W. Hall, M. Lynskey & L. Degenhardt

Trends in methadone-related deaths in the UK and Australia 1985-1995

NDARC Technical Report No. 69

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Wayne Hall, Michael Lynskey and Louisa Degenhardt
National Drug and Alcohol Research Centre,
University of New South Wales

ISBN 0 7334 0478 2

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ACKNOWLEDGEMENTS

We would like to thank the following persons for their assistance in preparing this report:

Ms Olivia Christopherson, the Office of National Statistics in the United Kingdom for her help in interpreting UK statistics on drug overdose deaths.

Dr Michael Farrell for providing copies of unpublished reports on opioid overdose statistics and the provision of methadone treatment in the United Kingdom and for comments on an earlier draft of the report.

Professor Griffith Edwards, and Drs Shane Darke, Adrian Reynolds and Deborah Zador for their comments on an earlier draft of the report.

Eva Congreve for her assistance in locating references for this report.

Patricia Ward, NSW Drug and Alcohol Directorate and Anne Lawrence, Pharmaceutical Services Branch, NSW Department of Health for their assistance in obtaining data on methadone patient numbers in New South Wales.

EXECUTIVE SUMMARY

This report analyses data on trends in opioid overdose deaths in general, and methadone deaths in particular, in the United Kingdom (UK) between 1985 and 1995. It places these trends in the context of the epidemiology of opioid dependence in the UK, the risks and benefits of methadone maintenance treatment for opioid dependence, and the risk factors for opioid overdose death.

The report begins with a description of the pharmacology and toxicology of the opioid agonist methadone. It describes its therapeutic uses in assisting opioid dependent persons to withdraw from heroin and its use as a maintenance treatment for opioid dependence. The benefits of methadone maintenance treatment for opioid dependent persons and the community are briefly summarised. The epidemiology of opioid and methadone overdose deaths is briefly reviewed. A distinction is made between methadone-related deaths that occur among persons who are enrolled in methadone maintenance treatment and deaths that occur among opiate users who have used diverted methadone.

The core of the report is an analysis of trends in heroin and methadone-related deaths in the UK between 1985 and 1995. Analyses are reported on trends in population mortality rates and the proportion of all deaths attributable to opioid overdose in the UK between 1985-1995. A comparison is also made of trends in opioid overdose and methadone overdose deaths in the UK and Australia. The comparison indicated that the two countries showed an overall increase in opioid overdose deaths between 1985 and 1995 with two important differences in pattern: (1) the UK had *lower* rate of opioid overdose deaths than Australia but (2) methadone played a contributory role in a *larger* proportion of opioid overdose deaths in the UK than Australia.

In the final section of the report some provisional conclusions are drawn about trends in the overall rate of methadone-related deaths in the United Kingdom over the period 1985-1995. The most plausible explanation of these trends is that the number of opioid dependent persons in the UK has increased over the period. The high rate of methadone involvement in these deaths probably reflects the greater availability of methadone and lower rate of supervised methadone dosing in the UK than Australia.

There are a number of possible explanations of the higher opioid overdose mortality in Australia, and the apparently lower rate of methadone involvement in these deaths. These possibilities cannot be distinguished on the basis of the available data. These are: that they are an artefact of different methods of classifying causes of death involving opioid drugs in Australia and the UK; that the UK has a much lower rate of opioid dependence, or a different pattern of dependence (e.g. much fewer heroin injectors) than Australia; and that the widespread availability of methadone in the UK has reduced the overall rate of opioid overdose deaths by increasing the number of dependent drug users who are in treatment, at the cost of increasing the proportion of overdose deaths in which methadone plays a role. The report identifies priorities for future research on opioid overdose and methadone-related overdose deaths in the UK, and makes some suggestions as to how the rate of methadone-related overdose deaths in the UK may be reduced.

1. INTRODUCTION

1.1 THERAPEUTIC USES OF METHADONE

The opioid agonist methadone may be used therapeutically with opioid dependent individuals to assist in withdrawing from opioid drugs and as an opioid maintenance agent. Methadone may also used for the control of chronic pain in palliative care for cancer patients or those with chronic pain of non-malignant origin. However, its use for the latter purposes will not be discussed in this report, as the vast majority of those who die from methadone and other opioid overdose are not receiving methadone for pain management. Opioid overdose deaths primarily occur in persons who have become dependent as a result of non-medical use of opioid drugs.

1.1.1 WITHDRAWAL

Methadone is widely used to withdraw people from opioid use. This may involve a rapid withdrawal over 10-14 days as an inpatient (Mattick and Hall, 1996), or a more gradual reduction in dose over 3 to 6 months as an outpatient (Gossop et al, 1998). In many countries the shorter form of withdrawal is the more common type of methadone assisted withdrawal. In the UK, the more protracted withdrawal regime appears to be more common. The National Treatment Outcome Research Study, for example, indicated that 19% of people in treatment for drug or alcohol problems in the United Kingdom were enrolled in a long term methadone reduction program (Gossop et al, 1998).

1.1.2 MAINTENANCE

Methadone maintenance therapy (MMT) was developed by Dole and Nyswander who believed that opioid dependence was a "physiological disease characterised by a permanent metabolic deficiency" that was best managed by administering a "sufficient amount of drug to stabilize the metabolic deficiency" (Dole and Nyswander, 1965).

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

1.1.2.1 Methadone Treatment in the United Kingdom

Since Dole and Nyswander introduced methadone maintenance in the US in the early 1960's, methadone has become widely used in the treatment for opiate addiction in many Western countries. Methadone treatment was introduced to the United Kingdom in 1970 and subsequently became the main treatment of choice for opioid dependence. A recent survey of pharmacies in England and Wales estimated that there were approximately

30,000 people receiving methadone treatment of some type from community pharmacies (Sheridan, Strang, Barber, and Glanz, 1996). They received these services from a variety of agencies including general practice and hospital settings, and in both private and National Health Service (NHS) practices. The National Treatment Outcome Research study (Gossop et al., 1998) indicated that 42.6% of those in treatment for drug dependence were enrolled in methadone maintenance.

Methadone treatment in the UK differs in several important respects from the model of MMT developed by Dole and Nyswander and widely implemented in the USA and Australia (Ward, Mattick & Hall, 1998). First, any medical practitioner in the UK is permitted to prescribe methadone for the purposes of treating opioid dependence (Farrell, Neeleman, Gossop, Griffiths et al., 1996). Second, although there are specialist addiction clinics, most UK patients are given a prescription of methadone that is filled by a pharmacist, often for a week or more at a time (Strang et al, 1996). Patients consequently consume their methadone at home rather than under direct clinical supervision, as is the norm in US and Australian MMT clinics. Third, there is minimal central regulation of MMT in the UK by comparison with the US and Australia. Until 1996 it was compulsory for medical practitioners to notify addicts to an Addicts register maintained by the Home Office but compliance was poor (Strang and Shah, 1985). Fourth, although there are guidelines for methadone prescribing, surveys of prescribing practice reveal widespread and unexplained variations between: different geographic areas in the UK (Strang and Sheridan, 1998), general practitioners and psychiatrists; and NHS and private practitioners (Strang et al, 1996). Fifth, it is consequently not always clear whether methadone is prescribed by general practitioners for maintenance or for extended withdrawal.

1.2 PHARMACOLOGY AND TOXICOLOGY OF METHADONE

Comment: Michael: suggests placing this section before therapeutic uses of methadone, however I've left it as is for your judgement.

Methadone is a synthetic opioid agonist. It has similar effects to morphine with two important differences in pharmacology. Firstly, methadone has a higher degree of oral bioavailability than morphine. When ingested orally 80-90% of methadone is absorbed through the gastro-intestinal tract as against only 40% of orally administered morphine. Once absorbed into the bloodstream methadone binds to blood proteins and, after repeated administration, accumulates in various tissues throughout the body, including the brain. Secondly, methadone has a considerably longer elimination half-life (24-36 hours) than morphine (three hours) (Ward et al, 1996).

These pharmacological characteristics make methadone an ideal maintenance opioid drug (Kreek, 1991). The oral route of administration avoids the risks associated with injecting, its long half-life allows for single daily dosing, and the fact that it accumulates in the body means that steady-state plasma levels are easily achieved after repeated administration. Methadone has no serious long-term side effects associated with chronic administration (Novick et al, 1990) and stabilised methadone maintenance patients do not experience the marked narcotic effects seen with shorter acting opioids such as heroin (Kreek, 1991).

There are nonetheless marked inter-individual variations in the disposition of methadone in the body. Bioavailability has been reported to vary between 41% and 99%, its half-life to vary between 4 and 91 hours, and its rate of clearance from the body has been reported to vary by a factor of almost 100. These variations indicate that there may be considerable differences between opioid dependent individuals in what constitutes an adequate dose of

methadone for either completing heroin withdrawal or maintenance treatment (Ward et al, 1996).

As with all opioid agonists, there is a risk of overdose death from methadone. A fatal dose of methadone in opioid naïve or non-tolerant individuals has been reported to be in the range of 40-60 mg per day. Doses considerably higher than this may be required for the purposes of averting withdrawal symptoms in opioid dependent persons, and doses usually in excess of 60 mg per day are required for maintenance purposes (Ward, Bell, Mattick & Hall, 1996).

There are two major overdose risks arising from the use of methadone for maintenance purposes. For opioid dependent and tolerant individuals, the major risks arise during the process of induction onto methadone maintenance. In persons with impaired liver function normal doses of methadone may accumulate over the first week of treatment to produce toxicity and death (Drummer et al., 1992; Caplehorn, 1998). Persons who exaggerate their extent of opioid use when being assessed for MMT may be given doses of methadone that prove fatal (Caplehorn, 1998). In Australia, the estimated risk of these deaths is 0.2% pa of patients inducted into methadone maintenance treatment (Zador & Sunjic, 1998).

