

Benzodiazepines and cocaine as risk factors in fatal opioid overdoses



Small grants publications

This series of publications was commissioned in 2005, to short timescales.

Contributors were asked to contribute research that increased our understanding of effective treatment and harm reduction.

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April 2007 >> Research briefing: 31

The National Treatment Agency for Substance Misuse

The National Treatment Agency for Substance Misuse (NTA) is a special health authority within the NHS, established by Government in 2001, to improve the availability, capacity and effectiveness of treatment for drug misuse in England.

Treatment can reduce the harm caused by drug misuse to individuals' well-being, to public health and to community safety. The Home Office estimates that there are approximately 250,000–300,000 problematic drug misusers in England who require treatment.

The overall purpose of the NTA is to:

- Double the number of people in effective, well-managed treatment between 1998 and 2008
- Increase the percentage of those successfully completing or appropriately continuing treatment year-on-year.

Reader information

Document purpose	To describe the risks of benzodiazepine and cocaine use to heroin and methadone users
Title	Benzodiazepines and Cocaine as Risk Factors in Fatal Opioid Overdoses
Lead author	Phillip Oliver
Publication date	April 2007
Target audience	Primarily providers and commissioners of drug treatment services in England.
Circulation list	Managers and commissioners of treatment services Co-ordinators and chairs of local partnerships (e.g. drug action teams and crime and disorder reduction partnerships) Service user and carer groups Commissioners of pharmaceutical enhanced services local pharmaceutical committees Regional government department leads on drugs Central government department leads on drugs.
Description	This report describes a study comparing a group of people who died from fatal opioid overdoses with a similar living group of heroin users and comparing the contribution of benzodiazepine and cocaine use to the risk of a fatality
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Gateway/ROCR approval	The NTA is a self-regulating agency in relation to the Department of Health Gateway

Disclaimer

This publication is not a journal publication and does not constitute National Treatment Agency or Department of Health guidance or recommendations. The views expressed by this study are not necessarily those of the Department of Health or the NTA, but are based on externally refereed research.

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1 Executive summary

1.1 Aims

Heroin users are at considerable risk of early mortality, principally from opioid overdose. Understanding factors that influence the risk of overdose offers the potential to better inform strategies that aim to reduce these deaths. A risk factor is formally defined as an aspect of personal behaviour, inherited characteristic or environmental exposure that increases the risk of a person developing a disease or condition. Co-administration of central nervous system depressants such as benzodiazepines is currently considered, alongside loss of tolerance, to be one of the main risk factors for fatal opioid overdose. This status is however challenged by some empirical research. Meanwhile, cocaine use has been associated with an increased risk of non-fatal opiate overdose and more chaotic drug-using behaviours, but surprisingly does not appear to be a feature of fatal opioid overdose.

The present study was designed to assess benzodiazepine and cocaine use as factors in methadone and heroin-related fatal overdose, using an epidemiological approach known as a case-control study. The case-control method is considered to be more rigorous than cross-sectional and "correlational" studies which have predominately been used in previous research. The case-control technique allows us to test the hypothesis that use of benzodiazepines or cocaine affects the risk of opioid overdose, and measure the extent of this risk.

1.2 Study design

For this study we used a matched case-control design to estimate the relative risk of fatal opioid overdose associated with benzodiazepine and cocaine use. A group of individuals who died from a heroin overdose (the cases) were matched on age and gender to a similar group of living heroin users (the controls) on a one-to-one basis. We then compared each pair's recent use of benzodiazepines and cocaine using urinalysis data. This process was also repeated for a group of methadone overdose fatalities.

1.3 Sample groups

Cases were selected from a database held by the University of Sheffield containing toxicological findings from around 1,300 opioid-related deaths occurring throughout England and Wales during 1991–2004. We randomly selected 350 individuals (90% males, median age = 29 years) who died from a heroin overdose and all 260 available methadone-related fatalities (85% male, median age = 30 years). The two control groups were obtained from the Sheffield Primary Care Clinic for Drug Dependence (PCC). The control group for the heroin overdose fatalities were patients who had recently been referred for assessment, while the

control group for the methadone overdose cases were a group of methadone maintenance patients who had been in treatment for at least three months.

1.4 Outcome measures

The measure of recent benzodiazepine and cocaine use employed in this study was a positive urinalysis detection. Data for heroin and methadone cases was obtained directly from post-mortem toxicology reports linked to the toxicology database. Data for the heroin controls was taken from the individuals' urine test results at initial assessment, which were required to be positive for morphine (an active heroin metabolite) so as to ensure that the individual had recently used heroin. Data for the methadone controls was obtained from the urine test results closest to three months after the start of treatment where methadone was detected.

1.5 Methods

After selecting heroin and methadone cases from the toxicology database and extracting relevant data into a statistical program, controls were selected from anonymised audit urinalysis results of patients from the primary care clinic and matched by hand to the heroin and methadone cases on the basis of gender and age (\pm three years). This process resulted in 330 heroin-using pairs and 260 methadone-using pairs. Missing data meant that 299 heroin and 199 methadone pairs were analysed in total. The relative risks of fatal heroin overdose for individuals with evidence of recent use of benzodiazepines and cocaine were then estimated using odds ratios (ORs). This was repeated for the methadone group. An OR of one indicates that there is the same risk of fatal overdose for both users and non-users of the concomitant in question, while an OR of greater than one provides evidence that risk of fatal overdose is increased in the concomitant using group.

1.6 Findings

1.6.1 Heroin overdose

Recent benzodiazepine use, as evidenced by positive urinalysis, was observed in 48 per cent of the heroin overdose fatalities and 26 per cent of at entry methadone patients. After matching, the risk of fatal heroin overdose for those with evidence of recent benzodiazepine use was 2.4 times greater than those with no evidence of use (95% CI=1.64 to 3.60; $P < 0.001$). In contrast, cocaine use was seen in 16 per cent of heroin overdose fatalities compared to 41 per cent controls, which after matching, translated to a decreased risk of fatal heroin overdose (OR=0.26, 95% CI = 0.16 – 0.41, $\chi^2=40.83$; $P < 0.001$).

