Overdosing on opiates

Distilled for FINDINGS from the world's most thorough review of how opiate overdoses happen and how they can be prevented. In this issue the causes, next issue, the cures.

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Opiate overdose is a major cause of death among drug injectors and opiate addicts.[1 2 3 4] Largely due to this cause, 7–8% of untreated opiate addicts die each year,[5] a staggering death rate in a young population.[6] In Britain heroin overdose deaths doubled over the last half of the 1990s,[7 8] making it essential to clarify the extent and causes of overdose as a basis for developing prevention strategies. As a step in that direction we outline the key themes emerging from our review of the international literature, with the emphasis on what these might mean for Britain.

Extent Major health problem

Attempts to gauge the extent of opiate overdose are hampered by problems of definition which mean the statistics rest on shifting sands *Hard to pin down* p. 7.[9] But it seems clear that in Britain[7 10] and other countries[11 12 13 14] opiates, and in particular heroin, account for more overdose deaths related to drug misuse than any other drug, and that the problem has increased[13 15] to the point where it is a major cause of young deaths. Internationally, death rates among opiate addicts are about 13 times the norm for their age; accidental overdose accounts for 30–45% of deaths.[16] In many countries (the UK is one), overdose is and is likely to remain the leading cause of death among opiate addicts.[2 17 18]

Between 1974 and 1992 poisoning deaths in England and Wales involving heroin or methadone increased tenfold.[19] Between 1994 and 1998 the trend continued with an increase from 276 to 632 in heroin/morphine poisoning deaths due to drug dependence.[7 8] Largely due to opiate overdose, almost as many years of life among men are lost from drug misuse as from traffic accidents.[20] In Scotland drug-related deaths among addicts rose from 139 in 1994 to 227 in 1999, of which 163 involved heroin/morphine.[10] A spate of deaths in Glasgow in the early 1990s linked to polydrug use involving heroin was noticeable enough to prompt an official enquiry.[21][22] By the early 1990s drug misuse had become the leading cause of death among young adults in the city.[23] Drug users there ran a 1 in 10 risk of dying after 10 years of injecting; overdose was the main cause.[24]

Concern in Australia has been stimulated by a sixfold increase in the rate of heroin overdose deaths between 1979 and 1995.[25 26] By the end of this period, opioid (opiate-type drugs) overdose accounted for 7% of young adult deaths.[27] On a longer scale, the trends are even more dramatic – a 55-fold increase since 1964.[28]

People who overdose but escape death risk serious physical complications[29 30] and provide valuable clues to the causes of overdose, making it important to study non-fatal as well as fatal incidents. Such experiences are clearly common among drug injectors, affecting around half those sampled in various countries. Most experience overdose only once every few years, but a minority do so far more often. In a sample of London drug injectors in the mid-90s (nearly all recent heroin users) 38% had overdosed, typically only once. But a few (just 11) recalled overdose incidents running into double figures and were overdosing on a more than annual basis.[31]

Results were broadly similar among methadone patients in London[32] and Edinburgh[33] and in Norway, where again a minority of addicts had overdosed extremely often – 1 in 6 at least nine times.[34] In Australia overdose is more common than in Britain; in Sydney and Adelaide 20–30% of heroin users overdose each year.[26 35 36]

Causes Individual risk factors

While the pharmacological causes of opiate overdose are well-known (*The pharmacology of opiate overdose* p. 6), less clear is what makes heroin users more or less likely to succumb to these causes. Such factors can be identified at two levels. First is what *individuals* do or don't do which affects their risk of overdose. Partly because such behaviours are associated with certain groups, or certain circumstances, we can also identify *population*-level risk factors. First we discuss the individual factors, usually the ones most amenable to intervention.

Injecting bypasses safety mechanisms

Injecting greatly increases the risk of overdose.[18 20] Heroin is relatively ineffective when swallowed, and sniffing or inhaling naturally leads to incremental consumption, affording a chance to adjust the dose. Injecting bypasses these safety mechanisms.

In the 1990s the greater prevalence of injecting in Glasgow contributed to its high overdose death rate compared to Edinburgh.[37 38] In 1992 nearly all Glasgow's heroin deaths occurred following injection.[39] In Paris 80% of drug-related deaths in 1983 involved injected heroin.[40] In the Australian state of New South Wales during 1992–1996, 99% of heroin-related deaths followed an injection[41] – however, in Australia heroin is nearly always injected. In Sydney[42] and London[43] non-fatal overdoses also overwhelmingly involved injecting. In the British study, nearly a third of heroin injectors had overdosed compared to just 2% of heroin smokers.

Doubling up on depressants

Depressant drugs are heavily used by many heroin addicts. Among the most popular are alcohol[44] and benzodiazepines. Both cause respiratory depression,[45] the major mechanism of death from opiate overdose. Tolerance develops to heroin's impact on breathing but this does not transfer to the two non-opiate drugs.[22 45] Taken in the same time frame, their effects can fatally cumulate with those of heroin.[20] Heroin's effects on breathing can be countered through conscious effort and heroin rarely leads to unconsciousness which persists despite attempts to rouse.[45] However, alcohol and benzodiazepines (used as sleeping pills) often do; by depriving the victim of consciousness, they also deprive them and those around them of one way to prevent death. Whatever the mechanism, the evidence is overwhelming that what would otherwise

have been survivable doses of heroin sometimes become lethal in the presence of alcohol or benzodiazepines.[46] Recognised as long ago as 1977,[47] this risk factor still dominates research findings.

Many British heroin addicts regularly expose themselves to this risk by drinking heavily (28% of new treatment clients in NTORS, most of whom were heroin users[48 49]) and regularly using benzodiazepines (nearly 4 in 10[48]). Use of all three drugs is not uncommon. The extra risk from each occasion of use and the high number of occasions mean that polydrug use features prominently in overdose incidents.

