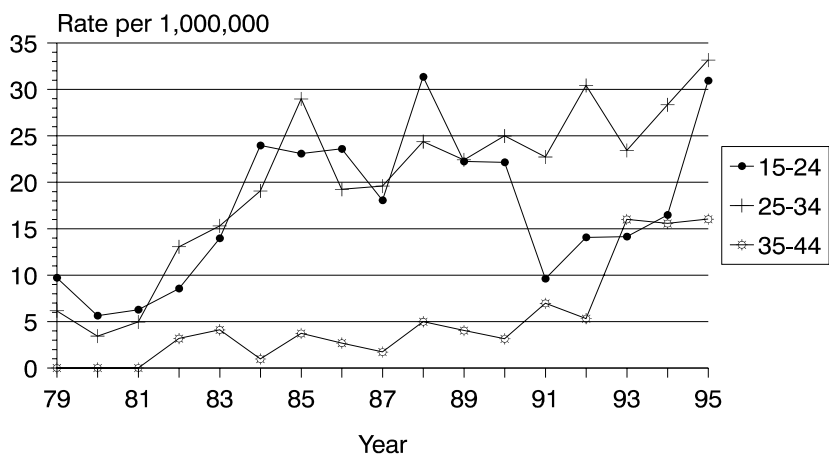


Figure 4

Age Cohort and Mortality

The numbers of death were calculated among men and women in the birth cohorts 1940-1949, 1950-1959, 1960-1969, and 1970-1979. This analysis indicated whether opioid overdose mortality risk depended upon when persons had initiated heroin use. Persons born between 1940 and 1949 had the lowest risk of initiation since most had passed the age of 25 before the first recorded post-war epidemic of heroin use in Australia in the late 1960s and early 1970s (Manderson, 1993). Persons born between 1950 and 1959 were at risk of initiating heroin use (ages 15 to 25) during an epidemic of heroin use in the mid 1970s. Persons born between 1960 and 1969 passed through adolescence and early adult life in the middle 1980s when there was another increase in the initiation of heroin use. Those born between 1970 and 1979 are now mid way through the risk period for initiation.

The analysis showed that 46% of all male overdose deaths and 50% of all female overdose deaths in the period occurred among those who were born between 1960 and 1969. Deaths among persons born between 1950 and 1959 accounted for another 38% of male and 33% of female deaths. Even among male deaths between 1991 and 1995, 50% occurred among men who were born between 1960 and 1969, and 27% among those who were born between 1950 and 1959. Deaths since 1970 accounted for 18% of male and 27% of female deaths between 1991 and 1995.

Most of the increase in opioid overdose mortality over the whole period 1979 to 1995, and more than two thirds of overdose deaths between 1991 and 1995, occurred among persons who initiated heroin use in the 1970s and 1980s. Recent initiations to heroin use among the youngest age cohort have just begun to be reflected in an increased rate of overdose deaths. If the mortality experience among the youngest cohort replicates that in the two older ones, then we can expect an epidemic of overdose deaths in this birth cohort within 10 to 15 years.

These mortality trends are highlighted when the cumulative overdose mortality is plotted for each cohort over the period 1979-1995. Cumulative mortality can be thought of as the total mortality rate between 1979 and any subsequent year in a cohort of 1,000,000 age peers. Thus, the cumulative mortality rate in 1995 is the cumulative rate of mortality among this birth cohort between 1979 and 1995. The rate at any year in between is the total mortality rate between 1979 and that year.

Figure 5 shows that for males the cumulative mortality rate was greatest among those born between 1950-1959 and 1960-1969. The cumulative mortality rate among those born between 1940 and 1949 was very low. That among the youngest cohort, born between 1970 and 1979, has begun to increase in the past several years as they have entered the period of risk of heroin initiation. Among females, there was a similar pattern but with a much lower cumulative mortality.

Cumulative Overdose Mortality 1979-1995

Male birth cohorts

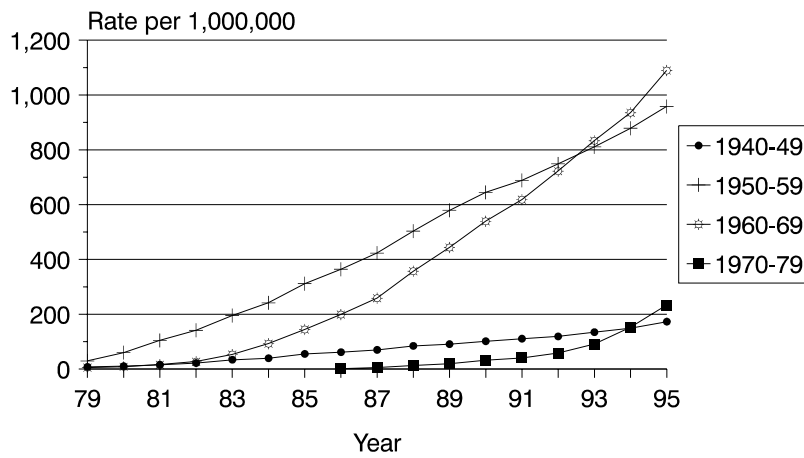


Figure 5

Discussion

There has been a statistically significant six-fold increase in the rate of opioid overdose mortality between 1979 and 1995. The overdose mortality rate in New South Wales was approximately twice that in Victoria, and three times higher than that in the other Australian states and territories. The rate of increase was much higher among males than females, and highest for men and women in the age group of 35 to 44 years. There was also a substantial rate of increase among those aged between 25 and 34.

This age-related pattern of opioid overdose mortality was reflected in an increase in the average age at death for males from 24.5 years in 1979 to 30.6 years in 1995.

Most of these deaths occurred among older heroin users who had initiated their heroin use in the late 1970s and the early 1980s. Deaths among younger recruits to heroin use have increased but they have not been a major contributor to the recent increase in opioid overdose mortality rate.

The sex difference in mortality reflects a combination of the greater likelihood of opioid dependence among males than females (Anthony & Helzer, 1991; Anthony et al, 1994) and greater risk taking among males than females (Plant & Plant, 1992). The differences between jurisdictions in overdose mortality closely parallel differences between the jurisdictions in rates of enrolment in methadone maintenance treatment (Hall, 1996), and probably reflect real differences in the prevalence of opioid dependence.

Possible Explanations of the Increase

Diagnostic changes

The first explanation that must be considered is that the mortality increase reflects a change in the diagnostic practices of pathologists and the conclusions reached by coroners as to cause of death. This is unlikely for a number of reasons. First, the change in diagnostic practice would have to be very marked to explain the six fold increase in mortality rate from these causes. Second, there is no evidence that such changes have occurred. Darke et al (1997) compared the conclusions as to cause of death by pathologists in heroin-related deaths in south western Sydney in 1992 and 1995. There was a doubling in the number of heroin-related fatalities between 1992 and 1995 but in both years the proportion of cases attributed to "narcotism" (opiate dependence) was 80%, and in the majority of these deaths other drugs were detected at autopsy. Third, the change in diagnostic practice would need to have varied strongly with the age and sex of the deceased to explain the observed trends. Fourth, a very similar pattern of results has recently been reported among opiate- and cocaine-related deaths in Spain between 1983 and 1991 (Sanchez et al, 1995).

An increase in the number of heroin users

This possibility is difficult to evaluate because of the lack of good estimates of the number of people who engage in an illegal and socially stigmatised act like using heroin (Hall, 1995). Nonetheless, indirect evidence is against the hypothesis that any such increase explains the increased opioid overdose mortality between 1991 and 1995. The increase in the age at death throughout the period for men and women, and the marked differences in mortality for the different age cohorts, suggest that deaths among younger recruits to heroin use has not made a major contribution to the increase. Rather, the rate of increase in overdose mortality has been steepest among adults in the 35 to 44 age group who initiated heroin use in the late 1970s and early 1980s.

Increased purity of heroin

The popular explanation for the rise in opioid overdose deaths is that it is the result of increased heroin purity. There is reasonable evidence that purity increased between

1992 and 1995 (Australian Bureau of Criminal Intelligence, 1996; Darke et al, 1997; Weatherburn & Lind, 1995). Increased heroin purity has, in all probability, made a contribution to the increase in opiate-related mortality, since the higher the blood morphine level, all else being equal, the easier it will be for a heroin user to overdose.

Nonetheless, heroin purity is unlikely to be the major explanation of the increase. First, mortality increased throughout the study period, rather than being confined to the last three years of the period. Second, retrospective analyses of overdose fatalities in 1995 found that it was still the case that a large proportion of fatalities had blood morphine levels that were below the conventionally defined fatal range, and polydrug use was still a feature of half of these cases (Darke et al, 1997). The average blood morphine level doubled but the proportion of users who had used heroin in combination with alcohol and benzodiazepines was unchanged.

Third, if increased heroin purity was the explanation of the mortality increase one would expect that most of the increase would be among newer recruits who would have the lowest tolerance for opioid drugs and are the least experienced in judging the purity of street drugs. But deaths among young, inexperienced users in the 15-24 age group were rare. Instead, the typical overdose fatality towards the end of the study period was a 30 year old male with a 12 year history of dependent heroin use. It seems more likely that increased heroin purity has increased the risk of overdose by amplifying the risks of pre-existing polydrug use (Darke and Zador, 1996).

Changes in patterns of opioid and other drug use

A number of changes in patterns of drug use could explain the increased rate of opiate overdose deaths between 1979 and 1995.

The first possibility is that opioid users may have adopted more risky patterns of heroin use, such as injecting alone, or in the street. There is also some evidence that street injecting has increased in the south western suburbs of Sydney (Maher, 1996), and this has been reflected in a doubling of the number of fatal overdoses in public places that have occurred in that region between 1992 and 1995 (Darke et al, 1997). It remains to be discovered to what extent these trends have occurred in other areas of Australia.

A second possibility is that there has been an increase in polydrug use among opioid users, especially an increased use of CNS depressants that are self-administered in riskier ways. The majority of Australian opioid users have traditionally used a wide range of other drugs, including alcohol and benzodiazepines (e.g. Darke & Hall, 1995) but there is no evidence that the prevalence of polydrug use has increased among persons who have died of opioid overdoses over the study period. In the Darke et al (1997) study, the proportions of cases in 1992 and 1995 in which alcohol, benzodiazepines and other drugs were detected were the same, as were the blood alcohol levels of cases in which alcohol was detected.

A third possibility is that changes in the route of administration of other CNS drugs over the period have increased the risk of opioid overdose deaths. There has been, for example, a trend in New South Wales for heroin users to inject preparations intended for oral consumption, such as, benzodiazepines tablets (Darke et al, 1995) and

methadone syrup (Darke et al, 1996a). Injectors of these substances are more likely to report a drug overdose (Darke et al, 1996 a,b), as would be expected because the peak plasma level of benzodiazepines and methadone is higher when they are injected rather than taken orally. When combined with heroin, the risk of overdose would be considerably increased by the injection of benzodiazepines or long-acting opioids like methadone.

A fourth possibility is that these more risky drug use patterns may be adopted as opioid users age. Older heroin users may find it more difficult to sustain a high rate of daily heroin injection so they use benzodiazepines and alcohol to manage their withdrawal symptoms. Their tolerance for opioids would be reduced and vary more day to day than younger more regular heroin users, making older users more vulnerable to the respiratory depressant effects of purer heroin when used in combination with alcohol and other CNS depressant drugs. It also may be that liver disease in older users (caused by chronic hepatitis) could make them less able to metabolise opioids, alcohol and other drugs, and hence, more vulnerable to polydrug toxicity.

These changes in drug use patterns may have contributed to increased rates of opioid overdose deaths in some locations in New South Wales. The extent of their contribution is difficult to estimate because it is uncertain how widespread the adoption of riskier drug use and injection practices has been. It also remains to be discovered whether there has been an increased resort to polydrug use as heroin users have aged.

An increased number of methadone-related deaths

It has been claimed in the media that there has been a marked increase in methadone-related deaths in the early 1990s among heroin users enrolled in methadone maintenance programs and heroin users not in treatment who use diverted methadone. The number of heroin users enrolled in methadone treatment has increased over the study period from approximately 2000 in 1985 to an estimated 20,000 in 1996, and the rate of increase has been highest in New South Wales which has the highest rate of overdose deaths. There is also evidence that oral methadone syrup is being injected by Sydney heroin users enrolled in methadone programs, and that diverted methadone is being injected by heroin users who are not enrolled in methadone programs (Darke et al, 1996a).

This hypothesis cannot be tested on these mortality data because no distinction is made in the ABS coding of cause of death between deaths attributed to heroin use and deaths attributed to the use of methadone. Nonetheless, there are a number of reasons why this explanation is unlikely to explain the increase in opioid overdose mortality. First, Zador et al's (1996) data on opioid deaths in 1992 found that 80% of opioid related deaths were due to heroin. There is no evidence that this proportion has changed. Second, Sunjic and Zador's (1997) analysis of deaths among patients in the NSW methadone program (see chapter 12) found that methadone maintenance had a substantial protective effect on mortality. Mortality from all causes among those in methadone treatment was 26% that of heroin users who were not in methadone maintenance treatment, a finding that is consistent with the literature (e.g. Caplehorn et al, 1994; Ward et al, 1992). Sunjic and Zador also found that there had not been an increase in the *rate* of deaths among methadone program participants.

Implications

The data show that much of the recent increase in opioid overdose mortality has occurred among older heroin users. This suggests that it would be desirable to increase the recruitment of older heroin users into treatment. Peer education of drug users also needs to focus on persuading them of the overdose risks of using heroin in conjunction with other CNS depressants. Serious consideration should be given to a controlled evaluation of the impact of naloxone distribution on overdose fatalities among heroin users (Darke and Hall, 1997). Special efforts need to be made to prevent a future epidemic of overdose death among recent recruits to heroin use. These should include educational and other policies to reduce initiation of heroin use, and peer education to reduce polydrug use and risky injecting practices among young persons who have recently initiated heroin use.

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Fatal Methadone and Heroin Deaths in the United Kingdom: A Growing Problem?

by

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Introduction

There are calls to limit the usage of methadone in the management of opiate addicts as a result of reports of high methadone related mortality through overdose (Harding-Pink, 1993; Marks, 1994; Newcombe, 1996). The main aim of the present analysis was to examine the available empirical evidence and published data to determine what contribution methadone has made to opiate overdose deaths in comparison to other opiates, and to assess the trends in opiate related deaths over time.

Two approaches are taken in this presentation: the first is to examine the relationship and contribution of both methadone and heroin to overdose deaths in England and Wales between 1979 and 1993 (Neeleman and Farrell, 1997), and the second is to use a period of reporting to Home Office Addicts Index to make some preliminary assessment of the role of prescribed versus non prescribed methadone in opiate overdose deaths.

Marks and colleagues (Marks, 1993; Newcombe, 1996) have reported that methadone is associated with a nineteen times greater risk of overdose death than heroin, based on an analysis of official data from 1991. However, this analysis is based on the assumption that the denominator is 92% heroin addicts and 8% methadone dependent,

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giving a death rate of 1 per 2582 heroin users compared to 1 per 134 methadone users. If one assumes a denominator of 40% methadone users and 60% heroin users then the death rate is 1 per 1684 heroin users and 1 per 668 methadone users with a risk ratio of 3 to 1 for methadone to heroin. However, even these calculations are based on some major assumptions about the size of the denominator and are therefore likely to be crude estimates.

We obtained data by hand searching the Office of Population Census Studies tabulations of all self poisonings, accidental, undetermined and suicidal, between 1974 and 1992. This was done in preference to relying on aggregate data reported by the OPCS and the Home Office. The aim was to determine the rate of rise of deaths from heroin and from methadone (Neeleman and Farrell, 1997). We assumed that, given the fairly rapid expansion in methadone usage since the mid nineteen eighties, the proportion of opiate addicts dying from methadone poisoning should rise at a faster rate than those taking heroin. By using a proportionate mortality design we could avoid having to make assumptions about the size of the methadone or heroin taking population.

The time trend was analysed with logistic regression. Changes in the ratio of heroin to methadone deaths over time from baseline were compared by means of a ratio of ratios, which is analogous to a proportional mortality ratio.

There were 43,231 self poisoning deaths between 1974 and 1992. The number fell from 8,958 between 1974 and 1977 to 6,125 between 1990 and 1992 (-32%). By contrast, over the same period, lethal self poisonings involving heroin alone, and methadone with or without heroin rose from 7 to 90 (a 1186%) increase and from 26 to 240 (an 823%) increase respectively. The ratio between the number of poisoning deaths involving heroin alone and those involving other substances increased from 7/8951 (ie 0.0008; proportion 0.08%) in 1974-1977 to 90/6035 (0.01; proportion 1.5%) in 1990-1992. The summary proportional mortality was 1.76 indicating that the ratio in 1990-92 was 76% higher than that in 1974-77. For deaths involving methadone, rates ratios rose at a comparable pace (proportional mortality ratio 1.80). However, the rate in the last three year period was greater for methadone and indicated a departure from linearity.

Overall then, while the total number of deaths from self poisonings declined by 32% between 1974-77 and 1990-92, deaths from methadone and/or heroin rose by 900% (from 33 to 330) over the same period. The proportional contribution of opiate deaths to both accidental and suicidal self poisonings increased from 0.4% in 1974-77 to 5% in 1990-1992 (Neeleman and Farrell, 1997).

In a separate exercise, data on fatal methadone poisonings (suicides, open and accidental verdicts) among notified addicts were obtained for the years 1989-1992, as well as information on whether they were receiving methadone treatment at their last notification. Total numbers of notified addicts increased from 14,785 in 1989 to 24,151 in 1992. The proportion prescribed methadone increased from 54% (7,945) in 1989 to 71% (17,266) in 1992. The total number of deaths among notified addicts due to accidental methadone poisoning was 39 in 1989 (i.e. 264 per 100,000) and 76 in 1992 (i.e. 315 per 100,000). Deaths due to methadone amongst notified addicts who were not

on methadone treatment rose from 33 (i.e. 482 per 100,000) in 1989 to 56 (i.e. 813 per 100,000) in 1992. Deaths due to methadone amongst methadone prescribed addicts rose from 6 in 1989 (76 per 100,000) to 20 in 1992 (115 per 100,000). Poisson regression was used to examine linear trends in the change of rates from the baseline (the 1989 rate). All three time series fitted a linear model. Methadone-related death rates amongst all notified addicts and amongst those who had been on methadone treatment, did not increase significantly over the four year period (rate ratio per year increase 1.03 [95% C.I. 0.92-1.16] and 1.12 [95% C.I. 0.88-1.43] respectively). Amongst notified addicts who had not been notified as receiving methadone treatment, rates had risen by a factor of 1.15 (95% C.I. 1.0006-1.32) per year.

In each of the four years, rates of death due to accidental overdose from non-prescribed methadone were higher than those involving prescribed methadone. Expressed in rate ratios, notified addicts in 1989 who were not prescribed methadone were 6.4 times (95% C.I. 2.6-18.7) times more likely to die of accidental methadone ingestion than those who were prescribed methadone. The corresponding rate ratios in the following years were 1990-5.9 (95% CI 3.0-12.8), 1991-3.9 (95% CI 2.1-7.1) and 1992-7.0 (95% CI 4.2-12.3).

Comment

Overall, the data indicate that there has been a dramatic rise in opiate self poisonings in England and Wales at a time when all other forms of deaths from self poisonings have fallen. The current data does not support the contention that methadone is disproportionately contributing to opiate self poisoning deaths despite the rapid increase in usage. However the Home Office Addicts Index data indicates that between 1989 and 1992 methadone used in a non prescribed way disproportionately contributed to methadone related deaths. This would indicate that diversion of methadone into the black market carries serious negative consequences that have not hitherto been reported.

The principal difficulty with studies of this nature is to obtain an adequate estimate of the population at risk. Over the period 1989-1992, the increasing methadone self-poisoning rate amongst notified addicts is attributable to overdoses of methadone obtained from sources other than a prescribed course of treatment. Within the notified addict population, the vast bulk of methadone related mortality appears to occur in those not notified as prescribed methadone. A certain degree of misclassification may inevitably have been present if methadone was prescribed to an addict after his date of last notification and vice versa, but this should have produced underestimates rather than overestimates of rate ratios.

Much of the concern about the high mortality rates associated with methadone, should be directed at the diversion of this substance onto the black market, rather than its use in the treatment of opiate addicts.

An underlying death rate of approximately 1% per annum occurs within the notified opiate dependent population (Howes et al 1995). The available evidence indicates that methadone treatment is likely to significantly reduce the high mortality rate among this highly at risk population (Capelhorn et al 1994; Zador and Sunjic, 1998).