1.6.2 Methadone overdose

The results for the estimation of the relative risk of fatal methadone overdose associated with recent use of benzodiazepines and cocaine mirrored those presented for risk of fatal heroin overdose but with stronger effects. Seventy-one per cent of the methadone overdose fatalities (cases) had urines positive for benzodiazepines, while this was seen in only 26 per cent of current methadone patients (OR=9.16, 95% CI = 5.05 – 16.63, $\chi^2=78.72$; P <0.001). Risk of fatal methadone overdose was reduced by more 80 per cent for cocaine users (OR=0.16, 95% CI = 0.08 – 0.30, $\chi^2=42.05$; P <0.001).

1.7 Conclusions

The results of this study contribute to the growing body of research in attempting to better understand the aetiology and associated risk factors for fatal opioid overdose. Our findings support the status of benzodiazepine use as a significant risk factor for opioid overdose, especially for methadone-related death in which a near ten times increase in risk of fatal overdose was observed. Interpreting these findings within the context of the literature leads to three observations:

- 1 Benzodiazepines appear to have the potential, in terms of pharmacological interaction, of increasing the respiratory depressant effects of opioids
- 2 This effect is yet to be empirically observed in humans and may not be as sensitive as the contribution that alcohol makes to such deaths
- 3 The behavioural effects of benzodiazepines and the characteristics of their users could also be relevant.

The use of cocaine by opioid-dependent individuals is widespread and has previously been associated with poorer treatment outcomes, more chaotic drug use and more severe psychopathologies. Despite this, positive cocaine detections are, in comparative terms, rarely seen in fatal opioid overdoses. The results of this study are consistent with this pattern, which may be due to the antagonist relationship between opioids and cocaine with respect to respiratory depression, an interaction between the behavioural effects of cocaine and other risk factors for opioid overdose, or some other unidentified process.

Overall, it is clear that a number of factors influence fatal opioid overdose. Presently, our findings indicate opioid users who also use benzodiazepines have an increased risk of fatal overdose but

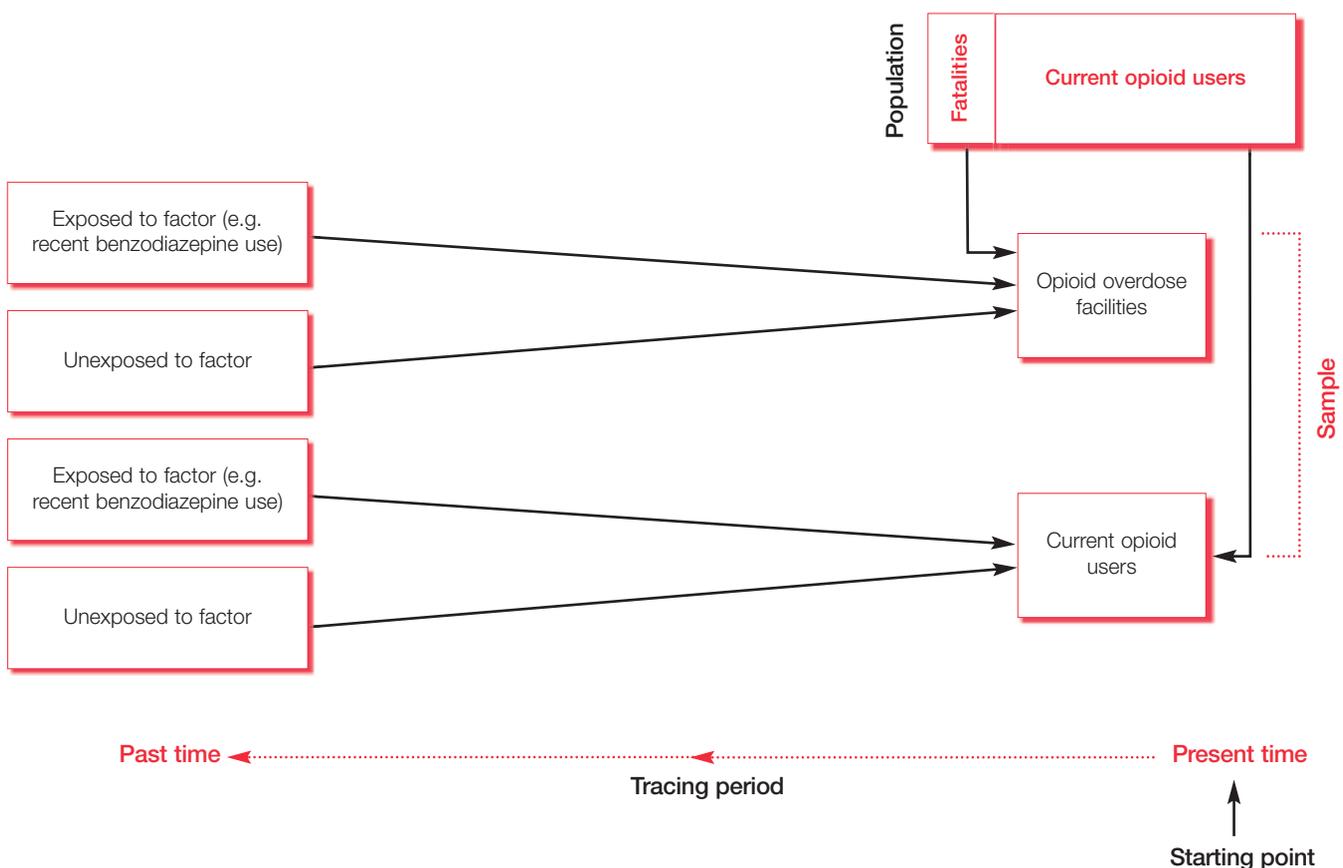


Figure 1: Diagrammatic representation of a case-control study to examine the influence of exposure factors on risk of fatal overdose (adapted from Petrie and Sabin, 2003)

the mechanism behind this is complex and may involve a behavioural component related to concomitant drug use. The most appropriate approach to preventing such deaths would appear to be public health education, vigilance, and careful prescribing. In this regard the recent introduction of daily dispensing of diazepam is to be welcomed.

1.8 Implications for further research

Future research directions should be aimed at further understanding the pharmacological nature of concomitant opioid overdose as well as exploring the behavioural characteristics of those with different apparent risks of fatal opioid overdose.