Methadone overdose deaths can also occur when therapeutically prescribed methadone is diverted and used by non-opioid tolerant individuals. Doses of methadone that are therapeutic in opioid dependent persons may be fatal if used by non-tolerant users. Opioid tolerant individuals who are unfamiliar with the effects of a longer acting agonist may overdose when they combine it with heroin, other opioids or CNS depressant drugs like alcohol and benzodiazepines.

Fatal methadone overdoses in persons who use diverted methadone are a potentially more serious public health concern than overdoses occurring in MMT. There are generally many more dependent opioid users who are out of MMT than in it, and an even larger number of non-dependent users of opioids (Hall, 1995). With due care, the number of deaths that occur in MMT can be minimised and those that occur may be accepted as a risk run to obtain the considerable benefits of MMT. The public is reasonably concerned about overdose deaths that occur as a result of methadone diversion, especially when these deaths occur in non-opioid dependent persons, or in opioid dependent persons who are not in treatment.

2. BENEFITS OF METHADONE MAINTENANCE TREATMENT

Ideally, the effectiveness of MMT for opioid dependence would be evaluated by randomised controlled trials in which large representative samples of patients were randomly assigned to receive either MMT or some ethically defensible alternative form of treatment. Few such studies have been conducted on MMT, or indeed on any other treatments for opioid dependence: five randomised-controlled trials have been conducted on the effectiveness of MMT. All of these trials have involved small numbers of patients (e.g. Dole et al., 1969) who have been followed up for rarely longer than one year. Assessments of the effectiveness of MMT have largely depended upon evidence from observational treatment outcome studies in which large groups of persons selecting different types of treatment have been followed over time to evaluate its impact on drug use, crime and other outcomes. Statistical methods have been used to assess the plausibility of alternative explanations of differences in outcome between MMT and other forms of treatment (Ward, Mattick and Hall, 1998).

2.1 ILLICIT DRUG USE

In the randomised-controlled trials conducted, methadone treatment has been shown to result in substantial reductions in illicit opioid use, despite small sample sizes working against finding differences. The positive findings of these trials have been corroborated by the results of controlled observational studies in which statistical forms of control have addressed the major alternative explanations of apparent effectiveness (Cook & Campbell, 1979). These controlled observational studies have generally shown that patients in MMT very substantially decreased their heroin use and criminal activity while they remained in treatment. The typical reduction in the frequency of illicit heroin use has been from two to three times a day to once or twice a week (Ward et al, 1998).

2.2 HIV RISK

MMT also prevents the transmission of HIV among injecting drug users by reducing the frequency of injecting and needle sharing (Ward, Mattick & Hall, 1992). In the Three Cities Study conducted by Ball and his colleagues (Ball & Ross, 1991; Ball, Lange, Myers & Friedman, 1988), MMT had a marked effect on whether or not patients injected, and on the frequency of injecting among those who continued to do so. These results are supported by Australian studies (Darke, Hall & Carless, 1990; Darke, Hall, Heather, Ward & Wodak, 1991). MMT has also protected patients from HIV infection in locations where HIV has spread rapidly among injecting drug users who have not been in treatment (Abdul-Quader et al, 1987; Schoenbaum et al., 1989; Novick et al. 1990). Findings of low seropositivity among methadone maintenance patients have been reported from Sweden (Blix & Grönbladh, 1988). Two large prospective cohort studies in the United States found that exposure to methadone maintenance during follow-up protected against HIV infection (Metzger et al, 1993; Moss et al, 1994).

2.3 OVERDOSE DEATHS

The risk of opioid overdose death is substantially reduced among individuals enrolled in MMT (Caplehorn, Dalton, Cluff & Petrenas, 1994; Caplehorn, Dalton, Haldar, Petrenas & Nisbet, 1996; Gearing & Schweitzer, 1974). Gearing and Schweitzer (1974) found that the mortality among 17,000 patients receiving MMT (7.6 per 1,000 pa) was similar to that in the general population (5.6 per 1,000 pa) and significantly lower than that among persons who left MMT (28.2 per 1,000 pa) and opioid users who were not in any treatment (82.5 per 1,000 pa). An Australian study of 307 heroin users enrolled in a methadone maintenance program in the early 1970's revealed that they were nearly three times more likely to die when they were not in MMT (Caplehorn et al, 1994). This was largely due to the reduced likelihood of those in MMT committing suicide or dying from a heroin overdose (Caplehorn et al., 1996). Zador and Sunjic (1998) have more recently corroborated these findings (see section 5.2.1).

2.4 CRIME

Many individuals seeking treatment for problems associated with illicit drug use have a history of criminal involvement. For example, Hall, Bell and Carrels (1993) reported that 73% of a sample of applicants for methadone maintenance treatment had a previous conviction for a property offence and 76% had been convicted for drug offences. Surveys of illicit drug users, many of whom are not currently in treatment, have also reported a high degree of criminal involvement. For example, Maher, Dixon, Lynskey & Hall (1998) reported that over two thirds of a sample of 202 illicit drug users had engaged in some form of property crime during the week preceding interview. MMT has been consistently shown to reduce both heroin use and crime while heroin-dependent persons receive adequate doses of methadone in programs with a maintenance treatment goal (Ball and Ross, 1991; Hall, 1996a).

3. EPIDEMIOLOGY OF OPIOID OVERDOSE

An opioid drug overdose is generally understood to be an excessive dose of an opioid which results in coma and respiratory failure (Proudfoot, 1988). Toxicological analysis and forensic examination are not always undertaken to assess the contribution of opioid use to deaths in young adults. When they are conducted, toxicological and forensic data may not be considered when the ICD code is determined. Countries also differ in their use of ICD codes, laws and regulations regarding registration of deaths, and in the extent to which information from death certificates is transferred to the death register (Danish National Board of Health, 1997). All these factors mean that opioid overdose deaths are often under-reported in national mortality registers.

Despite these problems with existing data, analyses over time of opioid overdose deaths *within* countries have provided useful information on trends in these deaths and on risk factors for opioid overdose (e.g. Darke & Zador, 1996; Hall & Darke, 1997). These difficulties indicate a need for caution in interpreting differences between countries in rates; they should not prevent researchers from learning what they can about these deaths from fallible data, and making suggestions as to how these data may be improved.

4. RISK FACTORS FOR OPIOID OVERDOSE DEATH

4.1 OPIOID PURITY AND INDIVIDUAL TOLERANCE

Variations in heroin purity are likely to be a contributory factor to overdose but they are unlikely to be the sole factor, as is often assumed in the media (Darke & Zador, 1996). Recent research indicates that the correlation between the purity of street seizures of heroin and the number of overdoses is moderate (Darke, Hall, Weatherburn & Lind, in press). However, studies of fatal opioid overdoses indicate that there is substantial variation in blood morphine levels among persons who die of apparent "heroin overdoses", many of whom do not have high blood morphine levels. There is also a marked overlap between the blood morphine levels of those who have died of a heroin "overdose" and live heroin users who have recently used heroin and heroin users who have died of other causes (Darke & Zador, 1996).

Most of those who die of heroin overdoses are older and experienced opioid users rather than the neophytes one might expect if heroin purity was the sole explanation of opioid overdose deaths (Darke & Zador, 1996). Hall and Darke (1997) found that the average age of those dying from opioid overdose in Australia in 1995 was 30.6 years. Similarly, Zador, Sunjic and Darke (1996) reviewed the coronial files of all heroin related deaths in New South Wales during 1992 and found that the average age at death among males was 30.3 years and 80% of these deaths involved regular and dependent heroin users. Only two deaths were identified among novice heroin users, both of which were classified by the coroner as suicide.

Overdose deaths are more common when an opioid dependent person resumes opioid use after a period of voluntary or involuntary abstinence. High risk situations for overdose fatalities occur after release from prison (Seamen, Brettle & Gore, 1998), after

detoxification when the user's opioid tolerance has been substantially reduced (Darke, Ross & Hall, 1996a), and after a period of voluntary abstinence in untreated opioid dependent persons (Tagliaro, Battisti, Smith & Marigo, 1998).

4.2 CONSUMPTION OF ALCOHOL, BENZODIAZEPINES AND OTHER DRUGS

A major risk factor for heroin overdose appears to be the concurrent use of heroin with alcohol and other drugs (Brecher, 1972; Darke, Zador & Sunjic, 1997; Darke & Zador, 1996; Fugelstad, 1994; Oppenheimer et al., 1994; Zador et al., 1996). In Australia, alcohol, benzodiazepines and heroin are used in combination (Darke & Hall, 1995). In the United States, heroin users typically also use cocaine, benzodiazepines and alcohol (National Institutes of Health, 1997). Such combinations increase overdose risk and make it difficult to decide which drug or drugs were responsible for the death (Gutierrez-Cebollada et al., 1994).

4.3 OTHER FACTORS

Contaminants and adulterants, which may have toxic effects, may be present in illicit opioids. In the United States, quinine in street heroin has been associated with overdose deaths in the late 1970s (Ruttenber & Luke, 1984). Apart from these findings in the US in the 1970s, however, there has been little evidence of a significant role for contaminants and adulterants in opioid related overdose deaths (Brecher, 1972; Darke & Zador, 1996).

Drug users are generally in poorer health than their peers, often with higher rates of malnutrition, tuberculosis, pneumonia, HIV infection, hepatitis B and C, sexually transmittable diseases, endocarditis and malaria (Donoghoe & Wodak, in press). These health conditions may physically weaken opioid users and may increase their vulnerability to overdose death.

A range of other factors has been associated with opioid overdose that may be important in developing interventions to reduce the number of overdose fatalities. For example, studies of fatal and nonfatal overdoses suggest that other people are often present during a fatal overdose (Darke, Ross & Hall, 1996b). Moreover, there are often hours between injection and death, suggesting that there is often time to intervene to prevent fatalities (Darke & Zador, 1996). A "typical" death by opioid overdose is therefore rarely solitary or instantaneous. These circumstances provide opportunities for others to intervene to reduce the fatality rate (Darke & Zador, 1996). Some injectors are more likely to overdose when injecting on the street (Klee & Morris, 1995; Darke et al., 1997) which provides a different set of opportunities for intervention.

