European Monitoring Centre
for Drugs and Drug Addiction

SELECTED ISSUE 2011

MORTALITY RELATED TO DRUG USE IN EUROPE:
PUBLIC HEALTH IMPLICATIONS

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Introductory note and acknowledgements

In-depth reviews of topical interest are published as Selected issues each year. These reports are based on information provided to the EMCDDA by the EU Member States, the candidate countries Croatia and Turkey, and Norway as part of the national reporting process.

The most recent Selected issues are:

- Guidelines for the treatment of drug dependence: a European perspective;
- Cost and financing of drug treatment services in Europe: an exploratory study;
- Treatment and care for older drug users;
- Problem amphetamine and methamphetamine use in Europe;
- Trends in injecting drug use in Europe;

All Selected issues (in English) and summaries (in up to 23 languages) are available on the EMCDDA website: http://www.emcdda.europa.eu/publications/selected-issues

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Mortality related to drug use in Europe: public health implications

Introduction

In recent decades, the overall level of illicit drug use in Europe has risen dramatically, and with it the number of deaths among the drug-using population, in particular among problem drug users. In the 21st century, a considerable share of premature or avoidable mortality among young adults can be attributed to illicit drug overdose, which accounts for an estimated 4% of deaths among those aged 15–39 in Europe ([1]). These deaths are often related to injecting drug use and, in most cases, involve a combination of substances (Best et al., 2000), but they represent only part of mortality among drug users ([2]). In addition, a substantial number of deaths are indirectly related to drug use, such as those from HIV/AIDS related to injecting drug use, accidents, violence and suicides. The high levels of mortality among drug users are a serious cause for concern both at the individual and the societal level.

The number of problem opioid users in Europe is cautiously estimated at about 1.3 million ([3]), and it is among these opioid users, particularly injectors, that we find the greatest share of morbidity and mortality related to illicit drug use in Europe. Heroin is the drug most often associated with overdose, although other drugs and alcohol are commonly present. Overdose represents a major cause of avoidable death associated with illicit drug use, and from 1990 to 2010, between 6 500 and 8 500 overdose deaths have

Mortality related to drug use: a complex phenomenon

Drug use can cause death directly by toxicity, either acute (e.g. overdoses) or chronic (e.g. cirrhoses or cardiovascular diseases), or by a variety of indirect effects including: facilitating the transmission of infectious diseases by certain patterns of use (e.g. sharing injection equipment); by circumstances surrounding drug dealing and social context (e.g. crime, violence); or by affecting the mental state (e.g. suicide) or psychomotor responses of the user (e.g. traffic accidents). In many cases of drug-related death, with the obvious exception of overdoses, drug use has contributed to but not caused the death by itself. Sometimes, it is difficult to assess if the death of a drug user, for example someone dying in a traffic accident, can be attributed to drug use. Furthermore, drugs are often found in post-mortem toxicology, although they may not have contributed to the death (Corkery, 2008).

In order to monitor some of the major components of drug-related mortality, the EMCDDA has defined an epidemiological indicator: 'Drug-induced deaths and mortality among drug users'. The indicator has two complementary components: deaths caused directly by and within a short time of the consumption of illicit drugs (commonly known as overdoses and referred to here as drug-induced deaths), and mortality among problem drug users.

The first and core component of the EMCDDA indicator is based on national statistics on drug-induced deaths, which are collected each year by almost all European countries. The second component, mortality among problem drug users is mainly based on longitudinal cohort studies. This component incorporates both overall mortality and cause-specific mortality (EMCDDA, 2011b). The number and type of overdose deaths can be seen as a reflection of the current patterns of drug use in society. Overall mortality, in contrast, can be influenced by other concurrent factors, such as the prevalence of HIV infection, violence related to drug dealing, and access to drug treatment. Together, these two components aim to fulfil a number of public health objectives: they can give an indication on the overall health impact of drug use and the different factors involved, and they can help to identify particularly risky patterns of use and potential new risk factors.

([1]) See Table DRD-5 in the 2011 statistical bulletin.
([2]) We focus on illicit drug use, in particular the more harmful forms of use and exclude alcohol, tobacco and medicine alone.
([3]) See glossary for a definition of problem drug use and Table PDU-1 in the 2011 statistical bulletin for available national estimates.

been reported each year in Europe. Somewhat surprisingly, however, given major increases in provision of drug treatment and effective HIV/AIDS treatment in Europe, the number of overdose deaths has been on the increase in most EU Member States in recent years.

But beyond overdoses, mortality related to drug use is a complex phenomenon, with a number of dimensions that require different data sources and methodology to help explain them ([4]).

This Selected issue focuses on mortality among drug users due to all causes, of which drug-induced deaths is only a component, albeit the one most well-documented. The publication begins with an introduction to mortality cohort studies and then reviews the findings on overall mortality rates in Europe. In the following sections, the available sources of data are examined to explore the main causes of deaths among drug users, including overdose, suicide, trauma and infectious diseases, as well as the latest information on risk and protective factors. The Selected issue finishes with a discussion of the public health implications of drug-related mortality and the options available for prevention and intervention.

Data sources

This Selected issue is based on a special data collection carried out in 14 European countries (Figure 1), supplemented by data routinely collected by the EMCDDA and results from the scientific literature.

Mortality cohort studies among drug users in Europe published since the mid-1990s provide a major source of data for this publication. The main European mortality studies that have been analysed here are presented in the Appendix. The studies have been selected primarily to cover as many countries as possible, and according to the size of the population followed up. Recent long-term follow-up studies conducted at national level and enrolling between 3 000 and 5 000 participants are available for Germany, Latvia, Poland, Slovenia, Sweden, Croatia and Norway. Studies conducted in other settings, such as juvenile correctional institutions, are available for some countries. While many of these studies have been published, some countries have provided cohort data that are as yet unpublished. The participants in the cohort studies analysed here are predominantly problem drug users, most of whom were engaged in opioid substitution treatment or some other form of treatment for opioid dependence at the time of their enrolment.

Figure 1: Countries participating in the special data collection for this Selected issue (yellow) and countries participating in the 2010 workshop on mortality data analysis or the EMCDDA mortality cohort COSMO group (blue star)
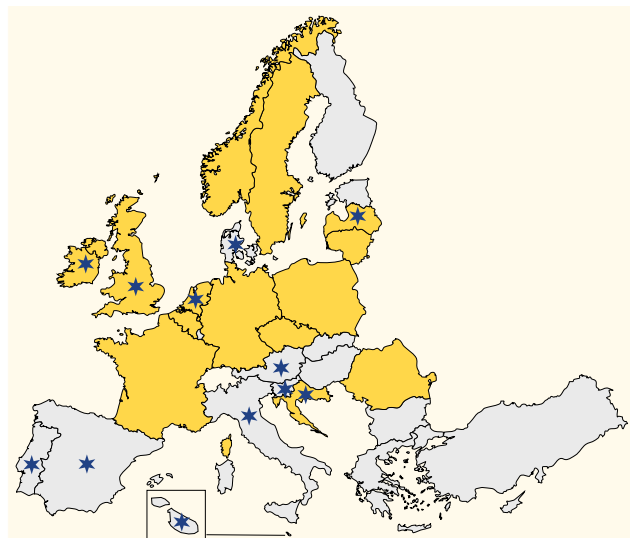
In addition to mortality cohorts, other follow-up studies, with different primary objectives or recruitment criteria can also be used to monitor mortality. Examples include the VEdeTTE Study in Italy (Bargagli et al., 2006a; Davoli et al., 2007; Ferri et al., 2007; Vigna-Taglianti et al., 2007), the primary objective of which was to assess treatment outcome, studies among those arrested for drug law offences in France (Lopez et al., 2004), and studies of injectors with hepatitis in the Czech Republic (Lejckova and Mravcik, 2005, 2007). Statistics on drug-induced deaths in Europe, derived from general mortality registries or special registries, usually medico-legal databases (EMCDDA, 2010b), have also been analysed in this Selected issue.

Finally, data from epidemiological surveillance of the general population are also used to identify trends in deaths related to HIV/AIDS among injecting drug users.

What are cohort studies and what do they tell us?

The information analysed in this Selected issue is mainly derived from longitudinal follow-up studies of groups — 'cohorts' — of problem drug users, which systematically identify the causes of all deaths among the cohort.

Cohort studies may be classified by whether they use an active or passive follow-up. Active follow-up studies allow researchers to measure behaviour over time, for example the

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([4])   See the box 'Mortality related to drugs: a complex phenomenon'.

duration of treatment over the years, or whether the person has changed his primary drug. Passive follow-up methods link records between lists of drug users and mortality registries, but cannot collect information on the subsequent drug-use or drug-treatment history of the participant after enrolment in the study.

Mortality cohort studies among problem drug users can determine overall and cause-specific mortality rates and can estimate the excess mortality of drug users, compared to their peers in the general population. Large-scale cohort studies can also help to determine the impact of interventions. For example, cohort studies provide insight into the trends of HIV/AIDS-related mortality among injecting drug users, which decreased dramatically after the introduction of effective HIV treatment. Cohort studies monitor the overall mortality risk and detect changing patterns in the causes of death (Darke et al., 2007a).

Findings from cohort studies can be used to produce national estimates of deaths among problem drug users. For that, mortality rates can be extrapolated from cohort studies to local or national estimates of the number of problem drug users (Cruts et al., 2008). Another approach that can be used to estimate the number of deaths due to drug use is to derive drug-attributable fractions from mortality cohort studies and apply these fractions to the causes of death that are most frequently related to drug use (e.g. HIV/AIDS, accidents, suicide and poisonings) and which are recorded in the general population mortality registries. Findings from cohort studies can also contribute to the validation of data from other sources, for example, the number of reported drug-induced deaths.

Cohort studies have both strengths and limitations when used for the study of mortality among drug users. The capacity to provide information on mortality from all causes among drug users, beyond drug-induced deaths, is the main advantage of mortality cohort studies. Their main limitation is that they underestimate the number of deaths when some subjects are lost to follow-up. In addition, the results may not be readily generalised to other populations of drug users.

