SUBSTANCE ABUSE DEPARTMENT

OPIOID OVERDOSE

Trends, Risk Factors,

Interventions and Priorities

for Action

SOCIAL CHANGE AND MENTAL HEALTH
WORLD HEALTH ORGANIZATION

Abstract

International illicit production of opioids has increased in recent years, as has illicit opioid use in many countries, especially the injection of heroin. The number of opioid overdose deaths, though difficult to assess, appears to have risen in a number of countries over the past decade but lack of agreement on the definition and classification of opioid overdoses and other drug-related deaths hampers comparisons between countries. There are many difficulties in defining and recording overdose and other drug-related deaths. Reliable cause-specific mortality data for opioid users is particularly lacking.

Research from a number of countries suggests that individual variations in tolerance and polydrug use are contributory factors to fatal and non-fatal opioid (primarily heroin) overdoses. Despite this evidence the view persists that opioid purity is the sole cause of opioid overdose deaths. This diverts attention away from potentially modifiable factors that may reduce overdose deaths. It also de-emphasizes the fact that overdoses often occur in the company of others which provide an opportunity to intervene. Delays in response to overdoses may be a major remediable cause of overdose deaths.

Deaths from heroin and other opioid overdose could potentially be reduced by: educating opioid users about the risks of polydrug use and injecting alone through, for example, peer outreach and social networks; improving their responses to the overdose of others, for example, by reducing fears of seeking emergency or medical assistance; teaching basic skills in cardiopulmonary resuscitation (CPR) to keep overdose victims alive until help arrives, and increasing the number of opioid users in treatment, particularly older heroin users, in methadone maintenance treatment.

Priorities for action include: better definitions and recording of opioid overdose and other drug-related deaths; the implementation and evaluation of preventive interventions based upon available knowledge; and more studies of risk factors for non-fatal and fatal opioid overdoses to improve preventive interventions.

Acknowledgements

Contents

1.   Introduction

This document briefly reviews international data on trends in illicit opioid use and opioid overdose deaths, in order to identify research priorities and strategies for preventing such. It was prompted by an International Symposium on illicit opioid overdose deaths, which was held in Sydney, Australia, in August 1997 and hosted by the National Drug and Alcohol Research Centre, a World Health Organization Collaborating Centre. Overdose from illicit opioid use was selected as a focus for the International Symposium because opioid use (and heroin use in particular) has increased in many developed and developing countries over the past decade. In many of these countries, opioid overdose deaths are a major cause of premature death related to illicit drug use and make a major contribution to the total number of deaths among certain populations in some countries. In Australia in 1995, for example, opioid overdose deaths accounted for 76% of all deaths due to illicit drug use, and 9% of all deaths, among young adults aged 15 to 44 years (*Hall & Darke, 1997*). In Glasgow (Scotland), just under one-third of all deaths among young adults aged 15-35 years were drug-related and the majority of these were opioid-related (*Frischer et al., 1997*).

The report begins with an overview of international trends in the nature and extent of the illicit use of opioids. A description is then given of mortality related to illicit opioid use and the difficulties in defining and recording drug overdoses. An analysis is provided of the risk factors that have been identified to date for illicit opioid overdose deaths. Most of these risk factors have been identified in recent studies of fatal and non-fatal opioid overdoses. They include: variations in opioid tolerance; variations in heroin and other opioid purity; polydrug use; contaminants and adulterants; and other risk factors related to the social environments in which opioid use occurs.

The analysis of these risk factors suggests a number of potential interventions that may reduce opioid overdose deaths. These include measures to reduce the incidence of opioid overdoses (e.g. outreach, the use of social networks and peer education about risk factors) and those that aim to reduce the fatality rate (e.g. better peer responses to opioid overdoses). The document concludes with priorities for action to better define and record overdose and other drug-related deaths and to reduce the toll of overdose deaths due to the illicit use of opioid drugs.

2.   Nature and extent of illicit opioid use

The 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. Accurate information on the nature and extent of heroin and other opioid use is difficult to obtain and interpret. The available evidence, however, suggests that there has been a global increase in the illicit production, transportation and consumption of opioids, especially heroin (*Childress, 1994; UNDCP, 1997*).

Heroin use has become increasingly common in some developed countries in North America and Europe and in Australia since the 1960s. More recently traditional patterns of opium use (mostly smoking) in some developing countries of southeast Asia (e.g. China, India, Nepal, Pakistan,

Thailand, and Viet Nam) have been replaced by the injection of opium solutions, heroin and buprenorphine (*Stimson et al., 1996; Stimson & Choopanya, 1998*). Opioid use and injection are also being reported in countries and regions where the illicit use of opioid drugs and opioid injection were previously unknown. This has been associated with new illicit opioid production in Colombia and Mexico (*International Narcotics Control Board, 1996*), and the establishment of new trafficking routes, such as through western and southern Africa and eastern Europe (*Adelekan & Stimson, 1997; International Narcotics Control Board, 1996*).

While illicit opioid use has generally been reported as increasing in recent decades, historical patterns of heroin use in some countries have been cyclical, with increases in illicit use being followed by periods of relative stability or even a decline in use. In Australia, an epidemic of heroin use occurred in the late 1960s and early 1970s which 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 and a new epidemic may be unfolding today (*Hall & Darke, 1997; Maher, 1996*). 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 southwest Asia, notably Pakistan. This form of heroin, which could be smoked, was attractive to young non-injecting users and fuelled an epidemic of heroin smoking (*Pearson, 1987*). There is recent evidence to suggest a new interest in heroin among the young in the UK (*Parker et al., 1998*). Recent evidence also suggests that the use of heroin has again become increasingly common in the United States of America. Unlike an earlier epidemic of heroin injecting in the US from 1964 to 1972 (*Boyle & Brunswick, 1980*), these increases in heroin use have occurred among younger users taking the drug intra-nasally (snorting) rather than injecting (*National Institutes of Health, 1997a*). This new "epidemic" of heroin use in the United States of America is in part associated with the availability of cheap, high purity heroin from South America (*National Institutes of Health, 1997a*). In Europe and the United States of America, the role of the media has come under some scrutiny for glamourizing heroin use and creating a climate in which heroin use is more socially acceptable, although there is no scientific evidence to prove that the media has encouraged increased use. Availability, price and purity are important influences on the extent and nature of illicit opioid use.

Heroin use is not increasing in all countries. In some European countries, for example the Netherlands, the number of young heroin users has been falling, whilst the number of older users has remained stable (*WHO, 1997a*). In Spain, the number of heroin users has stabilized in recent years, and the incidence of new heroin users may be decreasing. The mean age of heroin users and mean age at first heroin use has continued to rise in Spain since 1992 (*Delegacion del Gobierno para el Plan Nacional sobre Drogas, 1995*).

Heroin is not the only opioid of concern. The "traditional" opiates, such as opium and heroin, are increasingly sharing the scene with synthetic opioids (such as: buprenorphine; fentanyl; pethidine and methadone), diverted from medical sources. A range of locally-produced opioids is also used in different countries. In Western Australia and New Zealand, "home-bake" is manufactured from pharmaceutical preparations containing codeine and other opiates (*Black &*

Casswell, 1993). In Poland "kompot" and "soup" prepared from poppy straw are injected. In Ukraine "himier", a locally-produced solution also made from opiate poppy straw, is injected (*Rhodes & Fitch, 1997*). In Vietnam, "black water opium", prepared from the residue from opium smoking, is injected (*Power, 1993*).

Increased tolerance to opioids among users, declining purity of the drug, or changes in the availability of the type of opioids available, may lead some opioid smokers and snorters to make the transition to injection as their preferred route of administration. The mode of administration is changing in many regions. In Australia there is evidence of a new epidemic of heroin use among younger users, who initiated their use by snorting, but an important minority made the transition to injection once their opioid tolerance increased (*Maher, 1996*). The transition from opium smoking to heroin smoking and "chasing", then to heroin and buprenorphine injecting, is a familiar scenario in many developing countries, particularly those in which opium is produced or trafficking occurs, such as China, India, Nepal, Pakistan, Thailand, and Viet-Nam (*Stimson et al., 1996; Stimson & Choopanya, 1998*). There are now at least 127 countries and territories where injecting drug use occurs (*Ball, 1998; Stimson & Choopanya, 1996*). When users make a transition to injecting, the risk of overdose increases dramatically (*Gossop et al., 1996*) as does risk of HIV, hepatitis and other blood-borne virus infections.

Changes in route of administration are not always towards injection. Some countries have seen a transition from opioid injecting to smoking, chasing and snorting, particularly as drug purity has increased. Transitions from injecting to non-injecting use have also been reported as ways of reducing the risk of HIV infection. The transition from injecting to non-injecting heroin use has been observed in the United States and Europe (*Des Jarlais et al., 1994; De la Fuente et al., 1997; Griffiths et al., 1994*). In Spain, the route of heroin administration changed substantially between 1987 and 1997. At the beginning of the 1980s, 90% of heroin users who entered treatment were primarily injectors, by the late 1990s, about 50% were with notable regional variations. This change seems to have been due to the replacement of injection by "chinesing" which is the inhalation of the vapours produced when heroin is heated on aluminium foil (*De la Fuente et al., 1997*). This practice is common, particularly in European countries including the Netherlands and the UK. The United States Community Epidemiology Work Group (CEWG), which has a tradition of identifying 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 among younger heroin users, probably in a context of increasingly pure heroin. 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, 1997a*). The CEWG has also reported a new method of heroin use: heroin is dissolved and squirted into the nostrils using a syringe, nasal spray or dropper (*National Institutes of Health, 1997a*).

These changes in illicit opioid availability, the emergence of new patterns of heroin use, and shifts in the modes of administration influenced by variations in the purity and availability of different opioids, all affect the risks of transmitting blood-borne infections and experiencing an opioid overdose.