4.4 TIME TRENDS IN OPIOID OVERDOSE DEATHS

Hall and Darke (1997) examined trends in the number and rate of opioid overdose in Australia using national mortality data from 1979 to 1995. There was a corresponding six-fold increase in the rate (per million of the adult population aged 15 to 44) of fatal overdose from 10.7 in 1979 to 67.0 in 1995. There have been similar rises in the rate of fatal opioid overdose in: the Nordic countries (Steentoft et al., 1996), Spain (de la Fuente et al., 1995; Sanchez et al., 1995), Italy (Davoli et al., 1997), Austria (Risser & Schneider, 1994), the United States (United States Department of Health and Human Services, 1997) and England and Wales (Neeleman & Farrell, 1997).

5. ILLICIT METHADONE USE AND METHADONE DEATHS

5.1 EXTENT OF ILLICIT METHADONE USE

A study conducted in Washington DC between 1972 and 1973 when MMT had been widely implemented revealed that illicit methadone use was common among heroin users (Greene, Brown & DuPont, 1975). Among heroin users interacting with the Narcotics Treatment Administration (NTA), between one third (34%) and three fifths (57%) reported that they had ever used illicit methadone (Greene et al., 1975). The majority (60-70%) of those had used methadone within the past month but the daily use of methadone was uncommon (16%), with weekly or monthly use more common. The majority had bought it from a friend or heroin dealer.

It was feared that widespread illicit methadone would result in an increase in persons reporting a primary methadone addiction that preceded their dependence on heroin. However, even when illicit methadone was reported as readily available, only 20% of persons reported that they had tried methadone before heroin and only 1% reported a primary methadone addiction, even though heroin was scarce and methadone plentiful (Greene et al, 1975).

More recent data from the UK and Australia reports widespread use of illicit methadone. The NTORS study in Britain found that 49% of clients of treatment agencies reported having used illicit methadone in the 90 days preceding intake (Gossop et al, 1998). Fountain et al (1998) have reported the tactics used by UK opioid users to obtain methadone and other prescribed drugs for sale to other users. Darke, Ross and Hall (1996c) found substantial use of diverted methadone among heroin injectors in Sydney in 1995.

5.1.1 REASONS FOR ILLICIT METHADONE USE

The most common reported use of illicit methadone by heroin users has been to treat opiate withdrawal symptoms. One study found that 80% of those who had used illicit methadone had used it to self-medicate withdrawal symptoms (Greene et al., 1975). Only 10% reported using methadone for its euphoric effects.

McLellan (1998) reviewed American research on methadone diversion. He noted the media were preoccupied 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. He concluded that methadone diversion was an indication of unmet demand for methadone treatment since it was largely used to avert withdrawal symptoms. Oral methadone is less likely to be used for its euphoric effects but Australian data indicates that some users may obtain euphoric opioid effects by injecting methadone syrup (Darke, Ross & Hall, 1996c), and the same may be the case with diverted methadone ampoules in the UK (Strang et al, 1996).

5.2 PREVALENCE OF METHADONE-RELATED DEATHS

5.2.1 AUSTRALIA

Australia has a substantial MMT program that had approximately 19,000 heroin dependent persons enrolled in 1997. In 1995, MMT patients were estimated to represent 30% of all opioid dependent persons in Australia (Hall, 1995). Most MMT in Australia has been provided through specialist clinics in the public and private sector but there has been an expansion of delivery by general practitioners in recent years

Western Australia

A study conducted in Western Australia of all deaths attributed to opiates between the years 1974 and 1984 (Swensen, 1988) identified 108 deaths due to opioids. Of these, 19 were attributed to methadone and 24 to heroin/morphine, with the remainder due to other opiates. Methadone was freely available by prescription between 1975 and 1980, when 18 of the 19 methadone deaths occurred. From 1980 on all methadone was dispensed on a daily basis and all doses were supervised. There was only one overdose death attributed to methadone over the subsequent 4 years during which there were 15 overdose deaths attributed to heroin or morphine. There was no significant difference between the average age of those deaths that were due to methadone and those due to heroin.

South Australia

An investigation was carried out in South Australia of methadone-related deaths that occurred between 1984 and 1994. All methadone overdoses (with toxicity or related causes as the reason for death) were examined (Williamson, Foreman, White & Anderson, 1997) to see whether the person was enrolled in MMT and what form of methadone was involved (methadone syrup, which was exclusively prescribed for the treatment of opioid addiction, or physeptone tablets that were only prescribed for the relief of chronic pain).

During the study period, the average daily dose of prescribed methadone syrup increased, and some stable and long term patients receiving methadone syrup were allowed to have up to four take-home doses per week. Between 1984 and 1992, there were 9 deaths due to methadone syrup overdose, 4 of which involved persons who had not been prescribed methadone, and there were 8 deaths due to methadone tablets, 6 of which had been prescribed it. There were 94 other opioid deaths during the period.

According to the authors, in 1993 and 1994 there was an increased demand for MMT that was largely unmet. There was a concomitant increase in the number of patients who were prescribed methadone tablets by over half (58%). The number of methadone overdose deaths in 1993-1994 markedly increased compared to the previous 9 years, with 12 syrup and 18 tablet deaths (2 of which were probably suicides). The majority of these deaths (67% of syrup and 64% of tablet deaths) occurred among illicit opioid users who had used diverted methadone. There were 43 opioid overdose deaths in which methadone was not involved in the same period.

The two years in which there was unmet demand for MMT were those in which the number of methadone deaths increased markedly among persons who were not enrolled in

MMT, as did the number of overdose deaths due to other opioids. There was also a considerable increase in the number of persons who were prescribed methadone tablets while access to MMT was restricted.

New South Wales

Zador, Sunjic and Basili (1998) have analysed the causes of death among persons in the NSW methadone maintenance program between 1990 and 1995 when the number enrolled in MMT increased from 7,419 to 12,924. There were 211 deaths among program participants during this period. Most of these were males (72%) and the average age at death was 34 years. The overall mortality rate among MMT partic ipants was 26% of the rate in untreated heroin users, consistent with other findings (e.g. Caplehorn et al, 1994). Drug overdose accounted for 40% of these deaths (84 deaths), 24 of which occurred in the first seven days of treatment.

All methadone-related deaths in NSW between 1990 and 1995 – a total of 242 - were examined by Sunjic, Zador and Basili (1998). Methadone-related deaths accounted for 18% of opioid overdose deaths during this period. Ten percent of opioid overdose deaths (134 deaths) involved methadone syrup which is exclusively prescribed for the treatment of opioid dependence in New South Wales. The remainder of these deaths involved methadone tablets, both tablets and syrup, or the type of methadone could not be determined. A total of 72 of the deaths occurred among persons were enrolled in MMT at the time of their death. In 89% of these deaths, polydrug use (especially alcohol and benzodiazepines) was a contributory cause of death.

5.2.2 DENMARK AND NORWAY

A comparative study was conducted of drug-related deaths among drug addicts in Oslo, Norway and Aarhus, Denmark during the period 1980-1989 (Kaa & Teige, 1993). It included all cases of fatal poisoning among drug addicts examined in Institutes of Forensic Medicine of Denmark and Norway. Aarhus had a population of approximately 2 million people and Oslo had a population of 2.2 million inhabitants. The two countries differed in their treatment of drug addicts. Denmark used long term MMT whereas Norway did not, and Denmark extended the number of methadone places in the latter half of the study period.

Methadone was implicated as the cause of more overdose deaths in Aarhus (n = 33) than in Oslo (n = 6). The number of deaths per annum attributed to methadone increased in Aarhus from 4 in the first five years of the study period to 29 deaths in the second five years. There were more heroin overdose deaths in Oslo (n = 192) than in Aarhus (n = 75) and the total number of opioid deaths increased in Oslo but not in Aarhus.

The authors argued that the higher number of methadone deaths in Denmark was an indicator of methadone diversion in Denmark, which they supported by evidence that one third of medical drug seizures in Denmark in 1989 involved methadone (Kaa & Teige, 1993). A later study found that approximately half of the deaths that were attributed to methadone during the period 1987-1991 occurred among those who were not in MMT (Kringsholm, Kaa, Steentoft, Worm & Simonsen, 1994). The pattern of overdose deaths in this comparison suggests that ready access to MMT in Denmark may have produced a

lower rate of heroin overdose in Denmark than Norway at the cost of a higher rate of methadone involvement in opioid overdose deaths.

5.2.3 NORTH AMERICA

The District of Columbia 1970-1974

In February 1970, Columbia's Narcotics Treatment Administration (NTA) introduced a program of addiction treatment services that included MMT programs and the prescription of methadone by private physicians. By late 1971, approximately 3,800 persons had enrolled in an NTA program. Around this time, there was a severe shortage of heroin as a result of a nation-wide dock strike (Greene, Luke & DuPont, 1974a). One apparent consequence of the heroin shortage was an increased use of licit and illicit methadone in the District of Columbia (Greene et al., 1974a). The increased use of methadone prompted two studies of methadone related deaths.

The first study reviewed all deaths (n = 21) in which methadone was detected between October 1970 and March 1971 (Chabalko, La Rosa & DuPont, 1973). Multiple drugs were detected in the majority of cases but methadone was thought to have contributed to 90% of these deaths. In the same period, there were 38 deaths attributed to heroin overdose. Just under half (42%) of the methadone deaths occurred among patients in the public MMT program (n = 6) or patients of private physicians (n = 2). The remainder (n = 11) occurred among persons who used diverted methadone.

