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# Would legalizing illicit opioids reduce overdose fatalities? Implications from a natural experiment

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## ABSTRACT

Overdose is the leading cause of premature mortality among heroin users. We examine whether the provision of regulated and quality-controlled heroin to users in specified doses would reduce heroin overdose rates. We also address this in the context of the epidemic of prescription opioid use and deaths seen in recent years in the United States and internationally. We explore the extent to which any change in legal access to heroin would affect overdose rates, and note that this depends upon the validity of the two main assumptions that variations in illicit drug purity and/or the presence of drug contaminants are major causes of overdose. Toxicological and demographic data from studies of heroin overdose deaths do not support these assumptions. The surge in the use of pharmaceutical opioids provides an example of the legal delivery of opioids of known dosage and free of contaminants, where overdose deaths can be examined to test these assumptions. Rates of fatal opioid overdose have escalated, with increased rates of prescribing of pharmaceutical opioids. On the basis of the experience with prescription opioids, unregulated legal heroin access would not reduce overdose rates.

**Keywords** Heroin, legalization, mortality, opioids, overdose, oxycodone.

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## INTRODUCTION

Opioids make the largest contribution to illicit drug-related death, the predominant cause being overdose [1–8]. In such cases, death is due to the central nervous system (CNS) depressant effects of opioids, leading to a sustained reduction in respiration and consequent anoxia [9]. For every fatal overdose we would also expect there to be 25–50 non-fatal 'near misses' [10–16].

Heroin overdose has, rightly, attracted a great deal of clinical, research and public health attention. A core question is: how do we reduce the rates of non-fatal and fatal overdose? We examine the argument for a change in the legal status of heroin as a possible means of reducing overdose rates by addressing what is known about the toxicology and circumstances of overdose, and how these might inform such proposals. The recent epidemic in prescription opioid dependence and overdose, most prominently seen in the United States [17], is a natural experiment in opioid provision, with implications for future models of control and regulation. In examining this issue, we take no position on the legality, or illegality, of opioids. We are concerned solely with the specific scientific question of whether or not altering the legal status of opioids would help to reduce the mortality and morbidity due to overdose.

## OVERDOSE AND THE LEGAL STATUS OF ILLICIT OPIOIDS

Currently, the production and supply of heroin is proscribed world-wide, falling under the jurisdiction of the Single Convention on Narcotic Drugs, with specific exceptions in the United Kingdom and those countries providing experimental heroin-assisted treatment [18,19]. Arguments for an alteration in the legal prohibition of heroin range from ethical arguments on individual liberties, the stigmatization of heroin users, the criminalization of heroin users and the violence inherent in illicit drug markets to reduction in the harms of heroin use, and to its use as an alternative to methadone as heroin-assisted treatment [20–23]. We are concerned here with a specific harm, overdose, and what the literature and experience tell us with regard to legality.

There has been a lengthy and lively debate from advocacy for the legalization or decriminalization of heroin to its provision solely in medical settings [23]. Under all production and distribution proposals, however, the core is the provision of heroin to users in accurately labelled, specified doses of known purity [20,22,23]. The potential efficacy in reducing overdose by such provision relates to two broad factors that are not controlled in an unregulated market. The first is that each dose is of a specified quantity of the drug, in a known concentration. Each dose is controlled, and the risk of overdose from wide variations in the purity of each gram of heroin is thus eliminated. The logical consequence is that overdose rates would be reduced, to the extent to which they are related to such variations. The second factor imbedded in such proposals relates to drug impurities. Not only would doses be of known purity, they would be known to be free of potentially lethal impurities. Again, to the extent that impurities cause what are termed 'overdoses', their elimination from the market would contribute to reductions in drug-related death. Rather than the Russian roulette of current illicit drug markets, heroin would be distributed to users in the form of a pharmaceutical-grade injectable opioid. The overall argument is that the risk of overdose at the individual level would be substantially reduced, thus resulting in population-level reductions [23].

## WOULD IT WORK?

There is clear evidence that those in heroin-assisted treatment have reduced risk of death from heroin overdose [18,19]. While somewhat impractical, it is theoretically possible that if all heroin users were treated in highly supervised treatment programmes this would result in a major fall in mortality, if all doses were consumed in the supervised treatment setting with post-dose observation. The likelihood of such a treatment provision is minimal. In the community setting, where most drug use occurs, the extent to which any change in legal access to heroin would affect overdose rates depends upon the validity of the assumptions underpinning the argument: drug purity and drug impurity as major causes of overdose. We will now address each of these assumptions, before examining lessons to be drawn from the prescription opioid epidemic of recent years.