3.   Opioid-related mortality

Whilst the estimated worldwide production of heroin is reported to have more than doubled since 1985 (*Childress, 1994; UNDCP, 1997*), the prevalence of heroin use in general populations is generally comparatively low, when compared with alcohol, tobacco and other drugs such as cannabis. Typically less than 2% of the adult population have ever used heroin, and less than 1% meet criteria for heroin dependence, even in countries with a widely recognized heroin problem, such as the United States of America, Australia, and some European countries (*Anthony & Helzer, 1991; Anthony et al, 1994; Childress, 1994; Commonwealth Department of Human Services and Health, 1994; EMCDDA, 1996*). The number of drug injectors, predominately opioid injectors, worldwide has been estimated at 5.3 million (*Frischer et al., 1994*). This figure is a conservative one extrapolated from an earlier estimate (*Case et al., 1992*) and is likely, given the evidence for the spread of drug injection to countries where it was previously unknown, to be an underestimate.

In spite of their relatively low prevalence of use, heroin and other opioids cause widespread health and social problems. In many countries, opioids are the most commonly used drugs among those seeking treatment for illicit drug use and among illicit drug users coming into contact with the criminal justice system. In most countries of the European Union for example, between 70% - 95% of those entering treatment for drug problems are using heroin as their main drug (*EMCDDA, 1997a*). There are some exceptions, for example in some northern European countries amphetamines are the most commonly used drugs amongst those in treatment (*EMCDDA, 1997a; WHO, 1997b*). The same is also true in some countries outside of Europe, for example in the Philippines, Japan and the Republic of Korea *(WHO, 1997b)*. Opioid users have generally been shown to have higher mortality rates than users of other drugs, for example amphetamines (*Tunving, 1988*), but drug related deaths are often associated with polydrug use, including opioid/amphetamine combinations (see below).

3.1   Overall mortality rates among opioid users

Longitudinal and cross-sectional studies in Europe and the United States indicate that the yearly mortality from all causes (including HIV/AIDS) is between 1% and 3% among dependent opioid (primarily heroin) users *(Danish National Board of Health, 1997; English et al, 1995; EMCDDA, 1997a & 1997b; Frischer et al., 1997; Oppenheimer et al., 1994)*. These estimates include both injectors and non-injectors. For injectors alone, slightly higher all-cause rates have been estimated. Frischer and colleagues, in their review, suggest an annual all-cause mortality rate (including HIV/AIDS) among injectors of 3-4% (*Frischer et al, 1994*). Mortality rates among injectors (excluding HIV/AIDS) of 1-2% are reported (*EMCDDA, 1997a & 1997b*), similar to those rates recorded pre-HIV/AIDS *(English et al., 1995)*.

There is also evidence that mortality rates among opioid users have recently increased in some countries (*Darke & Hall, 1997; Danish National Board of Health, 1997*). An excellent review of the scientific literature on mortality among illicit drug users is to be found in the as yet unpublished report produced by the Associazione Italia per la Ricerca in Epidemiologia for the European Monitoring Centre on Drugs and Drug Addiction (*EMCDDA, 1997b*). The long-term

trend in drug-related deaths in countries of the European Union has been upwards since 1985. Many European Union countries had a sharp rise in the number of such deaths in the second half of the 1980s through to the early 1990s and beyond (*EMCDDA, 1997a*). Conversely, in some European countries, for example in Spain, the number of overdose deaths has stabilized or is decreasing (*Delegacion del Gobierno para el Plan Nacional sobre Drogas,* 1997).

In western Europe, dependent heroin injectors have a risk of premature death that may be 20 to 30 times higher than that among similar aged peers who do not use illicit drugs (*EMCDDA, 1997a*). In Glasgow, Scotland, drug injectors are 22 times more likely to die than their peers, and mortality rates have increased since the early 1980s (*Frischer et al., 1997*). Mortality rates among opioid users in Catalonia, Spain, increased from 13.8 to 34.8 (per 1,000) between 1985 and 1991 (*Orti et al., 1996*). In Amsterdam, the Netherlands, a mortality rate of 32.3 per 1000 was reported for drug injectors who were recruited through low-threshold methadone clinics and a sexually-transmitted disease clinic (*van Haastrecht et al., 1996*). In the same study, non-injecting opioid users had a mortality rate of 8.8 per 1000. In Milan, Italy, an overall mortality rate of 25.2 per 1000 was reported for injectors attending treatment centres. These rates remained under 16 from 1981 to 1986 before increasing rapidly to 63.8 per 1000 in the first half of 1991 (*Galli & Mussicco, 1994*).

A WHO multi-site collaborative study initiated in 1991, examined the mortality of injecting drug users in nine cities in eastern and western Europe and the United States (listed in Table 1 below), using as far as possible a common methodology. These injectors were mainly heroin users, with the exception of those from Moscow where a substantial minority were amphetamine-type stimulant users. They were attending treatment centres in the nine cities between 1980 and 1992. Mortality rates ranging from 3.2 per 1000 among female injectors in Liverpool to 35.5 per 1000 among male injectors in Barcelona were reported. Data from this study, including the mortality rates for men and women injectors in each of the cities, are summarized in Table 1 below. Mortality rates were higher for male injectors than for female injectors. Also of note are the comparatively low mortality rates reported for injectors in Liverpool (UK), compared with other cities in this study.

Table 1. Mortality rates (per 1000 person years) of injecting drug users attending treatment facilities in nine cities between 1980-1992

City	Study Period	Total N	Deaths N (female)	Mortality Rate Males	Mortality Rate Females
Barcelona (Spain)	1987-92	4201	460 (95)	35.5	25.0
Glasgow (UK)	1983-92	367	29 (10)	18.1	11.3
Liverpool (UK)	1984-92	815	15 (3)	5.3	3.2
Naples (Italy)	1980-92	3785	200 (8)	10.5	9.5
New Haven (USA)	1985-91	1588	58 (20)	13.3	9.7
Moscow (Russia)	1980-92	505	49 (8)	22.6	14.8
Rome (Italy)	1980-92	4660	639 (111)	12.7	12.5
Turin (Italy)	1978-92	6975	563 (101)	16.8	16.6
Warsaw (Poland)	1983-92	656	82 (13)	27.9	15.7

Source: WHO multi-site collaborative study on the mortality of injecting drug users attending treatment facilities in nine cities (unpublished report available on request from WHO/SAB).

3.2   Cause-specific mortality

Since heroin and other opioids are commonly used by injection, health risks including those of HIV and viral hepatitis transmission, are substantial (*Donoghoe & Wodak, 1998*). HIV/AIDS has had devastating consequences and is a leading cause of death for drug injectors in many countries. However, even prior to the advent of HIV/AIDS drug injectors had high rates of mortality. English and colleagues, on the basis of pooled data from twelve studies conducted prior to HIV/AIDS, estimated that opioid injectors had a relative risk of premature death that was 13 times greater than their non-using peers (*English et al., 1995*). High rates of mortality among drug users were also found, for example, in longitudinal studies conducted in the United Kingdom and the United States many years before the advent of HIV/AIDS. In the UK, Bewley and colleagues found mortality rates among heroin users followed up between 1954 and 1964 to be 28 times that of their peers (27 per 1000) and 39% of these deaths were attributed to overdose. Suicide and other violent deaths were also relatively common in this group (*Bewley et al., 1968*). In the US, opiate users followed up between 1975 and 1979 (pre-HIV/AIDS), had a mortality rate of 15.2 per 1000 (*Joe et al., 1982*). In Warsaw (Poland) and Moscow (Russia), male drug injectors had a high mortality rate, even in the absence of HIV/AIDS (27.9 and 22.6 per 1000). In Baltimore (United States) and Amsterdam (Netherlands), high mortality rates (17.1 and 16.0 per 1000) have been found among HIV-1 negative drug injectors (*van Ameijden et al., in press a*).

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 remains the leading cause of death

among drug injectors (*Darke & Zador, 1996; EMCDDA, 1997a & 1997b; Frischer et al., 1994; Oppenheimer et al., 1994; Perucci et al., 1991*). It has been suggested that the advent of HIV has focused attention on AIDS and away from deaths as a consequence of overdose (*Farrell et al., 1996*). In countries with low HIV prevalence among injectors, such as Australia, overdose is the major cause of death (*Darke et al., 1996a*). Even in countries where there is relatively high HIV prevalence among drug injectors, such as Italy and Spain, overdose continues to be an important cause of death (*Galli & Mussicco, 1994; Orti et al., 1996*). Some studies show that HIV-seropositive injectors are more likely to die of overdose than HIV-seronegative injectors (*Eskild et al., 1993; van Ameijden et al., in press a.; Zaccarelli et al., 1994*). Reported explanations for this include: enhanced susceptibility to overdose among immunosupressed injectors; suicidal behaviour and risk-taking psychosocial characteristics (*van Ameijden et al., in press b*). Overdose, nonetheless, remains poorly understood because of the methodological difficulties and confounding factors discussed below.

The WHO multi-site collaborative study recorded reported causes of death among drug injectors in nine cities, however, because of differences in recording procedures and a large proportion of non-defined or ill-defined causes in some cities these data are not strictly comparable. These data (summarized in Table 2 below) indicate that overdose and HIV/AIDS were the most commonly reported causes of death. Of particular note are the relatively high mortality rates among drug injectors even in the absence of HIV/AIDS in, for example, Moscow and Warsaw (see also Table 1 above). In Glasgow and Liverpool (UK), HIV does not seem to be an important factor in drug-related deaths. The early establishment of syringe-exchanges (1986 in Liverpool and 1987 in Glasgow), better access to drug treatment and other interventions introduced in the UK to prevent the transmission of HIV, seem to have been successful in these cities, particularly compared with the cities in Spain and Italy which introduced such measures much later. This hypothesis is also supported by evidence for the effectiveness of early interventions for the prevention of HIV among drug using populations presented elsewhere (*Ball, 1998*).

