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Clinical and Forensic Aspects of Heroin-Related Deaths: Prevalence, Contributors and Opportunities for Prevention

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Abstract

Heroin-related deaths are a significant public health concern however the extent of this problem as well as the impact and safety of interventions for this population are not clearly understood because the number of heroin-related deaths often underreported or misclassified. The aims of this research were to: accurately define and describe deaths involving heroin for improved public health and reporting purposes; to identify contributors to acute heroin toxicity as well as opportunities for intervention in order to reduce heroin-related deaths; and to examine the safety and efficacy of acute heroin overdose management in the out-of-hospital environment.

In order to improve heroin-related death attribution and reporting, a model was developed that incorporated both toxicological and investigative evidence of heroin use. Once validated, the model was then used to identify heroin-related deaths over a two-year period using the National Coronial Information System (NCIS). A total of 9060 potential cases were identified, reviewed and assessed based on the weighting of the evidence, with a total of 243 heroin-related death cases identified. To understand the extent and causes of the underreporting of heroin-related deaths, the identified cases were cross-referenced to data from the Australian Institute of Health and Welfare (AIHW) and Australian Bureau of Statistics (ABS) for heroin-related death data over the same time period. This study demonstrated that the actual number of heroin-related deaths in Victoria, Australia, are underreported by 47% compared to the number of deaths currently identified by the ABS and reported by the AIHW.

The potential for variation in the quality and quantity of street-level heroin to directly contribute to overdose was also examined. Street-level heroin seizures over a two-year period were obtained and the dose of heroin contained in 'cap' presentation determined. There were 983 samples analysed and it was demonstrated that 6% of samples that contained >2 times the median effective dose of heroin that may be expected by users which may directly contribute to overdose.

The safety of non-fatal heroin overdose in out-of-hospital environment was also examined using data linkage to pre-hospital Emergency Medical Services for each of the decedents. This study demonstrated that the treatment of uncomplicated heroin overdose in the out-of-hospital environment was safe, where there were 31 decedents treated by paramedics for a non-fatal overdose in the month prior to death, but in each case death occurred as a result of a subsequent and unrelated heroin use. An additional study examined the potential impact of take-home naloxone (THN) for reducing heroin overdose-related deaths. Results revealed that 79% of fatal

heroin overdose cases occurred at a private residence, where in 83% of cases the decedent was alone at the time of the fatal overdose event, and where there was someone else present, they were often incapable of providing meaningful intervention. This study demonstrated that THN could have led to a modest reduction in the number of fatal heroin overdose cases where there was the potential for appropriate and timely intervention by a bystander or witness. Findings from this research provide a unique and significant contribution to our understanding of this significant public health issues as well as add to the robust debate about the efficacy and challenges of different harm-reduction strategies.

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2. Stam NC, Gerostamoulos D, Pilgrim JL, Smith K, Moran L, Parsons S & Drummer OH. **Issues in the classification and reporting of heroin-related deaths.** Submitted (in review).

3. Stam NC, Gerostamoulos D, Gerstner-Stevens J, Scott N, Smith K, Drummer OH & Pilgrim JL. **Determining the effective dose of street-level heroin: a new way to consider fluctuations in heroin purity, mass and potential contribution to overdose.** Forensic Science International. 2018;290:219:226.

4. Stam NC, Pilgrim JL, Drummer OH, Smith K & Gerostamoulos D. **Catch and release: evaluating the safety of non-fatal heroin overdose management in the out-of-hospital environment.** Clinical Toxicology (Phila). 2018:1-7

5. Stam NC, Gerostamoulos D, Smith K, Pilgrim JL & Drummer OH. **Challenges with take-home naloxone in reducing heroin mortality: a review of fatal heroin overdose cases in Victoria, Australia.** Clinical Toxicology (Phila). 2018; Nov 17:1-6

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2. Stam NC, Gerostamoulos D, Smith K, Dietze PM & Pilgrim JL. **The differentiation and classification of heroin-related deaths: A model for the standardisation of investigation and reporting.** The International Association of Forensic Toxicologists (TIAFT) 54th Annual meeting (2016), Brisbane, QLD.

3. Stam NC, Gerostamoulos D, Dietze P, Gerstner-Stevens J, Scott N, Smith K & Pilgrim JL. **Determining the effective dose of street-level heroin: a new way to consider fluctuations in heroin purity, mass and overdose potential.** The Forensic and Clinical Toxicology Association (FACTA) conference (2017), Melbourne, VIC.

4. Stam NC, Pilgrim JL, Drummer OH, Smith K & Gerostamoulos D. **Opportunities and pathways for intervention by paramedics to reduce heroin-related deaths.** The Australia and New Zealand College of Paramedicine (ANZCP) conference (2018), Melbourne, VIC.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals and three submitted publications. The core theme of the thesis is the clinical and forensic toxicology of heroin. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Forensic Medicine, Monash University, under the supervision of Doctor Jennifer Pilgrim, Associate Professor Dimitri Gerostamoulos, Professor Karen Smith and Professor Olaf Drummer.