Nearly 40% of London injectors who had survived a heroin overdose had taken another drug on the last occasion.[50] In Sydney 72%[26] and in Adelaide 62%[36] of the latest heroin overdoses survived by heroin injectors had involved other drugs, typically alcohol, benzodiazepines or another opioid. The same risk emerged in studies at emergency units in Rome[51] and Barcelona[52] and in an analysis of blood taken from addicts found unconscious in Copenhagen.[53]

Fatal overdose is even more closely linked to polydrug use than non-fatal.[1] In London, nearly 60% of the fatalities witnessed by drug injectors involved two or more drugs, a much higher proportion than of non-fatal overdoses. Combinations of opiates and benzodiazepines were the main culprits.[50] In Scotland, heroin with benzodiazepines and alcohol were the dominant ingredients in overdose deaths of addicts in the early 1990s.[22 24] While the particular drugs have changed, mixtures of opiates and sedatives/tranquillisers continue to account for most such deaths.[10]

In Sydney[25] and in New South Wales generally,[54] heroin fully accounts for less than a third of heroin-related deaths. Among the added ingredients, alcohol (40% and 45%) and benzodiazepines (30% and 26%) dominated. Polydrug use (especially alcohol) was also the norm in the few non-injecting deaths.[42] Similar findings have emerged from Vienna.[55] In Sydney 9% of the deaths involved an antidepressant; heightened risk seems specific to tricyclics.[56]

While the risk from alcohol seems undeniable, findings on benzodiazepines are less consistent. The drugs were not mentioned in a study of non-fatal overdose among less severely dependent heroin users in London.[43] Analysis of overdose deaths in Australia suggests an elevated risk only when alcohol is also used.[54 57] Non-fatal heroin overdose in Barcelona was related only to high doses of benzodiazepines.[52]

Heightened overdose risk can be predicted from a history of regular and intensive use of other drugs, including alcohol, benzodiazepines or barbiturates;[25 34 40 58] the more types of drugs used, the greater the risk of overdose.[36] In Sydney[26] and Adelaide[36] each extra week of drinking alcohol in the last six months was associated with a 7% and 5% higher risk of overdose during that time. In the Adelaide study a penchant for drinking alcohol with heroin distinguished people who had recently overdosed. A history of benzodiazepine use may not (unlike alcohol) be linked to a greater risk of overdose, but taking them *at the same time* as heroin may still be.[35]

It is, of course, more than possible to overdose and die on heroin alone.[59] About half the overdose survivors among London injectors had taken only heroin before their last overdose.[50] Heroin was the only drug officially cited in most heroin poisoning deaths in England and Wales in 1994–1998[7] and accounted on its own for perhaps 20% of drug-related deaths.[60] In Australia a quarter of the heroin deaths in one study[54] and a third in another[25] involved only heroin.

Alcohol – the greatest risk

Among the drugs which heighten risk, alcohol deserves to be highlighted. Recent heavy drinking is one of the most consistent risk indicators. The danger is not normally due to any lasting damage to the body from alcohol but to its effects overlapping with those of heroin.

Just over half the London drug injectors who had survived an overdose had drunk alcohol on the last occasion, averaging 17 units.[31] At least 80% had consumed it with an opiate-type drug.[50] Alcohol's role was officially recognised in nearly a quarter of recent heroin poisoning deaths in England and Wales.[7] In Edinburgh and Glasgow in 1990–1992 a quarter of the addicts who died from overdose had consumed alcohol at the time; in Glasgow in 1992, nearly 40%.[22] However, in this and in another Scottish report,[10] alcohol levels were (when known) often relatively low. As with heroin, it could be that even these levels become dangerous with other depressant drugs.

In New South Wales[25 54] and Denmark[61 62] around 40% of heroin overdose deaths involved significant quantities of alcohol. In the same countries either most[53] or a large minority of heroin overdose survivors had at the time consumed alcohol.[26 36] But the relationship is not universal. In other cultures drugs such as benzodiazepines take on the role played elsewhere by alcohol.[52]

The link between alcohol and overdose does not simply reflect the fact many heroin users drink: several findings show that drinking actually heightens risk. In Sydney alcohol was detected in half the users who died from heroin overdose but just 1% of living users who had recently injected.[57] Alcohol remained in 74% of the bodies of the deceased during a local epidemic of heroin deaths in the USA; a detailed analysis provided convincing evidence that an increase in the use of alcohol with heroin was a major factor in the deaths.[63] Blood morphine and alcohol levels after heroin-related death have been found to bear an inverse relationship, just as would be expected if low doses of heroin become more dangerous the more alcohol is consumed.[25 46 54]

Taking too much

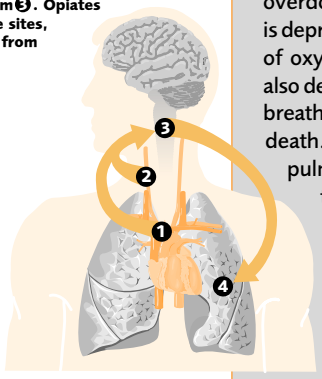
The most obvious cause of heroin overdose – accidentally taking too much – is one of the hardest to establish. *Potential* for risk is clear. Lack of product control and labelling coupled with the inability or unwillingness of users to adjust their intake to the mixture's strength[64] inevitably leads to uncertainty over how much heroin they are taking. However, in practice dose is

Golden Bullets

Essential practice points from this article

- Uncertain **strength** and fluctuating **tolerance** mean that the risk of overdosing while using illicit heroin cannot be eliminated.
- However, most overdoses and deaths are **avoidable**. Dose is rarely the sole cause – other factors turn the potential for risk into a real danger and these factors can be changed by the user and by interventions.
- Using **other** depressant **drugs** at the same time is usually the single most important factor. **Alcohol** and benzodiazepines are the major drugs.
- Other risk factors which can potentially be targeted by interventions are injecting, suicidal tendencies, resuming use after a break (often after imprisonment) and using in situations where no one else is available to summon help.
- The toxicity of available **heroin substitutes**/supplements attractive to addicts can have a major impact on the death rate.
- **Methadone** maintenance is the treatment which most effectively reduces the risk of overdose, but only while the addict remains in treatment.
- Without adequate controls drugs **diverted** from maintenance prescribing can increase deaths among non-patients but stringent controls could mean fewer addicts enter and stay in treatment, increasing their risk of overdose.