Table 2. Proportional mortality for major ICD-9 categories of cause of death among injecting drug users attending treatment facilities in nine cities 1980-1992

City	AIDS 042-044, 279.5		Mental Disorders 290-319		Injury & Poisoning 800-999		Disease of Circulatory System 390-459		Ill-defined Conditions 780-799		Other Causes		Total number of deaths
	N	%	N	%	N	%	N	%	N	%	N	%	N
Barcelona (Spain)	121	26.3	6	1.3	239	51.9	21	4.6	0	0.0	73	15.9	460
Glasgow (UK)	1	3.4	4	13.6	19	65.5	0	0.0	0	0.0	5	17.3	29
Liverpool (UK)	0	0.0	3	20.0	8	53.3	0	0.0	0	0.0	4	26.7	15
Naples (Italy)	35	17.5	32	16.0	50	25.0	6	3.0	41	20.5	36	18.0	200
New Haven (USA)	16	27.6	0	0.0	11	19.0	4	6.9	15	25.9	12	20.6	58
Moscow (Russia)	0	0.0	1	2.0	20	40.8	14	28.6	0	0.0	14	28.6	49
Rome (Italy)	188	29.4	177	27.8	94	14.7	38	5.9	13	2.0	129	20.2	639
Turin (Italy)	99	17.6	66	11.7	274	48.7	14	2.5	26	4.6	84	14.9	563
Warsaw (Poland)	0	0.0	4	4.9	26	31.7	4	4.9	35	42.7	13	15.8	82

Source: WHO multi-site collaborative study on the mortality of injecting drug users attending treatment facilities in nine cities (unpublished report available on request from WHO/SAB).

These data also highlight difficulties in defining and recording "overdose" and other drug related deaths, and the need for improvements in reporting procedures and definitions. These issues are discussed in more detail below. In this study, overdose deaths in Barcelona, Glasgow, Liverpool, Turin and Moscow were coded in the category "injury and poisoning" (ICD-9 800-999), however, this category could also include suicide by poisoning, accidents and homicide. The high proportion of deaths coded as "mental disorders" (ICD-9 290-319) in Glasgow, Liverpool, Naples and Rome suggests that some overdose deaths were recorded in this category. ICD-9 codes from 290 to 319 categorize the full range of mental disorders. ICD-9 292 refers specifically to "drug psychoses" and code 292.2 to "pathological drug intoxication". Code 304 refers specifically to "drug dependence" and 305 to "non-dependent abuse of drugs". Many deaths, particularly in Naples, New Haven and Warsaw were recorded as "ill-defined conditions". Some "overdose" deaths may also have been recorded in this category. In all cities many deaths were recorded under "other causes", again this could include overdose.

4. Methadone-related overdose

Opioid-dependent persons in opioid substitution programmes may be at risk of overdose. In addition the use of illicit or diverted methadone, and deaths associated with such use, has resulted in community and media concern in several developed countries including Australia, the United Kingdom and the United States. There have been a number of methadone-related deaths in Australia, for example, among persons enrolled in methadone maintenance programmes, as well as among heroin users who used methadone diverted from a legitimate source (*Harding-Pink,*

1993). These deaths, like heroin overdose deaths, are often associated with concomitant use of other drugs, including alcohol, benzodiazepines and heroin (*Sunjic & Zador, 1997*). Concern has been expressed about increasing numbers of deaths from methadone in some countries including: Australia (*Harding-Pink, 1993*), Denmark (*Steentoft et al., 1996*) and the United Kingdom, where between 1974 and 1992 the number of deaths involving methadone rose dramatically (*Neeleman and Farrell, 1997; Newcombe, 1996*). Methadone may produce overdose, for example when tolerance is incorrectly assessed, when doses are combined or when combinations of other drugs are taken, but overall the evidence indicates that methadone maintenance has a substantial protective effect on mortality from opioid overdose and mortality from all causes (*Caplehorn et al., 1994; Darke & Zador, 1996; Gronbladh et al., 1990; Sunjic & Zador, 1997; van Ameijden et al., in press a.*).

In the United Kingdom, despite significant increases in recent years in the number of drug users for whom methadone has been prescribed, the percentage of deaths has remained constant at around 0.25% (*Department of Health, 1996*). The increasing numbers of methadone and heroin deaths in the UK are reported to be associated with overall increases in the population at risk (*Neeleman & Farrell, 1997*). Similarly in New South Wales, Australia, whilst the number of persons enrolled in methadone treatment increased substantially between 1990 and 1995, the percentage of deaths remained constant. It has also been suggested that methadone-related deaths in New South Wales have been over-reported. Those cases recorded as methadone-caused deaths included all cases in which methadone was detected, however 89% of these involved other drugs. Furthermore almost half of these deaths occurred among individuals not registered in methadone maintenance treatment and were related to diverted sources of methadone (*Sunjic & Zador, 1997*). In the United States, Drug Abuse Warning Network (DAWN) data show comparatively low rates of methadone mentions among person attending emergency rooms for drug-related episodes and among drug-related deaths. Methadone maintenance has been widely evaluated and a majority of studies conclude that methadone maintenance is an important means of treating heroin addiction, reducing heroin use, reducing crime and lowering risk of premature death, including death from overdose (*Ward, Mattick & Hall, 1992; Mattick, 1994; Marsch, 1998*). Methadone maintenance has also been found to be effective in reducing the spread of HIV associated with injection drug use (*Des Jarlais et al., 1992; Marsch, 1998; Metzger et al., 1993*).

Research is necessary to investigate how to train staff better and regulate programmes in order to maximize the protective effect of methadone and minimize its contribution to opioid overdose mortality. Increased supervision and regulation of prescribers may help to minimize methadone overdose. Much of the international evidence from developed countries suggests that methadone programmes are best delivered by staff with specialized training and under close supervision. However, some community-based methadone programmes in developing countries, such as Thailand, provide only limited supervision to prescribers, but both mortality and overdose rates are reported to be low. Community-based programmes providing only limited supervision need careful evaluation.

5. Difficulties in defining and recording "overdose" and other drug related deaths

The lack of standardization in defining and classifying overdose and other drug-related deaths has been debated previously by the World Health Organization (*WHO, 1993*). The lack of a common terminology or classification system was seen as one of the major problems for international comparisons of drug-related mortality data (*WHO, 1993*). This point is well illustrated by the 1992 multi-site collaborative study on the mortality of injecting drug users attending treatment facilities in nine cities (see above), where "overdoses" were recorded as "mental disorders", "injuries and poisonings", as "ill-defined conditions" and with "other causes of death". An opioid drug overdose is generally understood to be an excessive dose of an opioid which results in coma and respiratory failure (*Proudfoot, 1988*). According to the *WHO Lexicon of Alcohol and Drug Terms* (*WHO, 1994*) an overdose is defined as: *"The use of any drug in such an amount that acute adverse physical or mental effects are produced"*. The World Health Organization has previously cautioned against the use of the term "overdose" (because of uncertainties regarding the association between drug purity, tolerance, consumption of combinations of drugs and alcohol and other factors and their relationship with drug-related deaths some of which are examined in more detail below) recommending instead the use of the ICD-10 classification of "**acute intoxication**" (*WHO, 1993*).

The current tenth revision of the *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* (*WHO, 1992*) allows for the classification of opioid overdose and other drug related deaths under a range of codes. The most appropriate ICD-10 codes may be *F10 to F19 Mental and behavioural disorders due to psychoactive substance use* with an appropriate fourth character subdivision. In the case of an opioid overdose this would be *F11.0 Mental and behavioural disorders due to use of opioids - acute intoxication due to use of opioids* for those with a substance use disorder.

Acute intoxication is defined by WHO as:

> "A condition that follows the administration of a psychoactive substance resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour, or other psychophysiological functions and responses. The disturbances are directly related to the acute pharmacological effects of the substance and resolve with time, with complete recovery, except where tissue damage or other complications have arisen. Complications may include trauma, inhalation of vomitus, delirium, coma, convulsions and other medical complications. The nature of these complications depends on the pharmacological class of substance and mode of administration" (*WHO, 1993 p.321*).

For those who do not have a substance use disorder, an overdose can be recorded under ICD-10 *T40 Poisoning by narcotics and psychodysleptics - hallucinogens*. Alternatively *X40-49 (accidental poisoning), X60-X69 (intentional poisoning) or Y10-Y19 (poisoning undetermined intent)* may be applied. For opioid the relevant codes are: *X42, Y62* and *Y12*. The current ICD classification does not allow for the recording of information regarding the route of administration (e.g. by injection).

Some countries have developed additional registers of drug-related deaths to provide better information (*Danish National Board of Health, 1997*). Changes in the tenth revision 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 may improve the classification and coding of drug-related deaths but its introduction will take time, 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 at the time of writing, although most have plans to introduce it over the next three or four years (*Danish National Board of Health, 1997*). ICD-10 allows for the recording of both underlying and contributing causes which should better capture drug-related deaths.

Countries which collect drug-related death data, even if classified according to the ICD coding system, experience other problems in ascertaining the cause of death. Toxicological analysis and forensic examination are not always undertaken to assess the contribution of opioid use to deaths. The technology required for such analysis and examination is often not accessible or affordable to those in developing countries. Different countries have different guidelines as to which deaths become subject to an investigation. For example in the United States, which has a relatively sophisticated system, only about 20% of all deaths are investigated by medical examiners or coroners, and this varies from State to State (*National Institutes of Health, 1997c*). Even in circumstances and countries where examinations are conducted, toxicological and forensic data may not be considered when the ICD code is determined. Countries also differ in their attitudes and traditions in the use of ICD codes, their laws and regulations regarding registration of deaths, and the extent to which information from death certificates is transferred to the death register (*Danish National Board of Health, 1997*). Even within countries there are differences. In the United States of America, for example, investigative practices vary between different jurisdictions (whether State, county, district or city). In some jurisdictions licensed physicians, and sometimes expert forensic pathologists, are required to perform the investigation, whilst in other jurisdictions the examiner need not even hold a medical qualification (*National Institutes of Health, 1997c*). The nature and extent of the investigation vary from country to country and between jurisdictions within countries. Again taking the example of the United States, in some circumstances a full postmortem is performed whilst in others only an external examination of the body is undertaken (*National Institutes of Health, 1997c*).