A second study (Green et al., 1974a, 1974b) examined the contribution that methadone made to 118 overdose deaths between July 1971 and December 1972. Of these deaths, 58 were heroin overdoses, 21 were attributed to heroin and methadone, and 39 were attributed to methadone alone. Methadone overdose victims were significantly younger (22 years) than heroin overdose fatalities (27 years) and 26% of the methadone deaths occurred in persons who were not and never had been tolerant to opiates. A further 21% of deaths occurred in persons who had a history of opiate addiction who were not opioid tolerant at the time of their deaths.

As a consequence of concern about methadone deaths, in February-March 1972, private prescribing of methadone ceased, security was increased at public clinics and take-away doses of methadone were reduced. In the period July 1971 to March 1972 before the restrictions were introduced, there were 47 (68%) heroin deaths, 16 (23%) methadone deaths, and 6 (9%) combination deaths (a rate of 104 overdose deaths per annum). Between April-December 1972, the annual rate of overdose deaths declined to 59 but the contribution made by heroin and methadone changed markedly: 22% were attributed to heroin, 47% were attributed to methadone (47%) or 31% to a combination of heroin and methadone. Overall opioid overdose mortality declined in 1973 to 19, comprising 14 (74%) methadone deaths and 5 (26%) heroin deaths (Greene et al, 1974a).

Texas 1987-1992

Concern about an apparent increase in the number of methadone-related deaths in Harris County, Texas in 1991, prompted an investigation of 91 deaths that occurred between 1987

and 1992 in which methadone was detected post-mortem (Barrett, Luk, Parrish, & Jones, 1996). In only 20% of these deaths was the deceased enrolled in MMT at the time of their death. The medical examiner attributed 11% of these deaths to methadone alone. The number of these deaths varied between 0 and 3 deaths per annum. In 85% of these deaths more than one drug was detected post mortem (half of which were diazepam). The authors concluded that methadone deaths did not increase in 1991 but deaths involving polydrug use that included methadone did increase.

British Columbia 1982-1986

Alexander, MacInnes & Beyerstein, (1988) reviewed all methadone-related deaths in British Columbia during the period 1982 to 1986, during which private MMT was freely available. There were 83 opioid overdose deaths in which methadone was detected post mortem, 74 of which were attributed to an accidental drug overdose. Methadone was considered the main cause of death in 26 cases and a contributory cause in 47 cases. Heroin was considered to be the major cause in one of the deaths.

5.2.4 UNITED KINGDOM

England

Clark, Milroy and Forrest (1995) reported on 18 overdose deaths involving methadone that occurred in Sheffield between 1991 and 1994. In all of these deaths methadone was regarded as the principal cause of death although other drugs were present in a substantial minority of cases. Of these deaths, 17 occurred in adults (14 of whom were male). Ten deaths occurred among persons who had been prescribed methadone for opioid dependence, and 7 of these deaths occurred within the first 4 days of treatment. In the 8 deaths that occurred among persons who had consumed diverted methadone, most had obtained the methadone from friends or bought it on the streets.

Cairns, Roberts and Benbow (1996) reported on 90 deaths that they attributed in whole or part to methadone that occurred in Manchester between January 1985 and December 1994. This represented 15% of all deaths attributed to alcohol and other drug toxicity during the study period. In 52 of the 90 deaths, methadone was regarded as the sole cause of death, with the remainder involving other drugs, alcohol or both. The mean age at death was 26 years and 88% of cases were males. In 36 cases the methadone had been prescribed, in 32 it was diverted and the source was unclear (although probably diverted) in the remainder. They present time series data that suggest that the rate of methadone overdose deaths in Manchester has risen with the rate of prescribing in the city.

Scotland

Lothian and Borders regions

Obafunwa & Busuttil (1994) reported an analysis of 352 deaths attributed to drug overdose in the Lothian and Borders regions of Scotland between 1983 and 1991. A third of these deaths (32%) were attributed to opioids (114), and equal numbers of these were attributed to methadone (18) and heroin (18). There was an increase in the number of deaths attributed to methadone over the period and a decrease in the numbers of deaths attributed

to heroin. Deaths attributed to heroin peaked in 1984 and fell significantly after 1986 while deaths attributed to methadone increased over the period.

A later study examined 125 accidental and suicidal overdose deaths in the region between 1989 and 1994 (Bentley & Busuttil, 1996). Methadone was found to be responsible for 30% of all overdoses (38 cases) and contributed to another 26 cases. Heroin overdose accounted for five deaths.

Edinburgh

Hammersley, Cassidy & Oliver (1995) reported an analysis of 12 drug-related deaths in Edinburgh in 1991. Two of these deaths involved methadone, one involved heroin, and five involved more than one drug. In 1986 the Lothian and Borders regions of Scotland (within which Edinburgh is located) implemented a policy of strict policing to reduce supplies of heroin while making methadone more readily available on prescription to addicts who requested it.

Glasgow

Cassidy, Curtis, Muir, & Oliver (1995) reviewed 62 drug-related deaths in Glasgow during 1992. In the majority of cases, more than one drug was found post-mortem. Heroin was found in 37 cases, benzodiazepines in 49 cases, and methadone in 2 cases, in both of which heroin and benzodiazepines were also detected. Benzodiazepines were found post-mortem in 89% of the heroin deaths.

5.3 RISK FACTORS FOR METHADONE DEATHS

Many of the risk factors associated with methadone deaths appear to be similar to those associated with heroin overdose deaths. Males are much more likely to die as a result of a methadone overdose. In Britain in 1995, 82% of those whose death was classified as accidental methadone poisoning were male. Similar figures have been recorded in the US (Chabalko et al., 1973; Greene et al., 1974a; Barrett et al., 1996) and Australia (e.g. Zador et al., 1996). The sex difference in rate reflects the greater numbers of males who become dependent on illicit opioid drugs (e.g. Ball & Ross, 1991; Darke & Hall, 1995).

Age may also be a risk factor for methadone overdose. In comparison with heroin deaths, methadone deaths in some studies have occurred among younger people (e.g. Greene et al., 1974a, 1974b) although not all studies report a difference (Swensen, 1988). Polydrug use, particularly the use of alcohol and benzodiazepines, is a significant risk factor for methadone overdose (Caplehorn, 1998; Cassidy et al., 1995; Gilhooly, 1997), as it is for heroin overdose deaths (Darke and Zador, 1996).

In studies that have examined the issue, the majority of methadone overdose deaths have occurred among persons who were not enrolled in MMT at the time of their death (e.g. Barrett et al., 1996; Cairns et al., 1996; Clark et al., 1995; Williamson et al., 1997). Some studies suggest that methadone deaths among those who are not prescribed methadone occur in younger persons (e.g. Clark et al., 1995; Williamson et al., 1997).

5.4 AN OVERVIEW

Research on methadone-related deaths has been sporadic and often opportunistic (See Table 1). These studies are often prompted by media reports about methadone-related deaths among persons not enrolled in MMT. They have been of limited utility because small numbers of deaths have been studied, the criteria used for attributing the deaths to methadone have not been made explicit or standardised, and rarely has any attempt been made to calculate mortality rates. Some studies have compared opioid overdose rates in settings in which methadone is available with settings where it has not, or with the same setting after efforts have been made to reduce methadone diversion.

A major problem with the literature is the lack of specification of the criteria used to classify the cause of these deaths. This makes it difficult to decide what contribution methadone makes to deaths in which other CNS depressants (such as alcohol, heroin, and benzodiazepines) are involved. It is also difficult to estimate the risks of methadone versus heroin since it is likely that any estimate based on the numbers in MMT will underestimate the size of the population who use methadone. This problem is one that is common to research on all illicit drug deaths, including those attributed to heroin. Without these estimates, it is difficult to estimate the relative dangers of methadone and other opioids. Nevertheless, these studies suggest a number of hypotheses that deserve more rigorous evaluation.

The first hypothesis is that increased availability of MMT and relaxation of controls on supervision of methadone dosing may be risk factors for methadone overdose deaths involving diverted methadone. In settings in which access to MMT increased (e.g. Denmark in 1980s, Washington DC in the early 1970s; Manchester in the late 1980s) or restrictions on dosing have been relaxed (Western Australia in the late 1970s), studies have reported an accompanying increase in opioid overdose deaths involving methadone.

Second, methadone overdose deaths that occurred among persons in MMT were much less common than those among persons who were not enrolled in MMT and who used diverted methadone. Deaths among persons enrolled in MMT were most likely to occur when patients were being inducted into MMT. Some of these occurred because patients exaggerated their history of opioid use, or because undiagnosed liver disease allows methadone doses that were below the fatal dose to accumulate over a number of days. Deaths during induction can be reduced by better assessment of dependence, use of lower starting doses of methadone and greater supervision during the first week of treatment (Drummer et al., 1992).

Third, evidence from some studies suggests that those who die as a result of ingesting diverted methadone may be younger users who have a low tolerance to opioids and are not experienced in using an opioid drug with a much longer half-life than heroin. Those who die of overdoses attributed to heroin tend to be older dependent opioid users and polydrug users (Darke & Zador, 1996).

Fourth, several studies (e.g. Greene et al, 1974a; Swenson, 1988) suggest that methadone-related overdose deaths can be reduced by increasing restrictions on take-away doses and increasing supervision of methadone dosing. These restrictions have on occasion been followed by a decline in overdose deaths involving methadone (Washington, DC in the early 1970s and Western Australia in the early 1980s). It is difficult, given the small

number of deaths in these studies, however, to exclude the possibility that the apparent decrease in methadone-related deaths after the implementation of the restrictions has been due to regression to the mean. The restrictions on methadone availability typically follow media concern about apparent clusters of methadone deaths and any apparent reduction in deaths that follows the restrictions is attributed to the restrictions; the possibility that the decrease represents chance fluctuations in a low base rate has not been tested. It would be preferable to have data over a longer period, or in a larger population, from a planned change in prescribing to properly assess this hypothesis.