### Purity

As we have opined elsewhere, the field of overdose is replete with myth [24]. The foremost of these myths is contained in the term 'overdose' itself. Overdose, typically, has been conceptualized as the consumption of a quantity, or purity, of a drug that is in excess of the person's tolerance. In fact, the toxicology of overdose consistently demonstrates moderate morphine concentrations (the major metabolite of heroin). Large proportions of fatal overdose cases have low blood morphine concentrations, in many cases below accepted toxic levels [25–27]. Indeed, Brescher [28], writing as far back as the early 1970s, noted that many overdoses appeared to be 'underdoses'. Furthermore, studies have demonstrated repeatedly that blood morphine concentrations in fatal cases are below, or similar to, those of living intoxicated heroin users, or of heroin users who died from of other causes [29–32].

It is now clearly understood and accepted that fluctuations in heroin purity have only a moderate relationship to the incidence of heroin-related death. This was demonstrated in the 1970s, when Desmond *et al.* [33] reported no correlation between heroin potency and overdose fatalities. Studies in the 1980s and 1990s found that variations in heroin purity accounted for only a quarter of the variance in overdose fatalities [34,35], while in 2000 Risser *et al.* [36] found no relationship between the purity of heroin seizures and heroin-related death.

The absence of a strong association between purity and overdose is consistent with the demographic and toxicological characteristics of overdose cases. The typical fatal case is a long-term, dependent, daily injecting drug user (IDU) aged in their 30s or older [1–6], and not the younger, inexperienced user with low tolerance. It is the older, dependent user, who we would expect to be tolerant to variations in purity, who contributes the bulk of deaths. There is also evidence that non-fatal overdoses typically commence after some years of regular, dependent heroin use [37]. These demographic characteristics are also reflected in the fact that these deaths are unrelated to day of the week or month [25,26,35].

Polydrug toxicity has emerged as the major factor in heroin overdoses. The overwhelming majority of opioid overdoses, both fatal and non-fatal, involve multiple CNS depressants, most notably alcohol and benzodiazepines [12–15,24–27,38,39]. Co-administration of other depressant drugs can substantially increase the likelihood of a fatal outcome, due to the combined respiratory depressant effects of these drugs. Thus, in the presence of other CNS depressant drugs, the usually well tolerated dose of heroin may prove fatal. Consistent with this, there is a negative correlation between blood alcohol and morphine concentrations, suggesting a functional reduction in opioid tolerance in the presence of alcohol [38,39]. The evidence is cogent: it is concomitant drug use, not drug purity, that is the primary vector of overdose. Consistent with this, variance in overall drug overdose deaths has been related to the number of multiple substance

deaths, and not variations in single-substance drug deaths [40]. Importantly, the pattern of polydrug toxicity is also true for both methadone and buprenorphine [3,25,41–43].

This is not to say, of course, that tolerance plays no role in overdose. Rather, it is to argue that most overdoses are due to combined drug toxicity, where a usually tolerated dose can kill. There are situations in which tolerance plays a more significant role, specifically after periods of opioid abstinence, such as the period immediately following imprisonment release or detoxification. The risk of death in these specific situations is elevated substantially [15,44–49]. However, such cases constitute a small minority, and it is questionable in the absence of opioid tolerance whether or not variations in purity are of relevance, as the risk of death is so high.

### Impurities

The second premise, concerning the argument that legal access to pharmaceutical heroin would reduce overdose deaths, is that it would mean that users are provided with a drug of high production quality that contains no lethal contaminants. This would be a cogent argument if contaminants were playing a major role in causing such deaths. This is not, however, the case. The evidence from toxicological analyses of blood, drugs and used syringes are quite clear. Harmful contaminants are rarely detected, which they most certainty should be if they were playing a major role in causing death after heroin administration [25–27,30]. Overall, one of the major things we have learnt over the past 40 years is that there is no toxicological evidence that contaminants play any great role in heroin overdose. Media alerts of 'killer' heroin, whether due to excessive purity or dangerous contaminants, simply do not fit the epidemiology, or toxicology, of opiate overdose.

## THE PHARMACEUTICAL OPIOID EPIDEMIC: A NATURAL EXPERIMENT IN PROGRESS

The preceding decade has seen an unprecedented increase in the prescribing and overdose rates of pharmaceutical opioids, and of oxycodone in particular [17, 48–60]. While seen in other countries [54,58], this phenomenon has been most prominent in the United States where, between 1999 and 2008, the sale of prescribed opioid analgesics increased by 300% [51]. The large increase in the prescribing of these drugs was reflected in non-medical use, with a 20% increase between 2002 and 2009 in the number of people in the United States who had recently used opioid analgesics for non-medical reasons [59]. Paralleling the increase in prescribing and use, between 2004 and 2009 rates of emergency room visits involving oxycodone rose from 28 to 89 per $10^5$, hydrocodone visits rose from 27 to 67 per $10^5$, and unintentional overdose deaths rose by 124% [17]. Indeed, the annual number of deaths attributed to oxycodone toxicity now exceeds the combined total of heroin and cocaine cases [51]. In examining this phenomenon, we are addressing a model of legal opioid delivery (by prescription), but with unsupervised dosing in community settings.