All these factors mean that opioid overdose deaths are often under-reported in national registers (*Lecomte et al., 1995; Rodriguez et al., 1993*). The same under-reporting has also been noted with regard to cocaine-related deaths (*Pollock et al., 1991*). In addition to the problem of under-reporting, national death registers are also often slow to report their results. Drug-related deaths can take more than a year to be nationally registered even in countries with sophisticated and well-developed reporting systems (*Danish National Board of Health, 1997; National Institutes of Health, 1997c*). Registers which are slow to report results are of limited use in detecting trends in illicit drug deaths in a way that permits rapid and effective intervention.

Despite these problems with existing data, there is good evidence from some countries, including: Australia *(Hall & Darke, 1997)*; Austria (*EMCDDA, 1997a*); Denmark (*EMCDDA, 1997a*); England and Wales (*Neeleman & Farrell, 1997*); Greece (*EMCDDA, 1997a*); Italy (*EMCDDA,*

1997a); Portugal (*EMCDDA, 1997a*); Scotland (Glasgow) (*Frischer et al., 1997*); and Spain (Catalonia) (*Orti et al., 1996*), that the number of illicit opioid overdose fatalities has increased in recent years. Even so, standard epidemiological techniques cannot easily be adapted to calculate rates of overdose and drug-related deaths because there are no reliable estimates of denominator populations of drug users in these countries.

Even when overdose mortality data are collected they are not comparable across countries because of the lack of standardization and categorization. There is typically substantial variation in the number of deaths between countries which raises the question of whether these differences are real or simply reflect differences in reporting and registration between countries (*Danish National Board of Health, 1997*). These problems suggest that comparisons between countries should not be made, however, in the absence of more reliable data they inevitably are.

The problems in studying opioid overdose deaths are compounded in attempts to study the prevalence and causes of nonfatal opioid overdoses. These appear to be common events in the careers of many illicit opioid users (*Darke et al., 1996*) but they usually do not come to medical attention, even in developed countries. When they do come to medical attention, good data may not be collected on them. There are even greater problems in studying these events in developing countries which do not have basic health care or systems for the collection of health data.

6.   Risk factors

6.1   Opioid purity and individual tolerance

Evidence from developed countries suggests that variations in individual tolerance appear to be a factor in opioid overdose deaths. Overdose deaths are more common after release from prison or after detoxification when the user's opioid tolerance has been substantially reduced (*Darke et al., 1996a*). Opioid users who "drop out" of treatment for their drug use have been shown to have a risk of death from overdose eightfold higher in the first twelve months after drop out compared with those retained in treatment (*Davoli et al., 1993*). There is a paucity of research evidence regarding tolerance to opioids, particularly for opioid users in developing countries. It is usual 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.

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*). 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 show high blood morphine levels (*Darke & Zador, 1996; Püschel, 1997*). 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 or heroin users who have died of other causes (*Darke & Zador, 1996*). Moreover, most of those who die of heroin overdoses, for example in Australia and Spain,

are older and experienced opioid users rather than the neophytes one might expect if purity was the sole explanation (*Darke & Zador, 1996*; *Delegacion del Gobierno para el Plan Nacional sobre Drogas,* 1997).

6.2   Consumption of alcohol, benzodiazepines and other drugs

A major risk factor for a heroin overdose appears to be the concurrent use of heroin with alcohol and other drugs (*Darke et al., 1997; Darke & Zador, 1996; Fugelstad 1994; Oppenheimer et al., 1994; Hammersley et al., 1995; Zador et al., 1996*). Polydrug use is common among drug users, and especially among heroin and other opioid users, in both developed and developing countries. In the United States of America, heroin users typically also use combinations of cocaine, cannabis, benzodiazepines and alcohol (*National Institutes of Health, 1997a*). In Phoenix, Arizona (United States of America), deaths have been associated with use of methamphetamine and morphine together. In the first eight months of 1996 five such deaths were reported (*National Institutes of Health, 1997b*). In Europe, the use of various combinations of cocaine and heroin, benzodiazepines and heroin, alcohol and heroin, are common. Heroin and barbiturate combinations are still common in some locations, for example Hamburg in Germany (*Püschel, 1997*), but not to the extent that barbiturates were used by heroin users during the mid-1960s and 1970s, for example, in the United Kingdom (*Power, 1994*). In many European Union countries, the majority of recorded drug-related deaths are of heroin users. Usually overdose is the cause of death and a mixture of drugs, including alcohol, involved (*EMCDDA, 1996 & 1997a*). In the Czech Republic, combinations of methamphetamine ("Pervitin") and heroin are typically used by drug injectors (*WHO, 1997b*). "Himier", (an opium solution), and "vint", (an amphetamine-type stimulant produced from ephedrine), are used in combination in the Ukraine (*Rhodes & Fitch, 1997*). In Australia, alcohol, benzodiazepines and heroin are used in combination (*Darke & Hall, 1995*). In Thailand, methamphetamine and heroin are often used together. In Viet Nam, morphine and a wide range of pharmaceuticals, including: benzodiazepines and barbiturates, are mixed in the syringe or a communal pot with "black water opium" and injected. Pethidine is also often mixed with the "black water opium" solution (*Power, 1993*). In India, drug injectors mix buprenorphine with benzodiazepines and antihistamines (*WHO, in press a*). Combinations of cocaine and heroin (called a "speed-ball" in the United States) are increasingly used in countries in Latin America. Such combinations increase overdose risk considerably and make it difficult to attribute causation to a specific substance used (*Gutierrez-Cebollada et al., 1994; Risser & Schneider, 1994*). The mechanisms by which combinations of drugs contribute to overdose risk are not clearly understood, and require further investigation.

6.3   Contaminants and adulterants

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 (*Ruttenber & Luke, 1984*). Crude preparation methods used for producing opioid solutions - such as "kompot" and "himier", made from opium poppy straw in Poland and the Ukraine and "home-bake" made, from over-the-counter medications containing opiates in Western Australia and New Zealand - use various toxic substances including gasoline, industrial solvents, sulphuric acid and sodium hydroxide. Impurities can originate during the manufacturing process or are introduced

later to increase the volume of the drug to increase profits from sale. Some substances are added to enhance the drug effects, for example different pharmaceuticals are added to "black water opium" solutions in Viet Nam (*Power, 1993*). Lack of access to clean water for preparing injecting solutions is a major problem for drug injectors from many developing countries. The role of such contaminants and adulterants in opioid-related overdose deaths is unclear and subject to much regional variation (*Darke & Zador, 1996*).

6.4   General health status of opioid users

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, 1998*). These health conditions may physically weaken opioid users and increase their vulnerability to overdose death. The health status of opioid users in most developing countries is even poorer than that in the developed countries and these factors may play an even more important role in opioid overdose in these countries. 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. These multi-site studies are currently being developed by the World Health Organization, Programme on Substance Abuse, in collaboration with the European Monitoring Centre on Drugs and Drug Addiction, the United Nations International Drug Control Programme, and experts from around the world *(WHO, in press b)*.

6.5   Other factors

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 et al., 1996b*). Moreover, the elapse time from injection to death is often measured in hours 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. Injection of opioids, as compared to other routes of administration such as smoking, also increases overdose risk (*Gossop et al., 1996*) and some interventions seek to discourage transitions to injection or to encourage heroin injectors to use non-injection routes.

7.   Interventions

Interventions may aim to prevent overdose or improve the management of overdoses that occur. Either type of intervention may target individual behaviour change or promote an environment that reduces the risk of an overdose. These interventions and mechanisms for their delivery are described below. As with any interventions those described here should be subject to careful evaluation.   It should be recognized that opportunities for such interventions, and the

circumstances which create such opportunities, vary across different social, political and cultural contexts.

7.1 Risk assessment and management

An intervention that can both prevent and improve the management of opioid overdose is the education of drug users and their peers who may be present during an overdose (*Darke & Zador, 1996*). Such education could cover: risk assessment; risk management; specific strategies for prevention of overdose and better management of overdose, including resuscitation techniques. In order to be effective such education should raise awareness of personal risk, influence attitudes and take into account social influences on behaviour. Education should be timely and relevant. Contextualizing education about overdose is important. This can be done in different ways for example by linking it to personal experience of overdose, embedding it in a broader framework of discussion about drug use or associating overdose with other health problems. Education on overdose can be delivered during one-to-one contact during counselling or outreach, or as a group activity in treatment programmes or in prisons, for example. All information on overdose should be factual and non-judgemental. Another option suggested by Trautmann is to organize meetings for drug users, their peers, drug service workers and medical professionals to discuss the issue. Such an option may be most effective when there has been an overdose death in the community.

Individual risk assessment covers three domains: the drug user's health status and tolerance; the substances being used; and the context of use. Individual risk assessment assumes that the drug user is able to assess his or her health status and opioid tolerance in order to titrate the dose to avoid overdose. When ill and malnourished, or after a period of abstinence, tolerance may be lowered and so doses need to be reduced. Drug users should also be aware of the type, quantity and purity of the substance(s) they use, and the risks of using combinations of different substances (particularly using opioids with alcohol and benzodiazepines - see above). Finally, he or she should be aware of the specific risks that might exist within the drug use setting, and how to seek assistance if necessary. These risks need to be assessed before each drug-using event.

Drug users may use a range of information to assess their overdose risk. These include: observation of others, monitoring media and other sources of information, exchanging information through informal and formal drug user networks, seeking medical advice, mapping drug using venues and sympathetic health services, and using test doses of drugs. This information should enable the user to modify drug-using behaviour to minimize overdose and HIV infection.

7.2 Outreach, peer education and social network interventions

Interventions to educate drug users and promote behavioural change need to reach those at risk and must be acceptable and credible to the drug users. Outreach strategies aim to deliver timely and relevant information and services to "hard to reach" or "hidden" populations. Some attempt

to establish links between drug users and health and other helping services. Outreach programmes operate in various regions of the world, with many utilizing drug users and ex-drug users as peer educators and outreach workers *(Grund et al., 1996)*.