Fifth, some studies suggest that there may be an inverse relationship between the number of heroin and methadone related deaths, with reductions in heroin overdose deaths being partially offset by an increased involvement of methadone in opioid overdose deaths. There is a suggestion from the comparison of mortality in Denmark and Norway that making methadone freely available reduced overdose deaths among those enrolled in MMT. If the proportion of opioid dependent person who are in MMT is a large enough proportion of all opioid dependent person in the population, then it may reduce the number of opioid–related deaths. If, however, this is achieved by liberal use of take-away doses, methadone diversion may increase the proportion of opioid overdose deaths that are attributed in whole or part to methadone.

All these must be regarded as hypotheses to be tested because the available data, for all the reasons indicated, are too weak to provide strong tests of them. Some suggestions are included below on the type of research that would provide more rigorous tests of these hypotheses.

Table 1: Findings of studies reporting the impact of changes in the availability of methadone on methadone and heroin related deaths

Location	Methadone availability	Year(s)	Period	Methadone deaths*		Heroin deaths*		Opiate deaths per annum	Ratio of methadone : heroin deaths
				N	pa	N	Pa	Pa	
Australia									
South Australia	Reasonable	1984-1992	9 years	17	1.9	92†	10.1	12.0	.18
	Limited	1993-1994	2 years	30	15.0	43†	21.5	36.5	.70
Western Australia	Extensive	1974-1981	6 years	18	3.0	9	1.5	4.5	2
	Limited	1982-1984	3 years	1	0.3	15	5.0	5.3	.07
Norway	Limited	1980-1989	10 years	6	0.6	192	19.2	19.8	.03
Denmark	Extensive	1980-1989	10 years	33	3.3	75	7.5	10.8	.44
United States									
District of	Extensive	Oct 1970 - Mar 1971	6 mths	19	38	38	76	114	0.5
Columbia	Extensive	Jul 1971–Mar 1972	8 mths	22#	33	47	70.5	103.5	.47
	Limited	Apr 1972-Dec 1972	10 mths	38#	45.6	11	13.2	58.8	.67
	Limited	1973	1 year	14	14	5	5	19.0	2.8
United Kingdom									
England									
Sheffield	Extensive	1991-1994	3 years	18	6	N/A	N/A	N/A	N/A
Manchester	Extensive	Jan 1985–Dec 1994	10 years	52	5.2	N/A	N/A	N/A	N/A
Scotland									
Lothian & Borders	Extensive	1983-1991	8 years	15	1.9	15	1.9	3.8	1
region	Extensive	1989-1994	6 years	64	10.7	5	0.8	11.5	12.8
Edinburgh	Extensive	1991	1 year	2	2	1	1	3	2
Glasgow	Limited	1991	1 year	0	0	10	10	10	0
Glasgow	Limited	1992	1 year	2	2	37	37	39	.05

* A "methadone death" or "heroin death" case may also have involved other drug(s), but has been classified as such for simplicity.
# If a death was described as involving methadone and heroin, it was classed as a methadone death
† Includes deaths due to heroin as well as other opioids

6. OPIOID USE AND OVERDOSE IN THE UNITED KINGDOM

6.1 OPIOID USE EPIDEMIOLOGY

6.1.1 HEROIN USE

Household surveys of drug use are likely to substantially underestimate the true extent of illicit opiate use in the community, as they are likely to under sample individuals who use illicit opiates and who are opiate dependent. These individuals are less likely to be living in general households and are therefore more likely to be excluded from the sampling frame of a household survey. It is also probable that illicit opioid users will be less likely to comply with requests to take part in a survey, and if they do participate, that they will conceal their opioid use.

Even so, illicit opiate use is probably relatively rare in the general population. It is typically reported at some time in their lifetime by around 1% of the adult population in Australia, the UK and the USA (Hall, 1996b). Large survey samples are accordingly required to estimate the prevalence of *heroin use* with any precision, and even larger samples are needed to estimate the prevalence of *heroin dependence* which occurs in as few as one in four of those who ever use heroin (Anthony et al, 1994).

In Britain there have been limited household surveys of illicit drug use. Illicit drug use has been inquired about in crime surveys, but respondents may be more likely to under-report in this context than in the context of a health survey. In the most recent British survey in 1995, 1% of British adults aged 16-34 years reported that they had used heroin in their lifetime (Judd & Fitch, 1998). The prevalence of heroin use in the past month was less than 0.5%.

One source of information about the number of drug-addicted persons in Britain is the Addicts Index of the Home Office. In 1989, 14,785 persons were registered on the index as addicted to opiates. By 1992, this number had increased to 24,151 and by 1995 there were 43,372 addicts registered on the Index (with opiates identified as the drug of addiction in the majority of cases). This figure is likely to be an under-estimate of the number of opiate dependent persons in treatment because a substantial proportion of doctors reportedly fail to notify their patients to the register (Strang and Shah, 1985).

According to the London Regional Drug Misuse Databases, in 1996/7, 56% of treatment applicants reported heroin as their main problem drug, while 18% reported methadone as their main problem drug. Since many services in the London area tend to be focused on opiate abuse treatment, these proportions may be inflated. Furthermore, those who cite methadone as their main problem drug may have been prescribed that drug by another physician.

6.1.2 ILLICIT METHADONE USE

In 1994, less than 0.5% of adults aged 16-59 in England and Wales were estimated to have used non-prescribed methadone (Judd & Fitch, 1998). In 1995, 1% of English adults aged 16-34 years reported ever having used either prescribed or non-prescribed methadone.

In a cohort of 1075 clients entering treatment for illicit drug use in the UK in 1995, 32-60% of applicants to a range of different types of treatment reported that they had used illicit methadone within the past 3 months (Gossop et al., 1997). In the past 90 days, the average number of days of methadone use varied between 25 and 46 days (depending on the treatment that clients were entering). Over half of those who applied to enter methadone maintenance or methadone reduction treatment reported using illicitly obtained methadone within the past 90 days, for on an average of 25 and 29 days respectively.

6.2 TRENDS IN UK OPIOID OVERDOSE DEATHS 1985-1995

6.2.1 METHOD

Trends in ICD-9 coded opioid deaths notified to the Office of National Statistics in the United Kingdom were examined between the years 1985 and 1995. This included deaths classified as accidental or undetermined poisonings, and deaths due to drug dependence or non-dependent abuse of drugs (Christopherson et al, 1998). Trends in the age at death were estimated from age groupings of the data (by assuming a mean age of 18 for those under 20 years of age and a mean age of 38 for deaths occurring in those over 35 years).

Data on methadone and heroin deaths were available only for the years 1993 to 1995. Data presented by Neeleman and Farrell (1997) provided more detail on trends in methadone and heroin related deaths between 1972 and 1992 because they were obtained by a hand search of Office of Population Censuses and Surveys (OPCS) tables by the authors.

Data from the Addict's Index were not used for these analyses for the following reasons. First, it is likely that the index underestimates the number of addicts receiving care because of a failure by doctors to notify new patients to the Addicts Index (Strang and Shah, 1985). Second, only those addicts who visit a doctor are notified to the Index. Third, the rules for notifying and recording patients in the Index have changed over time in ways that impair the utility of the data for epidemiological or comparative purposes (Howes et al, 1995).

A comparison was made between trends in opioid overdose between the UK and Australia in the survey period. Data on the number of deaths in Australia between 1985 and 1995 that were attributed to opioid overdose and accidental opioid poisonings were used to compare overdose death rates in the two countries. Information on the number of deaths in Australia attributed to undetermined poisonings were not included in the analysis because it was not possible to separate different drug types included in the category. Hence, any estimates of the rates of opioid overdoses in Australia will, if anything, be conservative by comparison with the UK rates.

Australia was considered an interesting comparison country because it is an English-speaking country that was formerly a colony of the UK, from which its legal and coronial systems have derived. The MMT system in Australia is very different from that in the UK. Access to MMT is much more restricted in Australia, with methadone prescribing by medical practitioners limited to licensed prescribers. There is central authority that monitors all MMT patients and limits the numbers of patients who can be prescribed the drug. There is also much more supervised administration of methadone doses in Australia than in the UK,

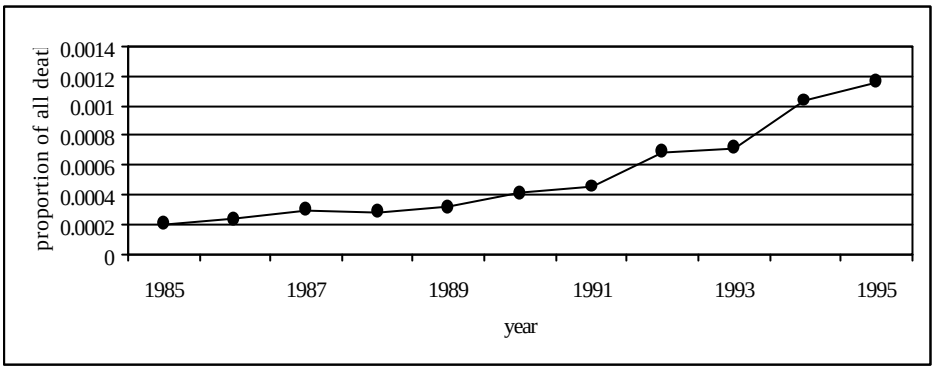
with take-away doses generally not permitted in the first three months of MMT. Australia also has extensive time series data on methadone and other opioid deaths with which to compare British data.

6.2.2 RESULTS

6.2.2.1 Trends in all opioid deaths

Figure 1 shows the proportion of all deaths attributed to opiates in the United Kingdom between 1985 and 1995. As is clearly shown, the proportion of all deaths attributed to opiates has increased six-fold over this period. In 1985, opiates were classified as contributing to 0.02% of all deaths in the UK. By 1991, this had risen to 0.05% of all deaths and by 1995 it had increased to 0.12%.

