



Heroin Overdose: Research and Evidence-Based Intervention

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ABSTRACT *Drug overdose is a major cause of premature death and morbidity among heroin users. This article examines recent research into heroin overdose to inform interventions that will reduce the rate of overdose death. The demographic characteristics of overdose cases are discussed, including factors associated with overdose: polydrug use, drug purity, drug tolerance, routes of administration, and suicide. Responses by heroin users at overdoses are also examined. Potential interventions to reduce the rate of overdose and overdose-related morbidity are examined in light of the emerging data in this field.*

KEYWORDS *Heroin, Mortality, Overdose.*

INTRODUCTION

Until recent years, heroin overdose received scant attention in the international research literature even though drug overdose remained one of the major causes of death among heroin users,¹⁻⁵ even in countries with high human immunodeficiency virus (HIV) seroprevalence among injecting drug users (IDUs). In recent years, however, research attention has been directed to the problem, including three comprehensive reviews.⁶⁻⁸ To date, the overwhelming majority of this research has been conducted in Europe and Australia. Recently, however, there has been renewed research interest in fatal and nonfatal heroin overdose in the United States.⁹⁻¹² This article examines current research regarding heroin overdose and how these findings may inform evidence-based interventions.

STUDY FINDINGS

Extent of the Problem

Opioid overdose is a major cause of premature death among heroin users.⁸ In Australia,¹³ the rate of opioid overdose deaths increased from 1.3 per million in 1964 to 71.5 in 1997. Similar increases have been documented in the Nordic countries, Spain, Italy, Austria, the United States, and the United Kingdom.⁸

The clinical significance of overdose extends beyond fatalities. Little attention, however, has been paid to nonfatal overdose, which recent research has shown to be extremely common among heroin users.^{11,14-19} Typically, a half or more of cross-

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sectional samples of heroin users report a history of overdose, usually on multiple occasions. Such high rates are clinically significant as nonfatal overdose has been associated with pulmonary conditions, muscular complications such as rhabdomyolysis, renal failure, cardiovascular complications, and anoxia-induced cognitive impairment.^{8,20}

Risk Factors for Overdose

Demographics Historically, males have been overrepresented among fatal overdoses, comprising over 80% of some series^{6,9,10,21-26} (Table 1). Contrary to popular misconception, it is not younger, inexperienced heroin users that are at greatest risk of overdose death, with the mean age of overdose fatalities in the late 20s to early 30s.^{6,9,10,22-28} Rather than novice users, it is long-term, dependent heroin users who are at greatest risk. Of particular significance, those who overdose are rarely in drug treatment at the time of their deaths.^{22,25,29-31} Enrollment in treatment has been demonstrated to substantially reduce the risk of both fatal²⁹ and nonfatal overdose.³²

Nonfatal overdose does not typically occur among new heroin users. Overdoses commence characteristically only after several years of heroin use.¹⁵ Similarly, nonfatal overdoses overwhelmingly occur when the person is not enrolled in drug treatment.^{15,16,18,32}

Polydrug Use Possibly the most important finding to emerge from heroin overdose research is the role of polydrug use. The overwhelming majority of overdoses, both fatal^{9,10,22,28,33,34-36} and nonfatal,^{11,15,19,37} involve the concomitant consumption of heroin with other drugs. The extensiveness of polydrug use among “heroin” overdoses suggests that “polydrug toxicity” is a better description of the toxicology of overdose.⁶ The major drugs associated with an increased risk of fatal and nonfatal heroin overdose are alcohol, benzodiazepines, and tricyclic antidepressants.

Alcohol is by far the most common concomitant drug and is present in a half or more of fatal overdose cases.⁶⁻¹⁰ An inverse relationship also exists between blood morphine and alcohol concentrations.^{22,28,38} Lower concentrations of morphine appear to result in death in the presence of alcohol. Alcohol is also strongly associated with nonfatal heroin overdose.^{15,18} Benzodiazepines are also frequently noted at autopsy,^{9,10,22,26,34,39,40} and the use of benzodiazepines is also associated with nonfatal heroin overdose.^{16,18,37} Given that both alcohol and benzodiazepines are central nervous system depressants, it is likely that there is potentiation of the respiratory depressant effects of these drugs when they taken with heroin.