Finally, comparability between studies can be compromised by differences in recruitment settings (e.g. treatment centres, outreach services, needle exchange services), populations of drug users enrolled (e.g. cocaine users, arrestees) and study design (e.g. enrolment of current drug users, retrospective studies of persons treated some years ago) (Degenhardt et al., 2011a).

Comparable mortality cohort studies: EMCDDA protocol

A protocol on conducting mortality cohort studies has been produced by the EMCDDA and national experts to assist European countries in carrying out useful and comparable studies (EMCDDA, 2011b). The EMCDDA protocol recommends the use of treatment centres as the setting for recruitment of patients into cohort studies.

Treatment centres are usually able to recruit a relatively representative sample of problem drug users in treatment, typically, opioid users. They are also an appropriate setting for the collection of personal identifiers needed to trace the participants in mortality registries. There are, however, limitations associated with recruiting drug users in these settings, as the findings are not necessarily transposable to other drug users, particularly those not in treatment.

To facilitate comparison across studies, the EMCDDA also recommends the use of prospective studies that focus on current drug users: participants are enrolled on entry to drug treatment and the study looks at mortality over the following months or years. Some studies are retrospective, that is to say the individuals have been enrolled in the past, at the moment of intake to treatment. However, in these studies, there might be gaps, errors, and non-standard data, which will be difficult or impossible to complete or correct.

The EMCDDA stresses the necessity of confidentiality and protection of identifiable personal data. Ethical approval and participants' consent are needed, as is compliance with national regulations and laws.

Key findings from recent mortality cohorts in Europe

Several tens of thousands of problem drug users have been enrolled in cohort studies over the last 20 years in Europe, and thousands of deaths have been recorded.

High mortality rates among problem drug users

Depending on recruitment setting (Degenhardt et al., 2011a) and enrolment criteria, most cohort studies carried out show mortality rates in the range of 1–2% per year among problem drug users (or 10–20 per 1 000 person-years) (see some examples in the Appendix). This rate appears to have been relatively stable over the last decade. Most of the participants in these studies are males (around 8 in 10), who at the time of enrolment were aged 15 to 34 years and were using opioids problematically.

How many Europeans may die every year because of problem opioid use?

Although it is difficult to obtain a precise figure, findings from cohort studies, in combination with figures on overdoses and estimates of the total number of opioid users in Europe, can be used in a number of ways to make crude estimates of the overall number of European deaths related to problem opioid use ([1]).

A first approach is based on the assumption, using the results of many mortality cohort studies, that overdose deaths account for between one-third and half of all deaths among problem drug users (see examples in Table 1). The estimated 7 600 overdose deaths in Europe for 2009 would therefore suggest an overall mortality of roughly between 15 200 (twice the number of overdoses) and 22 800 (three times the number of overdoses) (see estimation 1 below).

A second approach applies the range of mortality rates of opioid users observed in most cohort studies (between 1% and 2% per year) to the estimated number of problem opioid users in Europe (1 300 000) ([2]) to obtain a central estimate or range of between 13 000 and 26 000 deaths each year. See estimation 2a below. The estimate could be roughly refined by noting that opioid substitution treatment is expected to reduce the mortality rate during treatment by approximately two-thirds (Bargagli et al., 2007), and that the number of individuals reported to the EMCDDA as receiving opioid substitution treatment in a year is about half the estimated number of problem opioid users ([3]). Incorporating these figures into the calculation (mortality rates of between 0.33% — one third of 1% — and 0.66% — one third of 2% — applied to half the estimated number of problem opioid users) modifies the estimate to between 8 700 and 17 300 deaths (see estimation 2b below).

All estimations require caution, as they rely on the one hand on broad estimates of the proportion of overdoses to all deaths among opioid users, and on the other in combining estimates of mortality rates and the total number of opioid users in Europe. Nevertheless, there is some agreement between the results, and given the information that is available at present, these figures suggest a credible range for the number of deaths in Europe due to problem opioid use. Bearing in mind the data limitations and caveats mentioned above, it can be roughly estimated that somewhere between 10 000 and 20 000 problem opioid users die every year in Europe.

Estimates of overall mortality related to problem opioid use
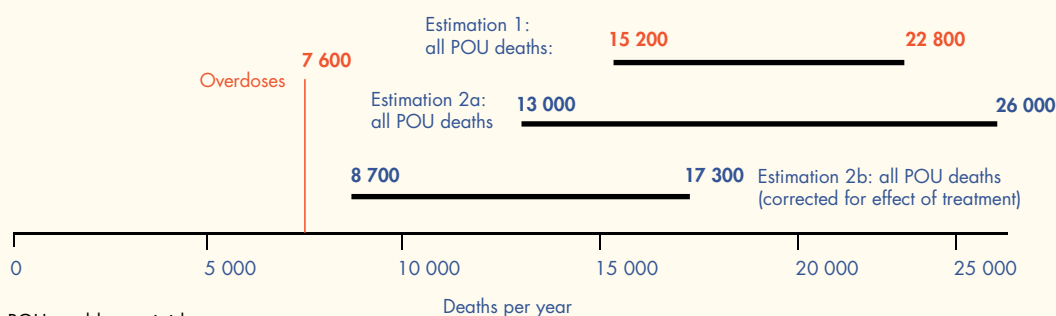
NB: POU, problem opioid users.

([1]) For more details on the computations and assumptions and limitations please see Drug-related deaths on the EMCDDA website.
([2]) See Table PDU-1 in the 2011 statistical bulletin.
([3]) See Table HSR-3 in the 2011 statistical bulletin 2011.

Compared to the general population, both male and female opioid users have very high mortality rates ([5]), and most of these studies show slightly higher rates of mortality among male than female participants. A recent international review found that the crude mortality rates for males were 1.3 times those of females. Looking at drug-induced deaths, the difference between genders was larger, with the rates of crude mortality due to drug overdose among males being 1.7 times higher than those of females (Degenhardt et al., 2011a).

Excess risk of death among problem drug users

Mortality cohort studies point to an excess risk of mortality for problem drug users compared with their peers of the same age and gender in the general population. Overall, the mortality for drug users is roughly 10 to 20 times that of the general population of the same age and gender ([6]). Comparison between studies needs to be undertaken with caution, however, as the values depend on the baseline levels of mortality, which differ across countries.

Although female problem drug users have similar or lower mortality rates than males, their excess risk of death is higher than that of their male counterparts, as illustrated in a recent study among opioid users in Latvia (Figure 2). This is primarily due to lower mortality rates among women than men in the general population, which in turn is largely due to fewer women dying from violent causes. Elevated excess risk in female drug users was illustrated by the COSMO study carried out in eight European cities (Bargagli et al., 2006b). Although overall mortality rates were consistently slightly higher among males, the excess risk for females was considerably higher than that for males. In Barcelona, the risk of death among drug-using women was 54 times that of women in the general population, whereas drug-using men had a risk 21 times that of men in the general population. In Rome, the respective figures were 38 for female drug users and 14 for male drug users (Bargagli et al., 2006b; Bird, 2010). The high mortality rates among drug users observed at that time (all studies started between 1990 and 1996) were due in part to the high HIV/AIDS mortality.

Excess mortality risk is usually higher in younger drug users than in older ones, again largely due to lower mortality rates among their peers in the general population. In a 2010 Romanian study, for example, the youngest group of drug-users enrolled (aged 15–19 years) had a 20-times higher risk of death compared with their same-aged peers, whereas the overall excess mortality rate for the whole study population was six.

Figure 2: Mortality rates in opioid users and excess mortality risk compared to the general population, by gender: a Latvian cohort study
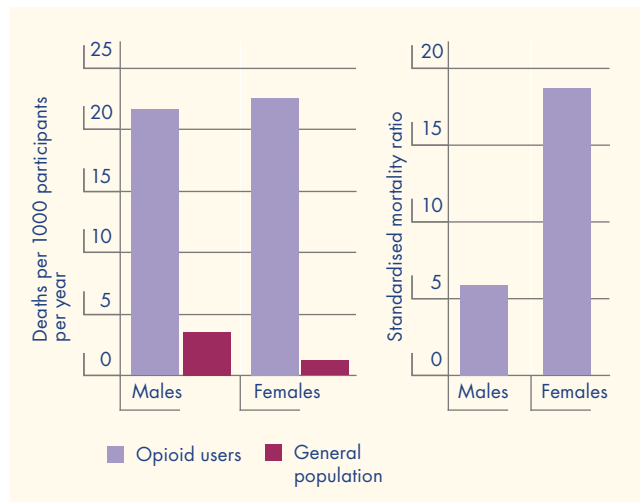
NB: Mortality rates in cohort participants (opioid users) compared to those in the general population, and the ratio between the two (standardised mortality ratios) for males and females aged 15–49. Follow-up period: 2000–09. Number of subjects followed up: 3 644.
Source: Trapencieris, 2010 (unpublished).

From a public health perspective, information on the levels of excess risk of death associated with drug-using behaviour can be a useful tool for epidemiologists and policymakers as they design and target interventions.

A number of European studies have estimated the excess risk of death associated with specific causes. For example, a study in France among people arrested for heroin, cocaine or crack use showed that the participants had considerably higher risks of mortality due to AIDS compared with the general population (24 times higher for males and 29 times higher for females), accidents (4 and 10 times higher) and suicide (3 and 13 times higher). In addition, male drug users in the study were 11 times more likely to die of homicide than their peers in the general population (Lopez et al., 2004).

Survival analysis provides an insight into the years of life lost, as the risk of death accumulates over time. After 10 years, with mortality rates of 1–2% per year, up to 20% of the drug users enrolled in a study can be dead. For example, a group of three studies conducted in Latvia with follow-up until 2010 recorded the deaths of 575 individuals. Overall, 1% to 2% of the participants died in the first year of the studies, by the end of the studies' fifth year between 4% and 7% had died, and between 15% and 18% of participants had died after 10 years.

([5]) See 'Excess risk of death among problem drug users'.
([6]) See mortality ratios in the Appendix.

What are the major causes of death among problem drug users?