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Death As A Result Of Consuming Opioid Drugs: A New Zealand Perspective

by

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Introduction

There are no New Zealand data relating to death as a result of consuming opioid drugs for New Zealand as a whole. However, there have been three regional reports: one from Auckland and two from Wellington, the two largest cities in New Zealand.

In 1983, Cairns and colleagues published data from the Auckland coroner's record for the years 1975 to 1982 and found that of 11,262 deaths, 394 (3.5%) were due to the primary action of a drug or a poison. Of these 45 were due to the accidental overdose of opioids. These comprised two groups: 36 who were considered to be accidental drug overdose in "drug addicts" where the most common drugs found on toxicological analysis were morphine/heroin, methadone and dextromoramide; and 9 deaths were due at least in part to accidental dextropropoxyphene use.

In 1992, Dukes and colleagues reported two sets of Wellington data. In the first (Dukes et al., 1992a), data was examined from the Wellington coroner's record, for the years 1970 to 1989, in which death was considered to be the result of drug or poison consumption. The autopsy report, toxicological report from the DSIR and the police report were examined for all cases which were categorised as suicide, accidental, therapeutic misadventure or uncertain. There were 130 deaths due to prescription drugs, of which 33 deaths were due to the consumption of opioid drugs, although a breakdown into the four categories was not fully reported. Of the opioid deaths, 16 (48%) were due to dextropropoxyphene. There were nine deaths (27%) due to methadone, three of which had myocarditis leading to uncertainty as to the cause of death. Of the seven deaths due to morphine, four were accidental and

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these all occurred in men under the age of 25 who were known intravenous drug users.

In the second study (Dukes et al., 1992b), a mortality study of 997 patients registered for treatment at the Wellington Drug Clinic was undertaken from the New Zealand death records. During this 18 year period there were 28 deaths due to primary drug overdose (23 accidental and 5 suicides) as follows: dextropropoxyphene (6), methadone (4), heroin (2), other opiates (4), barbiturates (6), chloral hydrate (2), multiple drugs (1) and one unknown. No breakdown of drugs for the accidental deaths versus the suicide deaths were reported. The total death rate from opioid overdose was therefore less than 1 death per year.

There is currently no central coronial record in New Zealand and each of the 74 offices is organised differently making it difficult to assemble national coronial data on deaths following the consumption of opioid drugs.

However, in New Zealand, all suspicious deaths reported to coroners in which there is a possibility of involvement of drug ingestion are analysed centrally by the Institute of Environmental Science and Research, (ESR) formally known as the DSIR. The fact that one laboratory conducts all analyses avoids the problem of variance between different laboratories. It has also fostered expertise in correlating toxicological findings with death. ESR toxicological reports, which include a judgement as to the probable cause of death, have provided coroners with quality data with which to make definitive legal judgements. Furthermore, all blood taken for analysis has for some time now been iliac vein samples, bringing about further standardisation in the establishment of data.

This paper reports data on death following the consumption of opioid drugs from the ESR covering the past two years. This period of time coincided with the development of significant methadone treatment waiting lists in New Zealand. Methadone maintenance treatment was established in the mid-1970s in New Zealand and by 1979 there were 219 patients being prescribed methadone (Sellman et al., 1995). This number increased slowly over the next 12 years so that in 1991 there were 537 patients. However, over the subsequent six years there was a surge in the numbers of patients being enrolled for methadone maintenance treatment which began to exceed 2,000 in 1995. This was the year that the new Health Reforms began to take effect in New Zealand with detailed service contracts under a funder/provider split. This development limited the numbers of patients on methadone, the result of which was the development of waiting lists for methadone treatment. There were 420+ patients estimated to be formally enrolled on methadone treatment waiting lists in 1996 (Sellman et al., 1996). The street value of methadone has increased from \$1 per mg to \$1.50-\$2 per mg over the last 3 years.

The main aims of this paper were:

1. to describe a current profile of New Zealanders who accidentally die following consumption of opioid drugs and to investigate whether this differs from that of suicides;
2. to investigate whether the profile of 1995/6 accidental deaths differs from that of 1996/7 data;

3. to compare the death rates in Auckland and Wellington from previous reports (Cairns et al., 1983; Dukes et al., 1992a), with the current 1995-1997 data to ascertain whether there has been any appreciable increase in the rate of deaths over the past 15 years.

Method

All deaths were examined that were referred to the Institute of Environmental Science and Research Limited between 1 July 1995 to 26 May 1997 and were judged to have been caused at least in part by the consumption of opioid drugs. The cause of death as judged by the ESR was recorded along with the demographic and clinical data available. Data were entered into the database Paradox and transferred to SYSTAT for statistical analysis. Chi square tests for contingency tables were used for comparing categorical data and t-test analyses for continuous data.

There were 78 opioid related deaths identified. Thirteen of these 78 cases were suicides, as evidenced by suicide notes or recent discussions of suicide with friends and/or relatives. 58 were considered to be accidental overdose. The remaining seven cases were due to the ingestion of opioid drugs as part of medical treatment and were also not included in further analysis. This provided a sample of 71 cases of death which involved the consumption of either unprescribed drugs or prescribed opioid drugs taken in an unprescribed manner.

Results

Subjects who suicided (n=13) were significantly older on average than those judged to have died through accidental overdose (n=58) (mean age 49.7 years (sd 19.4) vs 31.7 years (9.6), $t=4.82$, $p<0.001$). Only 5% of suicides were under the age of 20 years. There were no significant differences in other demographic variables (gender, ethnicity, marital status, work status). All five cancer patients were in the suicide group and all five patients known to be on a methadone treatment programme at the time of death were in the accidental group. Morphine was included in the drugs judged to be responsible for death more often in the suicide group than the accidental death group (85% vs 43%, Chi square=7.32, $df=1$, $p=0.007$). Methadone was included in the accidental death group more often than the suicide group (48% vs 15%, Chi square=4.71, $df=1$, $p=0.03$).

Closer examination of the 58 accidental deaths by year, 1995/96 (n=37), 1996/97 (n=21), showed that there was no difference in the demographic profile (age, gender, ethnicity, marital status, work status) of cases over the two years. There were, however, significant differences in the opioid drug profile. Morphine was more likely to be included in the drugs considered to be responsible for death in the 1995/96 group than the 1996/97 group (54% vs 24%, chi square=5.0, $p=0.03$). Methadone alone was considered to be the cause of death more commonly in the 1996/97 group compared with the earlier group (48% vs 22%, chi square=4.23, $p=0.03$). Overall, there were only 18 cases (31%) in which opioids were the only drugs detected. The main additional drugs detected were alcohol and benzodiazepines.

When accidental deaths were examined according to the place of death, there was a significant difference in the opioid death rate between the South Island and North Island of New Zealand. The main South Island cities (Christchurch and Dunedin) had about three times the death rate compared with the main North Island cities (Auckland, Hamilton and Wellington) ($p < 0.001$). Sixty-nine percent of deaths occurred in these five main cities. The rate of death was significantly higher in these five cities overall, compared with the death rate outside of these main metropolitan areas ($p < 0.01$).

Finally, trends in the rate of accidental deaths due to the consumption of opioid drugs were examined over the past 15 years in two New Zealand cities. The rates of death in Auckland and Wellington from the present data were compared to data of the death rate in the past from two previous studies (Cairns et al., 1983; Dukes et al., 1992). The mean death rate in Auckland from 1975-1982 was one death every 65 days (Cairns et al 1983) which is not substantially different from the one death every 58 days in Auckland in the present data. In Wellington there was one death every 243 days on average during the period 1970-1989 (Dukes et al., 1992) compared with one death every 116 days in the past two years.

Conclusions

1. The overall death rate in New Zealand from accidental opioid consumption currently remains relatively low (about 30 deaths per year);
2. There appears to have been some increase in the rate of accidental death involving opioids over the past 15 years, but there has not been a dramatic increase;
3. People who accidentally die following consumption of opioid drugs:
 - are not generally young novice users;
 - have often used multiple drugs;
 - are not currently in treatment;
 - are different to those who use opioids in completed suicide in that they are younger, less likely to use morphine and more likely to use methadone and not likely to be cancer patients;
4. There is evidence of a recent shift in the opioids used in accidental opioid deaths from morphine to methadone in New Zealand;
5. People who accidentally die following consumption of opioid drugs are not uniformly distributed across the country; South Island cities have about a three times higher death rate compared with North Island cities.

Discussion

New Zealand's geographical isolation has probably been a major factor in preventing the dramatic increase in opioid use and dependence seen in the Western World over the past

few decades. This has been despite the short distance between New Zealand and Australia which has shown such an increase. This isolation has ensured a paucity of opioids, particularly heroin, being imported into New Zealand. Nevertheless, there has been a five fold increase in the numbers of patients being treated with methadone maintenance treatment in New Zealand over the past six years (Sellman et al., 1996) suggesting a significant increase in the rate of opioid dependence. The homegrown industry of “homebaking” morphine and heroin from codeine based pharmaceutical products in New Zealand is well known (Bedford et al., 1987). This rate of growth in patient numbers is continuing although waiting lists remain, indicating ongoing demand for treatment.

Even though New Zealand’s opioid problem is not at the obvious epidemic level of other countries at the current time, it is important to not be complacent about the problem. It is anticipated that there will continue to be growth of opioid dependant numbers in the region of 15% in the foreseeable future (Sellman et al., 1996). This is likely to be associated with a similar increase in opioid related accidental deaths unless there are a number of significant changes. Listed below is a set of ten practical suggestions on how to help reduce the death rate amongst those who use opioid drugs in New Zealand. They are not placed in any particular order of priority.

1. Embark on an assertive strategy of recruiting people with opioid dependence into effective treatment. In the first instance the aim could be to eliminate the waiting lists in various regions. For the vast majority of people with opioid dependence, effective treatment means opioid substitution therapy. In New Zealand at the current time this consists, almost exclusively, of methadone maintenance therapy. This would mean increased numbers of methadone places. An assertive strategy could additionally mean the development of outreach workers whose aim it is to attract users into treatment who are more resistant to treatment. These may well be individuals at greatest risk of overdose death.
2. Establish service protocols related to service contracts, which actively encourage the retention of people in opioid substitution therapy, particularly “difficult” patients who are likely to be at most risk of overdose death, if discharged from treatment.
3. Continue to facilitate a shift in therapeutic culture for the treatment of opioid dependence, supported at the highest political levels, away from detoxification towards retention in substitution therapy, as the most effective form of intervention.
4. Actively encourage the development of alternative opioids such as buprenorphine and LAAM for use in opioid substitution therapy. Because of the mixed agonist/antagonist nature of buprenorphine, death following overdose is likely to be rare. LAAM as an additional alternative to methadone may help recruit new patients into treatment given its longer half-life, allowing less than daily attendance at pharmacies and clinics for administration of medication.
5. Invest in the training of alcohol and drug clinicians, beginning with assessment skills. Specific attention needs to be given to attempting to identify new recruits who may be at increased risk of death from opioid overdose, in much the same way suicidality is a prominent concern of clinicians when assessing patients with major depression. A number of possible risk factors related to death from opioid overdose are:
 - history of previous overdoses;
 - propensity to “nod” or “snore” on opioid drugs;

- personality traits of impulsivity, high novelty seeking or grandiosity;
 - severe opioid dependence;
 - use of other drugs, particularly alcohol and benzodiazepines;
 - dysphoria.
6. Establish a methadone induction protocol requiring all patients initiated on substitution therapy to be routinely reviewed three hours after the opioid dose (around peak level) on the third day of treatment as well as following any increases in dose.
 7. Link “takeaway” doses to measures of improved psychosocial functioning for example educational involvement and employment rather than either, time in treatment or (by itself) urinary drug screen status.
 8. Make naloxone (short-acting opioid antagonist) highly available to people with opioid dependence. Strategies could include selling naloxone “over the counter” and distributing it with educational material at needle exchanges and methadone programmes.
 9. Widely distributing educational material targeted towards people with opioid dependence, beginning at needle exchanges and methadone programmes. This information would include specific warnings about mixing opioids with CNS depressant drugs, particularly alcohol and benzodiazepines, as well as providing informative instruction about loss of tolerance to opioid drugs occurring as a result of the short term reduction or cessation of opioid drug use.
 10. Facilitate improved collaboration between the police, emergency services especially ambulance services, pharmacists and treatment providers with two main aims in mind:
 - to better identify high risk individuals in the community who should be actively encouraged to gain treatment;
 - to encourage opioid users to ring for assistance, without fear of prosecution, when an overdose occurs.

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Overdose among Australian injecting drug users: findings from the Australian Study of HIV and Injecting Drug Use (ASHIDU)

by

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Introduction

The Australian Study of HIV and Injecting Drug Use (ASHIDU), like other Australian research, demonstrates that overdose among injecting drug users is so ubiquitous and takes such an unacceptable toll of this population that it is imperative that action to prevent it be increased.

We have used the term 'overdose' although we know that Shane Darke and Deborah Zador, who deserve much of the credit for drawing attention to overdose in Australia, have suggested that the correct term should be "multiple drug toxicity" (Darke & Zador, 1996, p. 1770). The question of whether ASHIDU data can be used to support the multiple drug toxicity thesis, will be addressed.

There is very little literature which deals with the specific risk of overdose among younger IDUs, and although the ASHIDU was not designed to examine youth in particular, quota sampling was used to obtain a reasonable proportion of younger IDUs. In this paper we have examined age differences in the overdose data - in most cases with two age groups: those up to the age of 25, and those aged 25 and over - in order to examine whether there are characteristics of younger overdose victims that put them in need of specific prevention strategies.

Background and Methodology of ASHIDU

The ASHIDU was a cross-sectional, multi-city study which was designed to investigate aspects of injecting risk behaviour in Australian IDUs (Loxley, Carruthers & Bevan, 1995). Data were collected during 1994 from 872 IDUs in roughly equal numbers in Adelaide, Melbourne, Perth and Sydney. Quota sampling within cities was used to ensure adequate numbers of IDUs who were female, under 25, had never received treatment and/or lived in the outer suburbs of cities.

Respondents, who had all injected within the previous three months, were recruited by advertising, "snowballing" and networking. They were interviewed individually and anonymously using a questionnaire developed for the study, and offered \$20.00 remuneration for the time spent in the interview process.

Although the primary purpose of the ASHIDU was to examine issues relating to the transmission of blood borne viral infections, questions were asked about a number of other issues, including overdose. Overdose was defined as: "Any occasion that you lost

consciousness while using and needed assistance to come round”. These data do thus not specify opioid overdose, although, will become clear, opioids are the drug type most frequently cited as being implicated.

Results

The Study Group: Age and Gender

The mean age of the total group was 28.5 years. Of the 872 respondents, 41% were ‘younger’ (up to 25), and 59% were ‘older’ (25 and over). Mean ages of the younger and older groups were 21.4 and 33.4 years respectively. Sixty five percent of the total group were male and 35% female. Age and gender interacted as shown in the following figure:

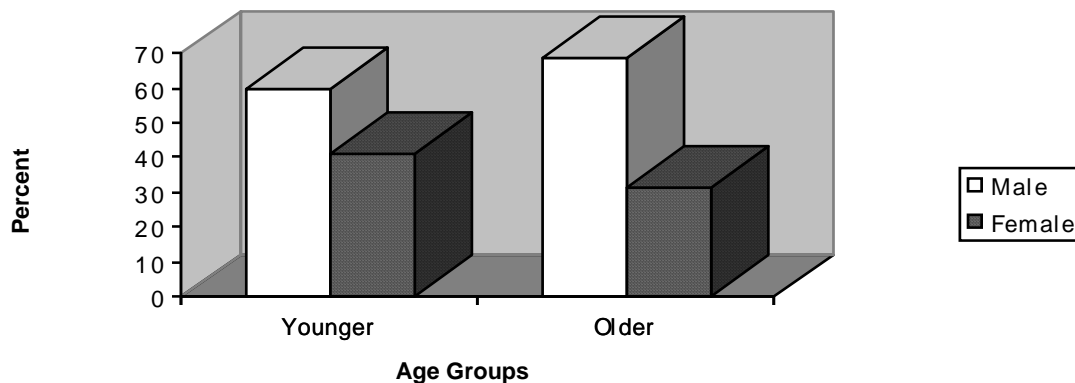


Figure 1: Age by gender

Figure 1 shows that there was a higher proportion of women among the younger respondents. It is not clear whether this is a cohort effect (that is, the proportion of women to men will remain relatively constant as these IDUs get older) or whether women are more likely than men to drop out of injecting drug use as they get older.

Experience Of Others' Overdose

All respondents, regardless of overdose history, were asked whether they had witnessed a fatal overdose. One of four reported that they had, at least once, but there was a significant age difference: 19% of younger compared to 29% of older respondents had witnessed at least one fatal overdose. There was also a significant gender difference with 27% of males, and 21% of females having witnessed a fatal overdose. Once again, age and gender interacted.

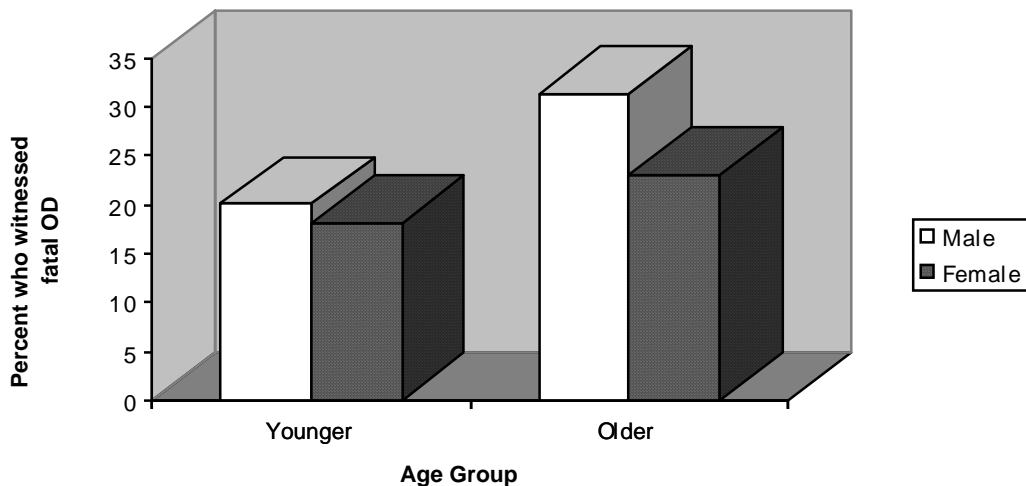


Figure 2: Percentage of those who had witnessed at least one fatal overdose by age and gender (n = 215)

Figure 2 shows that while there was no gender difference among younger respondents, older men were more likely than older women to have witnessed a fatal overdose. The mean number of fatal overdoses that respondents had witnessed was 2.8 (range 1 to 50), with no age or gender differences.

Given that 25% of respondents had witnessed a fatal overdose, it is hardly surprising to find that almost three quarters (74%) had witnessed at least one non-fatal overdose (82% of older respondents versus 63% of younger ones). However, in this case there was no gender difference, which perhaps relates to the ubiquity of the experience. On average, respondents had witnessed 7 non-fatal overdoses (range 1-50) with younger respondents having witnessed an average of 5.6 and older an average of 7.9 non-fatal overdoses.

Personal Experience Of Overdose

Just over half (53%) of the respondents (44% of the younger and 60% of the older) reported that they had had at least one overdose. A closer look at the relationship of age to overdose suggests that duration of years as an injector was a more powerful influence than age (although of course the two are closely related). In fact, the relationship between duration as an injector and overdose is very similar to that found for duration as an injector and hepatitis C. In order to show this more clearly, both have been put on the same scale in figure 3.

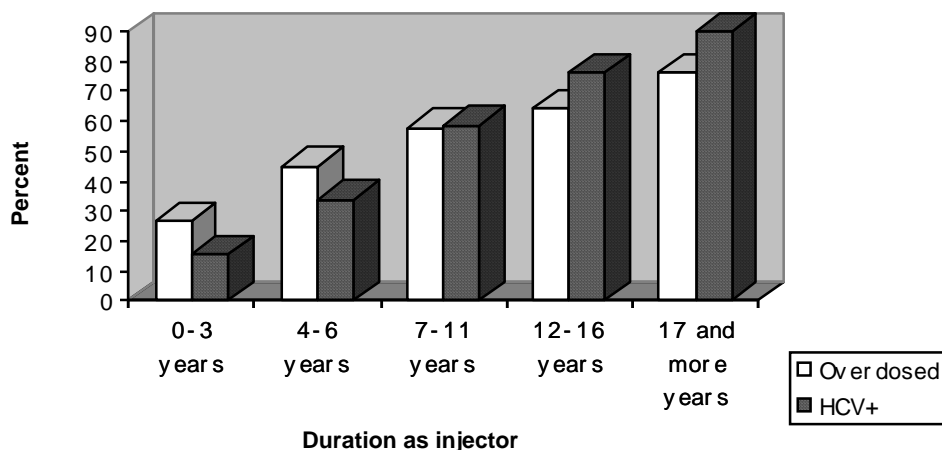


Figure 3: Experience of overdose and experience of HCV by duration as injector (n=787)

Unfortunately, we were not able to test all respondents for hepatitis C: either because they declined to give us blood, or because there was insufficient blood in a sample. There were no differences, however, in the rates of overdose between those who were, and those who were not, tested for hepatitis C.