Finally, Australian research has linked tricyclic antidepressant use with both fatal^{22,25} and nonfatal⁴¹ heroin overdose. The antidepressants detected among Australian fatalities are almost exclusively tricyclics^{22,25} despite the fact that Australian heroin users predominantly use selective serotonin reuptake inhibitors (SSRIs) (which may reflect their relative cheapness).⁴¹ It should be noted that postmortem toxicology analyses in Australian jurisdictions test for the presence of SSRIs and other classes of antidepressants, so this finding is not a methodological artifact. Risk of nonfatal heroin overdose would appear to be increased significantly by tricyclic antidepressant use, but not by SSRI use.⁴¹ To date, however, the relationship between antidepressants and overdose has not been examined outside Australia.

TABLE Factors associated with heroin overdose

Variable	Comment	References
Demographics		
Gender	Fatalities: overwhelming male. Nonfatal: no gender difference.	6,9,10,14–18,21–26
Age	Mean age of fatal cases in early 30s. Nonfatal overdose commences after several years of heroin use.	6,9,10,14–18,22–28
Dependence	Long-term dependent users predominate. Fatal cases typically have 10-year heroin use careers.	6,9,10,22–28
Treatment status	Fatal and nonfatal cases rarely enrolled in treatment.	15,16,18,22,25,29–32
Polydrug use		
Alcohol	Present in a half or more of fatal overdose cases. Strongly associated with nonfatal overdose. Inverse relationship between blood morphine and alcohol concentrations.	6–10,15,18,22,28,38
Benzodiazepines	Benzodiazepines frequently noted at autopsy. Benzodiazepines associated with nonfatal heroin overdose.	9,10,16,18,22,26,34,37,39,40
Antidepressants	Risk of nonfatal heroin overdose would appear to be significantly increased by tricyclic antidepressant use, but not by selective serotonin reuptake inhibitors.	22,25,41
Purity		
Purity level	Only moderately related to overdose.	28,42–44
Contaminants	Harmful contaminants rarely detected.	6,22,44–47
Tolerance		
Older heroin users	Emerging evidence of reduced heroin use in the period prior to death.	50–52
Prison	Immediate postrelease period has high risk of overdose.	15,18,22,25,54,55
Route of administration		
Injection	Substantially increased risk of fatal and nonfatal overdose.	17,19,22
Smoke/oral/nasal	Documented cases of heroin deaths by nonparenteral routes.	57
Suicide		
Overdoses and suicide	Deliberate heroin overdose unusual. Almost all overdose cases unintentional. Nonopioid overdose and violent means most common suicide methods employed.	15,22,63–68

Heroin Purity The most long-standing and widely accepted explanation for death due to heroin is the result of a quantity or quality of heroin in excess of the person's current tolerance to the drug.⁶ A natural consequence of this view is that fluctuation in heroin purity is the major cause of heroin-related deaths. Research, however, has failed to support this view.^{28,42-44} In the United States, Desmond et al.⁴³ reported a nonsignificant correlation between heroin potency and number of deaths, while Rutenber and Luke²⁸ found heroin purity accounted for only 24% of the variance in heroin overdose fatalities. In Europe, Risser et al.⁴⁴ found no relationship between the purity of heroin seizures and number of heroin-related deaths. In Australia, variations in heroin purity accounted for only a third of the variance in overdose deaths.⁴²

Overall, heroin purity appears to have only a moderate relationship to heroin-related fatalities. It should also be noted that harmful contaminants are rarely detected in either syringes or the bodies of overdose cases; instead, relatively innocuous substances such as caffeine and sucrose are most commonly detected at autopsy.^{6,22,44-47}

Tolerance One of the puzzles surrounding fatal drug overdose is the predominance of experienced, long-term heroin users among fatalities. Such a population would be expected to have a high tolerance to opioids, yet large proportions have low blood morphine concentrations, in many cases below, or similar to, those of living heroin users or heroin users who died of other causes.^{34,48,49}

