

Systemic disease among cases of fatal opioid toxicity

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ABSTRACT

Aims To determine levels of systemic disease among cases of death due to opioid toxicity. **Design** Analysis of coronial cases. **Setting** Sydney, Australia. **Cases** A total of 841 cases of death due to opioid toxicity (1 January 1998–31 December 2002). **Findings** Ventricular hypertrophy was present in 5.9% of cases and severe coronary artery atherosclerosis in 5.7%. Severe coronary pathology was more pronounced among older cases. Pre-existing bronchopneumonia was present in 13.2% of cases. Hepatic pathology was the most common type of pathology, and was far more marked among older cases. Cirrhosis was present in 25.3% of those aged > 44 years. Levels of renal pathology were comparatively low, but were related significantly to increasing age. Systemic disease in more than one organ system was present in 24.4% of cases, and was related to increasing age (44% of those aged > 44 years). The only pathology for which gender was an independent predictor among opioid cases was ventricular hypertrophy, more common in males. **Conclusions** Systemic disease, most prominently liver disease, is common among fatal opioid toxicity cases, and may be a factor in understanding the dynamics and age demographics of opioid-related death.

Keywords Disease, mortality, opioids, pathology.

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INTRODUCTION

Opioid overdose remains a major cause of premature death among heroin users, and has increased dramatically in recent decades [1–4]. The primary mechanism of death is opioid-induced respiratory depression, although hypoxia-induced cardiac arrest and arrhythmia may also occur [5–7]. The factors contributing to opioid-related death, however, remain poorly understood. While the demographic characteristics are well documented, they present a number of puzzles. Males constitute the overwhelming bulk of fatal heroin and methadone overdose [2,4,8–12]. While an excess of males is not surprising, given the over-representation of male opioid users, they constitute substantially higher proportions of fatalities than would be expected. Even more puzzling, it is not the inexperienced novice user who is most at risk, but long-term, dependent users. In fact, the mean age of overdose fatalities is in the late 20s to early 30s, representing use careers of a decade or more [2,4,9].

The toxicology of opioid overdose is even more puzzling. Morphine concentrations of fatal heroin overdoses

are skewed consistently towards lower concentrations [2,10,13–16]. Indeed, morphine concentrations are likely to be no higher than overdose survivors or living heroin users [16–19]. Furthermore, fluctuations in heroin purity appear to have only a moderate relationship to the incidence of heroin-related death [20,21].

The characteristics of opioid overdose can be explained partially in terms of polydrug use. The overwhelming majority of opioid overdoses involve the concomitant consumption of other drugs, particularly alcohol, benzodiazepines, tricyclic antidepressants and cocaine [1,2,4,8–13]. Alcohol and benzodiazepines, the most commonly detected drugs, are central nervous system (CNS) depressants, as are opioids. It is likely that there is potentiation of the respiratory depressant effects of these drugs when taken with an opioid, which may partially explain the low morphine concentrations seen in many cases. In fact, negative correlations between morphine and ethanol concentrations have been reported [2,10,18,22]. Similarly, there is recent evidence of an increase in benzodiazepine and tricyclic antidepressant use during the weeks preceding death [10,23,24].

The possible role of alcohol may also provide insight into the over-representation of males, as male opioid users are more likely to be alcohol-dependent [25] and to have alcohol present in fatal overdose [2].

Recently, there has also been interest in the natural history of opioid use as a possible explanation for some low-concentration overdoses [10,15,26,27]. Many users in these studies appeared to have cut down their use, or had periods of abstinence, immediately prior to death. The low blood morphine concentrations detected in many fatal cases may thus reflect less frequent use and correspondingly lower tolerance to opioids.

One possible contributory mechanism that has not been explored, however, is systemic disease [28]. While polydrug use may explain partially low blood morphine concentrations, and the predominance of males, it is less successful in explaining the relationship to age. The natural history of drug use, referred to above, does not explain deaths among older, tolerant cases who had not reduced their opioid use. There may, however, be a natural history of major systemic disease that underlies many, otherwise seemingly inexplicable, overdoses [28].