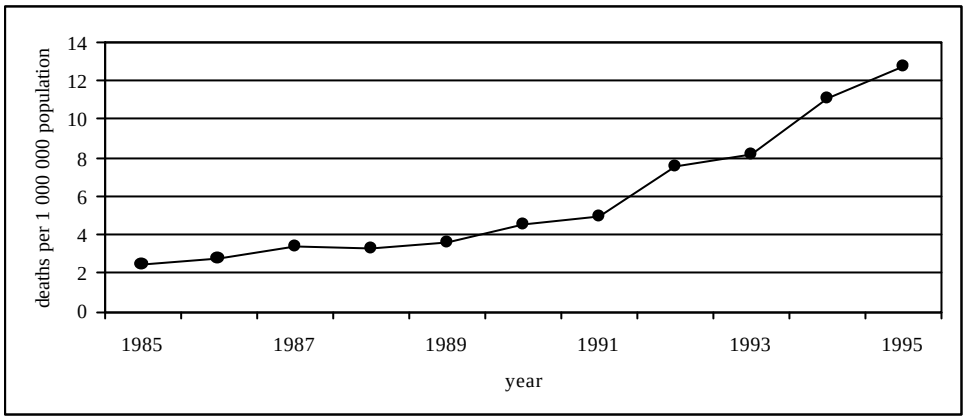
*Figure 1: Proportion of all deaths attributed to opiates between 1985 and 1995 for persons in the United Kingdom**



* Information on deaths in Northern Ireland was not available for the years 1985 to 1990. However, for the years in which it was available there were few deaths, so it is unlikely that the rate would change significantly.

The rate of opioid deaths among the UK population also increased during this period from 2.4 per million in 1985 to 12.7 per million in 1995 (see figure 2).

Figure 2: Deaths per million population attributed to opioid overdose in the United Kingdom between 1985 and 1995*

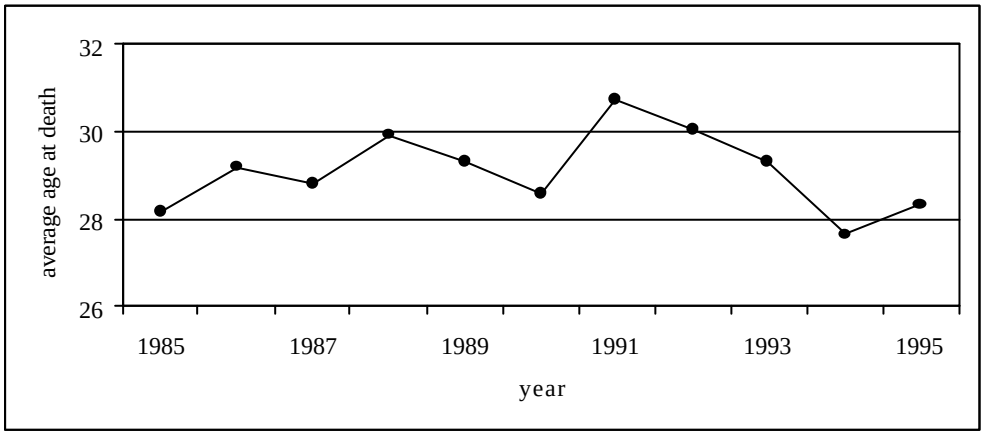


* Information on deaths in Northern Ireland was not available for the years 1985 to 1990. However, for the years in which it was available there were few deaths, so it is unlikely that the rate would change significantly.

6.2.2.2 Trends in the average age at death

As can be seen in Figure 3, there was no evidence of an increase in the average age at death in the UK. This is in contrast to opioid overdose deaths in Australia which have shown a steady increase in average age at death from 24 years in 1979 to 30 years in 1996 (Hall and Darke, 1997). There was some suggestion that between 1991 and 1995, the average age at death may have decreased but it is difficult to draw strong conclusions in the absence of data on exact age at death for persons under 20 years or over 35 years.

*Figure 3: Average age at death of persons in the United Kingdom whose deaths were attributed to opioids between the years 1985 and 1995**



* Includes deaths due to drug dependence or non-dependent abuse of drugs only

6.2.2.3 Methadone and heroin overdose deaths

Age at death

A comparison of the median ages at death between the years 1993 and 1995 (the only years for which data were available) revealed very little difference in age at death in persons whose deaths were attributed to methadone and other opiates. There was not a great deal of difference between the two groups in comparison to the variation in median age over the period 1985 to 1995 for all opioid related deaths.

*Table 2: Comparison of the mean ages of persons whose death was attributed to methadone or to any other opiate, between 1993 and 1995, in Great Britain**

	Methadone	**Other opiates**
1993	29	30
1994	27	27
1995	27	27

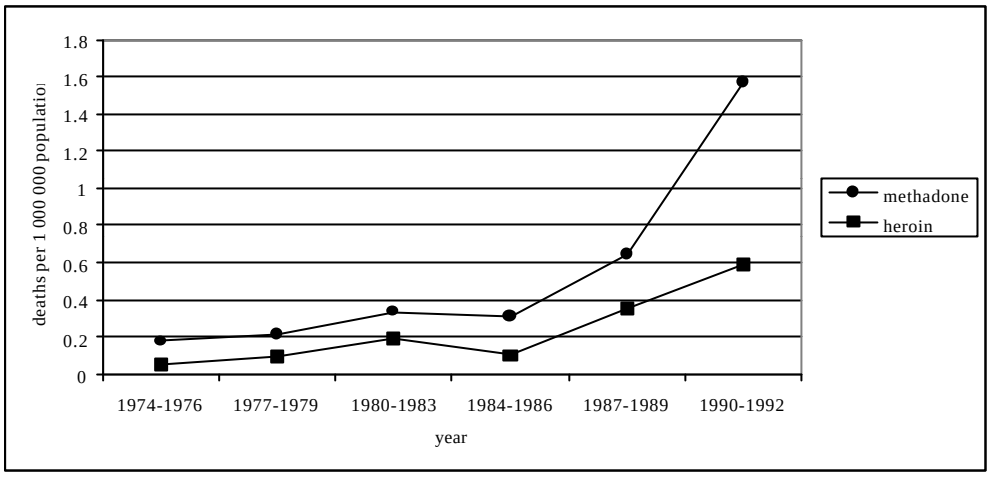
* Includes deaths due to drug dependence or non-dependent abuse of drugs only

6.2.2.4 Trends in methadone and heroin overdose deaths 1972 - 1992

Neeleman & Farrell (1997) reported an analysis of trends in heroin and methadone-related proportional mortality due to accidental poisoning, suicide and undetermined causes in England and Wales between 1972 and 1992. Their aim was to test claims (e.g. Marks, 1994; Newcombe, 1996) that methadone was a more lethal opioid than heroin in the UK. They concluded that the proportion of self-poisoning deaths attributed to methadone and heroin had both increased during the period but there was no statistically significant difference in the rate of increase of deaths attributed to heroin (76% pa) and methadone (80% pa). For both heroin and methadone deaths, the rate of increase was larger between 1990-1992 than between 1972 and 1989. These patterns persisted when the gender of those who had died was taken into account.

The estimates of Neeleman and Farrell (1997) are likely to overestimate the number of methadone-related deaths in the UK because they classified all deaths involving both methadone and heroin as "methadone deaths". The authors chose this method of coding so that their analysis would err in the direction of over- rather than under-estimating the number of methadone-related deaths to ensure that any bias in their test of Marks and Newcombe's hypothesis operated in favour of the hypothesis.

Figure 4: Deaths per million population in England and Wales attributed to methadone and heroin between the years 1974 and 1992*



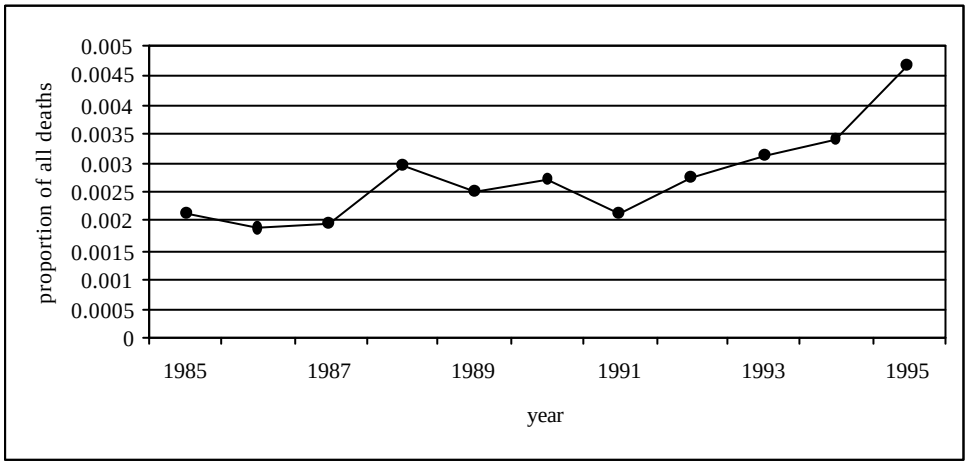
N.B. Data taken from an article published by Neeleman & Farrell (1997). Data for overdoses during the year of 1982 were not available; Neeleman & Farrell (1997) therefore extended the period to include 1980, 1981, and 1983.

- Neeleman & Farrell (1997) classified deaths in which both methadone and heroin were involved as "methadone deaths".