Receptors in the aorta ❶ and carotid artery ❷ sense lack of oxygen or excess carbon dioxide in the blood and relay messages to breathing control centres in the brain stem ❸. Opiates depress neural activity at these sites, preventing the control centres from stimulating breathing ❹.



The pharmacology of opiate overdose

The primary mechanism of death in overdoses involving opiate-type drugs is depressed breathing resulting in a lack of oxygen reaching the body. Opioids also depress heart function, but typically breathing is affected first and causes the death. Depressed breathing may cause pulmonary oedema – excess fluid in the lungs.[114 135] This can be rapid enough to be a cause of death, but may also be much more gradual and less of a factor.[45]

Opioids affect breathing by suppressing activity at neural control sites such that these become less sensitive to chemical changes which normally stimulate breathing, particularly rising concentrations of carbon dioxide.[45 135] Because respiration is the key factor in overdose, its restoration is also the key resuscitation objective.[114]

Apart from depressed breathing, overdose is characterised by 'pinpoint' pupils and stupor or coma. If respiratory depression persists, lack of oxygen may lead to abnormally low blood pressure and dilated pupils.[114 136] Tolerance to respiratory depression develops more slowly than tolerance to the other effects of opioids and remains relatively incomplete even after prolonged use.[45]

often not the decisive factor.

The most direct evidence comes from overdose survivors. In Britain[43] and elsewhere[51 65] about half attribute overdose incidents to taking too much or to unusually strong doses. However, such statements may be based on nothing more than an assumption that they *must* have taken too much or they would not have overdosed.

Blood morphine levels after fatal overdose are a more objective indicator of dose, but an imperfect one as they vary with the time between heroin use and death[59] and with details of the autopsy procedure.[25 45 57] In the USA,[63] Australia[25 57] and Spain,[52] high blood morphine levels did distinguish those who died or dangerously overdosed after taking heroin from those who did not and the average differences can be substantial. However, so too can the overlaps between levels in the deceased and in survivors.[47 52 57] In Denmark half those who died following injection of heroin or morphine had relatively low blood levels.[62] In two Australian studies a fifth[25] and a third[66] of the deceased had levels so low that they would not have threatened a non-tolerant user.

Such findings raise questions over how often dose is the sole cause of death. Supplementary use of alcohol[57 62] and benzodiazepines[25] often seems to potentiate the risk from high doses of heroin, while in a Spanish study the potentiator seemed to be reduced tolerance due to infrequent use.[52]

If routines such as splitting the dose actually do protect heroin users from overdose, this would provide indirect evidence that inadvertently taking too much is a significant risk. One Australian study found this was the case,[26] another that it was not.[36]

Recognising the role played by other factors should not lead us to discount heroin itself. In many countries it is the drug involved in the greatest number of overdose deaths. The fact that opiate antagonists usually lead overdose victims to recover suggests that without heroin, the overdose would not have occurred. In other words, heroin is nearly always an *essential* ingredient, even if it is often insufficient on its own to cause overdose or death.[59]

Deliberately taking too much

In a group who customarily take large amounts of dangerous drugs, deliberate overdoses can be hard to distinguish from accidents.[1] Nevertheless, suicide is clearly a major contributor to the death rate. Underlying this is the fact that addicts suffer mental health problems typified by anxiety and depression[20 67] to a far greater extent than the general population, problems particularly linked to opiate use[68] and even more common among those who overdose.

In NTORS, 62% of drug users entering treatment in England (mainly heroin users) reported feeling hopeless about the future. 29% had recently contemplated suicide, thoughts which severely troubled 9%. Opiate addicts imprisoned in England and Wales were nearly four times more likely to exhibit personality disorder than non-addicted prisoners, six times more likely if they had also been dependent on stimulants.[69] Many such troubles have been diagnosed: 1 in 10 of the NTORS sample had recently received inpatient psychiatric treatment and 1 in 7 outpatient.[48]

Poor mental health and feelings of hopelessness[70] are associated with overdose. Even when the last incident had been an accident, nearly half the overdosers among methadone patients in London and Edinburgh reported thoughts of suicide; when the last incident had been deliberate, nearly 80%.[33] Depression and psychiatric problems are common in the histories of people killed by drugs in England and Wales,[71] two-thirds of whom are drug abusers.[60] Among addicts in treatment in Norway, suicide attempts were related to psychiatric problems and to intake assessments of depression, anxiety, and suicidal ideation.[34]

While survivors can be asked about their intentions, establishing how many drug users die after deliberate overdose is more difficult. In Britain suicide is recorded only when there is strong evidence of intent, but most open or undetermined verdicts are likely to have been suicides.[24 72] Especially among dependent drug users, overdose suicide is almost certainly under-reported[60 72] and opiate overdose is far more commonly recorded as undetermined.[73] When unproven cases are taken into account, studies in Glasgow,[24] Manchester[74] and London[2] suggest that a third of all drug-related deaths of opiate addicts could be due to deliberate overdose, though samples were mainly identified through treatment services.