Outreach and peer education is becoming more common in some developing countries. In India and Nepal, for example, outreach interventions, such as needle and bleach distribution, and HIV prevention programmes provide opportunities for overdose prevention and management *(Chatterjee et al., 1996; Kanga, 1996; Maharjan et al., 1996; Peak et al., 1995)*. The "drop" overdose campaign, developed by the Drug and Alcohol Services Council of South Australia and SAVIVE is one example of a formal overdose education campaign targeting heroin users *(Drug and Alcohol Services Council, 1996)*. The Centre for Education and Information on Drugs and Alcohol (CEIDA) has been funded by the New South Wales (Australia) Health Department to evaluate a pilot peer education project targeting injecting drug users at risk of heroin overdose *(CEIDA, 1997)*. The project - the CEIDA Overdose Project - aims to reduce the frequency of overdose through behavioural changes that decrease individual risk and the creation of support networks of drug users, knowledgeable in overdose prevention and management.

In some countries drug users have self-organized to form drug-users organizations. Currently, these groups are involved principally in advocating on behalf of drug injectors and for implementing HIV prevention programmes. Some are also involved in issues relating to overdose. CEIDA has produced a booklet, together with drug users and ex-users called "Don't mix with your fix", this provides information about overdose, illustrated by stories about overdose experiences. Overdose is also addressed in newsletters of drug user groups, such as The Spike Collective of New Zealand *(Spike Collective, 1995)*. Analyses of drug users' social networks have been shown to offer opportunities to examine HIV and other risk behaviours and for developing and implementing interventions for prevention of drug use and HIV transmission *(Needle et al., 1995)*. Social network analysis has a similar potential for interventions to reduce and manage overdose.

7.3   Strategies targeting individual risk reduction

Drug users can adopt specific measures and behaviours that may reduce the risk of overdose. Some of these are simple and relatively easily implemented. Examples of individual overdose risk reduction strategies promoted in Australia include: testing the purity of the substance by using a small amount and splitting the dose (administering the drug in two or more doses); injecting slowly; avoiding combinations 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 among strategies promoted in Australia *(CEIDA, 1997; Drug and Alcohol Services Council 1996; Spike Collective, 1995)*. Some opioid users, however, may have little control over the administration of their drug and so may not be able to take precautionary measures. For example, it has been reported that in "shooting galleries" in Hanoi and Ho Chi Minh City, Viet Nam, the drug dealer manages all aspects of the opioid administration, including preparing and drawing up doses, providing the injecting equipment and injecting the client. It has been suggested therefore that outreach education also needs to target dealer-injectors as well

as the drug users (*Power, 1993*). Such interventions are controversial and should be carefully evaluated.

7.4   Increasing access to emergency and other health services

In many countries, particularly developing countries, the majority of overdose incidents are managed in the drug use setting, without involving formal emergency or health care sectors. There are various reasons for this: the overdose incident may be adequately managed by those present at the incident; there may be limited access to even the most basic health care services; 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 for fear of the legal consequences of being involved in an illegal activity (*Darke et al, 1996b*).

Strategies need to be developed which increase access to and use of services. This may require training of health professional staff to better understand drug users and provide services to them; training community health workers and volunteers in overdose interventions; reviewing requirements for reporting illicit drug users to authorities to ensure confidentiality of information; educating drug users on how to access services; and dispelling their fears about using such services. In Australia, those present at an overdose are encouraged to call an ambulance and reassured that the police will not be involved.

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. There is as yet no evidence as to the effectiveness of this intervention in reducing drug-related mortality (*Frischer et al., 1997*).

7.5   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 who are often present, including family members, in such environments. "Injecting rooms" aim to reduce deaths from drug overdoses, reduce the transmission of blood-borne infections (including HIV) through needle sharing and minimize public nuisance by providing a safe and supervised environment for drug users to inject (*Dolan, 1997*). In the Netherlands drugs can be used under "hygienic" supervision at "user locations". This provides opportunities for education and counselling. These locations also serve to minimize public nuisance. Such interventions are considered highly controversial and are not acceptable in some countries, but have been implemented to varying degrees in several countries including Germany, the Netherlands and Switzerland. Similar interventions have also been considered in Australia (*Mundy, 1997*). These interventions are associated with a "new" public health response to drug-related problems, however, similar services were available, for example, in the United Kingdom in the early 1970s. Day centres for drug injectors supplied needles and syringes and provided "fixing rooms" where prescribed drugs could be injected in a relatively sterile and safe

environment (*Turner, 1994*). The effectiveness of creating "safer" drug-using environments in different settings and their impact on rates of drug overdose need further assessment.

7.6   Opioid antagonists

The role of opioid antagonists, such as naloxone and naltrexone, in resuscitating people who have an opioid overdose is controversial (*Moss, 1997; Darke & Hall, 1997*). Naloxone is widely used in many Australian states by ambulance staff to resuscitate users who overdose. Some have advocated the distribution of naloxone to opioid users who are at high risk of overdosing (e.g. *Strang et al., 1996*). In the UK naloxone has recently been made available as a nasal spray and a pilot study is planned to distribute the spray to heroin users in south London. This may be an option in developed countries but it is likely to have a limited role in developing countries because of the cost of the antagonists. If naloxone is more widely used, its implementation will need to be accompanied by adequate training of health professionals and drug users to reduce the risks of inadequate naloxone dosing. The pilot study in south London will involve the training of drug users and their partners in the correct way of administering naloxone as well as basic resuscitation techniques. Since naloxone is a short-acting antagonist - about 30 minutes to an hour - a person who has been revived may later overdose after the effects of the short-acting drug are overridden by the effects of large doses of longer-acting opioids, such as heroin or methadone.

7.7   Drug treatment

Opioid substitution programmes, notably those which use methadone as part of a structured maintenance programme, have been shown to reduce overdose fatalities and mortality from all causes (*Caplehorn et al., 1994; Gronbladh et al., 1990; Darke & Zador, 1996; Sunjic & Zador, 1997; van Ameijden, in press a*). Attending high-dose methadone maintenance programmes has been strongly associated with lower overdose mortality (*Caplehorn et al., 1994; van Ameijden, in press a*). Some studies also suggest that low-threshold maintenance programmes with higher dosages offer the most protection (*van Ameijden, in press b*). Methadone maintenance treatment has been subject to much controversy (*Kirn, 1988*), which has resulted in many thorough studies, which in turn provide evidence of the effectiveness of such treatment (*Marsch, 1998; Ward et al., 1992*). Opioid substitution treatment has been available in the United States of America since the early 1960s and extensive evaluation has shown such treatment to be very effective *(Ball & Ross, 1991; Ward et al., 1992; WHO, in press a)*. Methadone maintenance treatment was shown to reduce heroin use and involvement in crime in the 1970s in the United States (*Dole & Nyswander, 1976; Dole & Joseph, 1978*). Since the late 1980s there has been a dramatic expansion of methadone maintenance in some developed countries, such as in western Europe and Australia *(Ward et al., 1994)*. All the countries of the European Union now have opioid substitution programmes, but to a widely varying extent. In some of these countries the number of people receiving such treatment has increased dramatically in recent years (*Farrell et al., 1995; EMCDDA, 1997a*). In spite of the evidence, mainly from developed countries, that opioid substitution can reduce mortality from HIV, overdose and other causes, it is frequently argued that such approaches are not appropriate, feasible or affordable in developing countries. While these difficulties are recognized, programmes have been established in many developing countries

in Asia, in countries in transition in Central and Eastern Europe and to a lesser extent in some African countries (*Ball et al., 1998*).

In some countries, including Australia, the United States, and some countries in Europe, guidelines for clinical practice in establishing and operating opioid substitution programmes include strict rules for prescribing that aim to minimize the risk of overdose during induction into methadone treatment and overdoses produced by diverted methadone (*Swiss Federal Office of Public Health, 1996; Drugs Advisory Committee, 1992; WHO, in press a*). Training and accreditation courses for prescribers have been established in some countries to ensure rational and safe prescribing (*Drug and Alcohol Services Council, 1994*). The importance of ensuring adequate training of service providers, particularly prescribers and those administering the substitute drug, is well recognized (*WHO, in press a*). It is argued that a balance needs to be struck in regulating substitute prescribing between attracting drug users and retaining them in treatment to reduce overdose, and imposing strict regulations that compromise access to or the effectiveness of treatment. Reports from community-based opioid substitution programmes in developing countries such as India, Nepal and Thailand indicate that overdose incidents are uncommon, even though strict guidelines do not exist and medical supervision is somewhat limited (*WHO, in press a*). It is suggested, therefore, that such guidelines should be both practical and flexible to suit local contexts and be subject to evaluation and periodic revision.

While methadone is the most widely used opioid in substitution treatment, a wide range of other opioids is also used. The use of mixed agonist-antagonist drugs, like buprenorphine, in opioid substitution programmes may also reduce overdose risks (*Cowan & Lewis, 1995; Walsh et al., 1994*). The literature also indicates that buprenorphine may have some advantages over methadone. Because buprenorphine is a partial agonist, its agonist effects reach a ceiling, and the risks of respiratory depression and fatal overdose are reported to be almost nil, except where it is combined with other drugs (*Cowan & Lewis, 1995; Walsh et al., 1994*). A review of the comparative overdose risks of buprenorphine, methadone and other opioids is to be found in *Mattick et al., 1998*. Buprenorphine maintenance programmes have been established in India and tincture of opium is used in northern Thailand (*WHO, in press a*). Other less widely used and, on the whole, less well evaluated opioid agonist drugs include: l-alpha acetyl methadol (LAAM) (*Rawson et al., 1998*); oral morphine; ethylmorphine; codeine; naloxone and tincture of opium. In most programmes the substitute drugs are provided in an oral form, however, in a minority of cases they are provided in an injectable form. The first scientifically evaluated large-scale study of opioid prescribing, including injectable heroin, morphine and methadone has been completed by the Swiss National Government (*Uchtenhagen et al., 1997*). There is also a wide range of programme models for the delivery of such treatment including: through specialized clinics, general practitioners, and community-based programmes. Other variations in programme design include: the duration of treatment, ranging from short-term withdrawal to long-term maintenance, where stabilization is the immediate goal rather than progression to abstinence and dosage.