Four broad categories of causes of deaths among drug users have been identified, including overdoses, disease, suicide and trauma (Darke et al., 2007a), and the following section of the report is structured around these. Among diseases, conditions related to blood-borne viruses (HIV, hepatitis B and hepatitis C viruses), neoplasms, liver diseases, and diseases of the respiratory and circulatory systems can be associated with drug use. Trauma refers to serious or critical wounds or bodily

injuries such as from accidents (traffic accidents, falls, drowning) and violence, and includes assault and homicide.

Among problem drug users, in particular, cause of death may not be clear-cut. Those with severe drug problems, especially opioid users, comprise a very vulnerable population. Often, they have additional problems such as psychiatric co-morbidity, social exclusion, difficulties to

Table 1: Causes of deaths in selected recent cohort studies among problem drug users in Europe							
Country and reference	Total number of deaths	Ill defined, unknown, unspecified (%)	Overdose (%)	HIV/AIDS (%)	Suicide (%)	Trauma, accident (%)	Others (%)
Germany (Soyka et al., 2006)	28	3.6	39.3	10.7	10.7	10.7	25.0
Italy (Ferri et al., 2007)	190	11.1	36.8	20.0	1.6	14.2	16.3
Latvia (Trapencieris, 2010, unpublished)	269	1.1	14.9	10.8	11.9	13.0	48.3
Malta (Calleja, 2010, unpublished)	55	0.0	47.3	1.8	10.9	21.8	18.2
Romania (Botescu et al., 2010, unpublished)	116	4.3	33.6	3.4	13.8	7.8	37.1
Slovenia (Selb, 2010, unpublished)	69	0.0	36.2	0.0	24.6	21.7	17.5
United (Bloor et al., 2008)	38	2.6	57.9	7.9	15.8	7.9	7.9
United Kingdom (Farrell and Marsden, 2008) [1]	442	0.0	57.0	0.0	8.1	22.6	12.2
United Kingdom, England (Hickman et al., 2003)	33	12.1	63.6	0.0	0.0	6.1	18.2
United Kingdom, Scotland (Kimber et al., 2010) [2]	112	0.9	38.4	38.4	7.1	0.0	15.2
United Kingdom, Scotland (McCowan et al., 2009)	181	8.3	33.1	7.7		7.2 [3]	43.6
Norway (Clausen et al., 2009)	213	2.3	53.1	8.0	4.7	8.9	23.0
Croatia (Pejak, 2010, unpublished)	174	12.6	54.0	0.6	0.0	8.0	24.7

[1] Newly released prisoners.
[2] Long-term follow-up with enrolment from 1980 to 2006. Localised HIV epidemic. Deaths before long-term cessation.
[3] Includes suicide.
NB: The studies presented here have been selected for the completeness of the information provided on causes of deaths, and are not intended to be representative of the population of problem drug users in Europe. As most studies are from low-HIV prevalence countries, the impact of HIV is probably far less than in other countries such as Spain, Italy and Portugal. Comparison of the studies should be made with caution as they differ in settings and enrolment criteria. More information, including study period, population, recruitment setting and mortality rates is available in the Appendix.

access services, alcohol use and dependence, which can cause considerable harm in their own right.

Results from a selection of studies presented in Table 1, which are also supported by results from other reports, show that while there can be great variation between studies, a rough generalisation can be made that between one-third and half of deaths among drug users are due to overdose, while between one-fifth and two-fifths are due to suicide and trauma. Less than a tenth is reportedly due to HIV/AIDS. A substantial proportion of drug users die from other causes, which in the studies cited here typically account for about a quarter of all deaths, though this category can represent up to half of recorded deaths in some cohorts. The category 'other causes' appears to include mostly somatic and chronic conditions, such as liver disease, cardiovascular and pulmonary causes, cancer, and other infections. Deaths from unknown causes are rare in this selection of studies, but they can account for a high number of deaths in some mortality studies. In general, comparison between studies needs to be made with caution, as the studies' populations and settings vary, as do the coding procedures of causes of deaths.

Overdoses

Opioids, particularly heroin, are by far the drugs most often implicated in overdoses ([7]), with fatalities primarily linked to respiratory depression. In Europe, there are around 7 500 cases reported every year, and numbers have been stable or increasing for the last five years in most reporting countries (EMCDDA, 2011a; Vicente et al., 2009).

In a multi-site EMCDDA study conducted in eight European countries, overdoses accounted for between 28% and 60% of the reported deaths among participants (Figure 3). An exception to this finding was Portugal, where overdoses accounted for 7% of the deaths among drug users; this was due to the high proportions of deaths either caused by HIV/AIDS, or ill-defined, of which some were likely to be overdoses (Bargagli et al., 2006b). Results from recent mortality cohort studies in Europe suggest that drug-induced deaths often represent between a third and a half of the overall number of fatalities among problem drug users (see examples in Table 1).

Figure 3: Causes of deaths in the EMCDDA COSMO studies, and in more recent selected studies in Europe
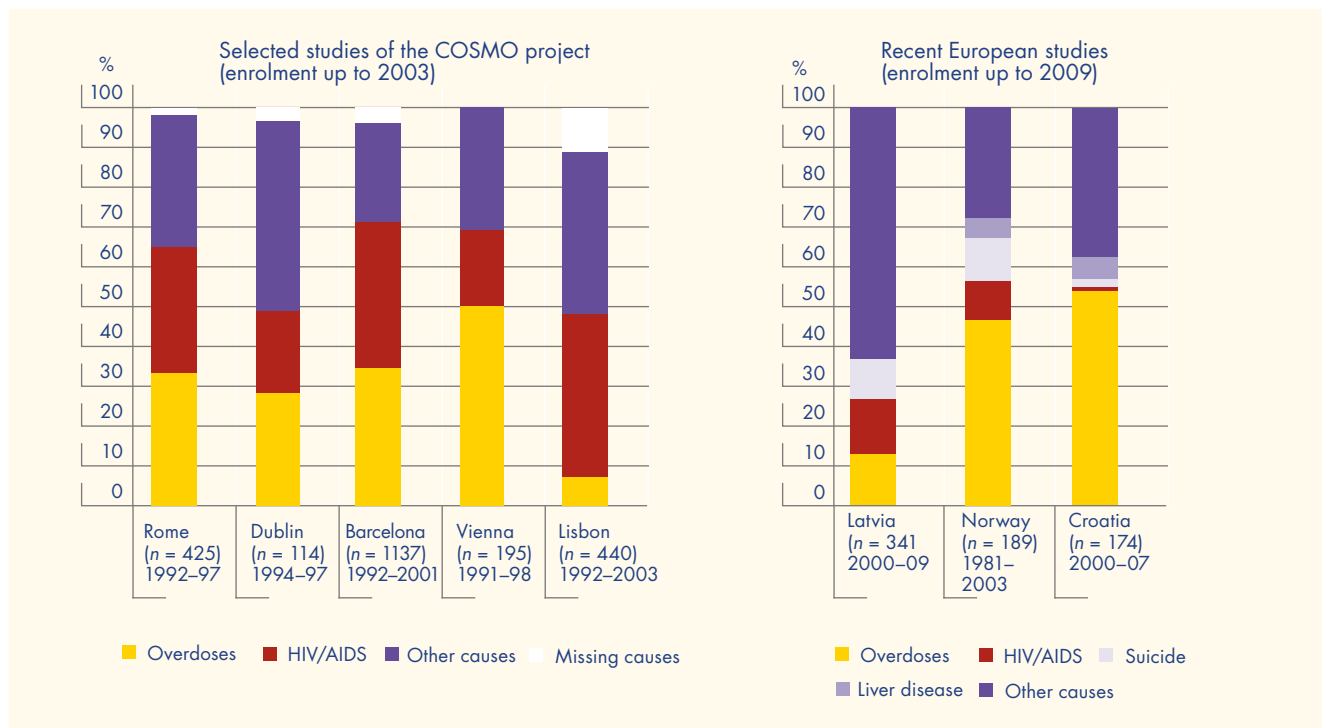
Sources: Bargagli et al. (2006b) and Reitox national focal points.

([7]) See the box 'Mortality among cocaine and amphetamine users'.

Those dying of drug overdose are predominantly in their early to mid-thirties, and have a long history of drug use. In recent years, the mean age of drug-induced deaths reported in Europe has been increasing, pointing to an ageing population of problem opioid users in many EU Member States ([8]). Gender appears to play a role too, and on average, male users have a higher risk of dying of overdoses than their female counterparts. A recent review found that among opioid users, male overdose-related mortality was 1.7 times that for females (Degenhardt et al., 2011a). Explanations put forward for this include greater social isolation of male drug users (Darke et al., 2007a), and higher rates of alcohol use among male overdose cases (Bird and Robertson, 2011).

The injection of illicit drugs carries the greatest risk of overdose, but all routes of administration can result in a fatal overdose. The majority of overdose deaths involve drug combinations, with alcohol and benzodiazepines being frequently associated in drug-induced deaths. The presence of diazepam was recorded in almost one-fifth (18%) of cases reported in 2006–07 in a study carried out in Scotland (Bird and Robertson, 2011). In Ireland, between 1998 and 2007, benzodiazepines were implicated in nearly a third (31%) of all deaths by poisoning, with the annual number increasing from 65 in 1998 to 88 in 2007.

Each year, the presence of substances used in substitution treatment (methadone and buprenorphine) is reported in a number of overdose or poisoning deaths. Most are due to misuse or, in a small number of cases, to problems occurring during treatment. The role played by the substance is often unclear, as polydrug use is frequent and other drugs are often present. Factors involved in such deaths may include loss of opioid tolerance, excessive dosage or inappropriate use, such as irregular and non-therapeutic use.

A case vignette of an overdose death from the United Kingdom ([1])

The average drug death victim from this area would be a white 33-year-old man who had used drugs since he was 16. Around that time he would have left school and gained employment or started an apprenticeship. His childhood would have been disrupted, and he would have had a family history of psychiatric difficulties and/or substance misuse. He may have suffered physical or sexual abuse and possibly spent time in care. At first, he would have used a cocktail of drugs including cannabis, amphetamines, LSD and ecstasy, moving on to heroin about four years later. He would have started injecting at around 24 years of age. Throughout his life, he would have maintained meaningful and close relationships with his friends and family members, and would not have been socially isolated. He would have had children; however, they would not have lived with him.