One of the few British studies of addict suicide investigated trends over the 25 years from 1968, the first quarter century of hospital drug dependency clinics.[73] Nearly 70,000 opiate or cocaine (a much smaller number) addicts aged 15–54 were notified by doctors. By 1992, 298 had been officially recorded as having committed suicide, 45% by overdose. Though suicides declined steeply over the 25 years, in1988–1992 rates were still four times higher than normal for men and 11 times for women. Restrictions on barbiturate prescribing (suicide drug of choice for addicts in the '60s and '70s) contributed to the decline. However, this study did not analyse open/undetermined deaths, of which there were 322, potentially doubling the addict suicide rate.

Treatment and in particular methadone maintenance reduces overdose overall but does relatively less well at preventing deliberate overdose. In British samples, during methadone treatment deliberate non-fatal opioid overdose is twice as common as accidental,[33 64] while outside treatment the reverse is the case.[31] A suicide/open verdict accounts for a much higher proportion of methadone deaths among people being prescribed the drug than those using it illicitly.[75] Among opiate injectors sampled from non-treatment settings, deliberate overdose seems less common – 1

in 10 in a study in London.[43]

Scandinavian studies confirm that suicide accounts for a significant minority of addict deaths (about 1 in 7)[76] and that treatment suppresses accidental death more than suicide.[34] Among them is the Grönbladh study *The Swedish experience* p. 17. This found that suicide accounted for 13% of all heroin addict deaths but for nearly half (7 out of 16) during methadone treatment.[77] Another Swedish study found no accidental overdose deaths during methadone treatment but one suicide, while among heroin users denied maintenance there were 72 overdose deaths and 16 suicides.[76] In Australia, deliberate overdoses seem far less common. Three studies in New South Wales found these accounted for just 1% of non-fatal overdoses[26] and 4%[25] or 9%[54] of heroin-related deaths. In one study all five suicides of patients admitted to methadone maintenance occurred during periods *out* of treatment.[78] Whilst in treatment at a US methadone maintenance programme, no patients died from heroin overdose, but six did so within a year of leaving. Since most of the out-of-treatment deaths involved people diagnosed as mentally ill (mainly depression) it seems likely that some of these addicts took their own lives.[79]

These results are consistent with the view that addicts prone to suicide tend to enter treatment, that while in treatment the risk is modestly reduced, and that dropping out or being thrown out restores high risk.

Not being in (methadone) treatment

Evidence that opiate addiction treatment prevents drug-related deaths is by far the strongest for methadone maintenance.[2] The key report came from Sydney where heroin addicts admitted to a methadone maintenance programme were traced for over 11 years.[78] Whilst in treatment they were a quarter as likely to die from non-HIV related causes, mainly because of fewer accidental heroin overdoses.[81] A meta-analysis combining this with similar studies from the USA and Europe produced roughly the same ratio – a fourfold reduction in overdose deaths during methadone treatment. The strongest evidence was from the Grönbladh study in Sweden *The Swedish experience* p. 17.

A Dutch study found a similar lifesaving ratio.[82] Australian studies have confirmed that while on methadone far fewer addicts die from heroin[25 54] than would be expected from the number in treatment,[57] evidence for a protective effect. A Swedish study[77] was the basis for a calculation that, even pre-AIDS, methadone maintenance cost $5915 for every year that it prolonged lives, more cost-effective than other more accepted medical interventions.[5]

Non-fatal overdose shows the same pattern. Entering Glasgow's methadone maintenance service halved the proportion of patients experiencing overdose; as long as treatment was unbroken, virtually none did so.[83] In two Australian studies heroin users on methadone had not overdosed for two[36] or three[26] years but those not in treatment had on average overdosed a year ago. In another being in treatment more than halved the chances of a non-fatal overdose, even after taking into account treatment's influence on other important risk behaviours.[35]

Britain's methadone programmes have not been optimised to prevent overdose

How much protection maintenance affords varies with the regime. The meta-analysis which showed a fourfold reduction was based on high-dose programmes,[78] known to most effectively curb heroin use;[84] the typical ceiling dose in the Australian programme was 120mg and the annual death rate was 1%. At a Danish programme which in practice was more detoxification than maintenance, the rate was over 3%.[85] In the Netherlands the risk of accidental overdose death among patients on higher doses (55mg or more) was a third of that in patients given lower doses.[82]

Britain's methadone programmes have not been optimised to prevent overdose among patients or non-patients. 1.8% of addicts admitted to London drug dependency clinics in 1969 died each year over the next 22 years, about 12 times the norm for their age and sex.[2] The study covered periods when clinics moved away from maintenance towards eventual withdrawal,[2 86] when expulsion for non-compliance was not uncommon, and when methadone doses were typically below 50mg. Such practices make programmes less effective while addicts are in them and increase drop out rates, both of which would tend to reduce the impact on overdose deaths.[83 87]

In many other countries methadone prescribing is more strictly regulated with supervised consumption the norm.[33 88] With such controls, increasing access to maintenance treatment in Geneva was associated with a fall in the overall number of overdose deaths between 1994 and 1998 and a particularly steep fall in heroin/morphine deaths, but no increase in methadone deaths.[138] Without such controls, deaths due to methadone sold on the illicit market are more frequent[88 89] and can counterbalance deaths prevented among methadone patients, as in Hamburg after regulations limiting take-home doses were relaxed.[90] Relatively relaxed regimes have meant that in Britain most methadone overdose deaths (especially accidental[33 64 75]) have been among people not being prescribed the drug.[60 74] However, if controls are too strict, fewer addicts may enter and be retained in treatment, increasing the overdose risk.

Whilst *being* in methadone treatment is protective, there is no evidence that having *been* on methadone exerts a similar effect if the ex-patient has returned to heroin use *Drop/throw out from treatment* p. 16.

Starting methadone treatment

Though overall methadone treatment saves lives, sometimes methadone simply supplements illicit use rather than displacing it, heightening risk. The situation is made

Hard to pin down

Whether someone who survives has experienced a heroin overdose is often unclear. Physical examination commonly reveals substantially decreased respiration and pinpoint pupils,[29] but medical reports of this kind are rarely available to researchers. Instead they rely largely on what drug users tell them. But when intoxication is the objective, differentiating overdose from simply overdoing it is not straightforward.