There are certainly good reasons to suppose that systemic disease may play a significant role. Opioid users have many risk factors for poor cardiac health, including high levels of cocaine use, almost universal cigarette consumption and exposure to infection with endocarditis [1,6,29]. Cardiac damage may increase susceptibility to the effects of opioid-induced hypoxia. Of particular importance is the potential role of liver disease. High rates of hepatitis C (HCV) infection are noted among opioid users, and long-term infection may result in steatosis, fibrosing liver disease, cirrhosis and carcinoma [6]. In addition, high rates of alcohol consumption may also produce liver disease. Whatever the cause, reduced opioid metabolism among liver-damaged opioid users may increase overdose risk. The heavy tobacco use of opioid users increases risk for pulmonary disease, such as chronic bronchitis, bronchopneumonia and emphysema. Pulmonary disease is clearly of direct relevance to users of drugs that suppress respiration. Finally, opioid use has also been associated with renal disease, although the mechanisms are poorly understood [6]. Poorly functioning kidneys may, however, be relevant to overdose risk, as electrolyte imbalance and increased blood pressure may place strain upon the cardiovascular system and increase the risk of pulmonary oedema [30].

We would expect all these pathologies to be more prominent among older opioid users, due to longer risk exposure and disease progression, and they may help to explain why older users appear at particular risk. To date, no study has examined specifically the systemic pathology of overdose cases, or related this to

demographic characteristics. The current study aimed to determine levels of pre-existing systemic disease among fatal opioid overdose cases, and relate these to age and gender. Specifically, the current study aimed to:

- 1 determine levels of systemic disease among cases of death due to opioid toxicity; and
- 2 examine the relationship of systemic disease to the age and gender of opioid toxicity cases.

METHODS

Case identification

Autopsy reports and police summaries of all cases of death by heroin/methadone overdose, and of death by hanging, between 1 January 1998 and 31 December 2002 were retrieved from the database of the Department of Forensic Medicine. Permission to inspect the files had been received from the both the NSW State Coroner and the Sydney South-west Area Health Service human research ethics committee. The Department of Forensic Medicine is located in central Sydney, and is the primary forensic pathology centre in New South Wales (NSW). All cases were reviewed by the authors.

In NSW a case must be reported to the Coroner where, *inter alia*: a person dies a violent or unnatural death; a person dies suddenly and the cause is unknown; a medical practitioner has not issued a death certificate stating the cause of death; the deceased was not attended by a medical practitioner in the 3 months prior to death; the person died within 24 hours of having been administered an anaesthetic; the person died within a year and a day of an accident to which the cause of death may be attributable; the person died in a psychiatric hospital or a variety of other institutions administering care or treatment (e.g. child-care centres); and the death occurred while the person was in police custody. All such cases, including all those presented in this study, undergo a standardized forensic autopsy with examination of all major organs, including microscopy of representative samples of tissue. All major organs are removed and weighed, and multiple samples of tissue (the exact number will vary from case to case) are taken from each organ for histology. Quantitative toxicological analysis is performed in all non-natural deaths. Cause of death is determined by the forensic pathologist on the basis of circumstances of death, the comprehensive autopsy findings and the toxicological analyses. It is important to note that this is a retrospective study. As such, the autopsies reported were not collected prospectively for the study, but were standard forensic autopsies performed as part of the medico-legal responsibilities of the Department of Forensic Medicine.

All cases autopsied at the Department of Forensic Medicine between 1 January 1998 and 31 December 2002 were identified in which the cause of death was attributed to opioid toxicity, due either to morphine (the major metabolite of heroin), methadone or the acute physical sequelae of such toxicity (e.g. hypoxic brain damage). All cases were also identified as illicit drug users. A total of 841 cases was identified. Almost all (95.4%) were accidental overdoses, the remainder being cases of probable suicide.