He would have been known to at least two services, intermittently, including his GP, criminal justice services and specialist substance misuse services during the five years prior to his death. In the six months before his death, he would have been arrested at least once. He would have committed crimes linked to his drug use, with charges such as possession of drugs or theft. At the time of his death, he would have been unemployed, living alone or with other adults and would not have changed accommodation type during those six months. He would have been classed as single, but may have been in an on/off relationship. He would have been known to his GP, but would not have sought or received pharmacological treatment for his drug dependency. During this time, he would be using a cocktail of illicit and prescribed substances.

On the day of this death, he would have purchased at least one 'tenner' ([2]) bag of heroin alongside alcohol and benzodiazepines. He would have shared these among friends/co-users and injected in their presence. He would have died in the presence of others who, believing him to be asleep would have been slow in attempting to revive him. Resuscitation would have only been conducted when instructed to do so by the ambulance, and would be partial in nature. He would have died at or near his resident home address, over a weekend, during the winter months. His blood sample would have revealed a cocktail of depressants such as morphine, benzodiazepines, alcohol and methadone. His cause of death would most likely have been classed as 'adverse effects of heroin/morphine'.

([1]) This case vignette is a summary of an aggregate profile, derived from the characteristics of individual cases recorded in Fife (Scotland) between 2008 and 2010, originally published in Neufeind et al. (2011). This 'profile' may not be representative of other drug user populations. It is presented to give an insight. Overdose victims are individuals and although there are common circumstances, each death is different. Context information is available from the report on Scotland's National Drug Related Deaths Database published in January 2011 (Graham et al., 2011).
([2]) GBP 10 (EUR 11.40).

([8]) See Figure DRD-3 in the 2011 statistical bulletin and EMCDDA (2010c).

Deaths due to buprenorphine poisoning are infrequently reported, despite the spread of its use in substitution treatment in most EU Member States ([9]). In France, where the majority of patients in opioid substitution treatment receive buprenorphine, the proportion of overdose deaths for which buprenorphine was recorded as the main substance involved was less than 10% in the latest year with available data (2008). In comparison, 36% of overdose deaths were attributed to 'heroin alone or combined with other products', and 29% to 'methadone alone or combined with other products' ([10]). Buprenorphine is a special case, though, for two reasons. First, because of forensic testing issues in some countries, as the substance might not be detected in post mortem analyses. And secondly, because buprenorphine is a partial agonist, which makes respiratory depression from buprenorphine overdose less likely than from other opioids such as heroin or methadone. Other synthetic opioids such as fentanyl have caused 'outbreaks' of overdoses in recent years, and these deaths should be closely monitored.

Finally, it is important to note that overdoses are likely to be underestimated. In some studies, up to half of drug user deaths can be classified as 'other causes', and some of these are likely to be overdose deaths. This is particularly likely in studies where high numbers of deaths are attributed to circulatory, or respiratory diseases, causes that should not be very common among young adults. Similarly, some causes such as death from 'inhalation of vomit' or 'heart failure, unspecified' could mask overdoses.

Deaths caused by diseases

HIV and hepatitis C virus infection (HCV) are the two most common infectious diseases associated with illicit drug use, and injecting drug use in particular. In addition to overdoses and HIV/AIDS, a high proportion of deaths among drug users are accounted for by liver disease related to hepatitis C infection (HCV) and/or heavy alcohol use. In the future, with an ageing population of heroin users in Europe, it is likely that other diseases, particularly non-infectious diseases, will become more frequent causes of death among drug users.

HIV/AIDS

Following the widespread use of highly active antiretroviral treatment (HAART) in the mid-1990s, mortality rates among problem drug users reported in recent studies in Europe are much lower than those in the pre-HAART era. For example,

in the EMCDDA COSMO group of studies, which enrolled opioid drug users in the early 1990s, HIV/AIDS caused more deaths than overdoses in both Barcelona and Lisbon. In Rome, the mortality rates for the two causes were about equal. At that time, the proportion of deaths among study participants due to HIV/AIDS reached 41% in Lisbon, 37% in Barcelona and 32% in Rome (Bargagli et al., 2006b). By contrast, recent studies generally show a lower proportion of deaths (usually less than 10%) due to HIV/AIDS in countries with low prevalence, although coding differences make comparison difficult (see Figure 3 and Table 1).

A French cohort study among those arrested for drug law offences showed that the mortality rate from HIV/AIDS fell six-fold between the middle and the end of the 1990s (Lopez et al., 2004).

Based on reported HIV/AIDS deaths and national AIDS surveillance data, it is estimated that there were around 2 100 HIV/AIDS-related deaths in Europe attributable to injecting drug use in 2008. Overall, estimated population mortality rates due to HIV/AIDS attributable to drug injection are low, with the exception of Spain, Italy and in particular Portugal and the Baltic countries (Mathers et al., 2010). In most countries, drug-induced mortality is now considerably higher than the estimated HIV/AIDS-related mortality among drug users ([11]).

Figure 4: Survival curve of three groups of HIV-positive persons by transmission group in the Czech Republic, 1987–2009
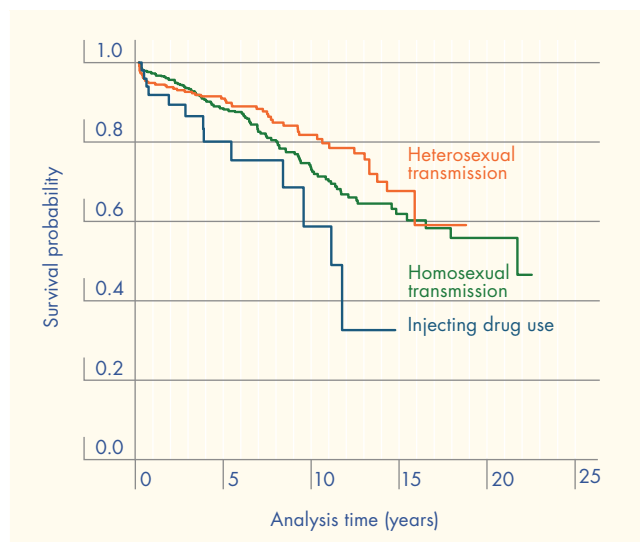
Source: Malý (2010) cited in the 2010 Reitox national report of the Czech Republic.

 ([9])   See Table HSR-1 in the 2011 statistical bulletin.
([10])   Based on data from the regional forensic network DRAMES, which does not record all overdose cases in France.
([11])   See Figure DRD-7 (part ii) in the 2011 statistical bulletin.

A review of cohort studies found that all-cause mortality among HIV-positive drug users, mainly enrolled pre-HAART, was almost three times that among HIV-negative users, and that the elevated mortality rates were accounted for by AIDS-related deaths (Degenhardt et al., 2011a). Compared to those acquiring HIV infection by other routes (such as sexual transmission), lower survival rates are reported among those acquiring the infection through drug injecting (Lert and Kazatchkine, 2007; Rodriguez-Arenas et al., 2006). For example in the Czech Republic, a statistically significant lower level of survival was found in those who contracted the infection through injecting drug use, compared to other transmission groups (Figure 4).

Hepatitis C

Hepatitis C virus (HCV) infection is highly prevalent among injecting drug users. The virus affects the liver and is spread primarily by exposure to human blood. In most developed countries, the predominant mode of HCV transmission is through injecting drug use, by shared use of injecting equipment. Surveillance data indicate that up to 63% of HCV cases in Europe are related to injecting drug use. Although the prevalence of HCV infection among injecting drug users varies considerably across Europe, of the 12 countries with national estimates of HCV antibody levels among injectors for 2007/08, eight reported levels of over 40%. High prevalence levels among young drug users and among recent injectors in certain countries suggest high rates of new infections (EMCDDA, 2011a). Many drug users are unaware of their infection, as illustrated by a study in Bristol that estimated that more than half of the injecting drug users who were HCV-positive were undiagnosed (Hickman et al., 2009). Once infected, very few clear the virus from their bodies. About three-quarters of all cases will go on to develop chronic infection and of these, around 7% will develop cirrhosis within 20 years of exposure to the virus. Of those with cirrhosis, each year 4% will experience liver failure and 2% will develop hepatocellular carcinoma.

Thus, the high prevalence of HCV is likely to cause significant morbidity and mortality over time by liver cancer and end-stage liver diseases. Where the information is available, some cohort studies among problem drug users show that 5% to 10% of the deaths could be due to viral hepatitis, but this is unclear as liver disease might be viral or due to alcohol, and the detailed information is not always available.

A recent Scottish study in a cohort of young injecting drug users (median age 31 years) suggested that problematic alcohol use may have played a larger role in liver-related hospitalisations and mortality than HCV infection (McDonald et al., 2011). Infected problem opioid users can and do survive long enough to experience harms from this slowly developing liver condition. This may be seen in the findings of a study on an ageing cohort of problem opioid users in Australia, where deaths caused by viral hepatitis were twice as frequent as those attributed to alcoholic liver disease (Gibson et al., 2011). Overall, the Australian study reported a mortality rate due to liver diseases of 1.4 deaths per 1 000 participants per year, 17 times higher than that among the general population.

The interaction between viral hepatitis and alcohol use must also be considered, as many drug users infected with HCV continue to use alcohol, as shown in a Spanish study of 497 HCV-infected drug users admitted into treatment, which found that 32% reported daily alcohol consumption (Sanvisens et al., 2011).

Other infectious diseases that are far less prevalent than HIV or HCV but which have a high risk of death include, endocarditis, which can be contracted through the sharing of contaminated injecting equipment (Darke et al., 2007a). Anthrax is another infectious disease that caused deaths among injecting drug users recently in Europe. Contaminated heroin caused more than 50 confirmed anthrax cases and 17 deaths in an outbreak among heroin users in Scotland in 2009–10, and a small number of cases were also reported in Germany (Wiessing et al., 2010).