To guide respondents researchers have listed symptoms indicative of overdose such as: "difficulty breathing, turning blue, lost consciousness and unable to be roused, collapsing"[26] rather than defining what is or is not an overdose. Unsurprisingly, many drug users do not find it easy to report how many overdoses they have had, complicating our understanding of prevalence and problems. This applies also to observations of other people's overdoses.

While death is usually unmistakable, whether overdose was the cause is a matter of interpretation; recording practices vary and coroners' beliefs and methods influence verdicts. Even in hospital emergency units, alternative definitions have led to a twofold or greater variation in the recorded rate of drug-related deaths.[29] With such considerations in mind, the EU's drug monitoring centre warned against making comparisons between drug-related death rates in member states.[15] The World Health Organisation has counselled against use of the term 'overdose' but their preferred formulation – acute intoxication – is so wide as to include effects sought and experienced by drug users daily.[18]

TIP Evidence of morphine in the blood of a drug user almost invariably signifies prior heroin use; once ingested heroin is rapidly changed into morphine.

worse by methadone's long duration of action, by the relatively small margin between a safe and a dangerous dose,[20] and because (especially in patients with impaired livers[89]) methadone levels build up over the first few days.[91] Risk of fatality is greatest at the start of treatment.

Between 1990 and 1995 there were 105 drug-related deaths during methadone maintenance in New South Wales, over 4 in 10 in the first week of treatment. Though nearly all involved other drugs, excessive starting doses of methadone and over-rapid increases might have contributed.[92] Studies reporting similar findings[93 94] include an investigation into methadone deaths in Glasgow.[95] This identified failure to examine for and respond to continued illegal use of drugs in most of the 19 cases where the deceased was in treatment.

One plausible mechanism is that early in methadone treatment drinking and drug use have yet to be stabilised and many patients continue to use on top of their prescription.[90 96] This becomes more dangerous when induction regimes fail to identify it and adjust the treatment accordingly or provide doses of methadone which are too high or increased too quickly. Two British studies[2 97] taking in periods when heroin was at least as likely to be prescribed as methadone also found elevated mortality early in treatment, suggesting that the risk is not confined to methadone.

Drop/throw out from treatment

Just as entering treatment can be risky, so too can discharge or drop-out.[1 98] Risk due to loss of tolerance is created by interventions which interrupt heroin use without successfully treating addiction, yet do not provide a lasting supply of a heroin substitute. Detoxification is a prime example. After accounting for other factors, in the year after leaving detoxification in Italy opiate injectors were 10 times more likely to die than addicts still in treatment. Later the excess risk subsided, suggesting that leaving treatment rather than the nature of the leavers was largely to blame.[99] Other research has confirmed that detoxification has a poor post-discharge overdose record[24 85] – in one US study of deaths, 22 times worse than methadone maintenance.[80]

Maintenance programmes with high drop/throw-out rates also place their former patients at risk of overdose death. The risk has been convincingly demonstrated in Sweden where limits on methadone created natural experiments in what happens when treatment is denied[76 77 100] ▶ *The Swedish experience*. Findings were similar at a US programme where within 12 months 8% of patients who had left had died, all after drop/throw out. None were back in treatment and heroin overdose caused six of the nine deaths.[79] Other US studies have confirmed that patients retained on methadone are much less likely to die from overdose than premature leavers.[80 101]

No overdoses occurred among new patients who stayed continuously in methadone treatment in Glasgow but nearly a fifth whose treatment was interrupted overdosed, perhaps because interruptions also reduced treatment's impact on injecting. At intake 'interrupted' patients were much more likely to be have been using benzodiazepines daily, placing them at greater overdose risk but perhaps also contributing to the interruptions, a third of which were sanctions for behaviour such as taking other drugs or misbehaving at the pharmacy (where at first all patients had to consume their methadone).[83]

Evidence that risk increases because methadone maintenance is withdrawn rather than because the more incorrigible patients are the ones thrown out comes from a Swedish study which showed that morbidity dropped when dischargees re-entered treatment,[100] and from another in which nothing about the patients who left treatment prematurely could explain why they died at a greater rate.[77] Studies of what happens when programmes are closed or curtailed provide further evidence.[102 103]

Risky to resume use after a break

Tolerance to heroin's effects on breathing takes time to develop, but the partial protection it affords wanes rapidly after a break or after reduced use.[20] Users may not be aware[45] that what for them was a safe dose could then become dangerous. Even the well-informed may not be able to judge the strength of a batch of heroin and titrate intake to their loss of tolerance well enough to avoid danger.[22 26] Purity variations,[64] irregular income, unsettled lifestyle, imprisonment, and short-lived attempts to stop, can all make for fluctuating consumption and tolerance.[104]

Several studies suggest the risk is real. In London nearly a third of the heroin users who had experienced overdose identified resuming use after abstinence as a cause.[43] 40% of drug-related deaths in Paris in 1983 (overwhelmingly heroin-related) occurred shortly after an interruption in drug use.[40] In Italy[59] and the USA[63] the irregularity of recreational heroin injecting has been associated with an elevated risk of fatal overdose. In Italy[59] and Amsterdam,[82] recent infrequent and/or relatively low levels of heroin use seemed to pose a greater risk of death than more regular use.