Autopsy findings

Information was collected on age (years), body length (m) and weight (kg), and body mass index (BMI) was calculated (kg/m^2). Circumstances of death and brief case histories were obtained from accompanying police summaries to the coroner. Information was recorded on all major pathology noted in autopsy reports, including coronary, pulmonary, hepatic and renal pathology. Information of particular relevance to cardiac pathology included ventricular hypertrophy (enlargement of the myocardium of the ventricle), ischaemic heart disease and coronary artery atherosclerosis. Atherosclerosis was classified as severe on the basis of direct comment by the forensic pathologist in the post-mortem report or by cross-sectional area narrowing >75%. Pulmonary pathology included bronchopneumonia, bronchitis, pulmonary fibrosis and emphysema. Cases in which bronchopneumonia may have developed after a period of hospitalization on life support, subsequent to overdose or hanging, were excluded from all analyses, as were cases of aspiration pneumonia. Hepatic pathology included lymphocytic infiltrate of the portal tracts (indicating active infection), steatosis (fatty infiltration), fibrosis, cirrhosis, hepatomegaly (enlarged liver) and necrosis. Renal pathology included nephrosclerosis (hypertensive changes in kidney tissue), fibrosis and cysts. For the purposes of presentation, pathology among opioid cases was presented in four age bands: 15–24 years ($n = 143$), 25–34 years ($n = 350$), 35–44 years ($n = 273$) and >44 years ($n = 75$).

Statistical analyses

Medians were reported where distributions were skewed, and Mann–Whitney *U*-tests or Spearman's rank order correlations were conducted. For bivariate group comparisons odds ratios (OR) with 95% confidence intervals (CI) were reported. The independent relationships of age and gender to the pathology of opioid toxicity cases were determined by logistic regression, with age, gender and BMI entered into each model. Adjusted odds ratios (OR) and confidence intervals (CIs) were reported for all

regressions. All analyses were conducted using SPSS for Windows (release 13.0) [31].

RESULTS

Demographic and physical characteristics

The mean age of cases was 32.9 years [standard deviation (SD) 8.3, range 16–64 years] and 81% were male. Only one case was older than 58 years. The mean body weight was 76.0 kg (SD 16.4, range 34–153 kg) and mean body length was 1.74 m (SD 8.3, range 1.45–2.01 m). The mean BMI was 25.1 (SD 4.8, range 11.2–57.4), with 4.3% of cases categorized as clinically underweight (BMI < 18.5). HCV serology was available for 655/841 of opioid cases, of which 71.3% tested positive (males 71.9%, females 68.8%). Positive serostatus for the four age bands were: 15–24 years (55.6%), 25–34 years (63.0%), 35–44 years (86.6%) and >44 years (75.4%). HIV serology was available for 656/841 cases, of which 3.2% were positive.

Toxicology

Blood toxicology was available for 805/841 cases. Morphine was detected in 91.9% and methadone in 11.9% of cases. The median blood morphine concentration among morphine-positive cases was 0.50 mg/l (range 0.05–35.0 mg/l). Females had significantly higher blood morphine concentrations than males (0.60 versus 0.40 mg/l, $U = 34\ 687$, $P < 0.01$). There was a significant negative correlation between age and blood morphine concentration ($\rho = -0.13$, $P < 0.001$), with younger ages associated with higher concentrations. Median blood morphine concentrations for the four age bands were: 0.60 mg/l (15–24 years), 0.50 mg/l (25–34 years), 0.40 mg/l (35–44 years) and 0.40 mg/l (>44 years). The median blood methadone concentration among methadone positive cases was 0.60 mg/l (range 0.02–9.50 mg/l).