6.2.2.5 Comparison of overdose deaths in the UK and Australia

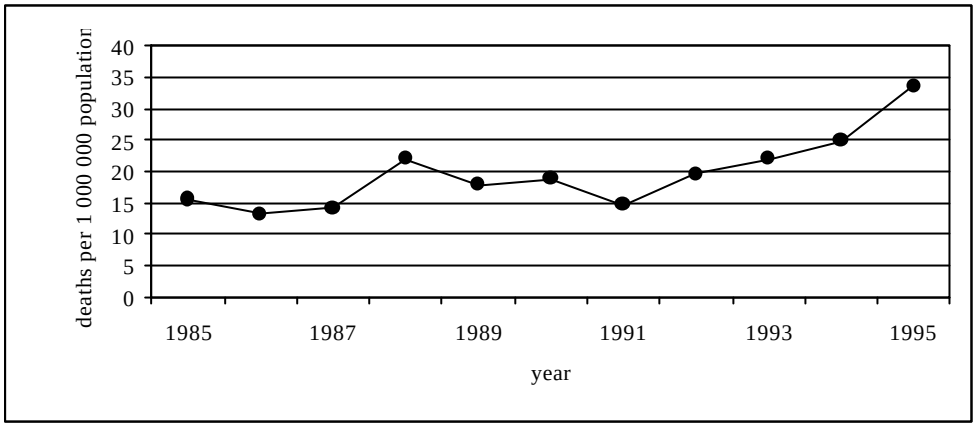
In Australia between 1985 and 1995, the proportion of all deaths attributed to opiates in Australia rose from 0.21% in 1985 to 0.47% in 1995 (Figure 4). In comparison, the proportions in the UK went from 0.02% in 1985 to 0.12% in 1995 (Figure 1). The Australian rate was higher throughout the comparison period than the UK rate but the magnitude of the difference decreased from 10 to approximately 4 times greater in Australia.

Figure 5: Proportion of all deaths attributed to opioids in Australia between 1985 and 1995



The prevalence of deaths attributed to opiates among the Australian population increased over the period from approximately 16 deaths per million persons in 1985 to 34 deaths per million in 1995, an increase of 113% (Figure 5). The prevalence of opioid overdose deaths in the UK increased from around 2 deaths per million in 1985 to 13 deaths per million in 1995, an increase of 550% (Figure 2). Again, the prevalence rate was significantly larger in Australia throughout the period but the difference decreased over time.

Figure 6: Opioid overdose deaths per million in Australia 1985 to 1995



The Australian Bureau of Statistics data on opioid deaths does not distinguish between deaths attributed to heroin and methadone. In New South Wales, which accounts for half of all opioid overdose deaths in Australia and has the highest prevalence of persons enrolled in MMT, an estimate of the proportion of opioid deaths attributed to methadone between 1990 and 1995 was 18% (Sunjic, Zador & Basili, 1998; Zador, Sunjic, & Basili, 1998). This contrasts with the UK where up to half of all opioid-related deaths were attributed in whole or part to methadone (Neeleman and Farrell, 1997).

6.2.3 DISCUSSION

The rate of opioid overdose deaths in the UK has dramatically increased between 1985 and 1995, whether this was assessed by the proportion of all deaths attributed to opioids or by the population prevalence of opioid overdose deaths. Approximately half of these deaths have been attributed to methadone throughout the period, with some suggestion that this proportion may have increased towards the end of the period.

Comparison with trends in Australia revealed that both countries observed an increase in opioid overdose deaths over the period 1985-1995. The mortality rate throughout the period was 4 to 10 times higher in Australia than the UK, whether measured by the proportion of all deaths due to opioid overdose or by the population prevalence of opioid overdose deaths. The rate of the increase may have been greater in the UK in the latter half of the period since the difference in rate narrowed substantially over the period.

6.2.3.1 A difference in classification of causes of death?

The first possibility that needs to be considered is that the differences between the UK and Australia are artefacts of differences in the way that overdose deaths are certified and statistics collated by the Office of National Statistics in the UK and the Australian Bureau of Statistics in Australia. It seems unlikely that there are large numbers of unexplained deaths in the UK. Non-natural deaths that occur among young adults in both countries are usually subject to a post mortem toxicological examination, if not a coronial inquest (Christopherson et al, 1998; Darke and Hall, 1998). Both countries used the ICD-9 classification throughout the study period but there was no information on how coroners and toxicologists made their diagnoses in each country, nor on the way in which these diagnoses were centrally coded by the national statistical offices.

The data were aggregated and reported in different ways. In the UK for example, the specific drugs involved in accidental, undetermined and suicidal deaths were separately reported whereas this was not done in Australia. However, these classificatory practices are more likely to under- rather than over-estimate the Australian opioid overdose rate by comparison with that in the UK. For example, the Australia opioid overdose rate in 1996 does not include 63 overdose deaths from undetermined cause in which the type of drug was not reported. Hence, although differences in classification and reporting systems may contribute to the difference in overdose mortality rates, it is unlikely to wholly explain the fourfold difference observed in the middle 1990s.

6.2.3.2 A difference in the prevalence of opioid dependence?

A second possible reason for the difference in rates may be that Australia may have a higher prevalence of opioid dependence than the UK. It is harder to exclude this possibility because of the paucity of data on the prevalence of opioid dependence in both countries. Nonetheless, the available data do not suggest that there is a four- to ten-fold difference between the two countries in the prevalence of opioid dependence. First, the limited survey data in the UK suggests that lifetime heroin rate of use is similar to that in Australia (1% among 16-34 year olds in England and Wales and 1% in Australian adults). Second, although the methods of data collection differ, the numbers of opioid dependent persons who are in some type of treatment are similar, given the population differences between the UK and Australia. There were, for example, approximately 43 500 addicts notified to the Home Office Addicts Index in 1996, compared with 19,573 persons involved in methadone maintenance treatment in Australia in the same year. A crude calculation suggests that the rates per million adults aged 15 to 44 years who are opioid dependent are similar (0.17% in the UK as against 0.23% in Australia). These crude rates do not take any account of the likely under-reporting of opioid dependence in both countries. If the Addicts Index under-reports 35% more than the Australian methadone register, then the difference in population prevalence of opioid dependence between Australia and the UK would disappear.

6.2.3.3 A difference in route of opioid administration?

A third possibility is that although rates of opioid dependence may be similar in Australia and the UK, the risk of fatal opioid overdose may be much lower in the UK where more heroin users smoke or "chase" than inject heroin (Strang et al., 1994, 1996). In the UK for example, around 40% of heroin dependent persons in treatment smoke heroin (Gossop, Marsden, Stewart, Lehmann, Edwards, Wilson & Segar, 1996; Howes, Strang, Taylor & Farrell, 1995) whereas in Australia injection was until very recently the sole route of heroin administration (Maher et al, 1998).

Heroin smoking carries a much lower risk of self-reported non-fatal overdose than injecting. Only 23% of a sample of London heroin users reported a non-fatal overdose (Gossop, Griffiths, Powis, Williamson, & Strang, 1996) compared with 68% of heroin injectors in Sydney (Darke et al., 1996b). Among these UK heroin users, the rate of non-fatal overdose among heroin smokers was only 1.6% compared with 40% among injectors (OR = 27.7 [95% CI: 6.7, 114.3]).

A crude estimate can be made of the proportion of the opioid overdose mortality differential between Australia and the UK that can be explained by the difference in the route of administration (see Appendix A). If we assume (1) that the prevalence of opioid dependence in the two countries is approximately the same, (2) that the relative risk of fatal overdose for injectors and smokers is the same as that for non-fatal overdose (Gossop et al., 1996), and (3) that 40% of dependent heroin users in the UK are smokers, then the opioid overdose mortality rate in the UK would be approximately 60% of that observed in Australia (see Appendix A). This calculation suggests that the difference in opioid mortality is not wholly explained by the difference in route of administration. Route of administration cannot be excluded as an explanation, however, because the overdose mortality difference between Australia and the UK would be explained if 70% or more of dependent heroin users (in and out of treatment) in the UK were heroin smokers rather than injectors.

6.2.3.4 A difference in MMT delivery?

A fourth possibility that needs to be considered is that the differences between the UK and Australia in opioid overdose mortality reflect differences in the way in which methadone maintenance is delivered in the two countries. It may be, for example, that allowing any registered medical practitioner to prescribe methadone leads to a greater proportion of heroin dependent persons being involved in methadone treatment and thereby being at lower risk of opioid overdose. If the proportion of opioid dependent people receiving methadone was a large enough proportion of all opioid dependent persons then the overall rate of opioid overdose deaths would be reduced. One cost of the increased availability of methadone may be that more overdose deaths occur as a result of diverted methadone. This hypothesis would explain the lower rate of opioid overdose death in the UK than Australia and the higher proportion of opioid overdose deaths that involve diverted methadone.

Again, some crude calculations can be done to assess the plausibility of this explanation of the difference in overdose deaths between Australia and the UK. If we assume that the prevalence of opioid dependence is the same in the two countries, that in Australia about 30% of dependent heroin users are in MMT (Hall, 1995), and the reduction in risk of fatal overdose while in methadone is (OR = 0.24) (Caplehorn et al., 1996), then the plausibility of

the hypothesis can be assessed by determining by how much the two countries would need to differ in the proportion of opioid dependent persons in treatment to explain the observed difference in overdose mortality. These calculations (see Appendix B) indicate that the difference in the penetration of MMT in Australia and the UK would need to be marked (80% or more in the UK versus 30% in Australia) to explain the difference in mortality rate. This does not of course exclude the possibility that the different methods of MMT make some contribution to the observed differences in opioid overdose deaths.

The four explanations that have been considered (differences in classification, prevalence of opioid dependence, prevalence of heroin smoking, and penetration of methadone treatment) are not mutually exclusive. They could each explain some of the observed difference in opioid overdose mortality between the UK and Australia. No attempt has been made to estimate the ways in which these explanations may jointly explain the difference in mortality because such calculations would be even more speculative than those that have been reported in Appendices A and B.

7. IMPLICATIONS

This report has reviewed the literature describing the pharmacology of methadone, its therapeutic use and efficacy as a treatment for opioid dependence and trends in the prevalence of methadone related deaths in the United Kingdom. The major questions raised by this report and their implications for future research are discussed below.