Figure 3 shows that the prevalence of overdose, like HCV, rises very rapidly, so that almost 60% of those individuals who have been injecting for between 7 and 11 years have either experienced an overdose, or become HCV positive, or both. The chance of either outcome continues to rise with duration of injecting. It is clear that with overdose, as with hepatitis C, there is a very narrow window of opportunity when people first start injecting, to put in place strategies to prevent the first overdose.

Frequency Of Overdose

The data that follow have been collected from the subset of 465 respondents who had experienced at least one overdose. Almost one in three (29%) had overdosed once; another third (32%) had overdosed 2-3 times, 15% had overdose 4-5 times and the remainder (24%) had either overdosed more than five times, or couldn't remember how many times (which probably means that they had overdosed many times). Again, there was an age difference: as might be expected, younger respondents had had fewer overdoses than older respondents.

Drugs Ever Involved In Overdose

Respondents were asked after taking which drug types they had ever overdosed, and they were allowed to nominate as many as they liked. The responses for the whole group are shown in table 1.

Table 1
 Drugs ever involved in overdose for respondents who reported
 having ever experienced an overdose (n=464)*

| Drug | f | % respondents |
|-----------------|-----|------------------|
| Heroin | 376 | 81.0 |
| Benzodiazepines | 124 | 26.7 |
| Other opiates | 66 | 14.2 |
| Amphetamine | 45 | 9.7 |
| Barbiturates | 44 | 9.5 |
| Hallucinogens | 26 | 5.6 |
| Homebake | 25 | 5.4 |
| Methadone | 16 | 5.4 |
| Cocaine | 18 | 3.9 |
| MDMA | 12 | 2.6 |
| Other | 45 | 9.5 |

* Multiple response

Clearly, heroin was the most significant drug associated with overdose, and this is not surprising, nor is the extent to which other CNS depressants such as benzodiazepines or other opiates were nominated. It is more surprising that 10% nominated amphetamines, 6% hallucinogens and between 3 and 4% nominated cocaine or MDMA as drugs which had caused overdose.

Age differences found in the drug types implicated in overdose, relate mainly to the type of drugs which were popular with younger and older IDUs in 1994. Only the seven most frequently implicated drugs have been included in the Figure 4, and because these are multiple responses, the frequencies do not add to 100%.

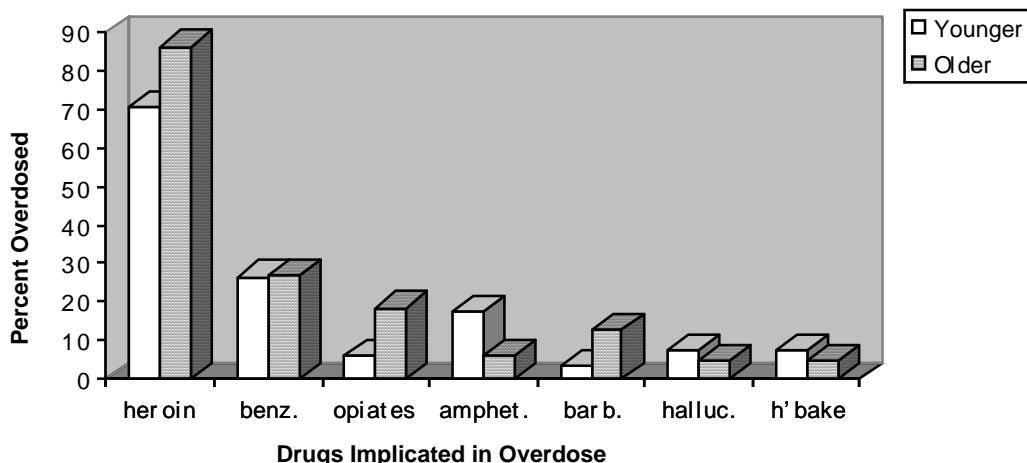


Figure 4: Drugs ever implicated in overdose by age groups (n=464).

Although heroin and benzodiazepines were the major overdose drugs for respondents of all ages, younger respondents were more likely than older to nominate amphetamines and hallucinogens as drugs that caused overdose.

We turn now to a more detailed description of the last occasion on which respondents had overdosed.

Main Drug Overdosed On The Last Occasion

The main drug involved in most (70%) overdoses was, as might be expected, heroin. No other single drug was reported by more than 10% of respondents. Drugs reported as primarily responsible for the last overdose have been reclassified as opioids (76%); other CNS depressants (11%); psychostimulants (6%) and other (7%). The relationship of these to age can be seen in Figure 5.

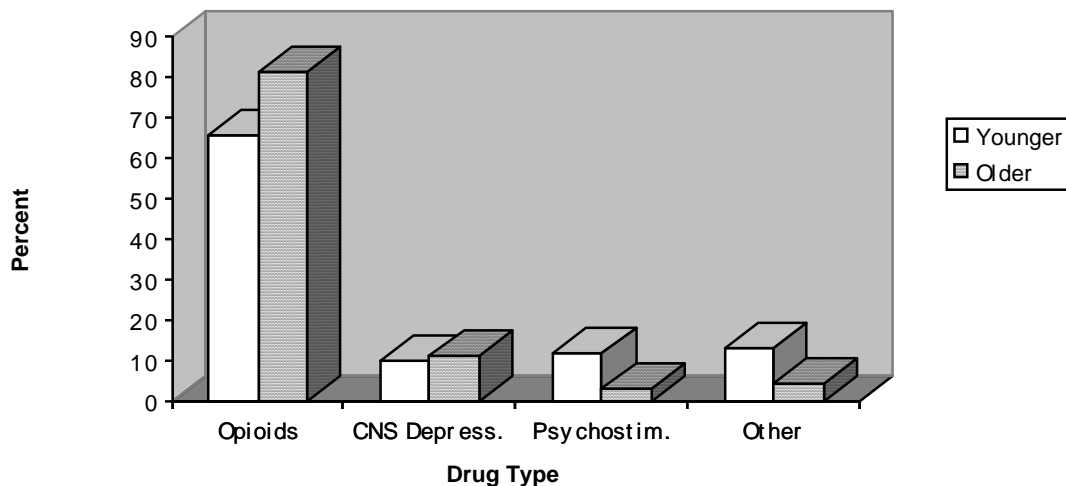


Figure 5: Main drug type implicated in last overdose by age (n = 459).

The overwhelming importance of opioids in the overdoses of both younger and older respondents is clear from this figure, but younger respondents were more likely than older to nominate psychostimulant or other non-CNS depressants as responsible for the last overdose.

Reasons For Last Overdose

Table 2 shows the responses given when respondents were asked what they believed to be the single major reason for the last overdose.

Table 2
Main Reason for the Last Overdose For Respondents Who Reported Having Ever Experienced An Overdose (n=465)

| Main Reason | f | % |
|---------------------------------|-----|------|
| 'Unexpected good quality' | 155 | 33.3 |
| 'Too many hits in a session' | 49 | 10.5 |
| 'Deliberate' | 49 | 10.5 |
| 'Had used a lot of other drugs' | 45 | 9.7 |
| 'Was just careless' | 44 | 9.5 |
| 'Had not used for a long time' | 30 | 6.5 |
| Other* | 93 | 20.0 |

* Eg. 'It was my first time'; 'I wanted the ultimate hit'; 'physical health was poor'

Table 2 shows that the most prevalent single reason for the last overdose, given by a third of respondents, was 'unexpected good quality'. The second highest group (20%) were other reasons which were generally related to the individual.

These responses have been recoded into three categories: those that relate to the drug (quality, quantity); the individual (eg deliberate, careless, tolerance etc.) and responses relating to concomitant use of other drugs. This results in 46% of respondents ascribing their last overdose to themselves; 44% to the drug and only 10% to the use of other drugs at the same time. There were no age differences.

Use Of Other Drugs On The Last Occasion

Despite most respondents not ascribing their overdose to the use of other drugs, 72%, said they were using other drugs at the time of their last overdose: most commonly alcohol (50%); cannabis (42%) and benzodiazepines (34%). Other drug types were used at the same time by fewer than 10%. The only significant age difference was in the use of cannabis, where 38% of younger respondents compared to 28% of older reported that they were using cannabis as well as the main overdose drug ($p = .03$).

Different patterns emerged from these data depending on the reported main overdose drug. The following table is based on those who reported that their last overdose followed the use of heroin.

Table 3
Use of other CNS depressants at the time of heroin overdose (n = 322)

| # other CNS depressants | f | % |
|-------------------------|-----|-----|
| None | 138 | 43 |
| One | 141 | 44 |
| Two | 36 | 11 |
| Three | 6 | 2 |
| Four | 1 | 0.3 |

Where a single other CNS depressant was used as well as heroin, this was mainly alcohol (n = 67) or benzodiazepines (n = 60). Where two CNS depressants were used, 15 of the 36 were combinations of alcohol and benzodiazepines, and there were 9 each of combinations of alcohol or benzodiazepines with one other drug. Where three drugs were used, 5/6 were combinations of methadone, benzodiazepines and alcohol. The one person who used four other drugs used another opioid, methadone, benzodiazepines and alcohol.

Action Following Overdose

Finally, we look at what happened to respondents after their last overdose: both immediately and in the longer term. For the following analysis, only those whose last overdose followed opioid use (n = 349) have been included. Immediately, the largest single group of respondents (44%) were looked after by their friends; 15% were admitted to hospital and 12% went to casualty; in 15% of cases an ambulance attended; 5% were given Narcan; 1% attended a doctor; and the remaining 8% either couldn't remember or had some other outcome. Thus almost half (48%) received some medical or paramedical attention after their overdose. There were no significant age differences.

City differences in actions taken following opioid overdose were also investigated. To control for the fact that there were variations in the rates in which respondents in different cities had been involved in treatment, only those who had ever been involved in treatment, and only those for whom the outcome was one of the major categories, have been included in this analysis. The patterns were consistent across age groups.

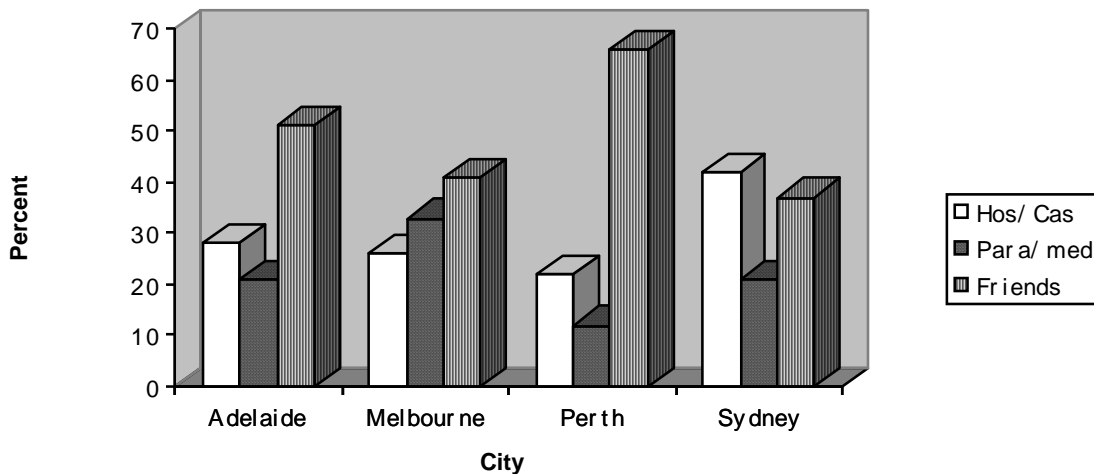


Figure 6: Actions taken after opioid overdose by city: respondents who had ever been in treatment.

Figure 6 shows that Perth respondents were more likely than others to be looked after by their friends, while Sydney respondents were more likely than others to be taken to hospital (either casualty, or admitted). Respondents in Melbourne were the most likely to use other paramedical or medical services.

In general, those who were admitted to hospital after an overdose (n = 99) reporting staying for an average of 5 days, but 70% stayed for only 1 or 2 days. A few had long stays, but these might have been related to admission to psychiatric wards. There were no age differences in the length of stay. 44% of those who were admitted to hospital reported being asked about their drug use.

Behaviour Change After Overdose

45% reported changing the way they used drugs as a consequence of the last overdose, and there were no age differences in the proportions who reported these changes.

The most common change reported, by around 1 in 3, was to use smaller amounts of drugs on subsequent occasions. 'Taking more care' when using other drugs was the next most common response (23%). Other popular outcomes included no longer using the primary overdose drug (19%), or some individual responses such as 'test dose of new batch'; 'gather information from dealer about drug purity' or 'control own use' (18%). Only 8% used the overdose experience as a catalyst to enter treatment, stop drug use or stop injecting.

These strategies have been compared by age, with the less popular strategies (entered treatment, stopped all use, stopped injecting) combined.

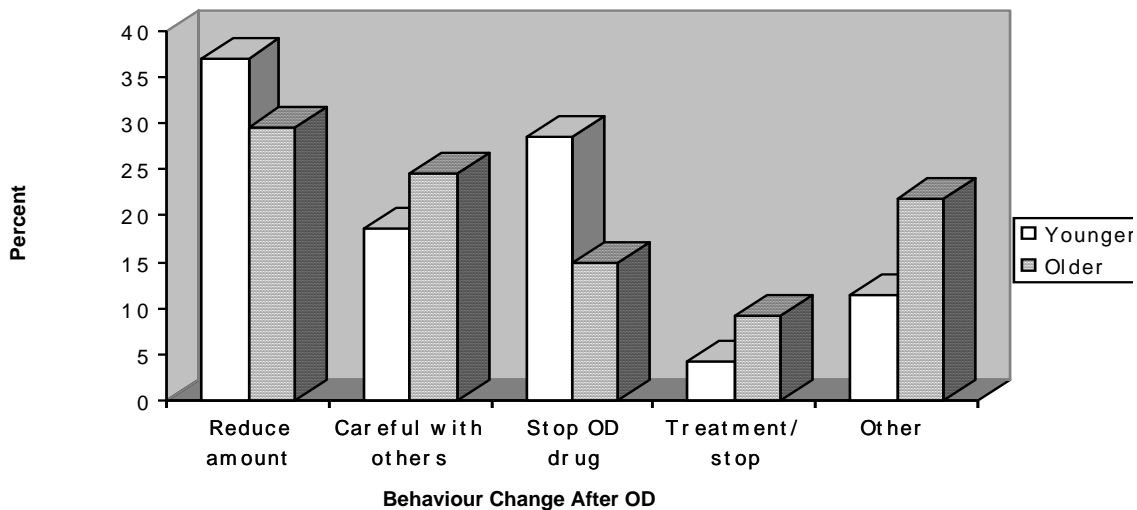


Figure 7: Behaviour Change After Overdose, By Age.

Figure 7 shows that younger IDUs were more likely to reduce the amount of the drug they were using, or to stop using that drug altogether, than older respondents who were more likely to be careful with the use of other drugs, or to adopt more individualistic strategies. Entering treatment or giving up use or injecting were not popular strategies with either age group.

There was a relationship between the type of change that followed an overdose, and the reasons respondents gave for having had the overdose, as shown in the following figure:

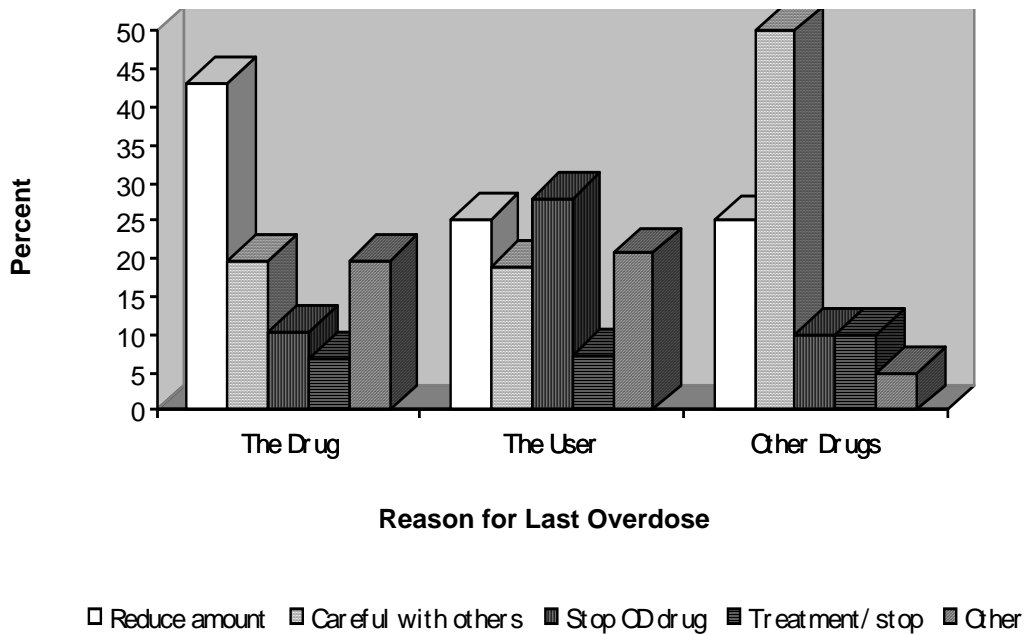


Figure 8: Behaviour Change After Overdose By Reasons Given For Overdose.

Figure 8 shows that those who felt that their last overdose was due to the quality or quantity of the drug used were more likely to say they would use less on the next occasion, while those (few) who ascribed their overdose to the use of other drugs at the same time, were more likely to say they would be careful with use of other drugs in the future.

Discussion

These data reinforce other Australian studies in demonstrating that overdose is a common experience among injectors. What is particularly disheartening, however, is that overdose becomes a common experience so early in an injecting career. According to these data, 27% of IDUs will experience at least one overdose within the first three years of injecting.

Younger IDUs and Overdose

There were few important differences in the pattern of overdose as experienced by younger and older respondents in the ASHIDU. If the age/gender interaction is a cohort effect, we can expect, all other things being equal, the proportion of female overdose cases to rise. Younger respondents had had fewer overdoses than older, but this appears to be a duration of injecting effect and again, without intervention, we can expect them to reach the same rates as the older respondents over time.

Although opioids were the drugs most commonly nominated as those that caused overdose

by respondents of all ages, younger respondents were more likely than older to nominate non-CNS depressant drugs. The question of whether these drugs caused 'overdose' precisely as defined in the questionnaire, or whether respondents had some other kind of unpleasant acute drug effect in mind, when they said overdose was caused by amphetamine or LSD, is one that merits more methodological attention.

Younger respondents were more likely than older respondents to use cannabis at the same time as the major overdose drug, although no less likely to use alcohol or other drugs. While the major concern has been with the toxicity produced by combinations of CNS depressants, we might also ask ourselves whether intoxication with combinations of drugs such as cannabis and alcohol, at times when heroin or other opioids are being injected, lends itself to carelessness and possible tragic outcomes.

Finally, after an overdose younger respondents were more ready than older respondents to stop using the overdose drug altogether. This may be a characteristic of some early stage IDUs that can be used to motivate long lasting and life saving behaviour change. It is clear, however, that there is a great deal that we do not know about the experience of younger IDUs and overdose. Given the clinical and anecdotal evidence which suggests that heroin is now so much more commonly used by younger IDUs than it was in 1994 when the ASHIDU was conducted, there is scope for research which is particularly focused at this sub-population.

Prevention

Many of the prevention strategies suggested by these data are well known and underway. Clearly, peer education which focuses on issues relating to multiple drug toxicity, understandings of tolerance and cross tolerance, the social context in which opioids are used, and appropriate user responses to overdose, is critical. Other prevention strategies might include exhorting hospital staff to take up the question of preventing further overdoses with IDUs who have been admitted as in-patients following an overdose.

The city differences in opiate overdose outcomes stress the importance of investigations and prevention strategies being linked to good understandings of local conditions. As an example, is it still the case, in 1997, that IDUs in Perth are less likely than IDUs in other cities to call for help when an overdose has occurred? And if so, why? And is it still the case that Narcan is used with only 5% of opioid overdoses?