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Being forced to take a break

Imprisonment seems particularly likely to pave the way for overdose. Drug users are forced to drastically cut back,[69 105] reducing tolerance without necessarily any lasting personal or social changes to prevent resumption of use. Lack of maintenance prescribing in British prisons means there is no way to maintain tolerance levels. Celebration of release with a cocktail of drugs including alcohol adds to the danger.[26]

The importance of this factor depends partly on the numbers at risk. Imprisonment is certainly a widespread[69 106] and frequent[107 108] experience among dependent drug users in Britain. At any one time in 1999, prisons in England and Wales probably held over 11,000 people previously dependent on opiates.[69 109] Short sentences mean that over a full year more pass in and out of prison.[69] In Scotland pre-prison opiate use is extremely common[110] and each year 9000 male drug injectors are released,[3] often to return to chaotic drug use.[106]

Research has documented the resultant damage. Across England and Wales overdose deaths are commonly seen in recently released prisoners.[71] In Edinburgh injectors were 34 times more likely to die from overdose within two weeks of leaving prison than during the rest of their time at liberty. Loss of tolerance was the prime suspect.[3] In Strathclyde, 1 in 5 methadone-related deaths occurred within a month of leaving prison, mostly in the first week.[111]

In Scotland accidental non-fatal overdoses also commonly occur among recently released prisoners[64] and in Glasgow imprisonment was the main cause of the interruptions to methadone maintenance which made it less effective in reducing non-fatal overdose.[83]

In Geneva,[112] Italy[59] and Australian cities,[26 36] fatal or non-fatal overdose, and heroin overdose in particular, have been found to be unusually common among recently released prisoners. The one dissenting study focused on a Sydney street dealing venue which probably posed such a high risk from other causes that any added risk from leaving prison was overshadowed. Even there nearly half the post-prison deaths happened within two day of release, mostly the same day.[25 113]

Intolerance kills – in many ways

Tolerance poses risks through at least two other mechanisms. First, by requiring higher doses to achieve the sought-after psychoactive effects.[114] Tolerance develops also to heroin's effects on breathing, but more partially and more slowly. Even after regular, long-term use, these effects could kill addicts who raise the dose in an attempt to reinstate heroin's psychoactive effects.[45]

If this happens in practice, it would be hard to disentangle from other causes. The

The Swedish experience

Ironically, Sweden's ambivalence about methadone maintenance has created the conditions for its value to be most convincingly demonstrated. The most important study was led by Leif Grönbladh. He tracked 166 patients admitted to the national methadone programme from its start to when in 1979 a five-year ban ended new enrollments.[77] Their fate was compared to a control group of 115 opiate addicts eligible for the programme but who did not get in before the ban, reducing bias due to self-selection or programme admission criteria.

Controls received detoxification and drug-free services but no maintenance during the tracking period, which for them lasted on average for six years. During this time 4 in 10 died, over 7% a year and 63 times the rate for Swedes of a similar age. 90% of the deaths were due to overdose, 80% to heroin-related overdose. In contrast, whilst in treatment 1.4% of patients died each year, eight times the expected rate – nowhere near as bad as among those refused treatment. A far smaller proportion (44%) died from overdose, none heroin-related.

Sweden's ambivalence about methadone created the conditions for its value to be most convincingly demonstrated

By the end of the study in 1988, over half the 166 methadone patients had been discharged. About 40% had left voluntarily on completion of a rehabilitation programme. They continued to do as well or better than when they and the other patients were in treatment, dying at four times the expected rate. In contrast, the 60% who had been forced to leave did about as badly as addicts who had never been in treatment. After seven years half had died, a 7% annual rate which was 55 times higher than expected. 22 of the 26 deaths were due to overdose, 16 involved heroin. Deaths were concentrated in the immediate post-release period.

Taking advantage of restrictions on treatment entry, another Swedish study was able to randomly assign opiate addicts to methadone treatment or (effectively) to no treatment. Two years later all the methadone clients had survived while two of the 17 waiting to be admitted had died.[137] Another Swedish study found that the annual death rate was 1% while patients were in a methadone programme but 2% among untreated opiate misusers. During an enforced break from treatment, hospital admissions rose only to fall again when the same addicts were allowed to return, evidence that treatment was indeed the active ingredient holding down injury and death.[100]

A third Swedish study found that nearly 90% of deaths among methadone patients were due to natural causes. In contrast, two-thirds of deaths among opiate misusers denied this treatment were from injecting heroin, contributing to a 4.4% annual death rate, the highest in the study. Strict admission criteria were thought on balance to mean that patients admitted to the programme were the more severe cases, lending added weight to the findings.[76]

best evidence comes from an Australian study which found that after taking account of other factors (including duration of use and use of other drugs), the more dependent a heroin user was, the more likely they were to have overdosed.[26]

The second risk arises from the fact that tolerance is partly a learned response cued by the environment in which the drug is usually taken.[115] In an unfamiliar environment, tolerance is markedly lower, potentially heightening the risk of overdose.[45] Indication that this can happen comes from the USA[116] and Barcelona[52] where non-fatal overdose has been associated with ingestion in unusual circumstances. But the evidence is weak and the risk is hard to disentangle from other risks such as irregular use, unusual drug mixtures, and use in public. Certainly overdoses and deaths can and commonly do occur in the subject's own home, where presumably many customarily consume their drugs.[26 32 39 54 75]

Street users die in haste

Taking drugs in public affords less opportunity to test the sample's strength and (especially where police pressure is high) places a premium on rapid purchase and ingestion to avoid detection. Public use is also associated with street dealing scenes where the seller is often unknown to the buyer. Such environments heighten risk.

Compared to 'private' injectors, in the north west of England nearly three times as many polydrug users who injected in public had overdosed. This ratio was reached after other factors had been taken into account, suggesting that public injecting was itself a risk factor rather than a proxy for some other factor.[117] Public injectors usually injected near and shortly after the purchase, a pattern also seen in Australia and suggestive of a hurried and unsafe procedure – perhaps why three times as many suffered vein problems. In London less dependent users were the ones most likely to resort to injecting their heroin in public.[118]

Drug-related deaths in Glasgow[39] and Paris[40] were commonly associated with circumstances suggestive of public injecting. In Sweden[77] opiate addicts refused methadone treatment were far more likely than methadone patients to die in public rather than private locations, suggesting that maintenance can reduce deaths partly by creating greater stability even if illegal drug use continues.