7.8   Drug and policing policies

Variations in drug purity play a role in overdose, although the evidence is unclear on how important or remediable this factor is. It has also been suggested that the purity of street drugs

is influenced by street level policing and other law enforcement activities. For example, the interruption of heroin supply networks may mean that heroin of high purity reaches the streets. Sudden increases in the purity of heroin could result in drug users unknowingly using excessive doses and possibly increasing the risk of overdose. Successful policing that reduces drug availability and purity may also unintentionally increase the transition from non-injecting to injecting opioid use which will, in turn, increase overdose risk. Those responsible for community policing and drug enforcement need to be aware of the potential health consequences of drug interdiction. They also have a role to play in improving responses to opioid overdose by reducing users' fears of calling for help in the event of an overdose.

8.   Priorities for action

The World Health Organization's Programme on Substance Abuse advocates a better coordinated response to reduce the risk of opioid and other drug related deaths. This response includes:

(1)   the improvement of the quality and comparability of information on the prevalence of opioid overdose and other drug-related deaths;

(2)   further studies to identify remediable risk factors that may assist in the design of effective overdose prevention and management interventions; and

(3)   the implementation and evaluation of effective overdose prevention and management interventions.

8.1   Improved quality of information

The first priority, improving information on the prevalence of opioid overdose deaths, may be achieved by better surveillance systems. This requires: *standardized definitions* of causes of drug-related deaths that distinguish between direct and indirect drug-related causes of death; *standardized reporting procedures*; and accurate and uniform coding, certifying and registration practices. The latter may be assisted by the use of the ICD-10 classification in a uniform way, including the full range of codes and information on the drugs involved. In the longer term, these data could be improved by encouraging toxicological analysis and forensic examination when drug use is thought to be a contributing factor to death and using this information when recording the cause of death. This option may not be feasible in developing countries where resources may not be available to provide the technology necessary for such analysis and examination. Improving surveillance systems, particularly national death registers, is a long-term project which will need to involve a range of national and international bodies. The difficulties in changing national laws and data collection procedures are well recognized.

Agreement on and training in the correct application of ICD-10 codes and in toxicological analysis and forensic examination will be required to improve the quality of information. WHO may have a role in this respect, particularly with regard to coordinating studies which examine and analyse differences in coding procedures between and within countries and in the preparation

of guidelines for the application of ICD-10 codes in a standardized way. A comparative coding study is also proposed and WHO is actively seeking partners in this respect. Further work is also necessary with regard to assessing the validity of opioid and other drug-related death data derived from different sources, for example, that from the health sector and that from law enforcement. Furthermore, during the current biennium (1998/1999) WHO will be producing a revised edition of the publication Medical Certification of Cause of Death (*WHO, 1979*). This edition has no reference to drug abuse and only a single line of guidance on the certification of poisoning on page 14. WHO will actively seek advice and guidance in the elaboration of a section related to the certification of deaths involving substance abuse.

8.2 Identify risk factors

In the shorter term and 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 a variety of special purpose research studies to better identify risk factors for opioid overdose. These include: cross-national, retrospective and prospective cohort studies of the health consequences of opioid and other drug use that use standardized methodologies and instruments. A prospective study of morbidity and mortality in cohorts of drug users has the further advantage that all disability and death in the cohorts would be captured (assuming an adequate follow-up of cases). A proposal for such a series of studies is currently being developed by WHO and other national and international collaborating partners *(WHO, in press b)*.

The results from these studies could be used to validate national registers as well as identifying risk factors for opioid overdose. Such studies should be complemented by in-depth qualitative investigations of the circumstances in which fatal and non-fatal overdoses occur. Studies of non-fatal overdoses that come to medical attention provide an under-used opportunity for better understanding the causes of opioid overdoses. Non-fatal overdoses are much more common than fatal overdoses and they enable more detailed information to be obtained about the circumstances in which the overdose occurred from survivors and peers.

8.3 Design and evaluate effective interventions

The third priority, the design and evaluation of effective interventions, can be pursued by implementing and evaluating peer-based education and social network interventions to reduce the incidence and fatality of opioid overdoses. Examples of such programmes are being tested in South Australia, New South Wales and in south London. These programmes attempt to reduce the occurrence of opioid overdoses by educating users about the risks of polydrug use and injecting alone. They also aim to improve users' responses to overdoses by teaching resuscitation skills, thereby reducing the overdose fatality rate. If these interventions succeed in changing drug users' behaviour and in reducing the prevalence and fatality of overdoses, our confidence in the role of polydrug use and user responses to overdose will be increased.

Opioid substitution treatments, particularly methadone maintenance, have been demonstrated to be protective against overdose. Other opioid drugs which are less widely used in treatment, and their role in reducing overdose, need careful evaluation. There is also a need for adequate

training of service providers, particularly prescribers and those administering the substitute drug. Treatment guidelines should be both practical and flexible to suit local contexts. Research findings on opioid substitution treatments and their role in reducing opioid overdose should be incorporated into clinical practice.

9. Related WHO activities

A number of initiatives of the WHO Substance Abuse Department are addressing the issue of opioid overdose. The WHO Drug Injecting Project (*WHO, 1996*) is collecting data on injecting drug use in twenty-one cities around the world, in both developed and developing countries, through rapid assessment methods and a survey, which include components on overdose. The project also assists sites in the development of comprehensive and integrated policies and programmes to reduce health risks associated with injecting drug use, including overdose.

The WHO Drug Substitution Project (*WHO, in press a.*) reviews and evaluates existing opioid substitution programmes, particularly in developing countries. It will 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 under way on a WHO multi-site collaborative project: Longitudinal Cohort Studies on Health Implications of Drug Use (*WHO, in press b*). These prospective and retrospective studies will examine the mortality, morbidity and the comparative health status of opioid and other drug users in different countries and will look specifically at opioid 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.

10. Conclusions

Evidence presented in this report shows that some deaths from heroin and other opioid overdose could be potentially reduced by relatively simple and for the most part inexpensive interventions. These interventions include: educating opioid users about the risks of polydrug use and injecting alone through, for example, peer outreach and social networks; improving their responses to the overdose of others, for example, by reducing fears of seeking emergency or medical assistance; teaching basic skills in cardiopulmonary resuscitation (CPR) to keep overdose victims alive until help arrives, and increasing the number of opioid users in treatment, particularly older heroin users in methadone maintenance treatment. The design and assessment of these interventions, however, require significant improvements in the quality of information on the prevalence and nature of opioid overdose and other drug-related deaths and non-fatal opioid overdoses.

11. References

Adelekan MF & Stimson GV (1997). Problems and prospects of implementing harm reduction for HIV and injecting drug use in high risk sub-Saharan African countries. *Journal of Drug Issues*, 12:37-48.

Anthony JC & Helzer JE (1991). Syndromes of drug abuse and dependence. Robins LN & Regier DA (eds). *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*, New York: The Free Press.

Anthony JC, Warner LA, & Kessler RC (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Study. *Clinical and Experimental Psychopharmacology*, 2:244-268.

Ball A (1998). Policies and interventions to stem HIV-1 epidemics associated with injecting drug users. In: Stimson GV, Des Jarlais DC & Ball A, (eds). *Drug Injecting and HIV Infection: Global Dimensions and Local Responses*, London: UCL Press.

Ball AL, Rana S, & Dehne KL (1998). HIV prevention among injecting drug users: responses in developing and transitional countries. *Public Health Reports,* 113:170-181.

Ball JC & Ross A (1991). *The Effectiveness of Methadone Maintenance Treatment,* New York: Springer-verlag.

Bewley TH, Ben-Arie O & James IP (1968). Morbidity and mortality from heroin dependence I: survey of heroin addicts known to Home Office. *British Medical Journal,* 1:725-726.

Bammer G & Sengoz A (1994). Non-fatal Heroin Overdoses. *Medical Journal of Australia,* 161:572-573.

Black S & Casswell S (1993). Recreational drug use in New Zealand. *Drug and Alcohol Review,* 12:37-48.

Boyle J & Brunswick AF (1980). What happened in Harlem? Analysis of a decline in heroin use among a generational unit of urban black youth. *Journal of Drug Issues,* 10:109-130.

Case C et al. (1992). How many injecting drug users in the world? Assessment of the epidemic potential Abstract PoC.42291. *Eighth International Conference on AIDS,* Amsterdam, Netherlands, 1992.

Caplehorn JRM et al. (1994). Retention in methadone maintenance and heroin addicts' risk of death. *Addiction,* 89:203-207.

CEIDA (Centre for Education and Information on Drugs and Alcohol) (1997). *Report of the Pilot Heroin Overdose Peer Eduction Project March 1997* (report available on request from CEIDA, PMB No.6, PO Rozelle, New South Wales 2039, Australia).

Chatterjee A et al. (1996). Evidence of effectiveness of street-based peer outreach intervention to change cleaning behaviour among injecting drug users in Manipur India. Abstract Th.C.422. *Eleventh International Conference on AIDS,* Vancouver, Canada, 1996.

Childress MT (1994). *A System Description of the Heroin Trade,* Santa Monica: Rand Drug Policy Research Centre.

Cowan A & Lewis JW (1995). *Buprenorphine: Combatting Drug Abuse with a Unique Opioid,* New York: Wiley-Liss, Inc.

Danish National Board of Health (1997). *Drug-related Death in Europe - Quality and comparability of data on drug-related deaths.* Final Report of the Working Group for Sub-task 3.3 of the EMCDDA Programme 1996/97 (unpublished document available on request from EMCDDA, Lisbon, Portugal).

Darke S & Hall W (1995). Levels and correlates of polydrug use among heroin users and regular amphetamine users. *Drug and Alcohol Dependence,* 39:231-235.