Finally, Shane Darke, in a recent seminar on overdose in Perth, talked about overdose myths one of which was the myth of the 'killer heroin'. The most common reason given for the last overdose in this study was the 'unexpected good quality' of the drug they were using, which suggests that this myth was alive and well. Despite this, 57% of those who overdosed on heroin were using at least one CNS depressant and 13% were using two or more at the same time. Clearly the risk of multiple drug toxicity was relatively unknown to these respondents, but it appears very likely that it played a large role in some of the overdoses. Respondents' behaviour change after an overdose - to the extent that there

was any - was related to the presumed reasons for that overdose, such that those who ascribed their overdose to the use of other drugs at the same time, were more likely to say they would be careful with use of other drugs in the future. This suggests that it is doubly imperative that IDUs understand the dangers of using combinations of CNS depressant drugs.

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Pharmacology of Opioid Overdose

by

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The dangers of opioid overdose have been recognised for as long as the use of opium itself. In the clinical context this danger is an important restriction on dosing with opioids for the control of pain. While it has always been recognised that use of heroin and other opioids in a non-medical context also carries significant risks, in recent years this has received increasing attention. This is due, in part, to the markedly increased rate of overdose in many countries.

The major consequences of opioid overdose are pulmonary oedema and respiratory depression. The role of pulmonary oedema is problematic. While it can be of relatively rapid onset and thus be a factor in death, it may also be of much more gradual onset and less of a contributing factor (Karlner et al, 1969). Pulmonary oedema is also a consequence of respiratory depression caused by non-opioid drugs. Thus, respiratory depression may be the primary event, with pulmonary oedema a complicating factor in some cases. The present review will examine the pharmacological basis of respiratory depression following opioid administration. Consideration will also be given to the role of drug interactions, as these have been important in the aetiology of overdose (Darke and

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Zador, 1996).

Control of respiration

The function of respiration is to maintain concentrations of oxygen and carbon dioxide within optimal ranges. This is achieved by intake of oxygen through inspiration and reduction of carbon dioxide concentration through expiration. This rhythmic process is effected by the lungs and associated musculature, but relies on appropriate neural input to the muscles. In contrast to the internally controlled rhythmicity of the heart, respiration is entirely dependent upon external input from the central nervous system (CNS).

While there are influences from cortical and other regions, control of breathing is localised principally in the brain stem. Two major groups of neurons have been identified, both within the medulla region of the brainstem. These have been termed the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). In addition, important input comes from the pons. The exact role of each of these structures is as yet unclear, despite considerable research. In particular, the search for a central pattern generator or oscillator as a source of the breathing rhythm has not produced a clear outcome. The most likely candidate is the DRG which, in turn, influences the VRG. Efferent fibres emanating from the VRG innervate the muscles of respiration. Thus, the VRG is likely to be involved in shaping motor output rather than being the source of the rhythmic pattern. VRG neurons are also influenced by innervation from the pons. While pontine regions are not essential for respiratory rhythm, they may play some role in influencing the timing of the different phases. For more detail on the physiology of breathing, the reader is referred to Bianchi et al (1995).

Neurotransmitters and the control of respiration

The generation of the respiratory rhythm requires phasic activation and inhibition. Researchers have now identified the major neurotransmitters and receptors involved in these processes (see Bonham, 1995, for a review). Within the VRG, excitation is mediated via excitatory amino acid receptors while the inhibition is mediated via GABA receptors. These are the most ubiquitous excitatory and inhibitory neurotransmitter systems in the CNS and they appear to play the central roles in the control of respiration. Several different sub-types of receptors for the excitatory amino acids (such as glutamate) have been identified. They can be categorised as NMDA, non-NMDA (e.g. kainate) and metabotropic.

NMDA receptors are the best characterised, with sites identified for glutamate, glycine and a PCP site. The NMDA receptor is believed to play an important role in memory (Rison and Stanton, 1995). Its actions are affected by drugs such as phencyclidine and ketamine (via the PCP site) and alcohol (at an unknown site). There is evidence of a role for both NMDA and non-NMDA receptors in the control of respiration in the DRG, VRG and pons.

GABA is the main inhibitory neurotransmitter in the CNS and acts via GABA_A and GABA_B receptors. The GABA_A receptor, which is linked to a Cl⁻ channel, is more widely distributed generally, and of greater importance in the control of respiration. A number of drugs as

well as endogenous compounds produce their effects via this receptor complex. These include benzodiazepines, alcohol, neurosteroids and barbiturates. GABA receptors are found in relatively high density in the DRG and VRG. Glycine may also play some role in producing inhibition in these centres.

Other neurotransmitters have the potential to modulate respiratory rhythm. These include serotonin, substance P and opioid peptides. The role of serotonin has not been clearly determined. In part, this is likely due to differential effects mediated through different serotonin receptor subtypes. In contrast, substance P seems to have a principally excitatory role: injections of substance P into respiratory regions of the medulla stimulate respiration. The effects of the opioid peptides are largely opposite to those of substance P, with decreased activity following administration of opioids into these brainstem regions. Much of this activity of opioids appears to be due to a reduction in glutamate-induced excitation (Bianchi et al, 1995).

Peripheral inputs to central respiratory centres

Adjustments in the rate and pattern of breathing occur in response to information from peripheral sources. One such source provides information on the degree of inflation of the lungs. Stretch receptors respond to inflation with input to the DRG via the vagus nerve.

Chemoreceptors which respond to changes in blood gases are located in the carotid and aortic bodies. They are composed of specialised cells which are stimulated by a decrease in oxygen and, to a lesser extent, by an increase in carbon dioxide or a decrease in pH. Like the stretch receptors, projections from the peripheral chemoreceptors eventually terminate in the DRG.

Opioid actions and effects

Opioids produce their effects through activity at three major receptor subtypes: μ , κ and δ . While agonists at each of the three receptor sub-types produce analgesia, there are also important differences in the effects they mediate. Most of the familiar opioid drugs such as morphine, methadone and fentanyl are agonists at μ opioid receptors. In contrast, κ agonists do not produce the euphoric and reinforcing effects of μ agonists. Delta agonists seem to have some reinforcing properties. With respect to respiration, drugs that have agonist activity at either μ or δ receptors cause respiratory depression. Kappa receptor agonists produce either no effect on respiration or cause a mild respiratory stimulation.

The μ receptor subtype is sometimes further subdivided into μ_1 and μ_2 isoforms (Pasternak, 1986). Analgesia is associated with activity at both isoforms, but possibly at different CNS sites: μ_2 receptors may mediate supraspinal analgesia and μ_1 , spinal analgesia. In the original schema, respiratory depression was μ_2 mediated. This could have important implications as it suggests that opioids could be developed with analgesic properties (and other μ -receptor mediated properties), but without respiratory depressant

effects. However, there is still considerable controversy about the validity of the μ_1 and μ_2 isoforms.

Within the system controlling respiration described above, there are several sites at which opioid drugs may produce an effect (Yeadon and Kitchen, 1989). At each of the sites the action of opioids is depression of neuronal activity. The first group of sites is comprised of the chemoreceptors. The inhibitory activity of opioids appears to be mediated principally by μ opioid receptors and results in diminished sensitivity to changes in oxygen and carbon dioxide outside normal concentration ranges. Opioids may particularly affect the magnitude of the response to increased carbon dioxide.

Opioid receptors are also found in central respiratory centres. Both μ and δ receptors are located in these regions. This suggests that opioid peptides such as β -endorphin and met-enkephalin may have an important role in respiration. However, despite the profound effect of exogenously administered opioids and the presence of opioid receptors at high concentrations on respiratory neurons, there is, as yet, no clear role for endogenous opioid peptides in normal control of respiration (Santiago and Edelman, 1985).

The effects of exogenous opioids on respiration include changes in both tidal volume and respiratory frequency. The nature of the effect depends in part on the concentration of the opioid. Low concentrations may have effects mainly on tidal volume, whereas at higher concentrations both tidal volume and respiratory frequency may be affected (Santiago and Edelman, 1985). There is some evidence to suggest that these two different parameters may be modulated by different opioid receptors, with μ opioid receptors mediating the depression in tidal volume and δ opioid receptors the depression of frequency (Morin-Surun et al, 1984), but this account is by no means definitive.

Opioid agonists, partial agonists and antagonists

Most instances of death through opioid induced respiratory depression result from heroin administration. Heroin (diacetylmorphine) is believed to have no significant opioid receptor activity. However, it is rapidly metabolised to 6-monoacetylmorphine and then to morphine.

Both of these compounds are μ opioid receptor agonists. While diacetylmorphine and 6-monoacetyl-morphine readily cross the blood-brain barrier, morphine itself is much slower to do so. Thus, heroin could be considered a prodrug which facilitates the entry of morphine into the brain.

Recently, two major metabolites of morphine, morphine-3-glucuronide and morphine-6-glucuronide, have been demonstrated to be pharmacologically active. While the action of morphine-3-glucuronide is not entirely understood, morphine-6-glucuronide is an agonist at μ and δ receptors. It is found in significant concentrations in the CNS after morphine administration (Wolff et al, 1995) and hence may contribute to the actions of heroin.

Tolerance is known to develop to most effects of opioids and respiratory depression is no

exception. Tolerance to respiratory depression in animals has been noted to be relatively slow and incomplete and there is some evidence that this is also the case in humans. The human studies have relied on observations of the effect of methadone because of the relative ease of access to patients on long-term methadone maintenance. Two studies (Marks and Goldring, 1973; Santiago et al, 1977) showed that tolerance to the respiratory depressant effects of methadone was incomplete. The latter authors differentiated tolerance to the carbon dioxide sensitive chemoreceptor mechanism which they suggested was complete, and tolerance to the hypoxia-sensitive chemoreceptor mechanism, which they suggested was incomplete. Whatever the mechanism, these results suggest that even long-term opioid users are at significant risk of respiratory depression.

In contrast to the effects of full opioid agonists, partial agonists such as buprenorphine appear to have less effects on respiration. Buprenorphine has been shown to produce dose related decreases in respiratory rate in the lower dose range, but no further decline with increases in dose (Walsh et al, 1995). Thus, partial agonists should be considerably safer than full agonists, with much lower risk of overdose. However, potentially fatal respiratory depression may still be produced by these drugs, particularly if they are co-administered with other drugs that produce inhibitory effects on respiration.

Finally, pure opioid antagonists such as naloxone and naltrexone have relatively little effect on respiration in healthy adults (Shook et al, 1990). As mentioned above, the role of peptides in mediating normal respiration is, as yet, unclear. The evidence for this comes principally from studies in which these antagonists have been administered. Their relative lack of effect on respiration has made it difficult to find a role for opioid peptides. Thus, therapeutic maintenance with antagonists such as naltrexone should not impair respiration. However, opioid antagonists will completely block or reverse the effects of agonists such as morphine. This is important in the treatment of opioid overdose where naloxone is the drug of choice.

One of the limitations associated with the use of naloxone is its relatively short half-life. This is not usually a problem in the treatment of heroin overdose, but if there is a component of the respiratory depression due to other opioid agonists with longer half-lives (such as methadone), then the effects of the full agonist may return after the naloxone has been cleared. An antagonist with a longer half-life, such as naltrexone or the more recently developed nalmefene, may therefore produce a similar reversal of the opioid effects, but with minimal risk of respiratory depression returning. However, in opioid dependent patients administration of an antagonist will precipitate withdrawal. The duration of withdrawal is dependent on the duration of action of the antagonist. While longer acting antagonists such as naltrexone may have benefits in terms of safety, they will also precipitate a long-lasting withdrawal syndrome (Hung and Hoffman, 1997).

Finally, it should be also be recognised that in the presence of a full agonist, a partial agonist such as buprenorphine will reverse a number of the effects of the full agonist and may precipitate withdrawal. However, this is unlikely to have any significant therapeutic use. Thus, following administration of heroin or morphine any respiratory depression may

be reversed by subsequent administration of buprenorphine, but a withdrawal syndrome may also be precipitated.

Opioid-drug interactions

There is now considerable evidence that many instances of overdose are due to the combined effects of opioids with other drugs. The major drugs implicated in this way are alcohol and the benzodiazepines. The potential for such interactions can be better understood by considering the actions of these compounds in the central respiratory regions.

As mentioned above, benzodiazepines produce their effects by action at the benzodiazepine receptor site on the GABA_A receptor complex. The effect of benzodiazepines is to enhance the effect of GABA, increasing Cl⁻ flux through an increased rate of channel opening. GABA_A receptors play a major role within the respiratory control centres and so there is potential for a significant effect of benzodiazepine administration. By themselves, benzodiazepines have less marked effects on respiratory rate than opioids, although pronounced respiratory depression can be produced when high drug concentrations are achieved (Gaudreault et al, 1991). However, the potential for interaction with opioids clearly arises from the combined inhibitory effects of both the opioid drug and the benzodiazepine via the GABA_A receptor.

Alcohol also acts via the GABA_A receptor. However, it does not bind to the benzodiazepine site, but at some other (unknown) location on the receptor complex. It also enhances the effects of GABA, increasing Cl⁻ flux, but via an increase in the duration of Cl⁻ channel opening. Thus, there is the potential for interaction between opioids and alcohol in a very similar manner to the interaction between benzodiazepines and opioids. In addition, alcohol acts at the NMDA receptor as a non-competitive antagonist. This results in a reduced effect of excitatory amino acids such as glutamate. The effect of alcohol then, is to produce greater inhibition via the GABA_A receptor site and reduced excitation via the NMDA receptor. These effects should be at least additive with the inhibitory effects of μ receptor agonists.

It is important to acknowledge that when respiratory depression is due to the combined actions of an opioid and non-opioid drug, specific opioid antagonists such as naloxone will block or reverse only that component of respiratory depression due to the opioid. Naloxone has no effect on respiratory depression due to other compounds, such as alcohol and the benzodiazepines.

Future research directions

While research to date has revealed something of the mechanisms underlying respiratory depression produced by opioid drugs, a number of questions remain unanswered. Clearly, more needs to be understood about the interaction between opioids and other drugs that

may induce respiratory depression. Research into the nature of these interactions may help in minimising the risks associated with the use of these drugs. While some studies could be carried out in humans, it would be useful to have an appropriate animal model with which to evaluate these interactions.

The role of metabolites of morphine in mediating respiratory depressant effects of heroin needs also to be determined. In most post mortem cases, concentrations of morphine alone are determined, or on some occasions, both monoacetyl morphine and morphine. Given that morphine-6-glucuronide may play an important role in the effects of heroin, it would be useful to assess this metabolite as well. Only one preliminary study has attempted to do that to date (Skopp et al, 1996). It is possible that some cases of overdose with relatively low concentrations of morphine present in the blood may be accounted for by significant morphine-6-glucuronide concentrations.

The role of tolerance also needs to be assessed further. It has been regarded as somewhat counterintuitive that most heroin overdose deaths occur amongst experienced users with long histories of opioid use (Darke and Zador, 1996). While tolerance can confer a protective effect, this is not necessarily the case as experience with barbiturates has shown. With these drugs, experienced users seemed to be at highest risk of overdose-induced respiratory depression. This may have been because of the relatively slower rate of tolerance development to the respiratory depressant effects compared to the therapeutic effects. Tolerance to opioids could also produce a similar narrowing of the difference between therapeutic/euphoric effects and respiratory depressant effects. Appropriate research on opioid tolerance could generate information of value to users, but also to prescribers of opioid drugs.

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Pathway for Classification of An Opioid – Drug Death

by

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Introduction

In an era of rising political, professional and community concern regarding the escalation in heroin related death rates around the world, the availability of reliable, valid and relevant data becomes imperative in order to monitor global trends, and to evaluate interventions designed to reduce the incidence of these fatalities. However, our experience in conducting research into opioid drug related mortality, including collation of data from coronial sources on the circumstances and toxicology of these cases of death, has exposed the complexities and inadequacies of current classification procedures for the accumulation of drug-caused mortality data in Australia. At the same time, the present classification system has not been systematically summarised nor made available in a readily accessible or easily understood format.

Based on our experience in the field, we have been able to assemble the chronological sequence of events involved in the process of ‘converting’ the forensic findings relating to individual cases of fatal drug overdose into statistical data. This paper will describe the pathway from the time of death of the deceased to the availability of data on opioid drug related deaths in Australia.

Discovery of the body

The body may be discovered immediately, some days, or even weeks after death has occurred. The body may be transported to a hospital Emergency Department for certification of the death, or directly to the mortuary if the person has been obviously deceased for some time and rigor mortis is established.

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1. South Western Sydney Area Health Service
 2. Central Sydney Area Health Service

If police attending the scene believe that the death occurred under suspicious circumstances, they may request that a forensic pathologist and/or coroner investigate the scene of the death.

A medical certificate can be issued where the cause of death is due to natural causes. A death becomes a coroner's case when a medical officer cannot certify it. This occurs where cause of death is unknown, or sudden, occurred in suspicious circumstances, or in gaol or another institution. All drug-related deaths are coroner's cases.

Post-mortem

A post-mortem examination is conducted of all coroners' cases. A forensic pathologist or a government medical officer (who in rural areas may be a general practitioner) may undertake this.

Division of Analytical Laboratories

All blood and tissue specimens in NSW taken at autopsy, along with any drug paraphernalia located at the scene of death are sent to the Division of Analytical Laboratories, NSW Health Department, Lidcombe for toxicological analysis. These results are then returned to the forensic pathologist/government medical officer for consideration in the determination of the medical cause of death.

Forensic pathologist

It is the role of the forensic pathologist to determine the medical cause of death only. No reference is made to the manner of death, for example accidental death, suicide, or homicide.

Inconsistent variation in the reported cause of an opioid drug related death can occur across pathologists and within the same pathologist from case to case. This arises as a result of the variety of terms which are used to describe cause of death e.g. "acute narcotism", "overdose", "toxicity" and "poisoning" among others. More importantly, there is variability in the likelihood that other psychoactive drugs detected at autopsy will be implicated, in addition to the opiate, in the cause of death. The interval of time between the post-mortem to a conclusion regarding cause of death, is usually at least six weeks.

Case management officer

The case management officer is a police officer based at the coroner's court. It is the case manager's duty to critically analyse and summarise the case for the coroner, ensuring that appropriate investigations have been conducted and that all relevant information is available.

Coroner

The coroner reviews all cases to determine whether a hearing can be dispensed with and the case closed, or whether a hearing should be held. A hearing is dispensed with, if the coroner deems it unnecessary, and/or the family does not request one. This occurs in the majority of cases of opioid related death, presumably because the cause of death is known and the death is accidental. If a hearing is dispensed with, no coronial finding is recorded, but the coroner may make notes in the file.

A coronial hearing is held if the death occurred in suspicious circumstances, the hearing is requested by a significant other, or it would be in the public interest to do so, for example a spate of deaths in similar circumstances.

The coroner reaches a conclusion regarding the cause of death based on the toxicological findings, forensic pathologist's conclusion, police report and expert witness' statements. The coroner determines the circumstances of death i.e. accidental death, homicide, or suicide. The finding of a suicide is only reached when evidence overwhelmingly indicates this.

If during the hearing, the coroner finds a prima facie case that an indictable offence has been committed, the hearing is terminated and the case referred to the Director of Public Prosecutions (DPP). The DPP then conducts a criminal investigation to determine whether another individual directly or indirectly caused the death of the case in question.

The time elapsed between scheduling of the hearing and the completion of the hearing may be several weeks to many months.

Registry of Births, Deaths and Marriages

The Registry of Births, Deaths and Marriages receives "cause of death" information from the coroner's court. In cases where a hearing has been held, the coroner's conclusion constitutes "cause of death information". In cases where the hearing has been dispensed with, the pathologist's finding is recorded as the cause of death. The death is then registered and a death certificate issued, which states the direct and antecedent causes of death. The Australian Bureau of Statistics then receives this information.

Australian Bureau of Statistics

The Australian Bureau of Statistics (ABS) has a national office in Queensland and sub-branches in each state and territory. The sub-branches collect information about causes of death of coroners' cases within their respective jurisdictions. The International Classification of Diseases – version 9 (ICD-9) criteria for a drug caused death are applied to each case of opioid drug related death. An interpretation of the cause of death for each case is made by the ABS clerk to determine the appropriate code. For example a pathologist may find the direct cause of death cardiac arrest, and the antecedent, methadone toxicity, in which case the ABS clerk will refer to the antecedent cause of death in order to code the death. Codes used to classify opioid drug deaths include: 304.0 Opiate dependence, 304.7 Opiate

dependence (including presence of other drugs), E850.0 accidental opiate poisoning, E950.0 Opiate caused suicide, E980.0 Opiate poisoning, cause uncertain. Code E980.0 is applicable to cases where the cause of death is known, but the manner of death i.e. suicide, accidental, homicide cannot be determined by the coroner.