The risks of street use have been most extensively researched in Cabramatta, a suburb of Sydney which in the early '90s became a centre for street dealing. Overdose deaths in the area rose steeply, largely due to an increase in deaths in public locations.[25] Threatened by police crackdowns, users tended quickly to inject the drug nearby rather than travel home[119] with their purchases frustratingly to hand. The accent on speed also entailed less careful potency testing of buys, hazardous injecting methods, fewer purchases of larger amounts, and dispersal of use to more isolated sites.[120 121]

Across Sydney in 1994 only 1 in 10 *non*-fatal overdoses among heroin users were in street settings,[26] yet in Cabramatta 9 in 10 *fatal* overdoses occurred in public, suggesting that the Cabramatta environment and the more desperate users[113] who resorted to it increased the chances of an overdose becoming fatal. The one potentially protective feature – that users purchased and consumed as a group[120] – did not act as such in practice; in just 19% of cases was an ambulance called prior to death.

Deliberately administering too much

Overdose inflicted by another person is rarely identified, but if the victim is a drug user incidents are easily mistaken for suicide or accidental overdose. In England suspicious deaths in one area led officers to thoroughly investigate each drug-related fatality. Within 18 months one overdose murder and an alleged manslaughter had been uncovered; other killings were suspected.[122]

Causes Population level factors

Certain demographic or environmental variables are associated with overdose. Because these are not about what drug users *do* but who they are and the society they live in, many would be hard to build an intervention around. However, all are potentially relevant to assessment of risk.

Availability of prescribed drugs

Apart from alcohol, in Britain the drugs opiate addicts use to supplement or stand in for heroin usually derive from legitimate prescribing. The more toxic the available substitutes are, the more overdoses will occur, especially if their toxicity augments that of opiates. In reverse, just such a shift in the toxic balance occurred in Britain in

the 1970s as barbiturates were replaced by the far less dangerous benzodiazepines.[123] [124] [125] Though prescriptions for sleeping pills and sedatives/tranquillisers increased overall, this change in their composition decreased risk, contributing to a fall in the death rate among opiate addicts.[97]

The impact on suicide was best documented. Over the 25 years from 1968 there was a drop in the degree to which the suicide rate among known opiate/cocaine addicts exceeded that of the general population.[73] At first barbiturates were involved in nearly 90% of drug overdose suicides but by 1988–1992 this had declined to under 5%. The changed toxic balance as barbiturates waned probably also contributed to a decline in the overall death rate among known addicts, evident from the last half of the 1970s. From being the clear leader, barbiturate-related overdose deaths fell until by 1981 a range of other drugs were at least as important.[97] A similar story can be told about non-fatal overdoses. Between 1975 and 1982 the number of (mainly) non-fatal overdoses among addicts seen at London casualty departments had halved, mainly due to a reduction of a fifth in incidents involving barbiturates, itself linked to prescribing trends.[126]

Availability of prescribed (especially opiate-type) drugs also influences the extent to which addicts resort to and die from illicit opiates. In 1991 buprenorphine prescribing was greatly curtailed in Glasgow. Immediately the city saw a steep rise in its previously low overdose death rate as addicts took heroin with their (mainly prescribed) benzodiazepines instead of the much safer buprenorphine.[45] In Hamburg the introduction of methadone maintenance with take-home doses led the drugs implicated in overdose deaths to swing from heroin to methadone as the latter became more available on the illicit market.[90]

Heroin purity rarely decisive

In theory an increase in heroin purity or in its variability could increase the overdose rate by creating a mismatch between amounts taken and users' tolerance levels. In practice the evidence is weak, partly because so many other factors are involved, and perhaps partly because the most common protective mechanism used by addicts (splitting the dose) is designed to deal with just such a risk. Purity appears to contribute to overdose deaths mainly by reducing the margin of safety above which use of other depressant drugs becomes dangerous.[25] [28] [63] Rarely is it the sole explanation for death rate fluctuations.

As in Vienna,[55] some studies find no link between heroin purity and overdose death rates. More commonly, increasing purity seems a contributory factor, as in Sydney,[25] where the range of purity levels – an indicator of the unpredictability of each dose– was also a contributory factor.[127] However, these relationships were weak. In contrast the link between heroin purity and heroin deaths was unusually strong in the US District of Columbia in the early 1980s, where the two rose together as street prices fell.[63] Here the upsurge in deaths was related to recreational use, possibly as cheaper heroin enticed drinkers into diversifying. If purity is to have an impact, it is likely to be most evident among inexperienced users.[28]

As in this study, rather than heightening risk from *each* episode of heroin use, purity and price may have their greatest impact by increasing the number of episodes. Increasing heroin purity and falling prices can widen the market, increasing the number of people at risk and the number who die. In Australia greater availability of cheap, relatively pure heroin encouraged the spread of its use, largely accounting for the rise in overdose deaths since the 1960s.[28]

Next issue: part II
Preventing overdose
Proven tactics, promising ideas, the obvious and the controversial, based on new studies and evidence reviewed in part I

Lengthy use no protection

Experienced and presumably more knowledgable heroin users might be thought less likely to overdose; if anything, the evidence suggests the opposite.

The longer someone has been taking heroin, the more likely they are to have overdosed[26] [36] and those who die have typically been dependent for many years.[25] [46] In Australia[54] and Paris[40] the few novice deaths tended to be suicide. Regardless of duration of use, use of other drugs, and current treatment status, three Australian studies found that the more dependent someone was on heroin the more likely they were to have overdosed recently[35] or ever.[26] [36]

Some of these findings could simply reflect exposure to risk: dependent users inject more often and risk occasions cumulate over a long career. However, the Australian studies suggest that the *current* risk of overdose increases with severity of dependence and to a lesser extent length of heroin use in ways which cannot be accounted for by patterns of drug use or treatment status.