Darke S & Hall W (1997). Providing naloxone to heroin users. *Addiction,* 92:1195-1199.

Darke S, Ross J & Hall W (1996a). Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. *Addiction,* 91:405-411.

Darke S, Ross J & Hall W (1996b). Overdose among heroin users in Sydney, Australia: II. Responses to overdoses. *Addiction,* 91, 413-417.

Darke S & Zador D (1996). Fatal heroin overdose: A review. *Addiction,* 91, 1757-1764.

Darke S, Zador D & Sunjic S (1997). Toxicological findings and circumstances of heroin-related deaths in southwestern Sydney, 1995. *National Drug and Alcohol Research Centre, Technical Report No. 40.*

Davoli M et al. (1993). Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users. *International Journal of Epidemiology,* 22:273-277.

De La Fuente L et al. & The Spanish Group for the Study of the Route of Heroin Administration (1997). The transition from injecting to smoking heroin in three Spanish cities. *Addiction,* 92:1733-1747.

Delegacion Del Gobierno para el Plan Nacional sobre Drogas (1995). *Plan Nacional sobre Drogas. Memoria ano 1995,* Madrid: Ministerio del Interior.

Delegacion Del Gobierno para el Plan Nacional sobre Drogas (1997). *Plan Nacional sobre Drogas. Memoria ano 1996*, Madrid: Ministerio del Interior.

Department of Health (1996). *The Task Force to Review Services for Drug Misusers: Report of an Independent Survey of Drug Treatment Services in England*, London: Department of Health.

Des Jarlais DC et al. (1992). HIV Infection among Intravenous Drug Users: Epidemiology and Emerging Public Health Perspectives in Lowinson JH and Ruiz P, (Eds). *Substance Abuse: A Comprehensive Textbook*, Baltimore: Williams and Wilkins.

Des Jarlais DC et al. (1994). Continuity and change within an HIV epidemic: injecting drug users in New York City, 1984 through 1992. *Journal of American Medical Association*, 271:121-127.

Dolan K (1997). The Swiss experiment. *Connexions*, 16:6:10.

Dole VP & Joseph H (1978). Long-term outcome of patients treated with methadone maintenance. *Annals of the New York Academy of Science*, 311:181-189.

Dole VP & Nyswander M (1976). Methadone maintenance treatment: a ten-year perspective. *Journal of the American Medical Association*, 235: 2117-2119.

Donoghoe MC & Wodak A (1998). Health and social consequences of injecting drug use In: Stimson GV, Des Jarlais DC and Ball A, (Eds). *Drug Injecting and HIV Infection: Global Dimensions and Local Responses*, London: UCL Press.

Drug and Alcohol Services Council (1994). *South Australian Methadone Prescribers Manual*, Adelaide: Drug and Alcohol Services Council.

Drug and Alcohol Services Council (1996). *Drop: Understanding Overdose and What to Do*, Adelaide: Drug and Alcohol Services Council.

Drug Advisory Committee (1992). *National Protocol for Methadone Programmes in New Zealand*, Palmerston North: New Zealand Department of Health.

English DR et al. (1995). *The quantification of drug caused morbidity and mortality in Australia, 1995 edition*, Canberra: Commonwealth Department of Human Services and Health.

Eskild A et al. (1993). Differences in mortlaity rates and causes of death betweeen HIV positive and HIV negative drug users. *International Journal of Epidemiology*, 22:315-320.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (1996). *1995 Annual Report on the State of the Drugs Problem in the European Union,* Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (1997a). *1997 Annual Report on the State of the Drugs Problem in the European Union,* Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (1997b). *Review of scientific literature of mortality among drug users and a feasibility study for a common methodology for monitoring overall and cause-specific mortality among drug users in member states of the European Union,* Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

Farrell M et al. (1995). Methadone provision in the European Union. *International Journal of Drug Policy,* 6:168-172.

Farrell M et al. (1996). Suicide and overdose among opiate addicts (Editorial). *Addiction,* 91:321-323.

Frischer M, Green ST, & Goldberg D (1994). *Substance Abuse Related Mortality: A Worldwide Review,* Austria: United Nations International Drug Control Programme.

Frischer M et al. (1997). Mortality and survival among a cohort of drug injectors in Glasgow, 1982-1994. *Addiction,* 92:419-427.

Fugelstad A (1994). Heroin deaths in Stockholm, 1986-1991. *Paper presented to the Fifth International Conference on the Reduction of Drug Related Harm,* Toronto.

Galli M & Musicco M for the COMCAT Study Group (1994). Mortality of intravenous drug users living in Milan. Italy: role of HIV infection. *AIDS,* 8:1457-1463.

Gossop M et al. (1996). Frequency of non-fatal heroin overdose: a survey of heroin users recruited in non-clinical settings. *British Medical Journal,* 313: 402.

Griffiths P et al. (1994). Transitions in patterns of heroin administration: a study of heroin chasers and heroin injectors. *Addiction,* 89:301-309.

Gronbladh L, Ohlund LS, & Gunne LM (1990). Mortality in heroin addiction: impact of methadone maintenance. *Acta Psychiatrica Scandinavica,* 82: 223-227.

Grund JP et al. (1996). Peer driven outreach to combat HIV among IDUS: A basic design and preliminary results in Rhodes T & Hartnoll R, (Eds). *AIDS, Drugs and Prevention: Perspectives on Individual and Community Action,* London: Routledge.

Gutierrez-Cebollada J et al. (1994). Psychotropic drug consumption and other factors associated with heroin overdose. *Drug and Alcohol Dependence,* 35:169-174.

Hall W & Darke S (1997). *Trends in opiate overdose deaths in Australia 1979-1995.* NDARC Technical Report No. 49, Sydney: National Drug and Alcohol Research Centre.

Hammersley R, Cassidy MT, & Oliver J (1995). Drugs associated with drug related deaths in Edinburgh and Glasgow, November 1990 to October 1992. *Addiction,* 90:959-965.

Harding-Pink D (1993). Methadone: one person's maintenance dose is another's poison. *Lancet,* 341:665-666.

International Narcotics Control Board (1996). *Report of the International Narcotics Control Board for 1995,* Vienna: United Nations.

Joe GW, Lehman W, & Simpson DD (1982). Addict death rates during four-year post treatment follow up. *American Journal of Public Health,* 72:703-709.

Kanga K (1996). Drug intervention awareness among IDUs in the slums Abstract MoD 242. *Eleventh International Conference on AIDS,* Vancouver, Canada, 1996.

Kirn TF (1988). Methadone maintenance remains controversial even after 23 years of experience. *Journal of the American Medical Association,* 235:2970-2975.

Klee H & Morris J (1995). Factors that characterize street injectors. *Addiction,* 90:837-841.

Lecomte D et al. (1995). Décès par toxicomanie en Ile-de France. *Rev Epidem et Santé Publ,* 43:560-572.

Loxley W, Carruthers S & Bevan J (1995). *In the same vein: First report of the Australian study of HIV and injecting drug use,* Perth: National Centre for Research into the Prevention of Drug Abuse, Curtin University of Technology.

Maharjan SH & Singh M (1996). Street-based outreach program for injecting drug users Abstract Mo.D.244. *Eleventh International Conference on AIDS,* Vancouver, Canada, 1996.

Maher L (1996). Illicit Drug Reporting System (IDRS): Ethnographic component. *National Drug and Alcohol Research Centre Technical Report No.36,* Sydney: National Drug and Alcohol Research Centre.

Manderson D (1993). *From Mr Sin to Mr Big: A History of Australian Drug Laws,* Melbourne: Oxford University Press.

Marsch LA (1998). The efficcacy of methadone maintenance interventions in reducing illicit opiate use; HIV risk behaviour and criminality: a meta-analysis. *Addiction,* 93:515-532.

Mattick R (1994). *Maintenance Approaches to Treating Drug Misusers: A Review of the Empirical Evidence*. A report prepared for The Task Force to Review Services for Drug Misusers and cited in Department of Health (1996) The Task Force to Review Services for Drug Misusers: Report of an Independent Survey of Drug Treatment Services in England, London: Department of Health.

Metzger DS, Woody GE & Mclellan AT (1993). Human Immunodeficiency Virus Seroconversion amongst Intravenous Users in and out of Treatment: an 18-month Prospective Follow-up. *Journal of Acquired Immune Deficiency Syndrome*, 6: 1049-1056.

Moss J (1997). Ambulances say 'no' to Narcan. *Connexions*, 17:3:29.

Mundy J (1997). No place to go. *Connexions*, 16:6:4-9.

National Institutes of Health, National Institute on Drug Abuse (1997a). *Epidemiologic Trends in Drug Abuse Community Epidemiology Work Group Advance Report June 1997*, US Department of Health and Human Services Public Health Service.

National Institutes of Health, National Institute on Drug Abuse (1997b). *Epidemiologic Trends in Drug Abuse Community Epidemiology Work Group December 1996 Volume I Highlights and Executive Summary*. National Institutes of Health NIH Publication No. 97-4204.

National Institutes of Health, National Institute on Drug Abuse (1997c). *Assessing Drug Abuse Within and Across Communities: A Guide for Local Community Epidemiology Work Groups*. National Institutes of Health NIH Publication.

Needle RH, Genser SG & Trotter RT (1995), (Eds.). *Social Networks, Drug Abuse and HIV Transmission*. NIDA Research Monograph 151 National Institute on Drug Abuse, NIH Publication No. 95-3889.

Neeleman J & Farrell M (1997). Fatal methadone and heroin overdoses: time trends in England and Wales. *Journal of Epidemiology and Community Health*, 51: 435-437.

Newcombe R (1996). Live and Let Die: Is methadone more likely to kill you than heroin? *ISDD Druglink*, Jan/Feb, 11:9-12.

New South Wales Users and AIDS Association (1996). Users experiences of discrimination: a report to the NSW Anti-Discrimination Board on discrimination against drug users. *Nuaa News*, 21:12-19.

Oppenheimer E et al. (1994). Death and survival in a cohort of heroin addicts from London clinics a 22-year follow-up. *Addiction*, 89:1299-1308.