Two recent studies^{50,51} that analyzed hair morphine concentrations shed some light on this puzzle. In both studies, hair morphine concentrations among fatal cases were significantly lower than those of current users, indicating lower levels of heroin use in the period prior to death than among living heroin-using controls. In addition, a recent study of Swedish overdose fatalities detected no hair morphine in a third of cases.⁵²

The rigors of the heroin lifestyle may mean that, after a decade or more of heroin use, many users reduce their use. There is evidence that they may also increase their use of other drugs, such as alcohol, to compensate for reduced heroin use.⁵⁰ The low blood morphine concentrations detected in many fatal overdose cases may thus reflect less frequent use and correspondingly lower and less stable tolerance to opioids among older heroin users. Increased use of central nervous system depressants in these circumstances would, in all probability, exacerbate the risk of overdose.

The issue of reduced tolerance is directly relevant to incarcerated heroin users and to heroin users recently released from prison. While many heroin users continue to inject while in prison, such use is typically sporadic,⁵³ so tolerance to the drug will be substantially reduced. There is mounting evidence that release from prison constitutes a high-risk period for both fatal and nonfatal overdose among heroin users.^{15,18,22,25,54,55} For instance, Seaman et al.⁵⁴ reported that the odds of a fatal overdose occurring in the 2 weeks postrelease were 34 times those in times spent outside custody. Darke et al.²² found that 2% of New South Wales heroin overdose deaths over a 5-year period occurred in prison, and that 5% died shortly after release. The use of heroin immediately following periods of enforced or voluntary abstinence will be associated with reduced tolerance and a subsequent increase in overdose risk.

Route of Administration The smoking of heroin has become widespread in recent years in Europe, Australia, and the United States.^{17,19,56-58} Studies of nonfatal over-

dose indicate that the risk of overdose is substantially less when the drug is smoked rather than injected.^{17,19} These data are consistent with the epidemiology of fatal overdose. In Australia, despite increased heroin smoking, 99% of overdose deaths result from the injection of heroin.²² The remaining 1% of deaths in heroin smokers indicates that, while noninjecting routes of administration reduce the risk of overdose, it is important to emphasize that death can, and does, result from smoking, snorting, and swallowing heroin.⁵⁷

Depression and Suicide Rates of major depression are extremely high among heroin users,⁶⁰⁻⁶² and the risk of suicide is 14 times that of the general population.⁶³ In light of these associations, it has been hypothesized that a large proportion of heroin overdoses are misclassified suicides.^{64,65} However, research findings are contrary to this view.^{15,22,62,66,67} In Australia, only 5% of fatal heroin overdoses were classified as suicides,²² and nearly all heroin users reported that their most recent nonfatal overdose was accidental rather than deliberate.^{15,66} Furthermore, the characteristics and histories of young overdose survivors have been found to be no different from those of overdose fatalities, but were significantly different from those who completed suicide.⁶⁷ International research on both completed and attempted suicide among heroin users indicates that deliberate heroin overdose is unusual, with nonopioid overdose and violent means being the most common methods employed.⁶⁸

Bystander Responses to Overdose

There is widespread exposure to drug overdose by others, with more than 70% of heroin users in cross-sectional samples reporting that they have witnessed an overdose.^{14,18,69,70} Two points need to be noted here. First, others appear to be present in the majority of both fatal and nonfatal overdoses.^{15,18,22,26,70,71} Second, instantaneous death appears to be unusual.^{22,26,34,71-73} These data indicate that there is time to intervene in the majority of heroin overdose deaths, and that in most cases, people are present who could intervene.

Responses at overdoses, however, appear poor.^{18,25,22,69-71} In 79% of cases reported by Darke et al.,²² no intervention occurred prior to death; similar results have been reported elsewhere.^{25,71} Few studies that have examined the responses of heroin users who witness heroin overdose are consistent with the lack of action among fatal cases.^{18,69,71,74} Calling an ambulance is rarely the first action taken, and if one is called, it may only be after considerable delay, increasing the risk of death or anoxia. By far the most common reason given for delaying seeking help is fear of police involvement.^{18,69,70}

Evidence-Based Intervention

We now know substantially more about heroin overdose and associated risk factors than a decade ago. Such data suggest a number of potential interventions that may reduce heroin-related morbidity and mortality. In reality, no one intervention is likely to provide a “masterstroke” that will eliminate the problem of overdose. It is more likely that a range of interventions is required to have a substantial impact on overdose-related morbidity and mortality.