Other diseases

Illicit drug use is also associated with a number of potentially fatal non-infectious diseases. Cardiovascular pathology is frequently reported as the cause of death among drug users, particularly older users. For example, a 37-year follow-up study among illicit drug users in Sweden showed that 20% of opioid users and 14% of stimulant users died from cardiovascular diseases, mainly ischemic heart disease and cerebro-vascular diseases (Stenbacka et al., 2010). There are some caveats though, as the coding of the causes of deaths are sometimes unspecific, and deaths attributed to cardiac causes might, in some cases, be due to overdose. Cardiovascular disease is also a consistent feature of heavy long-term use of psychostimulants, particularly cocaine and amphetamine ([12]). Non-infectious diseases that are commonly reported as the cause of death include lung diseases, such as pneumonia and chronic obstructive pulmonary diseases. Cancer accounts for a considerable

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([12])   See the box 'Mortality among cocaine and amphetamine users'.

Mortality among cocaine and amphetamine users

In recent years, cocaine has been detected in an increasing number of drug-induced deaths reported in European countries. Although the available data do not permit a clear picture of cocaine trends in Europe as a whole, an increase was observed before 2008 in Spain and the United Kingdom, the two countries with the highest rates of cocaine use in the general population; but most recent data suggest the numbers have decreased since then. Cocaine is very rarely identified as the only substance contributing to a drug-induced death.

A recent review on mortality among cocaine users (Degenhardt et al., 2011b) included nine studies in Brazil, Canada, the United States of America and three European countries (France, Italy, Netherlands). Crude mortality rates ranged from 0.54 to 4.6 per 100 person-years. The main causes of mortality, where known (Brazil, Canada, Italy, United States) included fatal gunshots (Brazil), overdose, HIV/AIDS and trauma and infections related to injecting, vascular diseases and suicide. The authors concluded that there are limited data available on the extent of elevated mortality among problematic or dependent cocaine users, and that it is unclear how generalisable the results may be to other populations. A recent Danish cohort study, however, among individuals in treatment for cocaine use, showed an excess mortality risk of 6.4 compared to same age and sex peers in the general population (Arendt et al., 2011). Dependent cocaine users show high rates of attempted suicide. Suicide attempts are not restricted to injecting cocaine users; a study in Australia showed that 10% of cocaine users who had never injected a drug also had this history (Darke and Kaye, 2004).

A review of the literature on mortality cohort studies among problem amphetamines users found that crude mortality rates ranged from 0 in Australia to 2.95 per 100 person-years in Thailand (Singleton et al., 2009). Studies carried out in Europe found mortality rates ranging from 0.49 in Czech Republic to 2.89 in the Netherlands, with studies also reported in Sweden and Finland. The Czech cohort study reported an excess mortality risk compared to non-using peers of 6.2. Only three studies reported on causes of deaths (102 cases), and the majority were due to violence, injuries, accidents, and overdoses. There was suggestive evidence that injection of amphetamines was associated with higher mortality than other primary routes of administration. The authors concluded that given the widespread extent of problem amphetamine use, the known non-fatal adverse effects of use and the mortality rates reported, cohort studies investigating the morbidity and mortality associated with such drug use should be a research priority.

proportion of deaths, particularly among older drug users, as evidenced in long-term follow-up studies. For example the Australian study mentioned above reported that 14% of the deaths were due to cancer (Gibson et al., 2011), similar to the 13% (109/860) of deaths due to cancer reported in the 37-year follow-up study in Sweden (Stenbacka et al., 2010).

In the case of deaths due to somatic problems, there are often multiple underlying causes of death recorded. A Norwegian study of a cohort of opioid users described 213 deaths, of which a third (32%) had a somatic cause. Three examples illustrate the very poor health among this cohort of drug users. Death was attributed to a combination of causes in the three cases: one to endocarditis, tuberculosis and hepatitis C; another to intracranial haemorrhage, hepatitis C and pneumonia; and a third to diabetes, stroke and kidney failure (Clausen et al., 2009).

Suicide and trauma

Cohort studies carried out in some European countries indicate that deaths from suicide or trauma account for between 20% and 40% of mortality among problem drug users.

Suicide

Suicide presents a major clinical challenge for those treating problem drug users. Many recent cohort studies in Europe, for example in the Czech Republic, Germany, Italy, Sweden and Norway, report that suicide accounts for between 10% and 20% of deaths among problem drug users (Table 1, Appendix).

Depression is a key risk factor for suicide, and the prevalence of depressive disorders among problem drug users is high; for example 25% of entrants to treatment for heroin dependence in an Australian study reported current major depressive episodes (Teesson et al., 2005). The suicide rate among heroin users has been estimated to be 14 times that in the general population (Darke and Ross, 2002). The authors concluded that the major risk factors for suicide among the general population also apply to the heroin-using population (gender, psychopathology, family dysfunction and social isolation). Heroin users, however, have extremely wide exposure to these factors. Younger users also appear to be at greater risk, with teenagers and those in their 20s having the highest suicide rates (Oyefeso et al., 1999). In addition, the greater the number of childhood problems that illicit drug users have experienced, the greater the likelihood of attempted suicide (Rossow and Lauritzen, 2001).

Heroin users are more likely than the general population to use some type of drug when committing suicide, and

the substances most often implicated are medicines (in particular benzodiazepines and antidepressants). Heroin appears to play a relatively small role in suicide among this group, and most illicit drug user suicides employ means other than their drug of dependence (Darke et al., 2007a).

A summary of studies carried out in Australia, Norway, the United Kingdom, Sweden and the USA found that between 17% and 43% of problem drug users had attempted suicide, compared to 5% or under among community samples, and a previous suicide attempt is a strong predictor of subsequent attempts (Darke et al., 2007a, b). As in the general population, illicit drug users that complete suicide are predominantly males, whereas those who attempt suicide are predominantly females.

Trauma

Trauma frequently accounts for at least 10% of deaths among drug users in Europe. Deaths caused by trauma mainly include those resulting from homicide, violence, accident and injury. Both contextual and psychological factors can explain why the rates of traumatic deaths are higher among illicit drug users than among the general population (Darke et al., 2007a). For those dependent on illicit drugs, the potential for violence is high, with many drug users turning to crime or sex work to support their drug use. An Australian study of 615 heroin-dependent users found that more than half of the men and a third of the women had been involved in at least one life-threatening accident, and two-thirds had been exposed to traumatic events including being threatened with a weapon, held captive or kidnapped. More than half of the women (54% of 208) had been raped, a risk 10 times higher than in males (Mills et al., 2005). At the psychological level, a number of common psychiatric disorders, often associated with dependent drug use, are characterised by impulsivity, risk-taking and violent behaviour.

Use of illicit drugs when driving is associated with increased risks of being involved in or causing an accident, and these risks increase when the drug is combined with alcohol or another substance (EMCDDA, 2008). In some studies, deaths due to road accidents represent a major component of overall trauma fatalities. Impairment due to intoxication may also increase the risk of fatal accidents such as falls from heights and drowning. A 37-year follow-up study

among illicit drug users in Sweden showed that 15% of deaths (127/860 deaths) were due to accidents or homicide. The most common types were transport accidents, falls, and deaths resulting from 'resisting the police' (Stenbacka et al., 2010). Around a fifth of the deaths in a Slovenian cohort were caused by trauma (including transport accidents, falls, assaults) (see Table 1), while 13% of the deaths in the Latvian cohort were due to trauma. In a Croatian study, traumatic deaths accounted for almost 10% of the total, and included various cranial, face, rest of the body injuries and wounds. Other studies, for example in Germany, Italy, Norway and Sweden describe 'traumatic deaths' as mainly relating to homicide, violence, accident and injury ([13]).

On average, drug users dying of trauma are often younger than those dying from chronic illnesses. This is illustrated by an analysis of drug-related deaths recorded in the Irish National Drug-Related Deaths Index (NDRDI) between 1998 and 2007 (Lynn et al., 2009) ([14]). It is important to note that the study did not classify deaths according to intent and, as a result, a sizeable proportion of the deaths ascribed to trauma will have been suicides, as suggested by the many deaths due to hanging or drowning. The median age of those dying from trauma between 1998 and 2007 was 27 years, and half of them (360) were aged between 20 and 29 years. In contrast, the median age of drug users dying from medical causes was 39 years, and the majority of them were aged between 30 and 44 years (Lynn et al., 2009)

Women with drug problems are at particular risk of a trauma-related death, as illustrated by a study in Vancouver that followed 572 young (not older than 29 years) active injecting drug users (including 268 females) recruited through self-referral and street outreach. Of the 14 women dying during the study, nine were murdered, one died from an accident, one from an overdose and three from somatic causes (Miller et al., 2007). Most of the cohort participants lived in very difficult circumstances: 40% had a history of sex abuse, and in the six months prior to the study 25% were homeless and 44% did sex work.

Risk factors for mortality

Mortality risk among drug users is heavily influenced by the drugs used and how they are consumed, with heroin being the drug most strongly associated with elevated mortality risk, and injecting the most risky form of administration. Risk of death is increased by older age, long-term use of drugs

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([13]) See the Appendix for details of the following studies: Clausen et al., 2009; Ferri et al., 2007; Fugelstad et al., 1997; Lejckova and Mravcik, 2005; Ødegård et al., 2007; Soyka et al., 2006; Stenbacka et al., 2010.

([14]) The NDRDI is an epidemiological database that records cases of death by drug and alcohol poisoning and deaths among drug users and alcohol dependents in Ireland.

(in particular a long history of heroin use) polydrug use, somatic and psychiatric co-morbidity, and not being enrolled in drug treatment (Rome et al., 2008; Warner-Smith et al., 2001).