Orti RM et al. (1996). Mortality trends in a cohort of opiate addicts, Catalonia, Spain. *International Journal of Epidemiology*, 25:545-553.

Parker H, Bury C & Egginton R (1998). *New heroin outbreaks amongst young people in England and Wales.* Police Research Group Crime Detention Prevention Series Paper 92, Home Office Police Policy Directorate.

Peak A et al. (1995). Declining risk for HIV among injecting drug users in Kathmandu, Nepal: the impact of a harm reduction programme. *AIDS*, 9:1067-1070.

Pearson G (1987). *The New Heroin Users*, London: Blackwell Scientific Publications.

Perucci CA et al. (1991). Mortality of intravenous drug users in Rome: a cohort study. *American Journal of Public Health*, 81:1307-1310.

Pollock DA et al. (1991). Discrepancies in the reported frequency of cocaine-related deaths, United States, 1983-1988. *Journal of the American Medical Association*, 226:2233-2237.

Power R (1993). *Rapid Assessment of the Drug Injecting Situation in Hanoi and Ho Chi Minh City, Viet Nam*, Unpublished report to United Nations International Drug Control Programme.

Power R (1994). Drugs trends since 1968. In Strang J & Gossop M, (Eds). *Heroin Addiction and Drug Policy: the British System*, Oxford: Oxford University Press.

Proudfoot AT (1988). Diamorphine overdose. In Scott DB, (Ed). *Diamorphine. Its chemistry, pharmacology and clinical use*, Cambridge: Woodheal-Faulkner.

Püschel K (1997). Determining the number of drug-related deaths. In: Council of Europe (Pompidou Group) and European Monitoring Centre for Drugs and Drug Addiction. *Estimating the Prevalence of Problem Drug Use in Europe.* EMCDDA Scientific Monograph Series No.1, Luxembourg: Office for Official Publications of the European Communities.

Rawson RA et al. (1998). A 3-year progress report on the implementation of LAAM in the United States. *Addiction*, 93:533-540.

Risser D & Schneider B (1994). Drug related deaths between 1985 and 1992 examined at the Institute of Forensic Medicine in Vienna, Austria. *Addiction*, 89:851-857.

Rhodes T & Fitch C (1997). *WHO Phase II Rapid Situation Assessment Pilot Visit Odessa, Ukraine 26-30 May 1997.* Unpublished report to UNAIDS and WHO.

Rodriguez B et al. (1993). Callidad de la certificacion de la muerte por reaccion aguda a opiaceos y cocaina entre los residentes del municipio de Madrid. *Rev San Hig Pub*, 67:401-409.

Ruttenber AJ & Luke JL (1984). Heroin-related deaths: new epidemiological insights. *Science*, 226:14-20.

Sanchez J et al. & The State Information System In Drug Abuse (Seit) Working Group (1995). Opiates or cocaine: mortality from acute reactions in six major Spanish cities. *Journal of Epidemiology and Community Health*, 49: 54-60.

Steentoft A et al. (1996). Death among drug addicts in Denmark. *Ugeskrift for Laeger*, 156:6215-6219.

Stimson GV, Adelekan M & Rhodes T (1996). The diffusion of drug injecting in developing countries. *International Journal of Drug Policy*, 7:4.

Stimson GV & Choopanya K (1998). Global perspectives on drug injecting. In: Stimson GV, Des Jarlais DC and Ball A, (Eds). *Drug Injecting and HIV Infection: Global Dimensions and Local Responses*, London: UCL Press.

Strang J et al. (1996). Heroin overdose: the case for take-home naloxone. *British Medical Journal*, 312:1435.

Strang J & Gossop M (1994). *Heroin Addiction and Drug Policy: The British System*, Oxford: Oxford University Press.

Spike Collective (1995). 'Lost the plot' *The Spike: News and Views for Injecting Drug Users*. Issue 17, Auckland, New Zealand.

Sunjic S & Zador S (1997). Methadone related deaths in New South Wales. *Medical Journal of Australia*, 166:54-55.

Swiss Federal Office of Public Health (1996). *Swiss Methadone Report: Narcotic substitution in the treatment of heroin addicts in Switzerlan*, Berne: Swiss Federal Office of Public Health.

Turner D (1994). The development of the Voluntary Sector: no need for pioneers? In: Strang J A & Gossop M, (Eds). *Heroin Addiction and Drug Policy: the British System*, Oxford: Oxford University Press.

Tunving K (1988). Fatal outcome in drug addiction. *Acta Psychiatria Scandinavia*, 77:551-566.

Uchtenhagen A, Gutzwiller F & Dobler-Mikola A (1997). *Programme for a Medical Prescription of Narcotics: Final Report of the Research Representatives*, Berne: Swiss Federal Office of Public Health.

United Nations International Drug Control Programme (UNDCP) (1997). *World Drug Report*, New York: Oxford University Press.

Van Ameijden EJC et al. (in press a). Pre-AIDS mortality and morbidity among injection drug users in Amsterdam and Baltimore: an ecological comparison. *Substance Use and Misuse.*

Van Ameijden EJC, Langendam MW & Coutinho RA (in press b). Dose-effect between overdose mortality and prescribed dosage in low-threshold maintenance programs. *Substance Use and Misuse.*

Van Haastrecht HJA et al. (1996). Predictors of mortality in the Amsterdam cohort of HIV-positive and HIV-negative drug users. *American Journal of Epidemiology,* 143:380-391.

Walsh SL et al. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology and Therapeutics,* 55:569-580.

Ward J, Mattick R & Hall W (1992). *Key Issues in Methadone Maintenance,* Sydney: University of New South Wales Press.

Ward J, Mattick R & Hall W (1994). The effectiveness of methadone maintenance treatment: an overview. *Drug and Alcohol Review,* 13:327-336.

World Health Organization (1979). *Medical Certification of Cause of Death: Instructions for Physicians on Use of International Form of Medical Certificate of Cause of Death.* Geneva: World Health Organization.

World Health Organization (1992). *International Statistical Classification of Diseases and Related Health Problems. 10th Revision.* Geneva: World Health Organization.

World Health Organization (1993). *Deaths Related to Drug Abuse: Report on a WHO Consultation, Geneva, 22-25 November 1993.* Geneva: World Heath Organization.

World Health Organization (1994). *Lexicon of Alcohol and Drug Terms.* Geneva: World Heath Organization.

World Health Organization (1996). *WHO Drug Injecting Project Planning Meeting Phase II. Bangkok, Thailand, 11-15 September 1997.* Geneva: World Health Organization.

World Health Organization Regional Office for Europe (1997a). *Smoking Drinking and Drug Taking in the European Region.* Copenhagen: World Health Organization.

World Health Organization (1997b). *Amphetamine-type Stimulants.* Geneva: World Health Organization.

World Health Organization (in press a.). *WHO Drug Substitution Project: Meeting on opioid substitution programmes in Asia, Kathmandu, 10-14 February 1997.* Geneva: World Health Organization.

World Health Organization (in press b). *WHO Multi-Site Collaborative Project: Longitudinal Cohort Studies on Health Implications of Drug Abuse, Report of the Phase I Planning Meeting, Rome, 23-24 September 1998.* Geneva: World Health Organization.

Zaccarelli M et al. (1994). Impact of HIV infection on non-AIDS mortality among Italian injecting drug users. *AIDS,* 8:345-350.

Zador D, Sunjic S & Darke S (1996). Heroin related deaths in New South Wales 1992: toxicological findings and circumstances. *Medical Journal of Australia,* 164:204-207.

Appendix I ICD-10 Codes

F10-F19 (mental and behavioural disorders due to psychoactive substance use)

F10 Alcohol
F11 Opioids
F12 Cannaboids
F13 Sedatives or hypnotics
F14 Cocaine
F15 Other stimulants (including caffeine)
F16 Hallucinogens
F17 Tobacco
F18 Volatile solvents
F19 Multiple drug use and use of other psychoactive substances

F10-F19 (mental and behavioural disorders due to psychoactive substance use)

Fourth character subdivision

.0 (acute intoxication)
.1 (harmful use)
.2 (dependence syndrome)
.3 to .7 (other disorders)

F10-F19 (mental and behavioural disorders due to psychoactive substance use)

Fourth character subdivision

.0 Acute intoxication

Complications may include trauma, inhalation of vomitus, delirium, coma, convulsions and other medical complications.

Pathological intoxication

T36-T50 (poisoning by (range of substances))

Excludes drug dependence and behavioural disorders due to psychoactive substance use (F10-F19) but includes overdose

T40.0-T40.9 (poisoning by narcotics and psychodysleptics (hallucinogens))
Excludes drug dependence and behavioural disorders due to psychoactive substance use (F10-F19)

T40.0 Opium
T40.1 Heroin
T40.2 Other opioids
       Codeine
       Morphine
T40.3 Methadone
T40.4 Other synthetic narcotics
       Pethidine
T40.5 Cocaine
	T40.6 Other and unspecified narcotics
	T40.7 Cannabis (derivatives)
	T40.8 Lysergide (LSD)
	T40.9 Other and unspecified
	psychodysleptics (hallucinogens)
	       Mescaline
	       Psilocin
	       Psilocybine

X40-X49 (accidental poisoning)

includes accidental overdose

X-42 accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens) not elsewhere classified

Includes: cannabis (derivative)
             cocaine
             codeine
             heroin
             lysergide (LSD)
             Mescaline
             methadone
             morphine
             opium (alkaloids)

X60-X69 (intentional poisoning)

X-62 intentional self poisoning by exposure to narcotics and psychodysleptics (hallucinogens) not elsewhere classified

Includes: cannabis (derivative)
             cocaine
             codeine
             heroin
             lysergide (LSD)
             Mescaline
             methadone
             morphine
             opium (alkaloids)

Y10-Y19 (poisoning undetermined intent)

Y-12 Poisoning by exposure to narcotics and psychodysleptics (hallucinogens) not elsewhere classified, undetermined intent.

= = =