Variation in reliability of classification can occur as coding is undertaken by various clerical officers of the ABS whose knowledge and training in interpreting information contained in coronial files may vary. It may take up to a year before the ABS has collated the opioid drug related mortality data for that year.

Illicit Drug Section – Commonwealth Department of Health and Family Services (CDHFS)

This section of the CDHFS obtains information from the Australian Bureau of Statistics on drug related deaths. This section is responsible for the calculation of aetiological fractions in relation to causes of drug related deaths. Cause of death data is published in reports, usually on an annual basis.

Discussion

The pathway described applies to the classification of all opioid drug deaths across Australia. The complete process may take 18 months before published data are available. Clearly, this delay impedes public health authorities' abilities to monitor trends in national and regional patterns of opioid drug death in closer proximity to the occurrence of these fatalities, and to plan more expeditious responses to detected changes in these trends. More precise identification of opioid drug related deaths as opioid and other drug related deaths (or polydrug deaths) will also substantially contribute to more effective interventions designed to reduce the incidence of these deaths.

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APPENDIX
Pathway For Classification Of An Opioid Drug Related Death

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| Death |
| Discovery of Body |
| Post Mortem |
| Division of Analytical Laboratories |
| Forensic Pathologists's Conclusion |
| Case management Officer |
| Coroner |
| Coronial Hearing |
| Director of Public Prosecutions |
| Registry of Births, Deaths & Marriages |
| Australian Bureau of Statistics |
| Illicit Drug Section Department of Health and Family Services |

Classification of Opioid Deaths - A Forensic Pathologist's Perspective

by

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Introduction

Heroin overdose is an all too common outcome of illicit intravenous opioid administration. According to all Coroners Acts in Australasia, deaths due to, or suspected of being caused by heroin overdose must be referred to the coroner for investigation. As part of this investigation, the forensic pathologist is expected to perform an autopsy which includes toxicological examination of tissues and body fluids.

As a result of the large number of heroin-related deaths country-wide, all forensic pathologists can be expected to develop expertise in the area of determination of cause of death in cases of apparent acute heroin overdose. Yet, despite the frequency of heroin overdose deaths, forensic pathologists have struggled to devise a standard nomenclature for these deaths.

Deaths associated with opioid administration may be due to the direct effects of the drug or its metabolites, the toxicity of diluents, adulterants or other material injected together with the drug, or the lifestyle and frequent infectious complications associated with illicit intravenous drug administration (Karch, 1996).

Acute infectious complications of parenteral administration of the drug include conditions such as infective endocarditis which is often right-sided (Dressler, 1989), massive hepatic necrosis due to hepatitis B or C virus infection, and septicaemia. However, the majority of these cases present as critically ill patients to emergency departments in hospitals, and tend to survive with long-term morbidity, and it is the minority that die prior to medical attention.

The relative importance of adulterants, diluents and other non-psychoactive substances in causing or contributing to acute death in Australasia is not known. However, pulmonary hypertension due to foreign particle embolisation is relatively infrequently diagnosed at autopsy (Hopkins, 1972). Death due to accidental or homicidal administration of substances such as battery acid and strychnine is frequently mentioned both "on the streets" and by more gullible pathologists and clinicians, but actual cases seem to be as rare as the proverbial hen's teeth, and this mechanism of

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death can probably be discarded in the vast majority of cases.

Most acute deaths associated with intravenous injection of heroin appear to die of the pharmacological effects of opioids. The patient is generally found dead at home, with drug administration paraphernalia in close proximity, and usually with other people present (Zador et al., 1996). Police investigations invariably reveal the deceased has been an intravenous drug user for a number of years, and the person tends to be “known to police”. At autopsy, the deceased invariably shows evidence of recurrent intravenous drug administration, with “needle track marks” in the antecubital fossae and other readily accessible parts of the body. Apart from generalised organ congestion at autopsy, autopsy findings are generally sparse, and it is often the absence of significant autopsy pathology that leads one to suspect a toxin rather than the presence of specific pathology (Helpern, 1966). Pathological processes such as chronic hepatitis due to hepatitis C virus infection, when present, are generally considered to be incidental findings associated with “dirty needles” and probably do not significantly contribute to the death.

Toxicological findings in apparently obvious heroin overdose deaths are puzzling, with generally low morphine levels detected in blood (Zador et al., 1996). In the majority of cases, the morphine concentrations are similar to those found in intravenous drug users dying from trauma (Baselt & Cravey, 1995), and it is highly unusual to find levels of morphine in illicit intravenous heroin users in the range seen in palliative care patients.

Despite these apparent anomalous toxicological findings, forensic pathologists accept that heroin injection kills acutely, usually as a result of the pharmacological effects of the drug. The exact mechanism of death in these cases is far from clear, and this has resulted in forensic pathologists using a variety of terms to circumvent the obvious fact that an overdose in the classical sense of the word did not take place. These terms can include, but are not limited to narcotism and acute narcotism (Helpern, 1966), heroin or opioid intoxication, heroin or opioid toxicity, acute narcotic overdose and narcotic/heroin/opioid poisoning.

This study investigates the various diagnostic approaches used by forensic pathologists to determine the medical cause of death in heroin-related deaths.

Methods

A representative sample of forensic pathologists in full time coronial practise throughout Australia were contacted telephonically. Three scenarios were presented, and following each scenario, the pathologist was asked to provide an opinion on what he/she would have written as the cause of death in this case. In all three cases presented, the following information was constant: the deceased was a known intravenous drug user, found dead in a hotel room in Kings Cross with drug injecting paraphernalia on the bedside table. There were recent and old needle puncture marks in the antecubital fossae, and apart from chronic hepatitis C virus infection, the autopsy was negative. The toxicological findings were varied as follows in the three scenarios (Table 1):

Table 1: Toxicological scenarios presented to pathologists.

| | Scenario 1 (High opioid, no alcohol) | Scenario 2 (Low opioid, elevated alcohol) | Scenario 3 (Low opioid, no alcohol) |
|----------------|---|---|--|
| Blood morphine | 0.5 mg/L | 0.05 mg/L | 0.05 mg/L |
| Blood alcohol | Nil | 0.10 g/100mL | Nil |
| Liver morphine | 2 mg/kg | 0.5 mg/kg | 0.5 mg/kg |
| Bile morphine | 40 mg/L | 40 mg/L | 40 mg/L |

Results

Ten pathologists were contacted and completed the telephonic questionnaire. The responses to the three scenarios are presented in tables 2, 3 and 4.

Table 2: High opioid, no alcohol scenario

| Scenario 1: High opioid, no alcohol | |
|--|---|
| Morphine toxicity/intoxication | 5 |
| Heroin overdose | 2 |
| Acute narcotism/narcotic O/D | 2 |
| Opioid toxicity | 1 |

Table 3: Low opioid, moderate alcohol intoxication scenario

| Scenario 2: Low opioid, moderate alcohol | |
|---|---|
| Combined effects of opiate and alcohol | 5 |
| Mixed drug overdose/toxicity | 3 |
| Heroin overdose | 1 |
| Acute narcotism | 1 |

Table 4: Low opioid, no alcohol scenario

| Scenario 3: Low opioid, no alcohol | |
|---|---|
| Morphine toxicity | 3 |
| Heroin toxicity | 2 |
| Acute narcotism | 2 |
| Undetermined | 2 |
| Opioid toxicity | 1 |

Discussion

This limited, telephonic survey of views of forensic pathologists has revealed a wide range of terms used to describe the cause of death in cases of opioid-related overdoses.

Accurate determination of cause of death is an essential part of death certification. Death certificate data should be accurate not only for the information of the next-of-kin of the deceased, but is also necessary for numerous societal functions, including the formulation of appropriate health and social policy, the detection of social trends, the collection of epidemiological data, and not least the provision of accurate data on which life-saving strategies can be based. Despite these important roles for accurate death certification, little formal training takes place in the field. Forensic pathologists, who arguably issue more death certificates than most medical practitioners, do not appear to have a consistent approach to determining cause of death for a category of case often encountered, namely cases of opioid toxicity.

Therapeutic, recreational, toxic and fatal concentrations of opioids in blood overlap, and in many cases are the same. Table 5 presents data from a range of sources, giving values typically found in a variety of cases (Baselt, 1995; Zador et al., 1996; Kintz, Mangin, Lugnier & Chaumont, 1989).

Table 5: Blood morphine levels in various categories of patients following administration of heroin.

| Typical blood morphine levels (in mg/L) | |
|--|-----------|
| Following 5 mg heroin IV | 0.02-0.05 |
| Following 200 mg heroin IV | 0.30 |
| In heroin IDU fatalities | 0.06-0.90 |
| In heroin IDU + alcohol fatalities | 0.17 |
| In heroin IDU suicides | 0.35-0.45 |
| In terminally ill patients | 0.5-3.0 |

In situations where a pathological condition having similar autopsy appearances can be either an incidental finding or the cause of death, forensic pathologists correctly take into account the circumstances of death and the presence or absence of other pathological findings to determine the cause of death. For example, a person with an obviously fatal gunshot wound to the head may have 90% narrowing of a coronary artery - the cause of death would be a gunshot wound to the head, and the coronary artery disease would be viewed as probably entirely incidental to the death. On the other hand, if a patient is seen to clutch his chest, collapse to the ground and at autopsy is found to have the same degree of coronary artery disease as the only pathology, the cause of death would be confidently given as ischaemic heart disease. Similarly, forensic pathologists use this process for determining cause of death in cases of apparent heroin overdose (Karch, 1996; Helpert, 1972). The general approach seems to be that scene evidence of illicit intravenous drug use, plus a history of recurrent heroin use, an essentially negative autopsy and detection of heroin metabolites (ie. morphine) in blood is sufficient for attributing death to the administration of heroin. This is despite the fact that low therapeutic levels of morphine (as in scenario 2 and 3) may be detected, or that significant quantities of other drugs may be found in blood, typically alcohol and benzodiazepines. Zador, et al. (1996) have previously investigated the reasons for forensic pathologists "preferring" a cause of death involving solely heroin, as opposed to including known respiratory depressant drugs such as alcohol and benzodiazepines in the diagnosis (Zador et al., 1996). As a result of this work, forensic pathologists appear to be modifying their approach to cause of death in cases of mixed drug administration - this is demonstrated by the fact that eight of the ten responses in scenario 2 did not limit the cause of death to the effects of heroin alone.

This limited survey of cause of death formulation has demonstrated a wide variety of responses to essentially everyday scenarios for forensic pathologists. Whether an attempt should be made to standardise the terms used by forensic pathologists to describe these deaths is open to debate. Although there are epidemiological and other statistical advantages for standardising the terminology, this approach would no doubt be strenuously resisted by the majority of forensic pathologists. Nevertheless, there are relatively few full-time specialist forensic pathologists in Australasia - less than 30 at present. It may be that modifying the behaviour of forensic pathologists in their assessment of cause of death in heroin-related deaths may be a cost-effective step towards a better understanding of the condition.

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Advances in the Management on Drug Overdose In An Outreach Setting

by

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Introduction

Kirketon Road Centre (KRC) is a primary health facility located in Kings Cross, Sydney. KRC is involved in the prevention, treatment and care of HIV/AIDS and other transmissible infections amongst injecting drug users (IDUs), sex workers and 'at risk' youth. KRC conducts an outreach program staffed by registered nurses (RNs) and counsellors which extends primary health & needle exchange services to 'hard to reach' clients in the Kings Cross and Darlinghurst areas including 'The Wall'. 'The Wall' is a site used to inject heroin and other drugs and opiate overdose is not uncommon. The initial role of outreach staff in the event of client overdose was to contact the ambulance service and provide basic life support (BLS). It was hypothesised that a more positive outcome could be achieved for these clients if the attending RN was authorised to administer naloxone.

Methods

In 1992 a protocol was developed by KRC for outreach RNs to administer naloxone intramuscularly in the event of opiate overdose. Safeguards to protect clients and the RNs included: standing order by a medical officer prescribing naloxone to be administered by RNs; training of RNs in BLS and naloxone use; that an ambulance still be called; advising the client about the risks associated with the short duration of naloxone if they choose not to go to hospital post-resuscitation; medical review and documentation of resuscitation and outcome.

Results

Following the introduction of this protocol, KRC outreach nurses have successfully

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administered naloxone to 86 clients following opiate overdose. There have been no subsequent reported deaths from opiate overdose among IDUs treated with naloxone, and clients continue to seek the assistance of outreach staff in overdose situations also providing an opportunity to educate IDUs about BLS.

Conclusion

KRC supports the continuation of this extended role of outreach RNs. Consideration should be given to extending the authority to administer naloxone to other outreach workers and even to IDUs themselves.

Deaths In Methadone Maintenance Treatment In New South Wales 1990 - 1995

by

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Introduction

Systematic classification of causes of death in methadone maintenance treatment (MMT) in Australia is not routinely undertaken, yet may reveal valuable information about mortality trends of heroin users in treatment. The purpose of this study was to determine the number of deaths of persons in (MMT), to describe the causes of death in MMT, and to estimate the all-cause mortality rate of all persons enrolled in MMT in New South Wales from 1990 to 1995. Implications of the findings of this study for policy and clinical practice will also be discussed.

This paper will present some of the key findings in relation to number and causes of death in MMT only. Data on mortality rate and risk of dying in MMT are reported elsewhere in the Proceedings from this Symposium. A full report presenting detailed results of this investigation will be available as a technical report (NSW Health Department, 1998, in preparation).

Method

Sampling Procedure

A list of all cases classified as "deceased" on the *Termination of Methadone Treatment* form (exit form) between 1 January 1990 and 31 December 1995 was obtained from the Pharmaceutical Services Section (PSS) of the NSW Department of Health. Deaths of all cases were confirmed with the Registry of Births, Deaths and Marriages (RBDM) prior to entry in the study. Cases were excluded if death occurred more than seven days after the last authorised dose of methadone, or if death was not confirmed by the RBDM. A total of 227 cases was identified by this procedure.

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 2. South Western Sydney Area Health Service

Collection of data

A data collection form was designed to record socio-demographic characteristics, the cause of death as specified on the death certificate on file at the RBDM, duration of (MMT), date and quantity of commencing dose of methadone, date and quantity of last authorised dose of methadone, and other variables relating to each subject's MMT. Data were obtained from *Application for Authority to Prescribe Methadone* and *Termination of Methadone Treatment* forms and other information contained in subjects' files located in the PSS.

Cause of death was categorised into one of four groups: drug related causes, medical illness, trauma and suicide. Where cases were classified as drug-related, relevant coronial files were examined to obtain information on results of toxicological analysis. A program was defined as the period of time between the date on the *Application for Authority to Prescribe Methadone* form and the date on the *Termination of Methadone Treatment* form. The current program was defined as the program the subject was registered in at the time of death.

Records for each subject were entered into the Epi-Info program for analysis.

Results

Number of deaths

Of the 227 deaths in (MMT), 16 subjects were excluded from the study. In eleven cases this was because the subject died more than seven days after receiving their last authorised dose of methadone. One subject died before collecting her first dose of methadone and in four cases, the subject's death certificate could not be located at the Registry of Births, Deaths and Marriages. The final analysis of deaths in MMT was conducted on 211 confirmed deaths.

The number of deaths ranged from 23 in 1990 to 47 in 1995 (see Table 1).

Demographic characteristics

Of the 211 cases of death between 1990 and 1995, 152 cases (72%) were male and 59 cases (28%) were female. The proportion of males and females receiving MMT in NSW during the same time period was 63% and 37% respectively. The mean age of male subjects was 34 years (SD=8, range 18 to 67) and the mean age of female subjects was 32 years (SD=7, range 20 to 48).

Table 1. Number of deaths in MMT in NSW, 1990 - 1995

| Year | Number of persons registered in MMT ¹⁵ | Number of deaths n = 211 |
|------|---|-----------------------------|
| 1990 | 7419 | 23 |
| 1991 | 7904 | 27 |
| 1992 | 8778 | 37 |
| 1993 | 10020 | 38 |
| 1994 | 11427 | 39 |
| 1995 | 12924 | 47 |

Causes of death in MMT

Causes of death were most often drug related (40% of cases), followed by medical illness (29%) of cases and trauma (14% of cases). In four cases the forensic pathologist's/coroner's findings as to cause of death were unavailable at the time of analysis.

Duration of MMT for cases of death

Table 2 shows the duration of MMT for cases of death. Over 50% of subjects had been in their current program for more than 12 months at the time of death. Eleven per cent of subjects had been in their current program for one week or less, and 35% for 12 months or less at the time of death.

Table 2. Deaths according to duration of current MMT program, NSW 1990 - 1995

| Duration | Current Program n = 211 |
|--------------------|----------------------------|
| 1 week or less | 24 (11%) |
| 8 days - 12 months | 74 (35%) |
| >1 year to 3 years | 47 (22%) |
| > 3 years | 64 (30%) |
| Unavailable | 2 (1%) |

The distribution of drug-related causes of death according to duration of MMT was exceptional. Two-thirds (64%) of subjects who died from drug-related causes had been in their current program for less than 12 months.

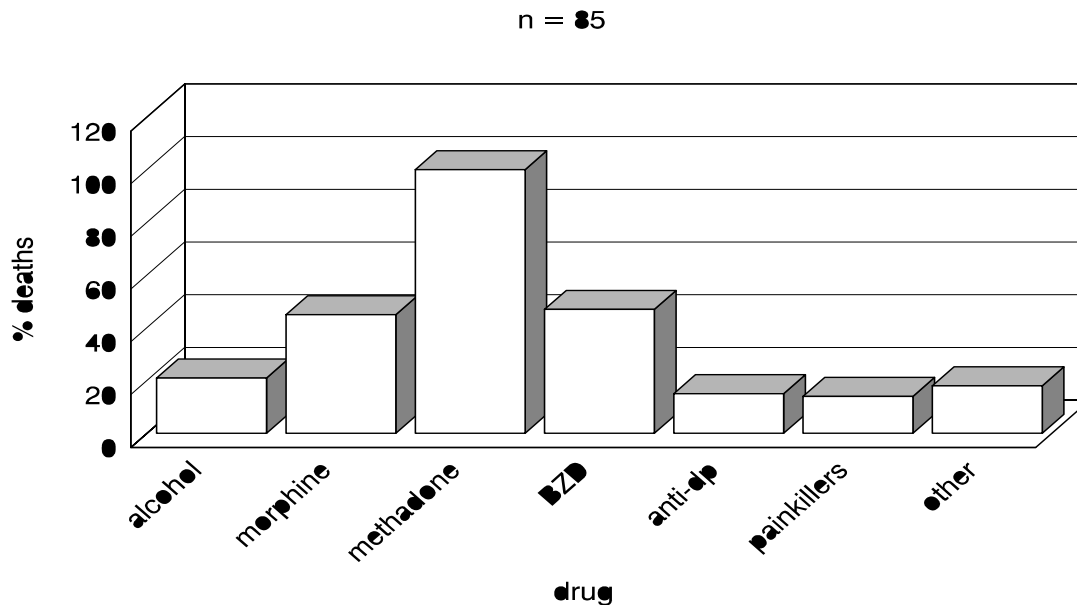
3. These figures differ from those released by the NSW Department of Health, which provide a snapshot of persons in treatment on one particular day. Our figures refer to recipients of MMT in a one year period and are therefore greater than those of the Department of Health.

Drug related deaths

After methadone (for which 100% of cases were positive), benzodiazepines were the most frequently detected drug class at autopsy. They were present in 40 cases (47%). Morphine was detected in 38 cases (45%) and alcohol in 18 (21%) cases (see Figure 1).

Eighteen per cent of subjects had a drug detected at autopsy other than those identified in the Figure.