Who is dying from these prescribed drugs? Cases comprise two distinct groups: established opioid-using IDUs, a sizable proportion of whom who inject the tablets, and a larger, older group of chronic pain patients [49,53,55,56,58,60]. Interestingly, we see again that the age profile of cases is skewed heavily towards older users, rather than young, inexperienced (and possibly low opioid-tolerant) individuals. In as many as half of cases the drug was not prescribed to the decedent [49,53,55,56]. Importantly, the toxicology mirrors those of other opioids, including heroin, in overwhelmingly involving the concomitant use of other CNS depressants, most notably benzodiazepines, alcohol and other opioids [52,53,55,56,58,60].

The situation observed in the pharmaceutical opioids epidemic is of direct relevance to our discussion, as it provides a real-world example of widespread licit opioid provision. We have widely available, labelled, legal opioids of known concentration, free of impurities. As prescription rates have increased, however, poisonings have increased dramatically. Of particular interest, a large proportion of these deaths are established heroin users who have begun to use this more readily available opioid. They are now injecting a licit opioid (albeit often not prescribed to them), rather than illicit heroin. Despite the fact that the drug is an impurity-free pharmaceutical of known dosage, toxicity deaths among this group have risen dramatically.

## WHAT CAN WE CONCLUDE?

The central question posed in this piece was whether or not a change to the legal status of heroin would have a substantial impact in reducing heroin overdoses. The short answer to this question would appear to be 'no', unless we developed a very comprehensive provision of heroin-assisted treatment, which we think is unlikely. The case that illegality contributes greatly to overdoses is based upon two assumptions, both of which do not stand up to scrutiny. The first assumption, that variations in purity are a major source of overdose, does not fit the demographic, epidemiological or toxicological characteristics of overdose. The second assumption, that impurities in illicit heroin contributes to death, has no evidence to

support it and much to disprove it. Finally, the epidemic of pharmaceutical opioid use and overdoses seen in recent years provides a model of the provision of an opioid of known concentration and purity, one which many existing heroin users have found to be to their taste. Importantly, the toxicological profile of these deaths is consistent with that of heroin and other opioid deaths. Wider use has resulted in more deaths. We must also view any such provision in light of the overwhelming predominance of injecting as the route of heroin administration [3]. Regardless of the opioid being considered, injecting is a route of administration that carries the highest risk of overdose [3], and transitions away from injecting to other, safer routes are rare [61,62].

A myriad of models could be proposed for the legalization of heroin. The model primarily addressed here is of provision in the manner of substances such as alcohol, where use is by the individual in a setting of their choosing [20]. Known dose and purity do not protect and any such provision, we argue, would not reduce overdose rates, but actually increase rates due to wider availability and more widespread, unsupervised use of these drugs. A far more restricted model, which could theoretically make a major impact on overdose rates, would be the provision of injectable heroin to be consumed solely in treatment settings, such has been trialled in Switzerland and the United Kingdom [18,19]. Rates of mortality are, indeed, significantly lower in such trials, a fact shared with treatment more broadly [3]. Importantly, if an adverse reaction occurs, there is medical support present. It is arguable, however, whether this would be comprehensively provided in most jurisdictions. Moreover, the issue of concomitant CNS depressant use would still be problematic, as alcohol and benzodiazepines could be consumed either prior to or after dosing, with an elevated risk of overdose. This has continued to be a major problem for clinic-based methadone and buprenorphine maintenance, fatalities from which demonstrate the polydrug profile seen in other opioid deaths [3,25,43,63,64].

Overall, this discussion has explored the issue of opioid overdose in the context of changing legal status and access to heroin. It is not an argument for, or against, changing the legal status of heroin, but simply an analysis of the specific impact of such changes on opioid overdoses and death. There are a number of other factors, such as movement into and out of treatment and prison, provision of naloxone and other anti-overdose strategies that may have an important impact in reducing overall death rates. There may well be factors associated with overdose of which the clinical and research communities remain unaware. These are important to consider, but in this instance were not the focus of our considerations. The evidence suggests that legalizing heroin would not result in major reductions in overdose deaths, as most deaths are not attributable to unstable purity or the presence of impurities. The recent epidemic in prescription opioid deaths presents a natural experiment, the results of which are consistent with this view. Any assertion that legalization, or at least unsupervised community use, would reduce the number of fatalities does not accord with the evidence, and is based upon false assumptions.

## Declaration of interests

None.

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