Mortality risks vary depending on both circumstances and personal and social characteristics of drug users ([15]). Major factors identified include male gender, low education level, unemployment (Antolini et al., 2006), history of psychiatric admission, benzodiazepine prescription, length of drug career, use of antidepressants in the past month, psychopathology, particularly major depression, and post-traumatic stress disorder (Darke et al., 2007a; McCowan et al., 2009). A history of opioid overdose also increases the risk, as shown by the ATOS study in Australia, which followed 615 heroin users over the period 2001–09. Drug users with a history of opioid overdose had a more than three times higher risk of death compared to those who had never overdosed. In addition to history of overdose, the ATOS study found that, independently of all other baseline characteristics, attempted suicide multiplied the risk by 1.4, being aged more than 30 years by 1.8 and use of benzodiazepine in the past month by 1.6 (Darke et al., 2011)

Ageing drug users are particularly at risk, both for drug-induced death and death from other causes. The available data on drug-induced deaths point to an ageing cohort of problem opioids users in many EU Member States (EMCDDA, 2010c). In the most recent data, drug users aged 40 or more accounted for over a quarter of all reported drug-induced deaths, and the mean age of the cases is increasing in many countries. This is especially so for the pre-2004 EU Member States, which compared to those joining the EU since 2004, have longer-standing heroin problems. This might be explained by an increased vulnerability due to the cumulative toxicity of the drugs over the years, and by their poor health, with lung, renal and liver dysfunctions associated with ageing, and other chronic conditions such as cancer, liver cirrhosis and chronic bronchitis. A long-term cohort study in Stockholm illustrated the differences in mortality risk profile

between younger and older users. It showed that cardiovascular disease and tumour were the most common causes of deaths in those aged more than 55 years, compared to accidents and suicide for those aged below 24 years (Stenbacka et al., 2010).

In terms of contextual factors, the period following release from prison is a time of particularly high overdose risk for drug users, due to relapse into heroin use and reduced tolerance to opioids. A recent meta-analysis of studies in the United Kingdom, Australia and the United States of America found a three to eight-fold increased risk of drug-related death in the first one to two weeks after release compared with weeks 3 to 12. The study found that the risk remained elevated up to at least the fourth week (Merrall et al., 2010). In Ireland, an investigation of deaths among drug users following release from prison between 1998 and 2005 showed a considerable risk of death at the time of release: out of 105 deaths observed after release from prison, 28% occurred within the first week of release with a further 18% in the first month. Opioids were implicated in 89% of all poisonings in the first month after release. Compared to other cases of drug-related deaths recorded in the national database in Ireland, former prisoners were very young (66% were aged between 20 and 29 years) and socially disadvantaged. They were more often unemployed (84%), in unstable accommodation, injectors and infected with HIV and hepatitis (Lyons et al., 2010).

Although being in treatment, particularly in opioid substitution treatment, is a protective factor against mortality (Brugal et al., 2005; Clausen et al., 2008; Davoli et al., 2007), there is a higher mortality risk linked to treatment drop-out and to relapse following drug-free treatment. In both of these cases, reduced tolerance to opioids can increase the risk of overdose mortality among drug users. With regard to medication-free inpatient treatment in Norway, a recent study suggests that the elevated risk of fatal overdose within the first four weeks of leaving is so dramatic that preventive measures should be taken (Ravndal and Amundsen, 2010).

([15])   More information is available on health and social responses as well as on drug users in prison in the 2011 statistical bulletin.

Public health perspectives and implications

This Selected issue presents an overview of mortality related to problem drug use (mainly opioid use) in Europe and the main components of this mortality. This final section briefly summarises the key findings, provides an overview of the main responses to mortality related to drugs, and addresses the implications for future public health policy and practice in this area.

Deaths related to drug use: a summary

During the last decade, many European countries have conducted cohort studies among problem drug users, mostly among those in treatment programmes, enrolled at the time of admission. Thousands of participants have been followed up, and their deaths recorded. These studies show extremely high rates of mortality among problem drug users (principally opioid users), with roughly 1% to 2% of study participants dying every year. Expressed another way, compared with their European peers of the same age and gender, problem drug users are 10 to 20 times more likely to die within a given time. Bearing in mind the data limitations and caveats ([16]), it can be roughly estimated that between 10 000 and 20 000 problem opioid users die every year in Europe. Eight in ten of these are male and most are heroin-dependent users. Based on cohort studies, the mean age of those dying is in the early to mid-thirties. These premature deaths result in hundreds of thousands of years of life lost at European level. Many of these deaths could be prevented.

The majority of deaths among problem drug users can be attributed to so-called 'external factors' such as overdose, suicide and trauma. Deaths directly related to drug toxicity (overdose or drug-induced deaths) are a major cause of death for problem opioid and cocaine users, and typically account for between one-third to half of the deaths among problem drug users. There is a strong polydrug-use association here, with alcohol and benzodiazepines in particular. Drug-induced deaths are associated with certain

high-risk situations such as lost tolerance to opioids after leaving prison or dropping out of treatment. In Europe, drug users older than 40 represent an increasing proportion of the 7 000 to 8 000 drug-induced deaths reported every year, particularly in the north of Europe and in the pre-2004 EU Member States.

After overdoses, disease is the second most important cause of death among problem drug users, particularly infectious diseases (HIV and hepatitis C), which are linked with sharing injection equipment. HIV/AIDS-related deaths among problem drug users declined substantially in Europe from a peak in the mid-1990s, but the estimated numbers and mortality rates are still high in some countries. It is estimated that in 2008, more than 2 000 HIV/AIDS deaths could be attributed to injecting drug use in Europe. In some cohort studies, up to one in five deaths among drug users are due to trauma and violence. Suicide also accounts for up to one in five deaths in some cohort studies. A considerable proportion of deaths among drug users remain poorly documented and understood (in particular suicide and trauma) and may be, to a large extent, more closely related to social exclusion, mental health problems and the life circumstances of problem drug users, than to drug use itself.

Treatment is protective

Cohort studies show that stable retention in drug treatment programmes, particularly in opioid substitution treatment, is a protective factor against drug-related mortality (Brugal et al., 2005; Clausen et al., 2008; Davoli et al., 2007) ([17]). Long-term opioid substitution treatment has been shown to reduce rates of illicit drug use, drug injection and thereby mortality, in particular through reduction of overdose risks, infections and by improving physical health. A 20-year cohort study in New South Wales estimated that the state-wide opioid substitution programme produced a 29% reduction in mortality across the entire cohort (Degenhardt

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([16])   See the box 'How many Europeans die because of problem opioid use?'
([17])   See the EMCDDA Best practice portal.

et al., 2009). A Cochrane review comparing heroin-assisted treatment with methadone maintenance showed an even stronger reduction of mortality for this type of intervention (ECDC and EMCDDA, 2011).

An analysis of registered opioid substitution clients in Norway over seven years found a significant reduction between mortality risk prior to treatment, and mortality among those accepted in opioid substitution treatment. While in treatment, risk of overall mortality among clients was halved compared to the pre-treatment levels, and risk of mortality due to overdose was reduced to one fifth (Clausen et al., 2008). The need for continuity and for retaining patients in treatment is also highlighted by the Australian ATOS study, which examined a cohort of heroin users who had been through a range of treatments and were re-interviewed after 12 months (Darke et al., 2005). The study showed that the total number of treatment days received over the follow-up period was associated independently with a reduced risk of fatal and non-fatal overdose. In this group, each extra treatment day was associated with a 1% reduction in risk of overdose over the one-year period. By contrast, more treatment episodes were associated with an increased risk of overdose, which the authors concluded may arise from a pattern of treatment and relapse, with substantial variations in tolerance. Thus, for example, 100 days spent in one treatment episode would in all probability be more effective in reducing overdose than the same number of days accrued over five separate treatment episodes.

There are, however, risks associated with treatment in some circumstances. For example, there is an increased mortality risk at the start of opioid substitution treatment, and immediately after stopping treatment (Cornish et al., 2010). For this reason, treatment needs to be continuous and long-term to achieve the best protective effect. A study in the United Kingdom estimated that if the average duration of opioid substitution treatment approaches or exceeds 12 months, it has a greater than 85% chance of reducing overall mortality among opioid users (Cornish et al., 2010).

Nevertheless, risk–benefit analysis shows clear advantages of appropriate provision of methadone maintenance treatment. With regard to methadone-related deaths in a population, a recent study in Scotland and England concluded that the introduction of supervised methadone dosing was followed by a substantial decline in deaths where methadone was involved. Between 1993 and 2008, there was at least a four-fold reduction in deaths due to methadone-related overdose per amount of methadone prescribed (Strang et al., 2010).

Overdose prevention

In addition to drug treatment, a number of other interventions can also reduce drug-related mortality (EMCDDA, 2010a). Overdoses are preventable and the risk factors are known (Darke et al., 2011). Preventive measures undertaken in many European countries include education of drug users on the risk of polydrug use (particularly co-use of benzodiazepines and alcohol with heroin), on recognising the signs of and managing overdose. With the aim of reducing overdose deaths, drug agencies in some countries provide take-home naloxone to heroin users, their peers and family. Facilities where health staff supervise drug consumption and intervene in emergencies also represent a key intervention for preventing overdose deaths at local level in some countries. Only a small proportion of overdoses result in death, and for each fatal overdose there may be up to 25 non-fatal ones (Darke et al., 2003; Warner-Smith et al., 2001). Many heroin users have overdosed more than once and overdose survivors are at elevated risk of dying of a subsequent overdose.

History of overdose and risk of future overdoses need to be considered when assessing drug users entering treatment, and all clients would benefit from overdose prevention training (see above). Reduced levels of opioid tolerance significantly increase risk of overdose and death for drug users leaving prison (Farrell and Marsden, 2008), and the World Health Organisation recommends a close linkage of prison health with community drug services in order to ensure continuity of care (WHO Regional Office for Europe, 2010).

Prevention and control of infectious diseases

Since the emergence of the HIV epidemic among injecting drug users in the mid-1980s, many European countries have implemented evidence-based measures to prevent and control infectious diseases among this group. In the 1990s, EU Member States started to develop common prevention policies in the field of HIV, and in the past two decades, prevention and treatment interventions have expanded significantly. According to reports from 2009, many countries have established needle and syringe programmes with adequate coverage among injecting drug users, and more than half of the estimated population of problem opioid users in the European Union received substitution treatment.