1.9 Acknowledgements

We are grateful for the assistance of Mr James Sutherland and Mr Saul Heng at the Sheffield Primary Care Clinic for Drug Dependence and Ms Michelle Horspool for their work on the collection of urinalyses data for the control group; to Dr Nicholas Seivewright and Dr Georgina Rowse for their comments on an earlier draft report; and to Dr Jenny Freeman for her input into the statistical methods.

2 Introduction

Annual mortality rates for users of heroin have been estimated to be between one and three per cent, with an excess mortality of up to 20 times that of age and sex-matched peers (Darke and Zador, 1996). Up to half of this excess mortality is believed to be due to fatal opioid overdose. Despite an increase in attention over the past decade, fatalities attributable to opioid overdose remain one of the most common causes of death among heroin users and continue to rise in many areas. The extent of the problem is such that the number of years of working life lost from drug misuse deaths in the UK now approaches that of road traffic fatalities (ACMD, 2000). Reducing opioid overdose deaths is therefore seen as one of the key performance indicators of the UK Government's revised drugs strategy. One way in which this may be achieved is through the identification of risk factors for opioid overdose.

In a meta-analysis of nine post-mortem studies of fatal heroin-related overdose carried out between 1976 and 2000, Warner-Smith *et al.* (2001) found that in addition to heroin, other central nervous system depressants such as benzodiazepines and alcohol were detected in up to 75 per cent of fatalities. Similar results have also been reported for methadone (Oliver *et al.*, 2001) and other opioid-related deaths (Pirnay *et al.*, 2004). Such findings however are not especially surprising given the population at risk – mostly heroin users who at one time or another are likely to engage in concurrent use of a variety of drugs of misuse. Benzodiazepines, for example, are frequently

prescribed to heroin users both in and out of methadone treatment (Darke *et al.*, 1994) and along with alcohol and cocaine, are among the most commonly used substances by this group.

More direct evidence for the role of concomitant substances in fatal opioid overdose has been provided by post-mortem toxicology studies, where research suggests that when opioids and other central nervous system depressants are co-administered, the amount of heroin required to overdose may be lowered. However, whereas this relationship has repeatedly been shown for alcohol (Ruttenber *et al.*, 1990, Zador *et al.*, 1996), such a relationship has not so far been seen for benzodiazepines (Zador *et al.*, 1996; Fugelstad *et al.*, 2003; Oliver and Forrest, 2005). As Capelhorn and Drummer (2002) point out, correlational studies such as those described are mainly descriptive in nature and thus for aetiological purposes have limited utility. In epidemiology, risk factors are typically identified and assessed through the use of analytic approaches such as cohort or case-control designs. To date, there has been a paucity of such research in this area. One exception is Davoli *et al.* (1993) who successfully used a case-control design to examine the risk of fatal overdose in a cohort of intravenous drug users. These researchers found fatal overdose risk to be associated with dropout from treatment, marital status and educational attainment, but did not examine concomitant drug use.

The purpose of this study is to assess the risk of fatal opioid overdose associated with recent use of two of the most commonly abused illicit substances by opioid dependent individuals. Specifically we intend to estimate the relative risk of fatal heroin overdose associated with recent use of benzodiazepines and cocaine in a group of heroin users, and estimate the relative risk of fatal methadone overdose associated with the same two concomitant drugs in a group of methadone users.

3 Methods

3.1 Study design

A risk factor is defined as an aspect of personal behaviour, inherited characteristic or environmental exposure that increases the risk of a person developing a disease or condition. For the present study, we employed a matched case-control design to evaluate benzodiazepine and cocaine use as risk factors in fatal opioid overdose. Figure 1 describes case-control designs that provide a convenient epidemiological method for determining risk factors associated with a particular disease or condition and are especially suitable for rarer events such as overdose fatalities, where a cohort design may be time consuming and costly. In a case-control study, a group of individuals with the outcome of interest (fatal opioid overdose in this instance) is compared to a

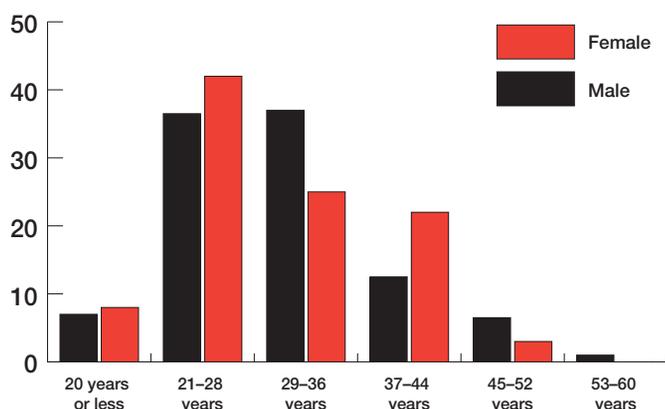


Figure 1: Distribution of age by gender for a random sample of 350 heroin overdose fatalities (314 male, 36 female) taken from the Royal Hallamshire Hospital's toxicology database

similar group of individuals without this outcome with respect to certain factors which are believed to increase (or decrease) the risk of the outcome of interest occurring.

An important consideration in the design of case-control studies is the identification and treatment of confounding factors. A confounding factor is an independent variable that distorts the association between another independent variable and the condition under study. For a variable to be confounding, it must therefore be associated with the exposure variable factor and be an independent risk factor for the condition. Several approaches exist to control for confounding factors. The effects of confounding can be adjusted by multiple regression during the analysis stage or via stratification (matching) at the design stage. The advantage of the latter is that inefficiencies due to too many or too few subjects per stratum are avoided (Breslow and Day, 1980) and it is this method which is adopted here.

In the present study, age and gender were considered to be potential confounders. While opioid fatalities tend to be male and cluster around 30 years of age (Cooper *et al.*, 1999; Sunjic and Zador *et al.*, 1999; Darke and Zador, 1996) previous (unpublished) research by the authors indicates that these factors may also be associated with concomitant drug use. It was therefore decided to match cases to controls on age and gender and conduct a matched analysis. Each case was matched to a single control and in order to minimise loss of data we aimed to match within four years of age.