The most commonly co-occurring drug was alcohol (40.0%). The median blood alcohol concentration (BAC) among alcohol positive cases was 0.12 g/100 ml (range 0.01–0.78 g/100 ml). Males were significantly more likely to have alcohol present (43.1 versus 27.0%, OR 2.1, CI 1.4–3.0). There was a significant negative correlation between blood alcohol and morphine concentrations ($\rho = -0.32$, $P < 0.001$). Other drugs present were: benzodiazepines (28.6%), antidepressants (10.4%), cocaine (8.0%), amphetamine (4.4%), cannabis (1.7%) and methylenedioxymethamphetamine (MDMA) (1.6%). The relationship of the three other commonly detected drugs to morphine concentrations was also analysed. The presence of benzodiazepines was not related to morphine concentrations (0.40 versus 0.40 mg/l, $P = 0.39$), but the presence of antidepressants was associated with

significantly lower morphine concentrations (0.30 versus 0.40, mg/l, $U = 26\ 689.5$, $P < 0.05$). Benzoyllecgonine concentrations (the major metabolite of cocaine) were correlated positively with morphine concentrations ($\rho = 0.14$, $P < 0.001$).

Cardiac pathology

Ventricular hypertrophy was present in 5.9% of cases and severe coronary artery atherosclerosis in 5.7% (Table 1). Only a single case of bacterial endocarditis was diagnosed, so no formal analyses were conducted. Increasing age was an independent predictor of ventricular hypertrophy (OR 1.06, CI 1.03–1.10), ischaemic heart disease (OR 1.10, CI 1.03–1.17) and severe arterial atherosclerosis (OR 1.12, CI 1.07–1.16) among opioid cases. Clear differences across age bands were seen, with 10.7% of those aged > 44 years being diagnosed with hypertrophy, compared to 2.1% of the youngest age band (Table 1). Similarly, 17.3% of the oldest age band of opioid cases had severe coronary artery disease, but none in the youngest age band.

Male gender was associated independently with a higher likelihood of ventricular hypertrophy (OR 5.72, CI

1.31–29.95), but not with ischaemic heart disease (OR 2.47, CI 0.31–19.46) or severe arterial atherosclerosis (OR 3.92, CI 0.98–11.01) (Table 1).

Pulmonary pathology

Pre-existing bronchopneumonia was the most common form of pulmonary pathology, present in 13.2% of cases (Table 1). Bronchopneumonia was more likely to be present among younger cases (OR 0.97, CI 0.94–0.99). By contrast, older age was a significant predictor of pulmonary fibrosis (OR 1.07, CI 1.03–1.10) and emphysema (OR 1.09, CI 1.15–1.14), both indicative of longer-term pulmonary disease. Age was not related significantly to a diagnosis of bronchitis (OR 0.99, CI 0.95–1.04). Among the oldest group, pulmonary fibrosis was reported in 17.3% of cases compared to 3.5% of the youngest age band (Table 1). A similar discrepancy was observable for emphysema, diagnosed in 13.3% of those aged > 44 years and between 1.4 and 3.7% of the younger age bands.

Gender was not a significant independent predictor of bronchopneumonia (OR 1.32, CI 0.73–2.39), bronchitis (OR 0.84, CI 0.34–2.09), pulmonary fibrosis (OR 0.75,

Table 1 Pathology among fatal opioid toxicity cases by age band and gender.