Deaths from infectious disease can occur a long time after initiation of drug use, and the prognosis is influenced by a range of factors, among them access to the appropriate

treatment. The roll-out of antiretroviral treatment had a major impact on HIV/AIDS mortality among drug users. Mortality from hepatitis C virus (HCV) infection attributable to injecting drug use is likely to represent a major burden

for public health in the future, with deaths occurring typically 20 or 30 years after infection. Alcohol co-dependence worsens the prognosis for HCV infection, and also needs to be addressed by treatment services. It has been shown that a pragmatic public health prevention approach can have a strong effect on reducing the spread of blood-borne and other infections among injecting drug users. Prevention is feasible and effective, if properly implemented. Joint guidance by ECDC and EMCDDA (2011) recommends a set of evidence-based key intervention components ([18]).

Key intervention components to reduce infections in people who inject drugs

Injection equipment. Provision of, and legal access to, clean drug injection equipment, including sterile needles and syringes, free of charge, as part of multi-component prevention, harm-reduction, counselling and treatment programmes.

Vaccination. Hepatitis A and B, tetanus, influenza vaccines, and, in particular for HIV-positive individuals, pneumococcal vaccine.

Drug dependence treatment. Opioid substitution treatment and other effective forms of drug treatment.

Testing. Voluntary diagnostic testing with informed consent for HIV, HCV (HBV for unvaccinated persons) and tuberculosis (TB) should be routinely offered and linked to referral to treatment.

Infectious disease treatment. Antiviral treatment based on clinical indications for those who are HIV, HBV or HCV-infected. Anti-tuberculosis treatment for active TB cases. TB prophylactic therapy should be considered for latent TB cases.

Health promotion. Health promotion focused on safer injecting behaviour; sexual health, including condom use; disease prevention, testing and treatment.

Targeted delivery of services. Services should be combined and organised and delivered according to user needs and local conditions; this includes the provision of services through fixed sites offering drug treatment, harm reduction, counselling and testing, and referrals to general primary health and specialist medical services.

Source: ECDC and EMCDDA (2011).

Prevention of suicide and trauma-related deaths

Suicide and trauma are among the causes of death for problem drug users that have received less attention, despite indications that they have a considerable public health impact. In contrast to overdose deaths, suicide and trauma are not specific to the drug-using population, but they are more frequent among drug users. This relates in part to the characteristics and difficulties experienced by problem drug users (depression, marginalisation and violence), and points to the need for comprehensive interventions, beyond drug treatment.

Suicidal intent is a major clinical problem among drug users in treatment and represents a substantial challenge for drug services; it is a problem that needs to be addressed in addition to the treatment of drug dependence. On treatment entry, drug users should be assessed for risk factors for suicide, such as depression, prior suicide attempts, psychiatric co-morbidity, family and social difficulties and dysfunction, and appropriate psychological and/or pharmacological treatment provided (Darke et al., 2007a).

Deaths among drug users due to trauma are poorly documented, and although they represent a considerable proportion of mortality among drug users, their full extent is not known. Understanding the role and risk factors for trauma, which accounts in some studies for up to one in five deaths, represents a significant research priority.

([18])   See the box 'Key intervention components to reduce infections in people who inject drugs'.

Towards a better understanding of drug-related mortality for more effective action

Improving our understanding of trends

Recent years have seen a substantial increase in the number of problem drug users accessing treatment in Europe, accompanied by a notable reduction in levels of injecting drug use. In addition, the evidence shows a major reduction in drug user deaths from HIV/AIDS since the introduction of HAART in the mid-1990s. Yet, in spite of these encouraging trends, the overall mortality rates among problem drug users in cohort studies have remained relatively stable, at 1% to 2% a year, and the numbers of drug-induced deaths have either remained stable or slightly increased in most reporting countries since 2003. This is a complex and surprising situation which needs further investigation and explanation.

Several factors identified in this Selected issue begin to help explain why total numbers of drug-related deaths and mortality rates have not decreased overall in Europe despite increases in protective factors. First, the population of problem drug users is ageing, as shown by the increased average age of reported overdose deaths in many countries. The cumulative effects of harmful lifestyles, including smoking, heavy alcohol consumption and injecting drugs, cause complex somatic problems. Older drug users are more at risk of dying of chronic conditions such as cancer, cardiovascular and neurovascular diseases, and moreover, it is estimated that the ageing process among older dependent drug users is accelerated by at least 15 years. At the age of 40, drug users may need a level of care corresponding to that required by non-substance using elderly people (EMCDDA, 2010c). In addition, a high proportion of liver diseases associated with long-term exposure to alcohol, as well as hepatitis, are more commonly reported in these ageing populations. These are key elements in the apparent increase in the proportion of deaths listed under 'other causes'. Secondly, deaths from suicide, violence and trauma continue to represent a sizeable proportion of all drug-related deaths. Finally, while drug treatment has an overall protective effect against mortality, some deaths continue to be linked to substitution drugs. This can include overdoses on substitution drugs obtained from illicit markets, as well as overdoses linked to both the start of opioid substitution treatment and stopping treatment.

From the studies analysed here, it has not been possible to identify clear geographical patterns or regional trends within Europe with regard to mortality rates and causes of deaths among drug users. This could be further investigated, in particular through comparable prospective studies among drug users enrolled in drug treatment. A better understanding of drug-related mortality in each country (or group of countries) is needed in order to ensure that interventions and policies are appropriate and targeted on those in need.

Improving information from cohort studies

Increased coordination and comparability between the many cohort studies that are underway in European countries could deliver deeper insights and be of considerable value, both at the national and European level. Improved cooperation and collaboration between treatment services and researchers conducting mortality studies may lead to a better understanding of the phenomenon.

Completing the picture of drug-related mortality in Europe will also require the implementation of cohort studies in those Member States that have not yet done so. The insights such studies offer into mortality among problem drug users and into the effectiveness of interventions require relatively little investment. There is no need to set up expensive multisite prospective studies, with extensive questionnaires and follow-up interviews. At the simplest level, all that is required is linkage of data between treatment centres and mortality registries, which can be achieved by cooperation between the institutions responsible of the respective databases — within the scope allowed by national regulations on personal data protection. The EMCDDA helps in this task by promoting standard methodology and offering technical assistance and by disseminating the findings of studies.

There are considerable difficulties in attributing accurate cause of death in many cohort studies. Large 'unknown' categories are evident in some studies, and there are limitations in accessing the data on the causes of deaths in some countries. For example in Poland, for data protection

reasons, as well as in Austria, where only the deaths related to overdoses could be documented in a recent cohort study.

Limited work has been carried out in Europe on the aetiological fractions of deaths caused by illicit drug use (e.g. the proportion of all deaths due to suicide in the population that can be attributed to problem drug use). Where studies have been carried out into the role of drugs in mortality among the population (e.g. Germany, Netherlands), the focus has been on the licit substances alcohol and tobacco. One cause of death for which the illicit-drug attributable fraction has been estimated for European countries is HIV/AIDS mortality ([19]), but other causes need to be included, and cohort studies can play an important part in this work.

Most cohort studies focus on treatment populations, and it is difficult to transfer their results to other more 'hard to reach' populations of drug users (e.g. those not in contact with drug treatment). These drug users should be a priority for new studies, as they are likely to be even more disadvantaged, and to warrant priority interventions. Similarly, there is limited information about mortality of problem or intensive users of drugs other than opioids ([20]).

Conclusion

Use of opioids, in particular heroin, continues to account for the majority of deaths related to illicit drug use in Europe. But as patterns of drug use continue to change, new studies are needed to monitor the effects of these changes on the public health impact of drug use. Cardiotoxicity of cocaine and, to a lesser extent, amphetamine warrants attention, as some countries report increasing levels of use. Similarly, synthetic opioids such as fentanyl have caused 'outbreaks' of overdoses in recent years, pointing to the need to closely monitor changes in patterns of drug use that may be associated with elevated risks of mortality.

Overall, Europe's population of problem drug users is ageing, and some countries are now reporting that over a third of overdose deaths are aged 40 or more. In addition to the risk of overdose death, the detrimental and cumulative effects of long-term drug use on the physical, mental and psychosocial health of these users places them at high risk of mortality due to other causes. The challenge for European countries is to provide for the special needs of this older population — success in this area will be reflected in improvements in the quality and length of life for this high-risk group.

([19]) See Table DRD-5 (part iii) in the 2011 statistical bulletin.
([20]) See the box 'Mortality among cocaine and amphetamine users'.

Appendix: Selected mortality studies among problem drug users in Europe, published since 1995 or reported to the EMCDDA

Table A1: Selected mortality studies among problem drug users in Europe, published from 1995 or reported to the EMCDDA

Country (study) reference	Timescale (enrolment) end of follow-up	Design (recruitment setting)	Inclusion criteria	Number of deaths reported	Person-years followed up (number of participants)	All-cause mortality rates per 1 000 person-years (95 % CI)	Excess risk (SMR) (1)
8 EU countries (COSMO group with EMCDDA), Bargagli, 2006b	1990–98	Drug treatment centres	Opioid users	3 221	159 030	From 10 (London, Dublin) to 20 (Roma) and 38 (Barcelona)	—
Bulgaria, unpublished *	(1999) 2008	Outpatient and inpatient treatment centres	Opioid users	71	6 011 (652; 532 males)	11.8	—
Czech Republic, Lejckova and Mravcik, 2005	1997–2002 and 2000–02	Hospitalised for drug-related behavioural disorders (a, n = 12 207; b, n = 2 824); injecting drug users with viral hepatitis (c, n = 1 998); substitution clients (d, n = 706)	Identified as drug users in three health registers; aged 15–49 at treatment intake	476	38 131 (18 772)	a 8.4 b 15.4 c 7.2 d 7.2	8 to 11
Czech Republic *	1997–2007	Problem drug users aged 15–39	Hospitalised in 1997–2007 with diagnosis of drug use-related disorders; patients in substitution treatment in 2000–07	1 045	72 741 (27 475)	6.5	4 to 11
Czech Republic, Zábransky et al., 2011	(1996–98) 2008	2 low-threshold centres; 1 inpatient centre; 1 juvenile correctional institution; 1 juvenile institution for vulnerable youngsters	Opioid users, methamphetamine users, other drug users	8	1 660 (185)	4.8 overall 7.2 for opioid users	9 (5–19) 14 (6–34) for opioid users
Germany (PREMOS-COBRA), Soyka et al., 2011	(2003–06) 2007	Patients from representative treatment facilities	Substitution treatment	131	(1 624)	11.5	—
Germany (COBRA), Soyka et al., 2006		Opioid dependent patients. Baseline and 1-year prospective follow-up data of the COBRA study	223 substitution physicians	28	(2 694)	10.4/1 000 persons	—