3.2 Participants

3.2.1 Case series

Data regarding heroin and methadone overdose fatalities over the age of 18 years were obtained from a forensic toxicology database held by the University of Sheffield. This database, which was developed for a previous NTA funded study, contains information on the toxicological analyses of around 1,000 heroin

and 300 methadone-related deaths which occurred during the years 1991 to 2004. The original source of the data contained within the database records are the results of toxicological analyses of samples from sudden or unexpected deaths conducted by the toxicology section of the Royal Hallamshire Hospital (RHH) at the request of various coroners throughout England and Wales. Since such deaths may have a variety of causes, each record was reviewed and rated by a senior researcher to assess the likelihood, on the basis of the information contained within these records, that the death was directly related to the toxicological consequences of heroin or methadone use. Each case was classified into one of four categories: where there was a clear indication that the fatality occurred as a toxicological consequence of heroin or methadone use, the detection was designated as "causative"; cases in which the toxicologist suggested a probable fatal attribute to heroin or methadone were classified as "suspected". A random selection of 350 heroin-related fatalities from the first group were selected as heroin cases, while due to smaller numbers, 260 of the methadone fatalities classified into groups one and two (13 were removed due to missing data) were selected as the methadone cases.

3.2.2 Control series

The principal consideration in the selection of control groups was similarity of the population and the availability of a reliable and comparable measure of recent drug use. Controls were therefore selected from two groups of patients at the Sheffield Primary Care Clinic for Drug Dependence (PCCDD). The control group for the heroin study was selected from a random sample of untreated "at entry" heroin users with positive urinalysis results for heroin. Similarly, controls for the methadone overdose group were randomly selected methadone maintenance patients who had been in treatment for a minimum of three months and who had positive urinalysis screens for methadone.

3.3 Measure of recent concomitant drug use

The measure of recent benzodiazepine and cocaine use employed in this study was a positive urinalysis detection. The issues surrounding the timeframe for the detection of cocaine and benzodiazepines in urine are complex; however, the generally accepted rule of thumb is that cocaine may be detected up to approximately four days after administration. Depending on the benzodiazepine in question and chronicity of use, benzodiazepines may be detected up to around six weeks after cessation of use; typically, however, therapeutic dosages are detectable for up to three days. Data for cases were obtained directly from post mortem toxicology reports linked to the RHH database. To account for rapid "on the end of the needle" deaths in which the concomitant drug may not have had time to be excreted into the decedent's urine, blood samples of cases were

also examined and combined with the urine test results. Separate statistical analyses are presented for pure urinalysis results and the combined urine and blood results. Data for the heroin controls were taken from the individual's initial urine test results on assessment that, as part of the study inclusion criteria, were required to be positive for morphine (an active heroin metabolite). Data for the methadone controls were obtained from the urine test results closest to three months after the start of treatment where methadone was detected.

3.4 Statistical analysis plan

The relative risk (RR) of fatal heroin or methadone overdose for individuals with evidence of recent use of cocaine or benzodiazepines in a group of heroin and methadone users was estimated using odds ratios. When employing case-control study designs, individuals are selected on the basis of their outcome status (for example, disease, event and death). It is not therefore possible to directly estimate the risk of the outcome occurring. An alternative measure of risk can be calculated in such instances using odds ratios (OR). In studies where the event of interest is said to be rare within the population, the OR approximates the relative risk (Hosmer and Lemeshow, 2000) and so ORs in the current context have the same interpretation. Therefore, an OR of one indicates that there is the same risk of fatal overdose in both the exposed (e.g. those with recent evidence of cocaine use) and unexposed groups, while an OR of greater than one provides evidence that the risk of fatal overdose is increased for the exposed group.

Odds ratios for the current study were calculated using the Mantel-Haenszel estimate along with exact 95 per cent confidence intervals. McNemar's Chi squared (χ^2) test was used to test the null hypothesis that the OR=1. All statistical analyses were conducted using STATA version 8.2 (StatCorp, 2003).

3.5 Sample size and power calculations

The sample size calculations for McNemar's test require, along with type II error level (α) and power ($1-\beta$), the anticipated odds ratio (ψ) and the percentage of cases that are expected to differ from their controls in terms of benzodiazepine or cocaine use (π). Based on conservative estimates for $\psi = 2.0$ and $\pi = 20\%$ and following the method of Machin *et al.* (1997), for $\alpha = 0.05$ and $1-\beta = 0.80$ approximately 350 pairs were required. As the maximum number of methadone cases that could be obtained was 273 we note that this analysis would have 75 per cent power with these parameters.

4 Results

4.1 Heroin fatalities

4.1.1 Matching

The distribution of age by gender (the two matching variables) for the heroin overdose fatalities (cases) is shown in figure 1. Most males were aged between 23 and 37 while female fatalities were distributed slightly more widely. Suitable matches were found from the PCCDD computerised audit records, resulting in a total of 330 successfully matched pairs. Of these 242 were matched to within one year of age (73 per cent of sample), 61 to within two years (cumulatively 92% of sample), 26 within three years and one within four years.

4.1.2 Sample characteristics

The overall sample comprised 89 per cent males. Median age of both cases and controls was 29 years. The mean (geometric) free and total morphine levels for cases at post mortem were 374 μ g/L and 578 μ g/L respectively. Where detected in blood samples (108 cases) the mean diazepam concentration was 272 μ g/L while for temazepam positive cases (47) it was also 272 μ g/L. Eleven of the cases were positive for cocaine at post mortem with a mean blood concentration of 48 μ g/L. Due to missing urinalysis data for some of the cases, it was only possible to analyse 299 matched pairs in total.

4.1.3 Relative risks associated with recent use of benzodiazepines

As shown in Table 1, recent benzodiazepine use, as evidenced by positive urinalysis detection, was observed in 26 per cent of at entry methadone patients (controls) and 48 per cent of the heroin overdose fatalities (Table 1). Where both urine and blood samples from cases were simultaneously considered for evidence of recent benzodiazepine use, the proportion rose slightly to 51 per cent.