Pathology	Age band (years)				Gender		
	15–24 (n = 143) % (n)	25–34 (n = 350) % (n)	35–44 (n = 273) % (n)	> 44 (n = 75) % (n)	M (n = 680) %	F (n = 161) %	All (n = 841) %
Cardiac							
Ventricular hypertrophy	2.1 (3)	4.6 (16)	8.4 (23)	10.7 (8)	7.1 (48)	1.2 (2)	5.9 (50)
Ischaemic heart disease	0.7 (1)	1.1 (4)	2.6 (7)	2.7 (2)	1.9 (13)	0.6 (1)	1.7 (14)
Endocarditis	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (1)	0.1 (1)
Severe coronary artery atherosclerosis	0.0 (0)	4.0 (14)	7.7 (21)	17.3 (13)	6.5 (44)	2.5 (4)	5.7 (48)
Pulmonary							
Bronchopneumonia	15.9 (20)	16.4 (52)	8.6 (21)	9.9 (7)	13.6 (84)	11.6 (16)	13.2 (100)
Bronchitis	4.9 (7)	2.6 (9)	3.7 (10)	2.7 (2)	3.1 (21)	4.3 (7)	3.3 (28)
Fibrosis	3.5 (5)	4.6 (16)	8.4 (23)	17.3 (13)	6.5 (44)	8.1 (13)	6.8 (57)
Emphysema	1.4 (2)	1.1 (4)	3.7 (10)	13.3 (10)	2.8 (19)	4.3 (7)	3.1 (26)
Hepatic							
Lymphocytic infiltrate	35.0 (50)	36.9 (129)	55.7 (152)	41.3 (31)	42.6 (290)	44.7 (72)	43.0 (479)
Steatosis	18.2 (26)	32.6 (114)	49.5 (135)	52.0 (39)	39.6 (269)	28.0 (45)	37.3 (314)
Fibrosis	7.7 (11)	9.1 (32)	13.6 (37)	12.0 (9)	10.4 (71)	11.2 (18)	10.6 (89)
Cirrhosis	2.1 (3)	4.3 (15)	9.2 (25)	25.3 (19)	7.9 (54)	5.0 (8)	7.4 (62)
Hepatomegaly	1.4 (2)	4.9 (17)	8.1 (22)	4.0 (3)	6.0 (41)	1.9 (3)	5.2 (44)
Necrosis	3.5 (5)	4.0 (14)	6.2 (17)	8.0 (6)	5.0 (34)	5.0 (8)	5.0 (42)
Renal							
Nephrosclerosis	1.4 (2)	0.9 (3)	4.4 (12)	9.3 (7)	3.1 (21)	1.9 (3)	2.9 (24)
Fibrosis	2.8 (4)	1.4 (5)	5.1 (14)	9.3 (7)	3.2 (22)	5.0 (8)	3.6 (30)
Cysts	1.4 (2)	0.6 (2)	2.2 (6)	1.3 (1)	1.2 (8)	1.9 (3)	1.3 (11)
Global							
> 1 system diseased	16.1 (23)	18.3 (64)	31.1 (85)	44.0 (33)	25.0 (170)	21.7 (35)	24.4 (205)

CI 0.38–1.46) or emphysema (OR 0.83, CI 0.32–2.16) (Table 1).

Hepatic pathology

High levels of liver disease were seen (Table 1). Lymphocytic infiltrate of the hepatic portal tracts was noted in 43.0% of cases and steatosis in 37.3%. There were clinically significant levels of serious hepatic pathology: fibrosis (10.6%), cirrhosis (7.4%), hepatomegaly (5.2%) and necrosis (5.0%). Older age was an independent predictor of the presence of lymphocytic infiltrate (OR 1.03, CI 1.01–1.05), steatosis (OR 1.07, CI 1.05–1.09), fibrosis (OR 1.03, CI 1.01–1.06) and cirrhosis (OR 1.11, CI 1.07–1.15), but not hepatomegaly (OR 1.03, CI 0.99–1.07) or necrosis (OR 1.03, CI 0.99–1.07). Serious liver pathology was particularly marked among the older age bands of opioid cases (Table 1). Among those aged > 44 years, cirrhosis was diagnosed in 25.3% of cases, steatosis in 52% and necrosis in 8%. Comparable figures for the youngest age band were 2.1%, 18.2% and 3.5%, respectively.

Gender was not a significant independent predictor of lymphocytic infiltrate (OR 0.93, CI 0.65–1.33), steatosis (OR 1.34, CI 0.89–2.03), fibrosis (OR 0.80, CI 0.46–1.39), cirrhosis (OR 1.40, CI 0.63–3.11), hepatomegaly (OR 3.01, CI 0.91–10.00) or necrosis (OR 0.91, CI 0.41–2.01) (Table 1).