Country (study) reference	Timescale (enrolment) end of follow-up	Design (recruitment setting)	Inclusion criteria	Number of deaths reported	Person-years followed up (number of participants)	All-cause mortality rates per 1 000 person-years (95 % CI)	Excess risk (SMR) (1)
Ireland (ROSIE), Comiskey et al., 2008	(2003–04) 2007	Inpatient facilities or outpatient settings	Opioid users, over 18 years, entering treatment	6	(404)	5/1 000 persons	—
France, Lopez et al., 2004	(1992) 2001	Data linkage (arrest data and national mortality data)	Arrested for offences related to heroin or crack cocaine	1 016	(~23 000) 82 % males	All 7.3 Females 5.3 Males 7.7	—
France, Marzo et al., 2008	(2003) 2006	50 prisons	Opioid dependents newly incarcerated	10	(500)	1 % per year	—
Italy (VEdeTTE), Ferri et al., 2007	(1998–2000) 2001	Public treatment	Heroin users	190	(1 376) 86 % males	All 12 Males 12.7 Females 8.4	Females 22.8 (16.5–31.5) Males 6.7 (5.7–7.8)
Latvia (multiple cohorts), unpublished *	(1999–2006)		11–44 years	279	19 566 (5 323) 79 % males	All 11.3 Females 8.7 Males 12.0	All 7.5 (6.65–8.43) Females 13.24 (9.66–17.72) Males 5.07 (4.44–5.76)
Latvia (treatment study), unpublished *	(2000–09) 2009	Outpatient treatment, public treatment	Opioid users, enrolled at date of first treatment	341	21 294 (3 644) 80 % males	21.6	All 9 (8 to 10) Males 6 (5 to 7) Females 19 (14 to 24)
Latvia, Riga (arrestees study), unpublished *	(2000–09) 2009	Drug testing facility	Subjects tested positive for opioid use, arrestees	416	24 873 (4 825) 81 % males	20.3	All 8.5 (7.7 to 9.4) Males 5.8 (5.2 to 6.4) Females 14.2 (10.7 to 18.4)
Lithuania, unpublished *	2001–07	Inpatient and outpatient drug treatment centres	All registered clients who applied for drug-related treatment	316	~4000		
Netherlands, Amsterdam, unpublished *	(1985–2009) 2009	Outpatient methadone treatment. Open cohort. No a priori fixed period of follow-up	Methadone patients living in Amsterdam who were born in the Netherlands, Surinam, the Netherlands Antilles, Morocco, or Turkey	94		4.3	4.5
Austria, unpublished *	(2000–08) 2008	Substitution treatment register linked to special mortality register. Only overdose deaths are available	Polydrug users including opioids	200, only overdoses	35 435 (9 716) 74 % males	Overdose mortality rate: All 5.6 Males 6.4 Females 3.5	—
Poland, unpublished *	(2000–04) 2006	Residential psychiatric drug treatment		1 744	96 038 (22 984) 75 % males	18.2	All 6.5 (6.2 to 6.8) Males 7.5 (7.1 to 7.9) Females 4.6 (4.1 to 5.0)

Country (study) reference	Timescale (enrolment) end of follow-up	Design (recruitment setting)	Inclusion criteria	Number of deaths reported	Person-years followed up (number of participants)	All-cause mortality rates per 1 000 person-years (95 % CI)	Excess risk (SMR) (1)
Romania, unpublished *	(2001–06) 2010	In- and outpatient treatment centres	Opioid users	116	20 188 (2 707) 835 males	All 9.2 Males 7.1 Females 11.3	All 6.5 (5.4 to 7.7) Males 6.3 (5.2 to 7.6) Females 8.7 (4.8 to 15.7)
Slovenia, unpublished *	(2004–06) 2006	Outpatient treatment centres	Clients first entering the treatment centre from 2004	69	8 548 (3 950) 76 % males, including 3 423 opioid users (87 %)	All 8 Males 8.3 Females 5	All 9 (7.1 to 11.4) Males 9.2 (7.2 to 11.8) Females 6.6 (2.7 to 15.8)
Sweden, Stockholm region, unpublished *	(1981–88) 2007	Inpatient treatment	Illicit opioid users	343	10 307 (678)	All 19 Males 23 Females 14	All 27.6 (24.9 to 30.7) Males 24.7 (21.8 to 27.8) Females 28.9 (23.2 to 35.2)
Sweden, Stockholm region, unpublished *	(1981–88) 2007	Inpatient treatment	Illicit amphetamine users	153	10 904	All 7 Males 7 Females 6	All 9.1 (7.7 to 10.6) Males 7.7 (6.3 to 9.2) Females 11.1 (8 to 15.1)
Sweden, Stockholm region *	(1981–88) 2007	Inpatient treatment	Illicit drug users HIV-positive at entrance	171	2 882	All 30 Males 30 Females 30	All 53 (46 to 52) Males 46 (38 to 54) Females 62.4 (47.2 to 80.9)
United Kingdom, (National Treatment Outcome Research Study), Gossop et al., 2002	(1995) 2000	Drug treatment patients		After five years: 62	(1 075)	12 PY survival: 1 year,:1.5 % died; 4 years: 5 % died; 5 years: 6 % died	—
United Kingdom, Scotland (Drug Outcome Research in Scotland), Bloor et al., 2008; McKegany et al., 2008	(2001–02) 2004–05	Treatment settings, prospective study of treatment effectiveness	15–54 years problem drug users starting a new treatment episode in 2001–02 (9/10 had used heroin in the past 3 months)	38	(1 033)	13.5 (95 % CI 10–18) Overdose mortality rate 8 (95 % CI 5–12)	12
United Kingdom, England, Hickman et al., 2003	(1997 to 2001)		Heroin users	33	(881)	1.61 per 100 person year	Females 17.7 Males 16.8
United Kingdom, Scotland, McCowan et al., 2009	(1993–2004) 1993–2004		Methadone patients	181 (after 12 years)	(2 378)	—	—

Country (study) reference	Timescale (enrolment) end of follow-up	Design (recruitment setting)	Inclusion criteria	Number of deaths reported	Person-years followed up (number of participants)	All-cause mortality rates per 1 000 person-years (95 % CI)	Excess risk (SMR) (1)
United Kingdom, Scotland (Edinburgh), Kimber et al., 2010; Macleod et al., 2010	(1980–2007) 2006	Primary healthcare setting	Opioid users prescribed and dispensed liquid methadone	228	10 390 (794) 68 % males	21.9	—
Croatia (Zagreb) *	(2000–06) 2007	In- and outpatient treatment centres	Opioid injectors	174	15 968 (3 059) 78 % males	All 10.9 Males 12.6 Females 4.9	All 10.3 (8.9 to 12) Males 10.4 (8.9 to 12.2) Females 9.9 (6.1 to 16.1)
Norway *	(1972–76) 1999	Infection medicine unit	Drug users enrolled in the unit	68	5 418 (214) 61 % males	—	—
Norway *	(1981–91) 2003	National Clinic for Drug Abusers (inpatient)	All drug users who received treatment	189	(501) 61 % males	23.4	—
Norway *	(1998–99) 2006	11 inpatient institutions	Problem drug users	36	(300) 70 % males	—	21
Norway *	(1998–2003) 2007	Outpatient treatment (short period inpatient included)	Opioid users	213	10 934 (3 789) 68 % males		

* Data reported to the EMCDDA by the national experts.
(1)   SMR, standardised mortality ratio.

Glossary

Cohort study: a type of longitudinal study that follows a group of people (cohort) over time, with the purpose of analysing risk factors and identifying events that occur to these people (e.g. illness, death). Cohort members may be tracked by re-contacting them or by record linkage, which involves checking their status in other databases (e.g. mortality registry).

Crude mortality rate: a measure of the number of deaths (in general or due to a specific cause) in a population, scaled to the size of that population, per unit time. It is typically expressed as either deaths per 100 or 1 000 individuals per year.

Drug-induced deaths: defined by the EMCDDA as those of 'people who die directly due to use of illegal substances, although these often occur in combination with other substances such as alcohol or psychoactive medicines. These deaths generally occur shortly after the consumption of the substance.' These deaths are also known as overdoses or poisonings.

Drug attributable fraction: the fraction of deaths (overall or due to specific causes) in a population to which drug use is the main or a contributing cause (e.g. the proportion of HIV/AIDS deaths that is attributable to injecting drug use).

Problem drug use: the EMCDDA operationally defines problem drug use as 'injecting drug use or long-duration/ regular use of opioids, cocaine and/or amphetamines'. Most cohort studies on drug users are conducted among problem drug users, and in particular among problem opioid users.

Standardised mortality rate: a crude mortality rate that has been adjusted for differences in age composition between the study population (here, drug users) and a standard population. The EMCDDA recommends using the European standard population to facilitate comparisons across studies.

Standardised mortality ratio (SMR): a measure of the 'excess risk of mortality' of a specific group (in this report, drug users), compared to their peers of same age and gender in the general population. It is calculated as the observed number of deaths in the study, divided by the number of deaths that would be expected, based on the age and sex specific mortality rates in the general population (e.g. an SMR of 15 means that the drug users in the study have a 15 times higher mortality than their peers of the same age and gender in the general population). The EMCDDA recommends using the European standard population as a reference to facilitate comparisons.

Survival analysis: a form of time-to-event analysis in which the event considered is the death of participants in the study, and time is measured from the participants' enrolment in the study (e.g. 90% survival after five years).

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(²¹)   Hyperlinks to online sources can be found in the PDF version of this publication, available on the EMCDDA website (http://www.emcdda.europa.eu/publications/selected-issues/mortality).

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