		At entry MMT patients (controls)	Fatalities (cases)
Recent use of BZDs – A	Yes	25.8%	48.3%
	No	74.2%	51.7%
Recent use of BZDs – B	Yes	25.8%	50.9%
	No	74.2%	49.1%

Table 1: Proportion of fatal heroin overdose cases and matched controls with evidence of recent benzodiazepine (BZD) use. A= Comparison of both urinalysis results. B= Comparison used urinalysis results for controls and considered both urinalysis and blood results for cases

2a		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	37	94
	-	39	101
OR = 2.41: 95% CI 1.64–3.60, $\chi^2 = 22.74$ ($P < 0.001$)			

2b		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	39	99
	-	37	96
OR = 2.67: 95% CI 1.81–4.01, $\chi^2 = 28.26$ ($P < 0.001$)			

Table 2a and 2b: Frequency counts and odds ratios for risk of fatal heroin overdose associated with recent benzodiazepine use ($n=271$ matched pairs). A comparison of urinalysis results is shown in Table 2a. In Table 2b, both urine and blood results were used to determine evidence of recent benzodiazepine use for the cases while controls used urine data only

A summary reflecting the matched nature of the data is shown in tables 2a and 2b. Frequency counts for the matched pairs are given in each cell showing the number of pairs in which: (++) both case and control displayed evidence of recent benzodiazepine use; (-+) the case but not the control was positive for benzodiazepines; (+-) the control but not case was positive for benzodiazepines; and (--) in which neither case nor control tested positive for benzodiazepines. The Mantel-Haenszel estimate of the relative risk is also given in this table (OR) along with exact 95 per cent confidence intervals and a test of the hypothesis that the odds ratio is equal to one (McNemar's χ^2).

When considering urinalysis results for cases and controls (Table 2a) the estimated relative risk of fatal heroin overdose for those with evidence of recent benzodiazepine use is given as 2.41 (95% CI=1.64 to 3.60). The results of McNemar's test ($\chi^2=22.74$; $P < 0.001$) indicate that this value is statistically significant. To account for the rapid deaths in which benzodiazepines may not have had time to be excreted into the urine, both urine and blood results for cases were examined (Table 2b). Using this data, the estimated relative risk of fatal overdose associated with benzodiazepine use was 2.67 (95% CI=1.81 to 4.01, $\chi^2=28.26$; $P < 0.001$).

		At entry MMT patients (controls)	Fatalities (cases)
Recent use of cocaine – A	Yes	40.6%	15.5%
	No	59.4%	84.5%
Recent use of cocaine – B	Yes	40.6%	15.5%
	No	59.4%	84.5%

Table 3: Fatal heroin overdose cases and matched controls with evidence of recent cocaine use. A = comparison of both urinalysis results. B = comparison used urinalysis results for controls and considered both urinalysis and blood results for cases

4.1.4 Relative risk associated with recent use of cocaine

Recent cocaine use was seen in 41 per cent of those entering methadone maintenance treatment (controls) compared to 16 per cent of heroin overdose fatalities (Table 3). No additional positive detections of cocaine were seen when the post mortem blood results for the cases were also considered. The matched-pair frequency counts for the four possible outcomes are shown in Table 4. In contrast to benzodiazepines, the estimated relative risk of fatal heroin overdose was decreased for those with evidence of recent use cocaine (OR=0.26, 95% CI = 0.16–0.41, $\chi^2=40.83$; $P < 0.001$).

4.2 Methadone fatalities

4.2.1 Matching

The distribution of age for male and female methadone overdose fatalities randomly selected from the RHH toxicology database is shown in Figure 2. Suitable matches were again found from the PCCDD client list, resulting in a total of 260 successfully matched pairs. Of these, 190 were matched to within one year of age (73 per cent of sample), 45 to within two years (cumulatively 90 per cent of sample), 24 within three years and one to within four years.

		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	17	25
	-	95	134
OR = 0.26: 95% CI 0.16–0.41, $\chi^2 = 40.83$ ($P < 0.001$)			

Table 4: Frequency counts and odds ratio for risk of fatal heroin overdose associated with recent cocaine use ($n=271$ matched pairs)

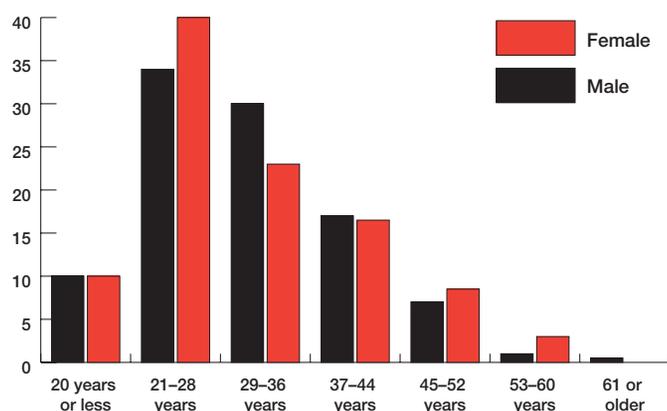


Figure 2: Distribution of age by gender for a random sample of 260 methadone overdose fatalities (220 males, 40 females) taken from the Royal Hallamshire Hospital toxicology database

4.2.2 Sample characteristics

Eighty five per cent of the matched pairs were male and the median age of both cases and controls was 30 years. The mean methadone blood level for cases at post mortem was 487µg/L. For cases in which it was detected (n=115) the mean diazepam blood level was 332µg/L while for temazepam positive cases (n=56) it was 850µg/L. Seven cases were positive for cocaine at post mortem with a mean blood concentration of 48µg/L. Due to missing urinalysis data for some of the cases, it was only possible to analyse 199 matched pairs in total.

4.2.3 Relative risk associated with recent use of benzodiazepines

The results for the estimation of the relative risk of fatal methadone overdose associated with recent use of benzodiazepines and cocaine mirror those presented for risk of fatal heroin overdose but with stronger effects. As shown in Table 5, recent benzodiazepine use was observed in 26 per cent of current methadone patients (controls) and 71 per cent of the methadone overdose fatalities (cases). When both urine and

		At entry MMT patients (controls)	Fatalities (cases)
Recent use of BZDs – A	Yes	25.5%	71%
	No	74.5%	29%
Recent use of BZDs – B	Yes	25.5%	73%
	No	74.5%	27%

Table 5: Proportion of methadone fatality cases and matched controls with evidence of recent benzodiazepine use (n=199). A = comparison of urinalysis results from cases and controls. B = comparison of used urinalysis results for controls and considered both urinalysis and blood results for cases

blood samples from cases were considered for evidence of recent benzodiazepine use the proportion rose to 73 per cent. The relative risk of fatal methadone overdose for both measures of recent benzodiazepine use is given in tables 6a and 6b.