7.1 HAS THE OPIOID OVERDOSE DEATH RATE INCREASED IN THE UK?

The analysis of trends in overdose deaths in the UK over the period 1985-1995 has indicated that the rate of opioid overdose mortality in the United Kingdom (population standardised) has substantially increased over the past decade. Up to half of these deaths involve methadone, most of which may occur among persons who are not enrolled in methadone at the time of their deaths.

It is more difficult to decide whether the rate of increase in opioid overdose deaths has been greater in the UK than in Australia. The problems raised in comparing rates of opioid overdose mortality between countries have been mentioned. Even allowing for differing reporting systems and methods of classifying and reporting drug overdose deaths, the available evidence suggests that *the rate of increase* in overdose deaths in the UK has been similar to that in Australia. However, the *rate* of opioid overdose deaths in the UK is substantially lower than the corresponding rates in Australia; while the proportion of these deaths that involved methadone was higher in the UK than Australia. Unlike Australia where there has been a steady rise in the average age of persons dying of opioid overdose, the age at death in the UK seems to have remained steady, or if anything, decreased over the last half of the decade.

If we assume that classification differences are not the whole explanation of differences between Australia and the UK, there are a number of substantive explanations for these apparent differences in rates and patterns of opioid overdose mortality, as discussed above. It is not possible to distinguish between these explanations on the basis of the available evidence, although some (e.g. route of administration) seem more plausible than others (such as differences in classification and the prevalence of opioid dependence).

7.2 WHAT ADDITIONAL INFORMATION IS NEEDED?

The following additional information would help to explain the causes of trends and patterns of methadone related deaths in the UK, and the very different rate and pattern of opioid overdose mortality in Australia and the UK.

First, better estimates are needed of the number of people in the population who use opiates by particular routes of administration (e.g. by injection and smoking) in the UK. This data is required because rates of opioid dependence and injection as a route of administration are related to the risk of opioid overdose death.

Second, there is a need for a more detailed description of the prevalence and role of licit (e.g. alcohol) and illicit drugs (heroin, methadone, and benzodiazepines) in fatal opioid overdoses

in the UK. If the quality of records permits, this could be done by retrospective analyses of fatal opioid overdose cases to discover how coroners and forensic pathologists assign a cause of death in these cases. This information may help to standardise the way in which these deaths are reported. If the quality of coronial records and forensic reports does not permit a retrospective study, then a prospective study of these deaths may be necessary. Studies of the clinical judgements of forensic pathologists using clinical vignettes (e.g. DuFlo, 1998) may assist in better understanding how these diagnoses are made by coroners and forensic pathologists.

Third, more information is needed about the drug use careers and treatment histories of those who are dying from opioid overdose. How many, for example, are opioid dependent and in treatment but not notified to the Home Office? How many have been voluntarily or involuntarily abstinent from opioids in the days, weeks or months prior to their deaths? What have been the circumstances in which they used the prescribed and illicit opioids that led to their deaths? This information could be collected as part of a prospective study of overdose deaths.

Fourth, more information is needed on the availability and source of diverted methadone in the UK. Where was the methadone obtained in overdose deaths? Where is methadone obtained by illicit opioid users? How is diverted methadone used by persons who are not in treatment? Is it to avert withdrawal or for its euphoric effects? Work by Darke et al (1996c) and more recently by Fountain et al (1998) shows that it is possible to collect these data from drug users.

An important issue is which opioid users provide the primary source of diverted methadone. Is it new users who enter MMT, patients who obtain multiple scripts from different doctors, or patients undergoing extended methadone withdrawal? The answer to this question will have implications for reducing methadone diversion. If, for example, a major source of diversion proved to be patients in methadone reduction then the use of non-opioid agents, such as, lofexidene, to complete withdrawal more rapidly could substantially reduce the amount of methadone that was diverted. If patients enrolled in MMT are a major source of diverted methadone, then greater supervision of dosing, and better regulatory controls to avoid double-scripting, may be required to reduce diversion.

7.2 WHAT CAN BE DONE TO REDUCE METHADONE RELATED DEATHS?

Methadone-related overdose deaths can probably be reduced by increasing controls on the way that methadone is prescribed. This may be achieved, for example, by restricting the right of private physicians to prescribe certain forms of methadone (e.g. tablets or injectable), by restricting patients to specialist MMT clinics during induction and stabilisation, and by substantially reducing or removing the right to take-away methadone doses early in treatment. There is suggestive evidence that these measures have reduced methadone deaths in other countries, such as, Western Australia in the 1980s and the USA in the early 1970s. A controlled evaluation of the implementation of these measures would provide useful information on their effectiveness, cost and side-effects.

There is some risk that increasing restrictions on methadone availability may reduce the number of patients in treatment. If this occurred, a reduction in methadone-related deaths may be offset by an increasing number of opioid deaths in which methadone does not make a contribution. In principle, this is an empirical issue that could be resolved by examining the

impact of increased restrictions on opioid overdose death rates, and the contribution that heroin and methadone make to them.

Other options might also be implemented in conjunction with any increased restrictions on methadone prescribing and administration. These should include education of prescribers and potential users of methadone about the risks of overdose. In the case of prescribers this would include education about the risks during induction and how to reduce them, and about the risks of methadone diversion. For methadone consumers, and illicit opioid users more generally, this would include information on the risks of methadone overdose in non-opioid tolerant individuals and the risks of combining methadone with other CNS depressant drugs, such as alcohol and benzodiazepines. Opioid users also need to be educated in elementary CPR (Darke & Hall, 1997), and encouraged to call an ambulance sooner than often occurs at present (Hall, 1996b). A more controversial option may be to trial the distribution of the opioid antagonist naloxone to opioid users (Strang et al., 1996). Ideally, the implementation of these interventions would be evaluated.

8. CONCLUSIONS

The data indicate that opioid overdose deaths in general, and methadone overdose deaths in particular, have increased in the UK over the past decade. The overall rate of opioid overdose deaths in the UK is substantially lower than Australia but the proportion of deaths to which methadone makes a contribution appears to be higher in the UK than Australia, and in many cases these deaths occur among illicit opioid users who use diverted methadone. It is difficult to be sure on the basis of available data, but it seems likely that the way in which MMT, and possibly methadone reduction, are delivered in the UK partly explain the high proportion of UK overdose deaths to which methadone makes a contribution.

The challenge facing the health service in the United Kingdom is to develop a system that maximises access to MMT for opioid dependent persons while reducing the risk of methadone overdose death from the illicit use of diverted methadone. It is desirable to reduce the diversion and recreational use of methadone, as this seems to be associated with a substantial proportion of opioid overdose mortality within the United Kingdom. The aim must be to do so in such as way that it does not adversely affect the access of heroin dependent persons to MMT.

To that end, it is worth considering trialing interventions that may reduce opioid and methadone-related overdose deaths. These include: different methods of delivering MMT in geographically separated areas in the UK to reduce diversion; and education of prescribers and users of methadone about the risks of overdose. The impact of these interventions on rates of methadone and other opioid overdose deaths could be evaluated. This would better be done as a planned activity rather than in the opportunistic and reactive way in which many studies have been done to date.

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APPENDIX A: POSSIBLE CONTRIBUTION OF THE ROUTE OF ADMINISTRATION TO THE RELATIVE RISK OF OPIOID OVERDOSE DEATH IN THE UK AND AUSTRALIA

Assuming:

1. The risk of overdose death pa in injecting heroin users = 0.01
2. The relative risk of overdose death pa in heroin smokers = 1/27.7 = 0.036
3. The prevalence of opioid dependence in the two countries is equivalent
4. All heroin dependent persons in Australia are injecting users

Then the overdose rate in the UK is given by

$$\text{Rate} = (0.01 * p_I) + (0.01 * 0.036 * p_S)$$

Where p_I = the proportion of heroin-dependent individuals whose principal route of administration is injecting

P_S = the proportion of heroin individuals whose principal route of administration is smoking

Proportion of heroin smokers in the UK	UK overdose rate[#]		Australian overdose rate	Relative risk
0.1	(0.009 + 0.000036)	0.00904	0.01	0.90
0.2	(0.008 + 0.000072)	0.00807	0.01	0.80
0.3	(0.007 + 0.000108)	0.00711	0.01	0.71
0.4	(0.006 + 0.000144)	0.00614	0.01	0.61
0.5	(0.005 + 0.00018	0.00518	0.01	0.52
0.6	(0.004 + 0.00022)	0.00422	0.01	0.42
0.7	(0.003 + 0.000252)	0.00325	0.01	0.33
0.8	(0.002 + 0.00029)	0.00229	0.01	0.23
0.9	(0.001 + 0.00027)	0.00127	0.01	0.13
1.0	(0 + 0.00036)	0.00036	0.01	0.04

APPENDIX B: POSSIBLE CONTRIBUTION OF METHADONE MAINTENANCE DELIVERY TO THE RELATIVE RISK OF OPIOID OVERDOSE DEATH IN THE UK AND AUSTRALIA

Assuming:

1. The risk of fatal opioid overdose per annum = 0.01
2. The relative risk of opioid overdose in MMT = 0.24[1]
3. The proportion of opioid dependent individuals in MMT in Australia = 0.30

Then the overdose rate in the UK is given by

$$\text{Rate} = (0.01 * 0.24 * p_{MMT}) + (0.01 * (1 - p_{MMT}))$$

Where p_{MMT} = the proportion of opioid dependent individuals enrolled in MMT

Proportion of those in MMT in the UK	UK overdose rate[#]	Australian overdose rate	Relative risk
0.30	0.00772	0.00772	1.00
0.40	0.00696	0.00772	0.90
0.50	0.00620	0.00772	0.80
0.60	0.00544	0.00772	0.70
0.70	0.00468	0.00772	0.61
0.80	0.00392	0.00772	0.51
0.90	0.00316	0.00772	0.41

[1] Estimate taken from Caplehorn et al. (1996).