Figure 1: Drugs detected at autopsy



BZD = benzodiazepines

antidep = antidepressants

Note: Total percentage exceeds 100 as some subjects were positive for more than one drug

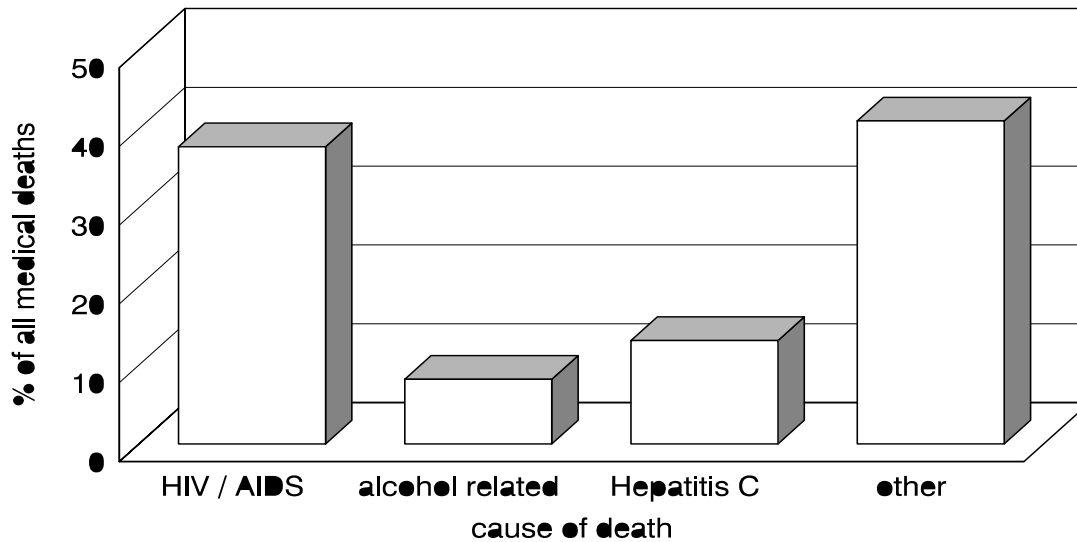
In 28% of cases, two drug classes were detected and in 42% of cases, three drug classes were detected in addition to methadone. Sixteen per cent had four or more drug classes detected. Over 90% of cases, therefore, were positive for psychoactive drugs other than methadone at time of death, a finding consistent with polydrug use. Only eight subjects (9%) who died of drug related causes were positive for methadone only.

Deaths due to medical illness

Figure 3 shows the deaths related to medical illness. More than a third of deaths due to medical illness were attributed to HIV/AIDS related conditions. Hepatitis C accounted for another 13% of medical illness related deaths. Alcohol-related diseases (e.g. cirrhosis of the liver), accounted for eight per cent (8%) of these deaths. Other medical illnesses included: Hodgkin's disease, myocardial infarct, malignant melanoma, haemopericardium due to dissecting aneurysm of the aorta, cerebral abscess and aortic valve endocarditis.

Figure 3: Deaths related to medical illness

n = 61



Trauma Related Deaths

The most common type of trauma related death was motor vehicle accidents where the subject was the driver, passenger or pedestrian (44% of cases). Stab wounds were the second most frequently occurring cause of trauma related deaths (20%) followed by hit and run accidents (10%) and bashings (10%).

Deaths during the first seven days of MMT

During the six year period from 1990 to 1995, there were 27 deaths in the first seven days of treatment. The mean age of cases was 27.5 years (range 19-38) and 78% were male. Drug related deaths accounted for 25 of the 27 deaths (93%) occurring in the first week of MMT. That is, of the total 85 drug-related deaths identified in the study, nearly one-third (29.4%) occurred during the first seven days of treatment. Of the remaining two deaths, one was related to medical illness (acute viral myocarditis) and one was unclassified due to missing data (the medical certificate could not be located).

Methadone dosing schedule for deaths in the first seven days of MMT

For each of the years 1990 to 1994, 80% or more of cases were commenced on 40 mg. In 1995 however only 29% of cases were commenced on 40 mg. The mean number of days in treatment at time of death was 3.9 days. Methadone dose on last day of treatment for 21 cases (78%) was consistent with state and national clinical guidelines on stabilization of dose during the first seven days of treatment. There were six cases whose increments of dose were more rapid than recommended by policy. In one case, the last ingested dose of methadone on day six was nearly four times his starting dose due to a clinic dosing error.

Toxicological findings for deaths in the first seven days of MMT

Blood methadone concentrations (n=23) at post-mortem showed that 91% were within the reference or therapeutic range of 0.04 - 1.0 mg/L (Division of Analytical Laboratories, NSW Department of Health). Blood methadone concentrations (BMC) of only two cases exceeded 1.0 mg/L.

As stated previously, 25 of the 27 cases (93%) were found by the pathologist or coroner to have died of drug-related causes. Four of these cases were excluded from further toxicological analysis because results were unavailable for three cases and because the fourth case died as a consequence of iatrogenic methadone toxicity. Of the remaining sample of 21 drug-related deaths, only three (14%) were positive for methadone only at autopsy. Thus, 86% of drug-related deaths in the first week of MMT were positive for one or more psychoactive drugs in addition to methadone at time of death, i.e. were poly-drug deaths. Coronial evidence for one poly-drug case suggested that he was inadequately assessed and may not have been sufficiently opioid dependent at time of entry into MMT.

Drug-related deaths positive for methadone only -- three case studies

Of the three cases of methadone-only drug-related death, one case died on day four of treatment with a BMC of 1.10 mg/L following a prescribed, ingested dose of 60 mg. The second methadone-only case died on day four of treatment with a BMC of 0.32 mg/L following a prescribed, ingested dose of 35 mg on the same day. The last case died on day 6 after a prescribed ingested dose of 80 mg and with a BMC at autopsy of 0.65 mg/L. All three deaths were attributed by the forensic pathologist/coroner to methadone toxicity.

Discussion

Two hundred and eleven patients died while registered in (MMT) in New South Wales from 1990 to 1995. Although the number of deaths per year increased so too did the total number of persons in MMT for each year. Analysis of the all-cause mortality rate for persons in MMT over this six-year time period has shown that it did not increase: the increase in number of deaths was proportional to the increase in numbers of persons entering MMT each year (Zador, Sunjic and Basili chapter). We believe that the number of deaths each year is small, given the overall total size of the NSW methadone program and given that opioid dependent persons are at substantially increased risk for premature mortality by comparison with the general population of the same age and sex (English et al., 1995).

The results show that the most common cause of death among MMT patients in New South Wales in the six years ending 1995 was drug-related. Nearly all of these deaths were polydrug cases:- in only nine per cent of drug-related deaths could methadone alone be implicated. Of some surprise was the high proportion of medical illness deaths due to hepatitis C. The finding that this viral infection alone accounted for 13% of medically-related deaths should alert both policy-makers and clinicians in the field that hepatitis C is already making a substantial impact on mortality among recipients of MMT.

The finding that a substantial proportion of drug-related deaths occurred in the first seven days of treatment is consistent with the increasing recognition that this is a high risk period of time for persons in MMT. A cautious approach to the prescription of methadone during the first seven days is advised based on the risk of cumulative toxicity from methadone if it is too rapidly administered. This caution needs to be balanced against the risk that newly inducted patients may resort to other psychoactive drug use while awaiting the stabilising effects of methadone.

Three drug-related deaths in the first week of treatment were not poly-drug related - they were positive for methadone only at autopsy and were considered to be methadone caused deaths by the forensic pathologist in each case. In one case the methadone dosing schedule and toxicological results suggest that she may have supplemented her prescribed dose with illicitly acquired methadone. Neither the second case's dose nor BMC was high, and although methadone toxicity was found to be the cause of death, insufficient opioid tolerance at the time of initial assessment for treatment cannot be excluded as a cause of his death. The third case appeared to be too rapidly inducted into MMT, as indicated by a prescribed dose of 80 mg on the sixth day of his induction into treatment.

In two of these cases, more judicious assessment and prescribing during induction may have averted these subjects' deaths. In the case of the third methadone-only related death, appropriate advice to avoid supplementation of the prescribed methadone dose during stabilisation may not have been adhered to by the deceased.

We believe that these findings are testimony to the overall safe performance of the New South Wales methadone program. However given the relatively high proportion of drug-related deaths occurring during the first week of treatment we urge the development and dissemination of safer clinical protocols for the induction of clients into MMT.

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All-Cause Mortality Rate and Risk of Dying in Methadone Maintenance Treatment in New South Wales in 1990-1995

by

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Introduction

Australian research into mortality rates among recipients of methadone maintenance treatment (MMT) to date has been limited. One study found that patients in MMT were one-third as likely to die as those who had left treatment (Caplehorn et al 1994). Another study of the same cohort concluded that MMT reduced the risk of death from accidental heroin overdose by one-quarter and also decreased subjects' risk of suicide (Caplehorn et al 1996). A South Australian study found that although an increase in methadone-related deaths had occurred in 1993-1994, these were predominantly due to methadone tablets (Williamson et al., 1997). Deaths from overdose of methadone syrup declined from 1984 to 1994 despite an increase in the size of the methadone program, leading the authors to conclude that the state's methadone program was relatively safe.

The studies cited above have involved various cohorts of injecting drug users (IDUs). However within Australia a paucity of data exists regarding the overall mortality rate for *all* recipients of MMT within a given jurisdiction. Furthermore, within the state of New South Wales, the state with over 55% of the country's 20,000 recipients of MMT, there is current community concern about the safety and effectiveness of MMT. Therefore it is timely to examine the all-cause mortality rate for the population of recipients of MMT across New South Wales, to compare this with the mortality rate for the general population in the same state, and with published mortality rate data for heroin users not in treatment.

Method

Sampling procedure

A list of identification numbers for all persons on the NSW methadone program between 1 January 1990 and 31 December 1995 was obtained from the Pharmaceutical Services Section (PSS) of the NSW Department of Health. Persons identified by the PSS as

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1. Central Sydney Area Health Service
 2. South Western Sydney Area Health Service

deceased were confirmed by cross-reference with records on file at the NSW Registry of Births, Deaths and Marriages which also provided information on cause of death for each case. Causes of death for persons in methadone maintenance treatment (MMT) were subsequently classified into one of the following four groups: i) drug-related, ii) trauma or injury, iii) medical illness and iv) suicide.

The all-cause mortality rate (MR) for persons in MMT between 1 January 1990 and 31 December 1995 was calculated using an incidence density approach in which we estimated the ratio of the total number of deaths during the period to the total number of person-days in treatment. It was not logistically feasible to calculate the total number of person-days in treatment for all persons enrolled in the NSW methadone maintenance program over this time period. Instead, the number of person-days in treatment was estimated from a random sample of the study population stratified by sex, age and year.

Statistical analysis

Data were entered into the SPSS for Windows 6.0 program for analysis. As the number of deaths in MMT was small, a Poisson distribution method was used to calculate 95% confidence intervals around mortality rates. As 99.7% of the random sample were aged between 15 and 54 years, deaths in the population of methadone maintenance recipients were compared with deaths in the 15 to 54 year age group in the general population of NSW.

Results

All-cause mortality rates

Mortality rates varied substantially between men and women, age groups, and years. For this reason, MRs for males and females in MMT for each year were pooled and compared with pooled rates in the general population of NSW in 1993 (the mid point of the study period).

Figure 1: Mortality rate by sex for population in MMT

The MR for males in MMT in NSW was higher than that for females over the six-year period (Figure 1). The increase in the MR for the total population in 1992 was not significant.

All-cause MRs for males, females and all persons in MMT during period 1990-1995 are set out in Table 1.

Table 1. All-cause mortality rate (MR) and risk of dying in MMT compared with general population in NSW, 1990-1995.

| Sex | MR* in MMT | Risk Ratio |
|-------------|------------|------------|
| Males | 581 | 2.9 |
| Females | 368 | 3.7 |
| All persons | 500 | 3.4 |

Risk ratios

Risk ratios (RRs) for males, females and all persons in MMT compared with the age and sex standardised general population in NSW are also set out in Table 1. Differences in RRs between males and females resulted from disparate MRs from 1990 to 1992. From 1993 to 1995 the RR of death for males and females in MMT was similar (Figure 2).

Figure 2: Relative risk of death in MMT compared to general population

Discussion

The data show that the MR for persons in MMT during 1990 to 1995 in NSW did not increase. Thus the increase in the number of deaths of persons in treatment over this time period was proportional to the increase in the total number of persons in MMT over the same period.

The pooled results of international research into all cause mortality among heroin users show that the RR of death among heroin users not in treatment is approximately 13 times greater than the general population (English et al 1995). The major finding from this study demonstrates that heroin users in MMT have only a threefold increase in risk of death compared with the general population. Assuming that heroin users in NSW face similar risks to users elsewhere, the results of this study indicate that heroin users reduce their risk of death substantially by entering MMT, with up to one-quarter of the risk for heroin users who are not in treatment. These results replicate the findings of earlier research in Australia (Caplehorn et al., 1996) and demonstrate the continuing effectiveness of MMT in reducing all-cause mortality among heroin users and therefore its value as a treatment modality for heroin dependence.

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Methadone Syrup–Related Deaths in New South Wales, July 1990 – December 1995

by

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Introduction

Recent political, coronial and local community preoccupation with the apparent increase in the number of methadone related deaths (MRDs) has the potential to limit expansion of methadone maintenance treatment (MMT) in NSW due to concern about the program's safety. However, there is little available local data to evaluate these concerns.

A number of international studies have noted an increase in MRDs associated with the expansion of methadone maintenance treatment programs for heroin dependent persons. An early British paper examined 12 MRDs between 1965 and 1969 and found that in 75% of cases, death involved legally prescribed methadone (Gardner, 1970). A later study identified 90 MRDs occurring in Manchester between 1985 and 1994 (Cairns, Roberts and Benbow, 1996). The authors found that in 36 cases, methadone had been prescribed to the deceased, and in 32 cases, diverted methadone was the source of the fatal dose. Methadone deaths increased over the duration of the study period, as did the number of methadone prescriptions.

Danish studies report similar findings. Kaa (1992) studied all drug caused deaths occurring in Denmark between 1980 and 1989 and found that methadone was the third most frequent cause of drug related deaths among illicit drug users. The author concluded that the increase in methadone deaths during the 10-year study period was the result of the growth of MMT in Denmark and the subsequent diversion of methadone to the black market. Other studies (Worm, Steentoft and Kringsholm, 1993; Kringsholm, Kaa et al., 1994) of drug

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related deaths in Copenhagen support these findings.

These studies have implications for MMT in NSW, the jurisdiction with the largest methadone program in Australia. Since 1985, the size of the NSW methadone program has significantly increased in response to the recommendations of the National Campaign Against Drug Abuse (Ward et al., 1992). Prior to 1985, a study of drug-related deaths in Western Australia found that methadone toxicity was the second most commonly reported cause of death, and noted that this occurred during a period when methadone takeaway doses were less restricted in that state (Swensen, 1988). A later study in Victoria examined 10 deaths occurring in patients who had recently commenced MMT, and found that in all cases, death was due to methadone toxicity as a result of inappropriate prescribing during the first week of treatment (Drummer et al., 1992).

Research into 200 opioid drug-caused deaths in NSW in 1992 found that 13% were due to methadone, 15 of which (60%) involved methadone syrup (Sunjic and Zador, 1996). Half of the syrup deaths occurred in persons not registered in MMT at time of death. A major finding of the study was the very high prevalence of other psychoactive drugs detected at post-mortem. Only eight per cent of cases were positive for methadone only. It was concluded by the authors that the high prevalence of other drugs detected at autopsy made it difficult to attribute the cause of death to methadone alone.

A review of MRDs in South Australia between 1984 and 1994 found that the majority of deaths were related to methadone tablet (Physeptone®) ingestion, and that death related to methadone tablets was almost eight times more likely than death related to methadone syrup. They concluded that the lower number of syrup-related deaths was due to the safe administration of the state's methadone maintenance program (Williamson, Foreman, White and Anderson, 1997).

No recent study has documented temporal trends in the total number of MRDs in NSW since the expansion of its methadone program. Of particular relevance, there is no published information to date in this state on the proportion of MRDs associated with syrup (the only form of methadone generally available in Australian methadone programs), the socio-demographic characteristics of cases of MRD, or the circumstances in which they occur.

This paper will present findings in relation to cases of methadone syrup death only. Full details of the results of this investigation are available from the NSW Department of Health as a Technical Report (pending publication).

Methods

Three hundred and seventy-five (375) cases positive for blood or tissue methadone at autopsy between 1 July 1990 and 31 December 1995 were obtained from the Division of Analytical Laboratories, NSW Health Department (data were unavailable prior to July 1990). Permission was obtained from the Department of Courts Administration to view the

coronial files for each of these cases. Two hundred and forty-two (242) of these cases were identified as accidental drug related deaths. One hundred and thirty-four (134, 55%) involved methadone syrup administration and were considered methadone syrup related deaths (MSRDs). Seventeen per cent (17%) of methadone detected drug deaths were related to methadone tablet (Physeptone®) administration. In two per cent (2%) of cases there was evidence of administration of both tablet and syrup forms of methadone, and in 25% of cases, the form of methadone could not be determined.

Two different sets of criteria (pathologist/coroner's finding, and clinical opinion of the investigators (SS and DZ)) were used to define a 'methadone related death'. This analysis was undertaken to compare the variation in sample size of MRD depending on which sets of criteria were used.

Wherever the forensic pathologist made reference to methadone (by name or use of other terms e.g. "narcotism") in the cause of death, the case was classified as methadone implicated. Otherwise, it was classified as a non-methadone drug related death.

The second set of criteria used to classify cases as a 'methadone related death' was based on the expert clinical opinion of two of the investigators (SS and DZ) independent of the findings of the pathologist or coroner. In the absence of any information to the contrary, methadone was considered to have contributed to death.

Toxicological analysis of all samples was conducted at the Division of Analytical Laboratories, NSW Department of Health, Lidcombe. Seven cases died in hospital following admission for management of drug toxicity. As interpretation of their toxicological results could be confounded by the prolonged interval of time between fatal administration of drug and onset of death, and by possible administration of other drugs during medical treatment, these cases were excluded from further analysis.

Statistical analysis

For continuous variables, t-tests were employed, and for skewed continuous data, non-parametric measures of variance were used. Categorical variables were analysed using chi-square. All analyses were conducted using Epi5-info statistical package (Dean, Dean, Burton and Dicker, 1990).

Results

One hundred and thirty-four (134) cases of MSRD (55% of the total number of MRDs) were identified between 1 July 1990 and 31 December 1995 (Table 1). Just over half of the MSRDs (n=72, 54%) were registered in MMT at time of death. Sixty-two (62) cases (46%) were not enrolled in MMT at time of death.

Table 1. Number of methadone syrup only, all forms methadone, and all MRDs in NSW, 1990 – 1995.

| Year | MSRDs# | % In MMT* | MRD** |
|--------------|------------|-----------|------------|
| 1990 | 6 | 67 | 13 |
| 1991 | 20 | 60 | 35 |
| 1992 | 18 | 61 | 41 |
| 1993 | 25 | 48 | 43 |
| 1994 | 32 | 38 | 59 |
| 1995 | 33 | 64 | 51 |
| Total | 134 | | 242 |

methadone syrup-related deaths

* % of MSRDS registered in methadone maintenance treatment

**methadone-related deaths (syrup, tablet and form undetermined)

The number of MSRDS per year increased from 1990 to 1995. During this time period, the proportion of MSRDS registered in MMT remained stable at about 60% or more per year except 1994, an atypical year during which 62% of MSRDS occurred in persons not in treatment (and except 1993 during which approximately equal proportions of deaths occurred both in- and out-of treatment groups).

Socio-demographic characteristics

The majority of MSRDS (both in MMT and not in MMT) were male (75% and 76% respectively), and single (64% and 57% respectively). Cases not in MMT (mean: 29 years, range: 14-53, SD=8.6) were significantly younger ($\chi^2=5.11$, $df=1$, $p=0.02$) than those in MMT (mean: 32 years, range: 19-54, SD=7.5). The majority of cases (86% in MMT, 73% not in MMT) were unemployed at the time of death.

Most cases (90% in MMT, 89% not in MMT) were known by witnesses or significant others to be drug users. The majority of cases, whether in MMT (92%) or out of MMT (74%), were known heroin users.

Route of Methadone Syrup Administration

Cases in MMT (74%) were more likely to have ingested methadone orally than cases not in MMT (47%) ($\chi^2=14.45$, $df=3$, $p=0.002$). Cases not in MMT were more likely to inject although this difference was not significant.