4.2.4 Relative risk associated with recent use of cocaine

Recent cocaine use was seen in 42 per cent of MMT patients (controls) compared with 12 per cent of methadone overdose fatalities (Table 7). No further positive detections of cocaine were seen when the post mortem blood results for the cases were also considered. The matched-pair frequency counts for the four possible outcomes are shown in Table 8 along with the estimated relative risk which was decreased for those with evidence of recent use cocaine by more than 80 per cent (OR=0.16, 95% CI = 0.08 – 0.30, $\chi^2=42.05$; P <0.001).

5 Discussion

This study was designed to assess benzodiazepines and cocaine use as risk factors for opioid-related fatal overdose using a more systematic approach than previous studies, which have relied for the most part on descriptive techniques. The advantage of using a case-control methodology over previous approaches is that it incorporates a control group against which to compare the prevalence of concomitant drug use and provides a measure of the strength of the association between the outcome and factors of interest in the form of a risk estimate – the relative risk. It therefore offers the potential to inform the decisions taken by both drug users and those involved their treatment when faced with options to use or prescribe concurrently. This section will summarise the findings of this study and discuss these in the light of the literature on opioid overdose.

5.1 Benzodiazepine use as a risk factor for fatal opioid overdose

Co-administration of central nervous system depressants is presently considered alongside loss of tolerance to be one of the main risk factors for fatal opioid overdose (White and Irvine, 1999; Warner-Smith *et al.*, 2001). The extent to which opioid overdose deaths involve other concomitants has even led some researchers to question the accuracy of term opioid overdose in view of the fact that “pure” opioid overdose is only seen in a minority of cases (Darke and Zador, 1996; Mirakbari, 2004). Opponents of this view however point out that, in most A&E cases of opioid overdose, acute respiratory failure can be rapidly reversed through the administration of opioid antagonists, suggesting that the contribution of any concomitants must therefore be negligible (Tagliaro and Battistini, 1999). Others have recognised the need for more rigorous study designs to confirm these largely observational findings (Capelhorn, Oliver *et al.*,

6a		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	31	110
	-	12	46
OR = 9.16: 95% CI 5.05–16.63, $\chi^2 = 78.72$ ($P < 0.001$)			

6b		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	32	113
	-	11	43
OR = 10.27: 95% CI 5.53–19.08, $\chi^2 = 97.61$ ($P < 0.001$)			

Table 6a and 6b: Frequency counts and odds ratios for risk of fatal methadone overdose associated with recent benzodiazepine use ($n=199$ matched pairs). A comparison of urinalysis results is shown in Table 6a. In Table 6b both urine and blood results were used to determine evidence of recent benzodiazepine use for the cases whilst controls used urine data only

2003). Additionally, as recognised by the recent introduction (in England¹) of instalment dispensing of diazepam, these drugs are frequently prescribed to individuals with heroin dependence. It is therefore important to more critically assess the role that these drugs play in fatal opioid overdose.

Our study showed that heroin and methadone overdose fatalities were more likely to have benzodiazepine positive urine samples than a group of controls matched for age and gender. Benzodiazepine use was associated with a 2.5 times increase in risk of fatal heroin overdose in a group of current heroin users and a near ten times increase in risk of fatal methadone overdose for methadone users. The estimated relative risk for fatal heroin overdose is similar to that found by Taylor *et al.* (1996) who found that self-reported use of temazepam was associated with a 2.7 times increase in risk of non-fatal overdose in a study of 1,018 Scottish drug injectors. The data on the prevalence of benzodiazepine use produced from the present study for both case and control groups are broadly congruent with previous research. Forty-eight per cent of the heroin overdose cases in this had urine samples which tested positive for a benzodiazepine at post mortem. This figure is slightly higher than that given by previous research based upon blood toxicology which ranges

		At entry MMT patients (controls)	Fatalities (cases)	Odds ratio
Recent use of cocaine – A	Yes	42.1%	12%	0.19
	No	57.9%	88%	
Recent use of cocaine – B	Yes	42.1%	12%	0.19
	No	57.9%	88%	

Table 7: Proportion of methadone fatality cases and matched controls with evidence of recent cocaine use ($n=199$). A = comparison of both urinalysis results. B = comparison used urinalysis results for controls and considered both urinalysis and blood results for cases

¹ The two remaining classifications were: (iii) deaths not related to drug use and (iv) those who could not be rated due to insufficient information (neither are included in this study).

between 25 and 40 per cent (Zador, Sunjic and Darke, 1996; Darke and Ross, 1999; Darke *et al.*, 2000; Gerostamoulos, Staikos and Drummer, 2001; Oliver *et al.*, 2003; Fugelstad *et al.*, 2003). The higher prevalence figure seen in our present data might however be expected given the wider window of detection for urinalyses testing. Around a quarter of the heroin control group had evidence of recent use of benzodiazepines which is consistent with self report data by heroin users at entry to methadone maintenance treatment (Ball and Ross, 1991).

Our findings suggest that the high prevalence of concurrent benzodiazepine detections in opioid-related fatalities represents a genuine risk factor for opioid overdose rather than simply being a feature of these deaths and as such implicates benzodiazepines in the causal pathway of fatal opioid overdose. However, in order to validate this finding it is necessary to impose more rigorous criteria than simply association alone. In addition to association, two of the main criteria for causality are biological plausibility and a dose-response relationship. Although these are not essential for causality to be demonstrated, they provide a useful guide for us to assess the role of benzodiazepines within the context of the present findings and the existing knowledge base.