HCV serology was not included in the multivariate analyses on hepatic pathology presented above, as this would have meant excluding 186 cases (22% of the sample) from the analyses. Bivariate analyses of those cases with serology, however, indicated that a positive HCV serostatus was associated with significantly higher rates of lymphocytic infiltrate of the hepatic portal tracts (69.0 versus 11.7%, OR 16.76, CI 10.31–27.34), steatosis (45.0 versus 28.2%, OR 2.08, CI 1.44–3.00), fibrosis (16.1 versus 2.1%, OR 8.80, CI 3.17–24.43), cirrhosis (10.9 versus 2.1%, OR 5.64, CI 2.01–15.83), hepatomegaly (7.5 versus 1.6%, OR 5.00, CI 1.52–16.45) and necrosis (7.7 versus 2.7%, OR 3.06, CI 1.18–7.92).

Renal pathology

Relatively low levels of renal pathology were seen. Increasing age was an independent predictor of nephrosclerosis (OR 1.14, CI 1.08–1.20) and fibrosis (OR 1.07, CI 1.03–1.02), but not cysts (OR 1.04, CI 0.97–1.11). No cases of heroin-associated glomerulonephritis were diagnosed. Among cases aged > 44 years, 9.3% were diagnosed with nephrosclerosis and 9.3% had fibrosis noted, compared to 1.4% and 2.8%, respectively, among 15–24-year-olds (Table 1). There were no gender differences for nephrosclerosis (OR 2.18, CI 0.49–9.73), fibrosis (OR 0.61, CI 0.25–1.48) or cysts (OR 0.54, CI 0.14–2.09) (Table 1).

Multiple organ pathology

Systemic disease present in more than one organ system was common, with 24.4% of cases having multiple organ pathology (Table 1). Multiple systemic disease was associated independently with increasing age (OR 1.06, CI 1.04–1.08), but not with gender (OR 1.08, CI 0.70–1.67). The relationship of multiple systemic disease to age was particularly evident when those aged > 44 years (44.0%) were contrasted with the 15–24-year-old group (16.1%). Specific interrelations between pathology in organ systems were as follows: hepatic/pulmonary (15.1%), cardiac/hepatic (9.0%), hepatic/renal (5.6%), cardiac/pulmonary (3.7%), pulmonary/renal (2.9%) and cardiac/renal (1.8%).

DISCUSSION

The current study found systemic disease, and most prominently liver disease, to be common among cases of fatal opioid toxicity. Cardiac and liver disease were particularly pronounced among older toxicity cases. Despite the general picture of poor health of cases prior to death, they were not typically underweight.

The most ubiquitous pathology seen was hepatic. Among cases tested, 70% were HCV positive and nearly half had evidence of current hepatitis. As would be expected, a positive HCV serostatus was related strongly to the presence of hepatic disease. Fatty changes were noted in over a third of cases, with an obvious age progression. Of particular clinical interest, however, was the extremely high level of cirrhosis among older cases. A tenth of those aged 35–44 years were diagnosed with cirrhosis, as were a quarter of those aged over 44 years. Such levels would be of major concern in any clinical sample, but particularly so among a group of drug users. It is known that the overall metabolic capacity of the liver is reduced in the elderly, due to factors such as decreases in liver mass, hepatic enzyme activity and hepatic blood flow [30]. These cases were not elderly, but had high rates of serious liver disease which may have serious effects on hepatic metabolism. The ability of cases with serious liver disease to metabolize opioids must be questioned seriously and may help explain the age demographics of overdose.

Approximately one in 20 cases had serious heart disease, either ventricular hypertrophy or severe arterial atherosclerosis. These figures, however, masked marked age differences. Among cases over 44 years, one in 10 were diagnosed with hypertrophy and one in five with severe atherosclerosis. These diagnoses were rare among younger cases. Importantly, levels of both diagnoses exceeded controls. Opioids do not induce heart disease directly. As discussed previously, however, both cocaine

and nicotine use are common, and both are associated with such disease. Poor cardiac health among older opioid users may well increase the risk of hypoxia-induced cardiac arrest and arrhythmia, and contribute to the age demographics of toxicity cases. Significantly, only a single case of valvular heart disease due to either healed or active infective endocarditis was diagnosed.