Setting and Geographic Region of MSRDS

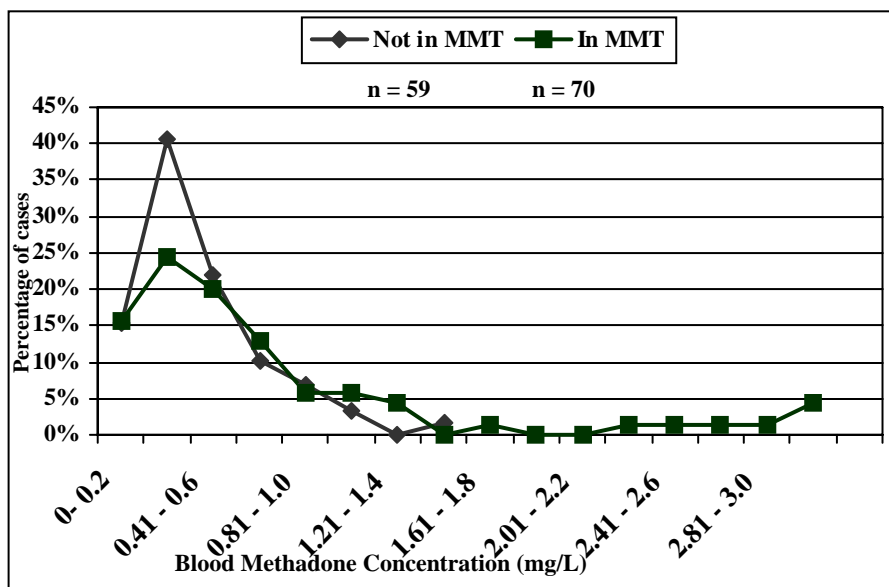
The most common setting for death was a home environment, either the person's own home or that of a family member or friend (73% in MMT, 88% not in MMT). Other settings included railway station/train (4% and 2% respectively) and hospital (10% and 10% respectively).

Twenty per cent (20%) of deaths in NSW occurred outside the Sydney metropolitan area. The most common region of residence and death for cases in MMT in NSW was south western Sydney (18% and 18% respectively), while western Sydney was the most common region of residence and death for cases not in MMT (27% and 26% respectively).

Toxicological findings

The range of blood methadone concentrations (BMCs) for cases of MSRSD (n=129) is depicted in Figure 1. Two cases were removed from the analysis because they were positive for tissue only, not blood, methadone and an additional three cases were excluded from this analysis because they died in hospital. The majority of BMCs are skewed toward the lower end of the range. Eighty-six percent (86%) of BMCs were within the reported therapeutic range of 0.03-1.0 mg/L (Division of Analytical Laboratories, NSW Health Department). The median BMC was 0.38 mg/L (range 0.07-5.5). A non significant difference was found between the median BMC of cases in MMT and cases not in MMT at time of death (in MMT median: 0.43 mg/L, range: 0.07-5.5, vs not in MMT median: 0.39 mg/L, range: 0.1-1.6, p=0.07).

Figure 1. Blood methadone concentrations detected at autopsy for methadone syrup related deaths in NSW, 1990 - 1995 (n=129).



A minority of cases (9% in MMT, 13% not in MMT) were positive for methadone only at autopsy. The median BMC for methadone-only cases was 0.455 mg/L (range: 0.23-2.8 mg/L) only slightly higher than the median for all MSRDS (median 0.43 mg/L, range: 0.07-5.5).

Eighty nine percent (89%) of cases had one or more drugs in addition to methadone 'on board' at the time of death. Benzodiazepines were most commonly detected (55% in MMT and 48% not in MMT), followed by morphine (39% in MMT and 35% not in MMT), and alcohol (24% in MMT and 33% not in MMT).

Comparison of cause of death according to forensic pathologist/coroner with clinical opinion of the investigators.

The forensic pathologist/coroner's conclusion regarding cause of death was compared with the clinical opinion of the investigators (SS and DZ) for each of the 134 cases of MSRDS. The forensic pathologist/coroner implicated methadone by name as a cause of death in 75% of cases. In a further 10% of cases, methadone was implicated by the use of terms such as "narcotism". In 34% of cases the pathologist/coroner did not implicate other CNS depressant drugs detected at autopsy in the cause of death.

In the clinical opinion of the investigators, methadone was a contributory cause of death in 84% of cases. In six per cent (6%) of cases the investigators did not believe that methadone contributed to the death, and a further 10% of cases were classified 'unable to be determined'. (In relation to this latter category, the investigators did not believe methadone was implicated in the cause of death, but they also could not be certain that it had not contributed to the cause of death). Clinical opinion implicated other CNS depressant drugs detected at autopsy in the cause of death in all cases of MSRDS.

Discussion

One hundred and thirty-four methadone syrup related deaths (MSRDS) occurred between July 1990 and December 1995 in NSW. These represented 55% of all methadone related deaths. However, it should be borne in mind that the vast majority of all opioid drug fatalities in NSW are heroin related (Zador, Sunjic and Darke, 1996).

This study found that the majority of methadone related deaths involved a combination of central nervous system (CNS) depressant drugs, most commonly benzodiazepines, morphine and alcohol. Half of all MSRDS were positive for two or more drugs in addition to methadone at autopsy.

The major disagreement between clinical opinion and the findings of the pathologist/coroner was in the role of other CNS drugs. Clinical opinion implicated other CNS depressant drugs in all MRD in which these drugs were detected at autopsy. By contrast, forensic pathologists and coroners only implicated such drugs as a cause of death

in a third of such cases. This latter practice may result in an over-reporting of methadone-related deaths by forensic authorities.

Determining the proportional contribution of methadone towards cause of death is difficult for several reasons. Firstly, it is impossible to determine an individual's opioid drug tolerance post-mortem. Secondly there is often inadequate information about the quantity of methadone and other drugs consumed. Thirdly, the presence of other drugs makes it difficult to determine the causal contribution of methadone to death.

Finally, Barrett et al (1996) have noted that "there is disagreement on what constitutes a toxic and fatal blood methadone level" (p.446). Thus, it is arguable that quantitation of blood methadone concentrations per se would appear to be of little diagnostic utility in the determination of the proportional contribution of methadone to the cause of death.

The implication of the finding that the majority of deaths in this study involved polydrug use, is that many of these deaths were potentially preventable. This suggests a need to better educate recipients of MMT of the risks of using other CNS depressant drugs in combination with methadone.

Almost half (45%) of cases of MSRDR occurred in drug users not in MMT at time of death. These cases were predominantly single, unemployed, males known to be drug users, that is, similar to cases of MSRDR in MMT. This may suggest that there is a greater demand for methadone treatment than is currently being met, therefore driving diversion of takeaway doses of methadone into the black market. An expansion of the current NSW methadone program and the development of strategies to attract high risk heroin users into treatment (for example, more publicly funded programs) may substantially contribute to the reduction of methadone syrup related deaths in NSW.

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Controlling the Public Health and Safety Problems of Opiate Use with Methadone: Is the Risk of Diversion Worth the Potential Benefits?

by

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It is a fact that opiate dependent patients typically have a range of medical, psychological, economic, legal and social problems. For example, studies by Rounsaville et al. (1982), Khantzian and Treece (1985) and Woody et al. (1983) have documented the high proportion of psychiatric diagnoses seen in methadone maintained patients. Ball (Ball & Ross, 1991) and Harwood (Harwood et al., 1988) have shown remarkable and alarming rates of individual and property crime among opioid dependent patients. Metzger and Platt (Platt & Metzger, 1985; Metzger & Platt, 1988) have shown the extreme problems of employment and deficits in job seeking skills among a significant proportion of these patients. Studies by Stanton and his colleagues have documented the serious family and relationship problems found in opiate dependent patients maintained on methadone (Stanton & Todd, 1982; Stanton, 1979). Finally, the problems of AIDS, Hepatitis, Tuberculosis and other infectious diseases are widely documented and growing rapidly among opioid dependent patients.

It is important to note that these problems, rather than the opiate use itself, are the major sources of concern to society. These "associated problems" are not only the source of substantial direct expense to the country but are in turn associated indirectly with deterioration in the quality of life for extended parts of the country. Thus, while methadone maintenance may be seen as a service to or even a privilege for the affected individual to the extent that it reduces his/her withdrawal symptoms and craving for opiates; to the extent that this form of treatment can be effective in reducing the social harm caused by these additional problems, methadone maintenance treatment may be seen as a public health benefit to society, similar to education and vaccination programs. However, it must be emphasized that the potential public health benefits derive from reductions in the associated problems of crime, loss of productivity, and disproportionate use of medical and social services for those in methadone treatment - and not merely from reductions in the use of opiates per se.

While it is a fact that these associated problems occur disproportionately among opiate abusing patients, there is debate about the origins of those problems and the appropriate role of methadone maintenance treatment in addressing them. If these additional problems were due entirely or even predominantly to the use of opiates and if

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the methadone medication by itself were effective in eliminating opiate use, then the provision of methadone alone would likely be effective both in reducing the target problem of opiate use and in bringing about the larger social goals of rehabilitation. It is well documented that methadone in adequate doses by itself can produce marked reductions in illicit opiate use (Yancovitz et al., 1991; McLellan et al., 1988). Further, it seems clear that these reductions in illicit opiate use as well as the accompanying stabilization of craving and affect in these individuals is a necessary precondition for achieving any additional rehabilitation. However, there is accumulating evidence that even large doses of methadone in the absence of additional counselling and medical and social services produce less than optimal reductions in opiate use. Methadone alone appears to have only a minimal effects on other drug and/or alcohol problems of these patients or their health, economic, crime and medical problems that are so important to society (McLellan et al., 1988; Ball & Ross, 1991). Thus, reduction of opiate use is a necessary but not sufficient condition for realizing the rehabilitation goals that are so important to society. Further, methadone by itself, even in adequate doses, produces sub optimal reductions in opiate use.

Over the past 10 years, numerous investigations have evaluated the benefits obtained by adding professional interventions to basic methadone maintenance. For example, in an initial investigation of the "active ingredients" of treatments, McLellan et al. evaluated the contribution of drug counseling services to the overall outcome of methadone maintenance (McLellan et al, 1993). Results showed that the drug counselor assignment was a particularly significant aspect of methadone maintenance treatment that could markedly enhance or detract from the other aspects of the program (e.g. the methadone dose, rules and regulations, etc.). Woody et al. (Woody et al., 1987; 1984) have shown the benefits of adding professional psychotherapy to methadone maintenance, while Metzger and Platt have shown similar benefits from adding employment and skills training (Platt and Metzger, 1985; Metzger and Platt, 1988). In the interests of space, this work is not reviewed here but full documentation is available in Woody et al (1983; 1984; 1987); General Accounting Office (1990); McLellan et al (1993; 1988) and Ball & Ross (1991).

A more recent study of different levels of services within a methadone maintenance treatment program goes directly to the question of the minimal conditions necessary for social rehabilitation and the effects of adding counseling and other services to methadone maintenance (McLellan et al., 1993). In that study, three groups of voluntary patients were randomly assigned at the beginning of their methadone maintenance treatment to receive different types and amounts of treatment services. All patients received initial physical examinations, laboratory testing and a short program of AIDS education. Thereafter, Level one patients received methadone maintenance (blocking doses of 60 mg or more) without additional counseling except on an emergency basis. Level two patients received the same methadone stabilization plus regular counseling by a trained rehabilitation specialist, but no additional services. Level three patients received the same services as level 2 patients, but in addition were also provided family therapy, employment, counseling and regular medical and psychiatric care on an as needed basis.

There were significant differences in the amounts of improvement shown among these

three levels. Those patients in level one showed some improvements in their opiate use but not their cocaine use, as well as minor improvements in employment, but no other changes. In fact, their family and psychiatric problems actually worsened, though not significantly. The simple addition of a counselor to this level of services (i.e. Level two) was associated with significantly enhanced improvement in most areas. The additional services rendered by the family therapists, physicians and social workers for level three patients produced still more changes. In summary, this work indicates that counseling and professional interventions can be added to standard methadone treatment and these interventions can produce significant improvements in drug use, employment and legal status in these multiply problematic individuals.

Risk of Diversion

While there are well documented benefits to the patient and to the public from well managed methadone maintenance treatment, there has also been much written in the public media and in research reports concerning the dangers of methadone "diversion" - the non-prescribed use of methadone by individuals who are either not medically eligible for methadone, or use methadone for non-medical purposes (i.e. to get "high"). There is realistic concern regarding the diversion of methadone since there is a dependence liability, overdose potential and it is a schedule II controlled substance. There are particular concerns regarding the diversion of methadone into the hands of children. For this reason the early regulations on methadone maintenance treatment (FDA, 1974) stressed the following:

- requirement that methadone be dispensed only by licensed and inspected programs;
- limiting the duration of detoxification doses that could be dispensed by hospitals;
- requiring and assuring that methadone patients enroll in only one program;
- specifying strict guidelines for the dispensing of "take home" doses; and
- denying take home doses to persons receiving over 100 mg/day.

These and other strictures served to make methadone the most regulated and constricted medication in the United States. Despite this level of control, there have continued to be worries about the availability of methadone and suggestions that it was ultimately becoming a "primary addiction" - that is, individuals were initiating their opiate addiction on "street methadone". Support for these worries came in the form of an early study by Chambers and Inciardi (1972) who interviewed 95 active heroin addicts in New York and found that 87% had been offered an opportunity to purchase illicit methadone in the past six months and that 13% had sold methadone. Another source of concern about diverted methadone came from reports by the Bureau of Narcotic and Dangerous Drugs (General Accounting Office, 1990) who reported that "methadone related deaths" had increased from 6% to 25% in New York from 1970 to 1972, while "heroin related deaths" had decreased over that time period. They attributed the deaths to the fact that methadone maintenance treatment programs increased in use over that time period.

They minimized the contribution of other sources of methadone, such as, theft at the manufacturing site, robberies from methadone clinics and illicit operations by staff at treatment facilities (including methadone treatment facilities). Based on street interviews they suggested that the major source of the diversion and attendant "methadone related deaths" was diversion by patients in methadone treatment programs.

An Examination of the Basic Data Associated With the Methadone Diversion Claims

Methadone has always been a controversial medication and it has had both unrealistically optimistic supporters as well as unrealistically pessimistic detractors. Consequently, it is important to examine the fundamental information that has informed opinions about methadone diversion over the years. This will only be summarized here but the interested reader should consult the fine chapter on this topic written by Prendergast in the Institute of Medicine Report on Methadone (Prendergast, 1995).

Although the television and print media have reported many sensational stories about methadone diversion over the past decade, there are actually three major "official" sources of data on methadone diversion that form the basis of our knowledge about this topic: Drug Use Forecasting (DUF) network, the National AIDS Demonstration Research (NADR) program and the Drug Abuse Warning Network (DAWN).

The Drug Use Forecasting system reports the drug use self reports of arrestees in 23 major cities across the country. The DUF statistics have regularly shown that fewer than 5% of arrestees had reported ever using "street" (i.e. diverted) methadone and less than 2% had used that methadone in the prior month.

Data from the NADAR study has provided information about the drug use patterns of injection drug users recruited into the AIDS risk reduction programs from around the country. This study asked 43,400 enrollees to report their use of "street" methadone over their drug using careers. Overall 27% reported ever using street methadone and 4% had injected it. However, 12% reported use of diverted methadone within the prior six months but only 2% reported using methadone from diverted sources twice a week or more.

The DAWN network reports drug and alcohol "related" deaths from medical examiners and hospital emergency rooms in major cities across the country. Specifically, any death where there is a measurable level of methadone in the deceased's blood, is officially counted as a "methadone related" death. Accepting for a moment this definition of a relationship, it is worth noting that in every city where DAWN data are collected, alcohol and heroin are always the drugs that are most likely to be mentioned in connection with deaths. In fact, methadone is typically ranked 19th or 20th of the twenty most mentioned drugs - with substances like LSD and marijuana being more likely to be "mentioned".

Perhaps the most cited studies of methadone related deaths from the DAWN network have been conducted by Gottschalk and his colleagues (Gottschalk et al., 1979; Gottschalk and Cravey, 1980). In these two studies, over 3000 methadone mentions

were studied in nine large cities. The findings suggested first that there were marked differences across the cities in the proportion of methadone related deaths, ranging from 47% in New York, to less than 11% in Los Angeles and 0% in most cities. This variability was studied by Gottschalk who evaluated the determinations made by the medical examiners across these cities. They concluded that the differences in "mentions" were not due to actual differences in use of methadone, but rather to "artificial" and "arbitrary" differences in the level of sophistication of the methods used by the medical examiners and to "personal and/or departmental emphases".

As these studies point out, there are substantial problems interpreting these "methadone related" death statistics. While "methadone related" may mean that there is no other cause of death - as in the case of a drug overdose - a death would also be counted as "methadone related" in situations where there has been a death by automobile accident or even murder, if there is a trace level of methadone present in the blood sample. Even when there is an apparent causal role for methadone in a reported death, it is still not possible to account for such important factors as tolerance or the effects of other drugs or alcohol in the cause of death. For example, even the presence of a relatively high level of methadone present in a decedent's blood level may have been quite appropriate for the individual: s/he may have been tolerant to a high dose and functional on a day to day basis. Finally, even when it can be established that methadone was "involved" in a death it is not always possible to determine whether the methadone came from a program or from illicit, diverted sources.

A more recent and more publicly visible example of the problems associated with defining and reporting "methadone related" deaths was seen in the case of Harris County Texas. Following a series of drug related deaths in that county in 1991, there was widespread publication of medical examiner reports by both the Houston Chronicle and the television show "60 Minutes". Both reported that individuals had died of "methadone related" causes between 1987 and 1990 at twice the rate of "heroin related" deaths. Further, these reports indicated that 80% of the decedents had not been enrolled in a methadone maintenance program, suggesting that the deaths were related to diverted methadone. These reports raised such concern that the 27 cases were investigated by three independent pathologists. Their results were dramatically different from the public reports. These investigators found that other drugs and/or alcohol were present in 85% of the deaths. Deaths could be attributed to methadone alone in only 3 cases and were rated as "contributing causes" in only 9 more cases. These reviewers indicated that while the number of deaths in which methadone were mentioned had increased in 1990 and 1991, there was no increase in the number of deaths that were definitely or even possibly attributable to methadone.

Who sells methadone to whom - and why?

Although the data cited above suggest that the amount and frequency of diverted methadone is substantially less than the sometimes sensational report suggest, there are still clear indications that some level of methadone is diverted and that more is diverted in areas of high concentrations of methadone programs (and opiate addicts). Thus it is worthwhile to ask about where diverted methadone comes from and about which individuals buy diverted methadone.

One of the best sources of information about the selling of prescribed methadone comes from studies by Spunt and his colleagues (Spunt et al., 1986). He interviewed 247 individuals drawn from methadone maintenance programs, current users not in treatment, and patients who recently withdrew from methadone. His interview data indicated that patients on methadone programs were the main source of diverted methadone, and none of his interviewees obtained methadone from any other source. Thirty-three percent of the patients in the methadone maintenance programs admitted to selling at least one of their take-home doses and 10% admitted to doing it regularly - three times per month or more. Why did they sell their methadone? Answers were not surprising. Most patients said they needed the money (sometimes for program fees). Many patients admitted that they didn't want to take their dose so they could use heroin. Finally, a small number of patients suggested they sold their dose to "help a friend" who was in withdrawal.

Spunt and his colleagues (1986) also collected data on the characteristics of buyers of diverted methadone and why they chose to use methadone that way. By far, the majority of diverted methadone buyers were heroin addicts who were either unwilling (because of perceived stigma or fear of identification by employers) or unable (due to long waiting lists or lack of money) to enter formal methadone treatment. The main uses of the diverted methadone were:

- to substitute for heroin when it was difficult or expensive to buy;
- to withdraw from heroin without formal treatment;
- to supplement methadone that had been prescribed by a program;
- to experience the euphoric effects of methadone (<1%).

It is important to note that none of the buyers of diverted methadone were first time users of an opiate - all had been regular users of heroin or other opiates. This is quite relevant to the dangers associated with diverted methadone and the issue of whether diverted methadone were acting to draw non-users into drug addiction. Though this study is the only one of its kind and should be replicated, the results are quite clear that there were essentially no users with a "primary problem" of diverted methadone.

Conclusions from Available Research:

There are four conclusions that derive from our initial premise regarding the rehabilitative goals of methadone maintenance treatment and the data presented regarding the benefits and dangers associated with methadone treatment delivery.

First, the available national data indicate that patients admitted to methadone treatments typically show a wide range of serious health and social problems in addition to their major problem of opioid dependence.

Second, data from three decades of controlled clinical trials and field research indicate

that these opioid dependent patients show improvement in, if not elimination of, their opioid addiction with the provision of adequate doses of methadone. This is important and is, in turn, related to reductions in opioid related crime and in the direct effects of needle exchange (e.g., AIDS, and other infectious disease transmission).

Third, improvements in the important social and self-support areas are at least in part related to the types and amounts of counseling and other social services provided during treatment. That is, there is little evidence that, at least at the initiation of methadone treatment, the provision of methadone by itself can lead to reductions in other important problem areas of non-opioid drug use, alcohol dependence, unemployment, psychiatric problems, and disproportionate use of health care services.

Fourth, data from the past fifteen years has shown that methadone is diverted and sold in an illicit manner in most large cities in this country. At the same time, the level of methadone diversion is low in all cities and it is typically diverted to persons with active heroin addiction, typically in the self-administered treatment of withdrawal. Thus there is little indication that there is a significant public health risk associated with the diversion that is associated with programmatic methadone maintenance treatment.