Opioid agonists such as heroin metabolites and methadone are potent respiratory depressants, exerting their effects at various sites within both the central and peripheral nervous systems (Yeadon and Kitchen, 1989). While pulmonary oedema is frequently observed in opioid overdose, it is the depression of respiration that is thought to be the most common cause of

		At entry MMT patients (controls)	
		+	-
Fatalities (cases)	+	13	11
	-	69	106
OR = 0.16: 95% CI 0.08–0.30, $\chi^2 = 42.05$ ($P < 0.001$)			

Table 8: Frequency counts and odds ratio for risk of fatal methadone overdose associated with recent cocaine use ($n=199$ matched pairs)

death (White and Irvine, 1999). Benzodiazepines are also respiratory depressants, though the mechanisms underlying these effects are different from those of opioids and the resulting depression is comparatively weaker. As of yet, the exact process underlying benzodiazepine and opioid interactions in respiratory depression remains to be established (Megarbane *et al.*, 2003), though some support for an additive effect in animal models has been published. McCormick *et al.* (1984) found that the respiratory depressant effects of methadone was increased by co-administration of diazepam, especially when both were used acutely, suggesting that novice users of both drugs were at particular risk. More recently, Gueye *et al.*, 2002 found similar findings for co-administration of buprenorphine and midazolam in rats, however these effects may not be as significant when opioids and benzodiazepines are administered through non-intravenous routes (Gerak *et al.*, 1998).

Whilst there would appear to be reasonable support for the biological plausibility of a mechanism in which the respiratory effects of opioids are enhanced in the presence of benzodiazepines, a perhaps more rigorous test of causality is a dose-response relationship (for example, one in which higher doses of benzodiazepines lead to an increased risk of fatal opioid overdose). One way in which such a relationship could be manifest is in terms of a toxicological correlation: lower doses of heroin would be required to cause a fatal overdose as blood levels of benzodiazepines increase. This can be tested (with some caveats) through examination of a series of blood toxicology results from opioid-related deaths, in which the levels of benzodiazepines (or any other concomitants) are correlated with levels of heroin or methadone. After taking into account other relevant factors, the resulting correlation would be expected to be negative. Exactly this type of relationship has previously been shown for the involvement of alcohol by the authors of this report and other research groups. For example, we recently found that after adjusting for other relevant factors, heroin fatalities with any quantity of ethanol present in their blood had average blood morphine levels 20–50 per cent lower than those without evidence of alcohol ingestion. This relationship has also been found in smaller scale studies from other countries (Ruttenber *et al.*, 1990, Zador *et al.*, 1996; Fugelstad *et al.*, 2003) and suggests that concurrent use of alcohol reduces the lethal heroin overdose threshold. This same research however has failed to find any correlation between benzodiazepine and opioid levels, and although one study suggests that such an effect may only be apparent at moderately high concentrations of benzodiazepines (Guitterez-Corroborla *et al.*, 2002), it would appear that the levels of benzodiazepines commonly seen in most opioid-related fatalities (for example Oliver *et al.*, 2003) may be insufficient to affect the lethal heroin or methadone concentration threshold.

Collectively, these strands of research indicate that while increasing doses of benzodiazepines (in contrast to alcohol) may

not have a simple inverse correlation to the amount of heroin required to overdose, concurrent users of benzodiazepines and opioids are nevertheless at increased risk of fatal overdose. In addition to toxicological risk, use of benzodiazepines by intravenous drug users has previously been associated with general risk-taking behaviours which may place the user at increased risk of experiencing opioid overdose (Darke, 1994a, 1994b). It remains unclear, however, to what extent these behaviours are due to the effects of the drugs themselves, for instance by affecting judgement during injecting, or because certain users of benzodiazepines have characteristics that place them more at risk of overdose. Some evidence suggests that opioid users who also use benzodiazepines do indeed have such characteristics. One study for example found that methadone maintenance clients with a history of benzodiazepine use had higher levels of depression, and poorer social functioning (both antecedents of suicidal behaviours) than those who did not use benzodiazepines (Darke *et al.*, 1993).

Distinguishing between effects directly related to benzodiazepines themselves and user characteristics has important implications for opioid overdose prevention methods because it suggests that focusing purely on strategies to reduce co-administration of opioids and benzodiazepines, either through educational methods or more restrictive prescribing, may have only limited impact in reducing fatal opioid related overdose. The identification of characteristics which increase the risk of fatal opioid overdose allows more focused prevention strategies and is the subject of a two-year study currently being conducted by our research group into the antecedents of fatal accidental overdose. In this study, the idea that fatal accidental overdose lies on a continuum bounded by fatal deliberate overdose opioid-related suicides – and therefore influenced by similar risk-factors – is being explored using the psychological autopsy technique (Appleby *et al.*, 1999). This study is collecting information not only on use of prescribed and non-prescribed drugs around the time of death but also on a wealth of psychosocial variables and will thus be well placed to explore the role of benzodiazepines in such deaths in greater detail than previously, for example by assessing whether use of this drug increases risk of overdose independent of other characteristics.

5.2 Cocaine use as a risk factor for opioid overdose

Concomitant detections of cocaine are seen much less frequently in fatal opioid overdose than central nervous system depressants such as alcohol and benzodiazepines and consequently cocaine is not generally considered to be a major epidemiological factor in these deaths. However, the main motivation behind the inclusion of cocaine in the present study was based upon research findings which suggest that cocaine use by injecting drug users may be associated with an increased risk of non-fatal opioid overdose. One study for example, found that drug injectors who reported

use of cocaine had a 1.8 times greater risk of experiencing a non-fatal overdose than those without evidence of cocaine use (Taylor *et al.*, 1996). Another similar study found that a recent history of injecting cocaine was associated with a 2.1 times increase in risk of non-fatal overdose (Ochoa *et al.* 2003). The results from our study suggest that this apparent increase in risk does not translate to fatal opioid overdose. Indeed, we found that heroin and methadone overdose fatalities were less likely to have cocaine positive urines than a group of controls matched for age and gender. The estimated relative risk of heroin or methadone fatal overdose for those with evidence of recent use of cocaine was 0.26 and 0.16 respectively, indicating that users of these drugs were at decreased risk of fatal opioid overdose in this study.