Two British studies provide corroboration. In London the risk of a user experiencing non-fatal overdose in their first year of injecting was 1 in 6 compared to 1 in 16 a year averaged across their injecting career.[31] However, many respondents had to recall incidents a decade ago, and risk may have been lower in the first year just because they were injecting less often. The second study was of injectors (two-thirds primarily using heroin) at a detoxification service in Glasgow. Their chances of dying in the next 12 months increased from near zero in their first year of injecting to 1 in 5 after 14 years,[24] a trend which could not be discounted as due to aging, onset of addicted patterns of use, or selective attrition.

One possible mechanism is that committed injectors who persist for years are also the ones prepared to take the greatest risks. Another is that as veins are used up, long-term injectors resort to more dangerous sites. Where injection sites were noted, over a third of the drug abusers who died from drugs in Glasgow in 1992 had resorted to the groin.[39] In London respondents who injected at sites other than the arm had injected for five years longer and overdosed twice as often as arm injectors.[31]

The culture of injecting

Where non-injecting administration is the norm, overdose can be expected to be less frequent. The contrast between death rates in Glasgow and Edinburgh is consistent with this expectation.[24] [128] [129] In the Netherlands just 4% of Surinamese heroin users inject and the same proportion have overdosed, while 37% of Dutch-born users inject and 29% have overdosed.[130]

Homelessness leads to unsafe use

Homelessness is common among addicts, but few studies have asked whether it is *more* common among those who overdose. This could happen if homeless addicts are left no choice but to risk injecting in public.[20] There is evidence for just such a mechanism.

In England's north west non-fatal overdose was unusually common among polydrug users who injected in public. 40% were homeless, nearly four times more than those who injected in private. They were also twice as likely to be living in the parental home, where many may have been unwilling to inject. As the researchers commented, "lack of predictably safe and private places to inject ... may increase the tendency to risk."[117] Unstable accommodation was strongly related to drug deaths in Hamburg[131] and (with other markers of social exclusion) to addict overdose in Norway,[34] where it remained so even after other factors had been taken into account.

Beyond homelessness, social exclusion is often unrelated to overdose. This was true of unemployment in addict samples in Sydney[57] [58] and Italy,[99] though in the latter those who died were over twice as likely to be single. Socio-economic deprivation in Britain is strongly associated with drug-related death, but this might simply reflect the distribution of addiction and injecting.[20]

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How a magazine for methadone clients portayed the risks of celebrating release from prison with drink and drugs

Women at greater risk but fewer die

In Britain three-quarters or more of drug users who overdose are men,[7] but this is just because there are more male users.[20] The risk faced by *each* female addict either of overdosing[33 43 69] or of dying from overdose or other causes[2 24] is roughly the same as for each male, possibly greater.[31] Compared to the same-sex general population,[6] female addicts are at greater *excess* risk of death than men.[2 24] Women addicts are also at greater excess risk specifically of suicide,[73] and suicides account for a much higher proportion of their drug-related deaths.[60]

As in Britain, in Australia[26 35 36] and Sweden[76] female heroin users were as likely to overdose as men and in Norway were more prone to suicide.[34] Where deaths are linked to a male-oriented drug culture, the relative equality of risk may be upset, as seems to have happened in Cabramatta.[113 132]

Older and perhaps slightly wiser

In Britain[7 20 21 24 39 60 111] and Australia,[25] overdose deaths, including those involving heroin, occur mainly among people in their late twenties and early thirties. However, in Scotland,[133] Spain[52] and Paris,[40] drug abusers tend to seriously overdose and die in their mid-20s. Though in the youngest age ranges deaths are few, excess mortality compared to the same-age general population is at its height – 22 times higher among 15–24-year-old addicts in London.[2] Because Glasgow's addicts die younger, excess mortality there is even higher – 72 times the norm in 15–19-year-olds and 28 times in 20–24-year-olds.[24]

Some of these statistics could merely reflect the age distribution of opiate injecting and the accumulation of risk.[25] The more interesting question is whether older users are more or less likely to overdose *each time* they take heroin. The answer is, all else being equal, probably less. Taking other factors into account, injectors in London were 11% less likely to have overdosed for each year they were older when they started injecting.[31] In Glasgow, injectors over 24 years of age were at less risk of overdose death per year of injecting than younger users.[24] In Adelaide, though just as dependent, heroin users who had avoided overdose in the last six months were on average older than those who had not.[36]

While a long heroin career does not in itself protect against overdose, these data hint that older users take fewer risks. Australian studies suggest age has an impact via variables such as drinking alcohol while using heroin.[26 36]

Genetic susceptibility is not the key

The metabolism of opiates and the physiology of respiration provide ample opportunities for physical differences determined by genetics or other factors to affect susceptibility to opiate overdose. The same potentially applies to the interaction between opiates and other depressant drugs which underlie many deaths.[45] However, in practice genetic anomalies do not seem a major factor in overdose deaths. The only one known to be important is very rare and, if others existed, these should quickly become apparent in new users, yet overdoses are most common in established users.[134]

A case for intervention

The evidence reviewed here shows that opiate overdose is highly prevalent among drug users and one of the main causes of premature death in young adults. However, overdoses do not occur at random: those who engage in polydrug and alcohol use, whose tolerance has dropped, who are not involved in treatment, and who use alone, are particularly at risk. Even when overdose is not prevented, physical damage and death can be.

This implies a dual focus for interventions: preventing overdoses, and preventing an overdose becoming a fatality. Researchers and practitioners are now working more actively on such interventions than ever before. The results of their work are the subject of part II of this review in the next issue of FINDINGS.

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