Treatment The least controversial way of reducing the frequency of opioid overdose is to increase the proportion of heroin users who are enrolled in treatment programs. As noted above, enrollment in opioid substitution treatment substan-

tially reduces the risk of overdose. The demographics of overdose indicate that a priority group is untreated older heroin users, who are at greatest risk. Motivating a group of long-term, high-risk heroin users to enter drug treatment to reduce overdose risk presents a major challenge. Increasing the availability of alternative pharmacotherapies to methadone maintenance, such as buprenorphine, may make maintenance treatment more attractive to older users who have not been interested in methadone maintenance or drug-free residential treatment.

Reducing Risk Factors Polydrug use plays a major contributory role in fatal opioid overdose. Heroin users need to be informed about the risks of combining heroin with other depressant drugs. Education of heroin users on the risks of polydrug use may help reduce the frequency of heroin overdose. It has been demonstrated that awareness of risk factors can be raised by means of such a campaign.⁷⁵ Changing actual behaviors may be more difficult.⁷⁵ Education on the increased risk of overdosing when resuming heroin use after a period of abstinence is essential, especially for older users. This is particularly relevant for heroin users about to be released from prison and could form a component of prerelease counseling about risks involved in the resumption of heroin use. Older heroin users also need to be discouraged from injecting alone, thereby denying themselves assistance in the event of an overdose.

Such information could be presented through needle-exchange programs and outreach services. Medical practitioners also need to be aware of the role of prescribed medications such as benzodiazepines and tricyclic antidepressants in causing heroin overdose.

Improving Responses at Overdoses Given the apparently poor responses to overdose, improving heroin users' responses to the overdoses of their peers may well reduce overdose fatalities and morbidity. Heroin users could be taught simple cardiopulmonary resuscitation skills to keep comatose users alive until help arrives. Users also need to be encouraged to call an ambulance immediately when overdoses occur. Their understandable fears of police involvement need to be addressed, and relations between ambulance officers and heroin users need to be improved. It has been demonstrated that interventions can improve the responses of heroin users when emergency medical systems and police have agreed on emergency protocols that bar/prevent/limit police from routinely attending overdose emergencies.⁷⁵

Provision of Naloxone Given the reluctance of heroin users to seek medical intervention, we and others⁷⁶⁻⁷⁸ have proposed that the provision of naloxone hydrochloride to heroin users be tested and evaluated. Naloxone hydrochloride is a narcotic antagonist that reverses the effects of acute narcosis, including respiratory depression, sedation, and hypotension. In the absence of opioids, naloxone has no pharmacological activity. Naloxone also has no abuse potential. Naloxone could be distributed through existing outlets such as needle and syringe exchanges, pharmacies, general practitioners, or treatment agencies. The ampoules of naloxone would be stored in heroin users' homes for use in the event of an overdose. The major advantage of providing naloxone to heroin users is that the opioid contribution to overdoses could be rapidly reversed if bystanders administered naloxone.

An evaluation of this option would need to assess the seriousness of potential problems with naloxone distribution. First, there are medicolegal complications for medical practitioners prescribing a drug that is most likely to be administered to

and by persons other than the one for whom it is prescribed.^{76,77} There are also significant economic costs in distributing naloxone sufficiently to have a wide impact on overdose morbidity and mortality.