Cocaine, or more accurately, crack cocaine is one of the most frequently used illicit substances among opioid users, with estimates (depending upon the setting and method of estimation) as high as 75 per cent for methadone maintenance patients and 92 per cent for general polydrug heroin users (Condelli *et al.*, 1991; Leri *et al.*, 2003). In contrast, published reports of post-mortem blood toxicology data following opioid overdose in general reveal very few concurrent cocaine detections, ranging from around one to five per cent (Darke and Ross, 1999; Zador *et al.*, 1996; Oliver *et al.*, 2003).³ This data, along with the results of the present study, are suggestive of a protective effect for cocaine in opioid overdose. However, despite being biologically consistent with the antagonist relationship between opioids and cocaine with respect to respiratory depression, it is unclear whether concomitant use of cocaine would positively influence fatal outcome, particularly at the blood levels typically associated with opioid overdose. Jorens *et al.* (1996) describe a heroin overdose survivor following co-ingestion of the amphetamine-derived stimulant 3,4-methylene dioxymethamphetamine (MDMA) and suggest that the antagonist effects of these two drugs probably saved the individual's life. However this person was reported to have taken a considerable quantity of MDMA (40 tablets, or 4g) and had not injected the heroin detected. In larger quantities cocaine is associated with considerable toxicity in its own right and this is known to be potentiated in the presence of heroin (Drummer, 2004). Co-administration of cocaine and methadone has also recently been associated with irregular heart function (Krantz *et al.*, 2005).⁴

If those who provided positive cocaine detections are assumed to be regular cocaine users, then an alternative (though not mutually exclusive) interpretation of these findings is that individuals who use opioids and cocaine concurrently have certain characteristics that are protective against fatal overdose, although there would appear to be little empirical evidence for this in the literature. Moreover, polydrug use in itself is considered a marker for more chaotic drug use and hence risk taking behaviour. Heroin dependent individuals who co-abuse cocaine also appear to have

poorer treatment outcomes and more severe co-morbid psychopathologies (Leri *et al.*, 2003). There remains however the possibility that cocaine use interacts with other risk factors for opioid overdose, for example by reducing the likelihood that an individual injects while alone, and future research could be directed at investigating this issue in greater detail, perhaps by exploring the role of cocaine in non-fatal opioid overdose.

5.3 Study limitations

As with all studies, this research has methodological limitations. In a case-control study, the control group is intended to provide an estimate of the exposure (recent use of benzodiazepine or cocaine in this instance) in the population from which the cases are drawn, and ideally therefore should come from the same population. However, the two control groups in the present study were probably more homogeneous than the heroin and methadone fatalities as they were selected from a group of heroin dependent methadone maintenance treatment clients. In this regard, while most of the cases will be regular users of heroin or methadone, a proportion⁵ will not and this sub-group may therefore be less likely to use benzodiazepines or cocaine. The consequence of this is that the control group may be expected to have higher rates of exposure than the overdose fatalities. This would manifest itself as a bias in the estimated odds ratio in the direction of zero but is unlikely to have affected the inference of this study to any great extent. A second issue is that cases were drawn randomly from a wide geographical region of England and Wales while the controls are limited to the Sheffield heroin using population. The differences observed between cases and controls with respect to benzodiazepine and cocaine use may therefore, in part, reflect differences in patterns of polydrug use between Sheffield opioid users and those in other parts of the country. Any such effect will have been offset by the fact that the majority of fatalities included in this study will have come from the Yorkshire region. Thirdly, the use of urinalysis tests which have timeframes in the order of days means that the findings only relate to use of benzodiazepines around the time opioid use. The results may not therefore be generalised to actual co-administration of these drugs. This fact also limits causal inference because the order of administration cannot be known. Finally, the prevalence estimate for benzodiazepine detections in the fatal methadone cases was considered high in comparison to previously reported data –

² Amendment (SI 2005 No 893) to the NHS General Medical Service Contracts Regulations 2004 (SI No 291)

³ In the present study, positive blood toxicology detections of cocaine were seen in 3.6% of heroin cases (n=330) and 2.7% of methadone cases (n=260).

⁴ Krantz *et al.* (2005) report on cocaine-related polymorphic ventricular tachycardia (torsade de pointes) in a methadone maintenance patient and discuss the possibility that this may occur through a common mechanism of influencing the QT interval.

⁵ Perhaps around 20%, based on our previous work (Oliver *et al.*, 2003).

possibly due to sampling variation. Consequently, the risk estimate for benzodiazepine use in fatal methadone overdose may have been inflated. These qualifications aside, the overall prevalence estimates of benzodiazepine and cocaine use in both cases and controls were otherwise consistent with previously published reports. Additionally the use of urinalysis data offers new insights into opioid-related death since it probably reflects more accurately the actual prevalence of concomitant use of these drugs in this population.

6 Conclusions

The results of this study contribute to a growing body of research attempting to further our understanding of the aetiology and associated risk factors for fatal opioid overdose. Our findings support the status of benzodiazepine use as a significant risk factor for opioid overdose, especially for methadone-related fatalities. Interpreting these findings within the context of literature base leads to three observations:

- 1 Benzodiazepines appear to have the potential, in terms of pharmacological interaction, of increasing the respiratory depressant effects of opioids
- 2 This effect is yet to be empirically observed in humans and may not be as sensitive as the contribution that alcohol makes to such deaths
- 3 The behavioural effects of benzodiazepines or characteristics of their users may also be relevant.

The likelihood is that these and other factors interact in fatal opioid overdose. Presently, our findings indicate that opioid users who also use benzodiazepines have an increased risk of fatal overdose – the mechanism behind this however is complex, and therefore, the most appropriate approach to preventing such deaths would appear to be public health education, vigilance, local monitoring and careful prescribing. In this regard the introduction of instalment dispensing of diazepam is to be welcomed.

A similar effect for the role of cocaine was not observed in this study even though use of cocaine is generally considered a marker for more severe forms of dependence and poorer treatment outcomes. Future research directions could be aimed at further understanding the pharmacological nature of concomitant opioid overdose as well as exploring the psychological characteristics of those with different apparent risks of fatal opioid overdose.

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8 Acknowledgements

We are grateful for the assistance of Mr James Sutherland and Mr Saul Heng at the Sheffield Primary Care Clinic for Drug Dependence and Ms Michelle Horspool for their work on the collection of urinalyses data for the control group; to Dr Nicholas Seivewright and Dr Georgina Rowse for their comments on an earlier draft report; and to Dr Jenny Freeman for input on the statistical methods.

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