Comments Regarding Regulations:

Based on these conclusions our recommendations regarding optimization of rehabilitation (i.e. public health value) in methadone and other opioid substitution therapies require recognition of the fact that methadone maintenance can be a public health service only if it is financially and professionally supported so that it can offer necessary rehabilitative services, and minimize problems associated with diverted methadone. It is clear from both scientific evaluation of existing treatment programs (Hubbard et al., 1986) and from inspection of the national media stories about methadone (Houston, Cleveland, etc.) that the present system of care offered by methadone maintenance programs has deteriorated badly over the past ten to fifteen years even while the number, chronicity and complexity of the problems presented by the patients have increased. At this point, there are few programs that are able to provide the range and intensity of counseling and social services that are necessary to optimize the effectiveness of the methadone maintenance treatment modality and perhaps more importantly, to even adequately return the social investment.

Given adequate financial support, methadone maintenance programs should be expected to perform the following services toward the goal of achieving its potential public health benefits:

- 1) Perform a comprehensive evaluation of the full range of medical, employment, alcohol, criminal and psychological problems of all patients admitted to methadone maintenance. As indicated above, it is in the public health interest for methadone maintenance programs to address the "addiction related" problems of unemployment, crime and infectious diseases. If these problems are to be addressed effectively they will have to be evaluated, and that evaluation will have to be a meaningful part of the initial treatment plan for all patients.

- 2) Offer on-site or proximal medical screening for diseases such as AIDS, Tuberculosis, Hepatitis and sexually transmitted diseases. These diseases are disproportionately represented in the opioid abusing population and represent a risk to all of society. There are typically few medical screening services available to these patients outside the methadone maintenance programs, and it is in the interests of the patient, the program and society to see to it that these diseases are recognized and treated.
- 3) Offer on-site counseling by certified and supervised addiction counselors. While it is not clear at this time how much counseling is needed for patients entering treatment or for how long, it is clear that the majority of patients entering treatment will require several sessions of counseling each week during the first months of stabilization. This level of counseling intensity should be available as a standard part of methadone maintenance treatment. It is also unclear whether a particular set of qualifications are required to optimize counseling efficacy, and how or whether individuals can be trained to become effective counselors. At the same time, it is clear that effective counseling can be evaluated and encouraged through ongoing supervision. Experienced professional supervision of counseling staff should therefore be a mandatory and regular part of methadone maintenance treatment.
- 4) Offer on-site services (preferably) or referrals (through contracted inter-agency agreements) to professional medical, social work, and mental health services. Again, it is important to stress that these services should not be considered "frills" in this time of increased accountability. Rather they are necessary ingredients for methadone maintenance programs to achieve the public health benefits that justify their existence. It is recognized that not all patients will need all of these professional services and the recognition of those who do need the services will be one of the duties of the admission assessment and the ongoing counseling. It is also recognized that it may not be possible or even cost effective for every program to have on-site professionals representing all the services that will potentially be needed by these patients. However, two points are relevant here. First, it has been historically difficult to connect opioid dependent patients with the services that they so clearly need, even when these services are available. There are problems with motivation, disorganization, distrust and confusion that prevent patients from accessing these services in the best of conditions. Second, there are well documented and very pervasive conditions where professional services have been denied methadone maintained patients merely because of the stigma associated with their condition. Therefore, it is recommended that those services which are most clearly needed by admitted patients (e.g. medical and social work) should be provided on-site by informed and accredited professionals. When referrals are required, it is typically not adequate to merely provide information or even a phone call to the referred agency. Effective provision of these services (again in the interests of public health) will usually require contractual arrangements between agencies, close working arrangements between responsible individuals at the program and the agency, and active follow-up by the referral program to insure that the services

are delivered.

In Summary

It bears repeating that these four recommendations can only be made given the expectation that methadone maintenance will be restored on a level of funding and professionalism that is commensurate with the severity of the disorder(s) that it is charged with addressing and with the (appropriate) public health expectations that have been placed upon it. This may be the most important general point that can be made and it has profound implications for regulations. It must be clear that without infusion of both financial and professional support, all changes in the regulations will be ineffective in increasing the potential benefit of this treatment modality.

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HEROIN OVERDOSE WORKSHOP - SUMMARY AND RECOMMENDATIONS

by

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Preamble

The aim of the workshop was to generate a list of recommendations to reduce heroin-related overdose. Invited speakers were asked to present recommendations based on their presentations for consideration by the group. Given the high quality of presentations and the resulting discussion, the participants decided that it was more useful, to generate a list of areas within which recommendations could be framed. This list, generated by workshop participants, formed the basis of a feedback presentation made by Margaret Hamilton to the larger group consisting of participants in both workshops (this and that which focused on methadone-related overdose). The following summary of the outcomes of presentations and discussions at the workshop is based on Margaret's presentation. It was circulated to all workshop participants in order to check for accuracy and to ensure the recommendations were supported.

General Comments

Urgent Problem

Clearly heroin-related overdose deaths are a significant problem requiring urgent attention. The experience of those at the local level is that these deaths are growing. This impression was consistent with the research evidence presented at the symposium. It was noted that the problem has resulted in a significant burden to the community which could be measured in terms of both human and financial costs.

Collaboration

It was noted that successful solutions to the problem can not be based on a "one size fits all" approach but need to maximise the available knowledge, skills and data to inform the collaborations right down to the local level. The collaboration needs to be between the various stake holders, primarily emergency services (ambulance and police) and drug users. The protocol developed for police attendance at drug overdoses

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in South Australia was cited as an example of best practice in this area.

Some workshop participants strongly expressed the view that more work was needed to be done with regard to supply side measures to reduce the rate of heroin overdoses. This included strategies at a national level to catch the 'Mr Bigs' of heroin supply, as well as enhancing police practice at a local level, such as, the overdose scene. There was a view expressed that there needed to be a review of legislative measures at both a federal and state level.

Resourcing

The acquisition of new knowledge through research and the development of relevant information materials, protocols, and skill sharing requires financial support, and a commitment to reduce heroin-related mortality.

Aboriginal Australians

There was an acknowledgment that issues related to Aboriginal Australians were largely absent from the discussions to date and that this needed to be redressed in future initiatives in this area.

Areas for Action

Information

The terminology used in this area needs to be refined, taking into considerations the different audiences. For example, in the media terms such as 'killer heroin' and 'heroin overdose' have the capacity to mislead the public (including heroin users) as they fail to acknowledge the data which point to the significant role of concomitant use of other CNS depressants, namely benzodiazepines and alcohol in the majority of deaths. For technical users of terminology such as those in toxicology and pathology settings the term 'multiple drug toxicity' may be a more accurate description of overdose deaths where a range of drugs including heroin are present post mortem. For others, in particular heroin users, other terms may be found which have more meaning for these groups.

The media portrayal of the heroin related overdose issue has been seen as a very powerful, yet not often helpful, contributor to the heroin debate in the community. Two practical suggestions included: (1) the development of a code of practice for the media regarding heroin-related overdose based on that in place for suicide; (2) running of workshops and briefings for the media (akin to those held early in the HIV epidemic) which may contribute to a more balanced and useful coverage of these issues.

Data collection needs to be systematic, comparable and then subject to analysis to extract meaning. This was highlighted in presentations during the symposium regarding the determinations of whether an overdose death was heroin-related. The complexity of the task is highlighted by the number of systems involved including forensic pathology, the Offices of the Coroner, the Departments of Public Prosecution, the Registry of

Births, Deaths and Marriages, the Australian Bureau of Statistics, and the Illicit Drug Services Section of the Department of Family Services and Health.

Recommendations:

That those who communicate information about heroin-related overdose use terms which accurately describe the phenomenon and take into consideration their target audience: the media and general public; heroin users & technical users, such as, coronial and forensic personnel.

That a code of practice for the media regarding heroin-related overdose be developed and based on that in place for suicide.

That workshops and briefings are held with staff media outlets to explain the issues regarding heroin-related overdose and facilitate more balanced reporting.

That procedures and protocols in place across all jurisdictions for the routine collection and analysis of heroin-related overdose statistics be reviewed and recommendations be formulated to make them more systematic and comparable and to allow prompt and useful data analysis.

Education and training

Issues which need to be addressed include: who is to be the recipient of training, what is to be covered, how, when and by whom? For example the 'who' might include heroin users, people not yet using, the general community, parents, police and ambulance officers, alcohol and drug workers, general practitioners, medical pathologists, the media, policy makers, etc. A strong recommendation was that the recipients of education and training need to be involved in the development and implementation of such initiatives and that training should be based on the principles of adult learning. There was a recognition that for some issues there was an opportunity to develop and implement strategies almost immediately. For other areas, such as practical guidelines for users on when to call an ambulance, research was needed to identify what was practical and acceptable to the target group.

Recommendation:

That training regarding heroin-related overdose be based on the principles of adult learning with the involvement of the target audience in its development and implementation.

The content of messages to be conveyed should be based upon scientific evidence regarding the risk factors for overdose.

Protocols and Guidelines

Protocols and Guidelines need to be formulated with the participation and endorsement of all stake holders. The 'products' of the development need to be well disseminated and the uptake and usefulness of protocols need to be monitored to inform their revision.

Sectors where there seemed to be an opportunity to develop protocols which could impact on heroin-related overdose included: ambulance services (including the use of Naloxone and protocols for its administration and dose titration, questions about when transport to hospital is indicated etc.), police (including guidelines for policing at fatal and non-fatal overdoses etc.) and users (e.g. first-aid, when to ring for an ambulance and what to say). There was a recognition that many of the protocols and guidelines need to be across and between sectors (e.g. users, ambulance services, police, accident and emergency departments, departments of public prosecution).

Recommendation:

That across sector protocols and guidelines for the prevention of heroin-related overdose be developed for police and ambulance staff, drug users and others involved.

Treatment

The evidence shows that treatment works and it is protective. More work is needed on how to attract people into treatment. There was general agreement on expanding the treatment options available, particularly in the pharmacotherapies including LAAM, Buprenorphine, Naltrexone, slow release methadone and heroin, although support was not unanimous for the latter. It was noted that more could be done to enhance the effectiveness of currently available treatment options, such as, expanding methadone treatment places to make it available for all eligible who want it, and strategies to improve clinical management skills of methadone service providers. More research is needed to add to existing data on the impact of disciplinary versus planned discharge from methadone as well as the provision of methadone maintenance while clients are still using other opioids.

Recommendation:

That places be made available in methadone or other opioid replacement treatment for all suitable dependent heroin users who request it.

That the provision of pre-release methadone in prison be considered in all jurisdictions given increasing risk of overdose following release from prison after tolerance to the effects of opioids has decreased.

Research

It was noted that there was a need for ongoing research and that there were a number of unanswered questions regarding heroin overdose, some of which were very specific and some more general.

In general there was a need for more epidemiological research and social and

psychological audits of both fatal and non-fatal overdoses. The possibility of clusters of heroin related deaths could be investigated in terms of locations, temporal effects and an analysis of cases looking at single and multiple episode overdoses. There was a suggestion that the technology applied to infectious disease epidemiology could be usefully applied to heroin-related overdose.

Recommendation:

That research into the following be resourced and undertaken:

- a trial of provision of Naloxone to users for peer administration
- further research on poly drug use and overdose prevention which acknowledges that many users will probably continue to use multiple drugs
- investigation of the possible role of sleep apnoea and other sleep disorders in overdose
- the role of the metabolite morphine-6 glucuronide in heroin related deaths where both blood morphine levels and levels of other CNS depressants are low
- investigations regarding sudden overdose deaths and how they differ from deaths which occur over a longer period, for example the possible role of the 'bolus effect'
- ethnographic investigations of the experience, context and meaning of overdose for heroin users to inform interventions in this area
- an evaluation of safer injecting rooms/places in locations with a significant problem of street injecting
- investigation of heroin overdose among special populations where the need for consultation and engagement with the target groups is especially relevant
- assisting in enhancing and analysing data bases held by existing stake holders such as ambulance and police.

Workshop – Methadone Related Deaths - Sydney 15.8.97

by

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Summary and Consensus Recommendations

Introduction

This workshop was convened as a result of professional and community concern about methadone related deaths. Concerns about methadone related deaths were first raised in Victoria in 1993. Since then, there have been a number of research studies into methadone related deaths (in Victoria, NSW and South Australia), and increasing concern internationally about the problem of methadone related deaths. Research data presented at the Opioid related deaths symposium (Sydney, August 14, 1997) had clearly identified 3 major areas of concern. These were:

1. Deaths during initiation of methadone treatment. The first week of treatment is a time of heightened risk of death, and imperative to find ways to minimize this risk.
2. Deaths associated with methadone diverted from treatment (that is, deaths of people not in treatment who obtained doses of methadone diverted from participants in the program).

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1. Prince of Wales Hospital, South Western Sydney Area Health Service
 2. Central Sydney Area Health Service
 3. North Western Health, Western Hospital, Footscray, Victoria

3. There are no adequate criteria for defining a methadone-related death, and this lack probably leads to over-attribution of mortality to methadone.

Deaths during initiation of treatment

Three related approaches to optimizing the safety of initiation of treatment are (1) adequate assessment to ensure that only people who are opioid dependent receive methadone, (2) safe induction schedules to minimize the risk of toxicity early in treatment, and (3) warning patients about the risks of other CNS depressant drug use in combination with methadone.

Assessment

Coronial findings in NSW and Victoria have included adverse comment concerning inadequate assessment procedures employed by some doctors. A key task for the workshop was to establish consensus views on what constitutes adequate assessment.

It was agreed that methadone maintenance treatment (MMT) is appropriate treatment for people over the age of 18, requesting treatment voluntarily, with established opioid dependence for at least 12 months, and able to give informed consent to treatment.

An adequate assessment should clearly document the following issues:

1. The diagnosis of opioid dependence, based on a documented history of features of opioid dependence.
2. Such a history should be backed up by corroborating evidence. The corroborating evidence could take a range of forms. The presence or absence of the following should be documented in the assessment record:
 - evidence of vein damage (track marks) consistent with repeated injection,
 - physical signs of opioid withdrawal
 - a verifiable history of previous detoxification or residential treatment for opioid dependence

In the absence of other corroborating evidence, a naloxone challenge may be indicated.

3. People with a clear history of opioid dependence do not have to be currently neuroadapted to be eligible for methadone. Assessment should document an estimate of the current level of neuroadaptation.
4. Informed consent is particularly an issue where patients have major mental illness,

in which cases the involvement of a psychiatrist experienced in management of drug dependency should be sought.

5. Documentation at assessment should include a review of patients health, social and psychological functioning.
6. Patients who are polydrug dependent, patients who are behaviourally disturbed and chaotic, and patients with intercurrent illness (particularly decompensated liver disease) are at high risk during initiation of treatment on an ambulatory basis. In these situations, the potential benefits of methadone treatment need to be weighed against the risks during initiation of treatment. Safety must be the primary consideration, and alternate treatment, or initiation of methadone treatment in a controlled environment may be required. In high risk situations, a second opinion should be sought from a D&A consultant before initiating methadone treatment.
7. Assessment should include the provision of information to prospective patients about the nature of methadone treatment, and the risks during induction into treatment. An information sheet, to be discussed with the patient as well as given to them, is recommended.

There was agreement in the workshop that people with less than 12 months opioid dependence should not generally be considered for methadone treatment, but referred to some other form of treatment. However, it was also agreed that for some people with shorter histories of heroin use, and for some people under the age of 18, methadone could be appropriate. In those situations, a second opinion from an experienced prescriber would be required before initiating treatment.

Induction into treatment

The first 2 weeks of treatment is a time of increased risk of death.

1. The long half-life of methadone means that on a stable daily dose, blood levels continue to rise for at least the first 7 days of treatment. This is the basis for recommendations in the Australian National Methadone Guidelines which limit dose increases during the first 7 days of treatment. There was considerable discussion of these guidelines, and the workshop endorsed the following slight revision of the National Guidelines:

“In general, the initial dose should be in the range 20-30mg and should not exceed 40mg. Caution should be exercised if a starting dose more than 30mg is to be used, because of the risk of overdose. Where doses need to be increased during the first 7 days, the increment should be no more than 5mg on any one day. In any event, the maximum dose achieved at the end of the first 7 day period should not exceed 40mg without clear documentation of the rationale for a higher dose. It is essential that a patient be reassessed by a methadone physician before any increase in dose.”

2. It was agreed that limiting the dose in the first week of treatment is necessary, but is not sufficient, to minimize toxicity during induction.

There is inter-individual variation in methadone metabolism. In a small number of cases of methadone deaths early in treatment, deaths in which no other drugs were detected, post-mortem blood levels of methadone were much higher than expected from the prescribed doses.

- This may in some cases be due to very slow methadone metabolism, something which cannot be screened for at this time, and which mean that even quite low starting doses may accumulate to toxicity.
- In other cases, patients may have taken methadone in addition to what was prescribed, something which is made more likely if they are given very small starting doses of methadone.

In most cases of fatal overdose, drugs in addition to methadone (particularly, benzodiazepines and alcohol) were present. In many of these cases, methadone levels were quite low, and toxicity is the result of synergy between other drugs, and a dose of methadone excessive for that patient's level of tolerance.

Therefore, while safety concerns suggest the desirability of lower starting doses, this not only fails to ensure safety, but doses which are too low may carry their own risks that patients will be more likely to "top up".

3. To optimise the safety of induction onto methadone, it was agreed that structured induction protocols needed to be developed. These should specify documentation required at assessment, consent, provision of information; starting dose, daily monitoring during the first week, and scope for review during the first week if dose adjustments are sought.

Specific points which should be included in such protocols included:

1. Most methadone overdose deaths during induction into treatment involve the concomitant administration of benzodiazepines or alcohol. At assessment, and during induction, patients need to be informed of the risks of these drugs in combination with methadone.
2. Patients with concomitant benzodiazepine abuse or dependence, or alcohol abuse, may require stabilization or detoxification prior to being commenced on methadone.
3. All patients should be carefully informed of the proposed dosing schedule, and what can realistically be expected from methadone treatment. The best way to

ensure that patients are “held” during induction into treatment is through clear information, realistic expectations, and the establishment of a therapeutic relationship.

4. In particular, to minimize the risk that patients new to treatment “top up” their methadone dose, it is important to inform patients about the effects of methadone. The onset of oral methadone is gradual, without the rapid peak effects (with euphoria) which result from intravenous injection. New patients may not recognise the effects of doses which approach or even exceed their level of tolerance. In this setting, they may take other drugs to “boost” the effect, which can be highly risky. Therefore, as part of gaining informed consent for treatment, patients need to be informed about the expected effects of methadone and risks early in treatment.
5. Patients in the first week need supervised dosing, and documented monitoring for signs of intoxication or withdrawal.
6. Nurses and pharmacists involved in induction into treatment should have experience and have received further training in recognising intoxication and withdrawal. Patients should not commence treatment in settings where such experienced staff are not available.

Deaths of people not in treatment

Annually in Australia, there are a significant number of fatalities due to methadone in which the deceased was not on a methadone program.

One important category of deaths is that of children, usually as a result of drinking their parent’s methadone. It was agreed that all methadone take-aways should be supplied in child-proof bottles. It was further agreed that in making the judgement about suitability for take-away, the presence of young children in a patient’s care, coupled with the stability and parenting skills shown by the patient, should be taken into account.

Another category, of indeterminate size nationally, is that of deaths resulting from taking physeptone tablets.

The largest group comprises people, usually with histories of multiple drug use, who overdose on methadone diverted from treatment.

Research on methadone diversion, and on methadone related deaths suggests that the factors associated with diversion are:

- Unmet demand for treatment, leading to a large demand for street methadone
- Availability of take-away doses leading to a supply of methadone.

It was also suggested in the workshop that the high price of treatment (up to \$50 per week in some jurisdictions) coupled with liberal availability of take-home doses provides a reason for people to sell methadone. There is no research evidence to support this hypothesis.

It was generally agreed that take-away doses have an important role in methadone treatment, as it is not desirable to insist on daily pickup for long-term patients who have done well and are reintegrating into the community. There was strong support for the proposition that to minimize methadone diversion, the availability of take-away doses should be restricted to patients who are stable and functioning well. It was also agreed that spelling out blanket criteria for stability was not easy. Rather, the grounds for prescribing take-away doses should be an assessment of risk and stability in each individual case, and must be documented in the patient's file. Such documentation should include self-report, general appearance, attendance for dosing, vein damage, and urine test results. External audit of take-away prescribing should be one aspect of quality assurance for methadone clinics.

Defining a methadone related death

Although there was general agreement that the broad label "methadone related death" was over-inclusive, there was no consensus on how to define methadone related deaths.