On a more immediate clinical level, the half-life of naloxone is shorter than that of opioids, which means that naloxone has a limited duration to reverse the effects of opioids. That is, a person whose narcosis has been reversed by the administration of naloxone can relapse into coma if the dose of a longer-acting opioid drug has been sufficiently large to persist beyond the half-life of naloxone. This can, however, be overcome by the administration of further doses of naloxone. The risk may be overrated. In Australia, overdose cases are typically treated in situ with naloxone, and these individuals are not hospitalized. Despite this, in New South Wales, the state in which a half of Australia's heroin users reside, only 0.004% of fatal overdose cases occurred after naloxone administration.²²

Interventions to Change Route of Administration While noninjecting routes of heroin administration can result in overdose, research indicates that the risk of overdose from these routes is substantially less than that of injecting. It has been suggested that interventions be designed to encourage heroin users to switch to noninjecting routes of administration, thus reducing the injection-related harms and the risk of overdose.⁷⁹ The only concern with such a policy is the possibility that it may increase the aggregate number of heroin users and may, in the longer term, increase the number of heroin injectors if a substantial proportion of smokers transition to injecting. As noted above, heroin smoking has become popular among new heroin users, particularly in Europe and, more recently, in Australia. However, studies of transitions between routes of administration indicate that existing heroin injectors are resistant to changing from injecting to other routes as injecting is highly reinforcing due to rapid drug onset (the "rush") and greater bioavailability.^{19,56} It would appear unlikely that large numbers of heroin injectors would be willing, or able, to change to alternative routes. To date, no formal trial of transitions to less dangerous administration routes has been implemented and evaluated.

Medically Supervised Injecting Rooms Safe injecting rooms are officially designated sites where heroin users can inject without fear of arrest and with the knowledge that medical assistance is available if the person overdoses. Such facilities exist in Switzerland (since 1986), Germany (since 1994), and the Netherlands (since 1996),⁸⁰ and a trial commenced in Sydney, Australia, in 2001. Evaluations of safe injecting rooms reported their acceptability among IDUs, reduced public visibility and nuisance from street injecting (e.g., discarded syringes), increased street drug user contact with treatment and medical services, and reduced rates of overdose.⁸⁰⁻⁸³

Clearly, such facilities would not be expected to reduce overdose deaths in locations where there is no substantial degree of street-based injecting. However, such facilities would appear to have a role in reducing overdose deaths and in reducing the sequelae of nonfatal overdose in locations where street injecting is common.

Heroin Maintenance Heroin prescription under medical supervision is an option that may play a role in reducing heroin overdose. The Swiss experience with heroin prescription suggests that, under appropriate conditions, it may be beneficial to the dependent heroin users who participate in the program.⁸⁴ Heroin prescription may reduce illicit opioid use, reduce crime, improve health, and probably reduce overdose death. However, public anxiety about heroin prescription and the cost of implement-

ing the Swiss model of prescribing, which costs substantially more than other maintenance treatments, means that heroin prescription is unlikely to be implemented on a scale that would make a significant difference to opioid overdose rates.⁸⁵

DISCUSSION

A great deal of progress has been made in the past decade in understanding heroin overdose. This recent progress is not due to methodological weakness in earlier research, but rather to the relative paucity of research on this issue. Worldwide epidemics of bloodborne viruses among drug users dominated research attention in the late 20th century. The area of overdose also suffered from a number of popular myths that limited research interest (e.g., heroin overdoses are due to the purity of the drug, overdose victims are young and inexperienced, etc.). Recent research has shifted attention to factors such as the role of polydrug use, the demographics of overdose, and responses at overdoses. The challenges that remain include the low morphine concentrations of many fatalities, the exact nature of the interaction between heroin and other central nervous system depressants, and the relationship between overdose and the natural history of heroin use. The area of the health consequences of nonfatal overdose is one that has only recently received research attention.⁸⁶ Given the extent of the problem, this field requires urgent research.

In summary, heroin overdose remains a major contributor to heroin-related morbidity and mortality. The past decade has vastly expanded our knowledge of heroin overdose, although we are far from fully understanding the dynamics of the phenomenon. Our knowledge, however, provides a basis on which to reduce the rate and consequences of heroin overdose. Compared to a decade ago, we are much more informed about the demographics, toxicology, and circumstances of overdose. In the short term, expanding treatment services would be the most politically palatable intervention option. In the long term, a range of more innovative options is needed, including reducing risk factors such as polydrug use, improving the responses of heroin users to overdoses, and providing take-home naloxone directly to at-risk heroin users. These are politically difficult issues to address, but they are issues that must be considered to substantially reduce the human cost of overdose.

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