The only pulmonary pathology of note was bronchopneumonia, diagnosed among one in seven cases. It is important to note that this diagnosis specifically excluded hospitalized cases and cases of peri-mortem aspiration pneumonia. Unlike other systemic disease, bronchopneumonia appeared more common among the young, so is unlikely to contribute to our understanding of the age demographics of opioid toxicity death. Bronchopneumonia, however, may increase risk of a fatal overdose occurring, due to impaired lung functioning in the presence of a CNS depressant.

Finally, levels of renal disease were low compared to the pathology already discussed. Again, however, this masked age differences, with approximately a tenth of those older than 44 years being diagnosed with nephrosclerosis and/or fibrotic scarring. Renal disease is a further indicator of the general clinical picture of poor health among the older opioid users seen in these data. It may, however, also be relevant to overdose risk, due to resultant strain upon the cardiovascular system. No cases of heroin-associated glomerulonephritis were diagnosed, which may be due to the relative difficulty in making the diagnosis at autopsy [32].

In addition to individual organ pathology, multiple systemic disease was common, being present in a quarter of cases. As in individual organ disease, multiple disease was related strongly to age, being present in nearly half the oldest age group. The global health of the older opioid case in this series was clearly extremely poor.

The high burden of disease among older opioid users provides new insight into potential factors underlying opioid overdose. While age was associated with increased risk of nearly all types of pathology, there were few obvious gender differences. Being male was an independent predictor only of being diagnosed with ventricular hypertrophy, and was not associated with multiple organ pathology. Higher levels of coronary pathology among males are typical of the broader population [30]. Overall, there were no large, substantive gender differences seen in this study upon which to hypothesize that disease underlies the gender discrepancy seen in opioid toxicity.

The morphine toxicology produced several findings of interest. First, the negative correlation between morphine and alcohol concentrations, seen previously [2,10,18,22], was confirmed. Overall, these data are consistent with the suggestion that lower morphine doses may result in death in the presence of alcohol. Secondly,

blood morphine concentrations had a moderate negative association with age. This may reflect the natural opioid use history postulated above [10,15,26,27], in that less frequent use in some users may have resulted in lower opioid tolerance. It may also reflect the higher levels of serious systemic disease seen among older cases, with lower doses resulting in death. Finally, female morphine concentrations were markedly higher than those of males. What this means is unclear, but may possibly reflect the higher levels of alcohol seen among males. The fact that there was a moderate positive relationship between morphine and cocaine concentrations is also difficult to interpret, but may be a marker for heavier drug involvement. The negative relationship between the presence of antidepressants and morphine concentrations is consistent with previous research demonstrating higher rates of non-fatal opioid overdose after consuming antidepressants [33].

The major theoretical implication of the current research is that systemic disease may play a role in explaining the factors determining opioid overdose. In particular, it may provide some of the basis for the age demographics seen among such cases. While blood morphine concentrations and polydrug use patterns are clearly part of the mechanisms of overdose, the current data suggest that systemic pathology must be added to these. This potentially has clinical implications for opioid substitution maintenance. The progressive disease burden of opioid users as they age implies that susceptibility to overdose may increase over time. A particular methadone dose once considered therapeutic may become more difficult to metabolize over time as systemic disease progresses, thereby lowering the threshold for overdose. Regular medical examinations and liver function tests would appear warranted.

The current study has limitations and research implications that must be noted. First, as a descriptive study of opioid toxicity cases, it is not possible to state definitively the role of systemic disease in causing these deaths. The data are certainly suggestive, but future research should compare the pathology of such cases with an appropriate control group, such as opioid users who died from other causes. Secondly, it is not possible to extrapolate from these data to pathology among living opioid users. A clear implication of the current research is that the systemic disease among living opioid users should be examined and compared to fatal cases, in order to understand better the role of disease in contributing to fatal opioid overdose.

In summary, systemic disease was prominent among opioid toxicity cases, particularly among older cases. Systemic pathology may well be a relevant factor in our understanding of the dynamics and demographic characteristics of opioid-related death.

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