In the case of experimental chapters 2, 3 and 4, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
Chapter 2	The attribution of a death to heroin: A model to help improve the consistent and transparent classification and reporting of heroin-related deaths.	Published	70%. Concept, designed the study, convened expert panel, developed the model NCIS search, case review, data analysis and writing manuscript including figures and tables.	1. **Dimitri Gerostamoulos**, input regarding toxicological evidence in model, reviewed and edited manuscript - 5% 2. **Paul Dietze**, reviewed and edited manuscript - 5% 3**. Sarah Parsons**, input into manuscript, input regarding pathology evidence - 5% 4. **Karen Smith**, reviewed and edited manuscript - 5% 5. **Belinda Lloyd**, input into manuscript - 5% 6. **Jennifer Pilgrim**, input regarding content and direction of study, development of model,	No for all co-authors

				reviewed and edited manuscript - 5%	
Chapter 2	Issues in the classification and reporting of heroin-related deaths.	Submitted (in review)	70%. Concept, designed the study, reviewed cases, data acquisition from ABS, AIHW and NCIS, data analysis and writing manuscript including figures and tables.	1. **Dimitri Gerostamoulos**, input regarding content, reviewed and edited manuscript - 5% 2. **Jennifer Pilgrim**, input regarding concept, reviewed and edited manuscript - 5% 3. **Karen Smith**, reviewed and edited manuscript - 5% 4. **Lauren Moran**, provision of mortality data, input regarding cause of death reporting and input into manuscript - 5% 5. **Sarah Parsons**, input into manuscript and pathology advice - 5% 6. **Olaf Drummer**, input regarding content and direction of study, reviewed and edited manuscript - 5%	No for all co-authors
Chapter 3	Determining the effective dose of street-level heroin: a new way to consider fluctuations in heroin purity, mass and potential contribution to overdose.	Published	70%. Concept, designed the study, data acquisition from Vic Police FSD, data analysis and writing manuscript including figures and tables.	1. **Dimitri Gerostamoulos**, input into study design, reviewed and edited manuscript - 5% 2. **Joanne Gerstner-Stevens**, provision of heroin seizure data, input into manuscript - 5% 3. **Nick Scott**, input into study design, statistics and manuscript - 5% 4. **Karen Smith**, reviewed and edited manuscript - 5% 5. **Olaf Drummer**, reviewed and edited manuscript - 5% 6. **Jennifer Pilgrim**, input regarding content and direction of study, reviewed and edited manuscript - 5%	No for all co-authors
Chapter 4	Catch and release: evaluating the safety of non-fatal heroin overdose management	Published	80%. Concept, designed the study, data linkage acquisition from Ambulance Victoria, reviewed cases, data analysis	1. **Jennifer Pilgrim**, input into study design, reviewed and edited manuscript - 5% 2. **Olaf Drummer**, reviewed and edited manuscript - 5%	No for all co-authors

	in the out-of-hospital environment.		and writing manuscript including figures and tables.	3. **Karen Smith**, facilitation of data as well as data linkage, reviewed and edited manuscript - 5% 4. **Dimitri Gerostamoulos**, input regarding content and direction of study, reviewed and edited manuscript - 5%	
Chapter 4	Challenges with take-home naloxone in reducing heroin mortality: a review of fatal heroin overdose cases in Victoria, Australia.	Published	80%. Concept, designed the study, data linkage acquisition from Ambulance Victoria, reviewed cases, data analysis and writing manuscript including figures and tables.	1. **Dimitri Gerostamoulos**, input into study design, reviewed and edited manuscript - 5% 2. **Karen Smith**, facilitation of data as well as data linkage, reviewed and edited manuscript - 5% 3. **Jennifer Pilgrim**, study concept, reviewed and edited manuscript - 5% 4. **Olaf Drummer**, input regarding content and direction of study, reviewed and edited manuscript - 5%	No for all co-authors

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I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 17/08/2018

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

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Chapter 1: Introduction

1.1 Literature review

Opioid drugs can be an effective tool for the management of severe pain however, they are also associated with potentially serious harms as a result of misuse, dependence, drug diversion and acute overdose (1-4). The use of heroin, as well as the non-medical use of opioid analgesic drugs is particularly prevalent in Asia, North America, Oceania, Eastern Europe and South-Eastern Europe (5-7). Morbidity and mortality resulting from the overdose of opioid drugs including heroin, oxycodone, fentanyl, methadone and codeine represents a significant public health issue with an estimated 70 000 to 100 000 people dying from opioid overdose around the world each year (2, 3, 8-11). Heroin use is associated with a disproportionately high level of morbidity and mortality for the overall number of users, where overdose is a major cause of concern for regular users of this drug and where most deaths are caused by overdose (12-16). In fact people who use heroin are at estimated to have a six-times higher risk of premature death compared to the general age-matched population, with most of those deaths attributable to drug overdose (17).

Opiate and opioid drugs

Opioid drugs are a structurally diverse group of compounds with different pharmacological properties, however they all share the same fundamental property of being able to produce morphine-like effects following administration and where antagonists such as naloxone can block these effects (18). Opioid is an umbrella term that includes both opiate drugs, or compounds derived specifically from the opium poppy, as well as synthetic opioid drugs. In the illicit manufacture of heroin, a raw opium mixture that contains a number of different opium alkaloids including both morphine and codeine, are typically processed through an acetylation stage where diacetylmorphine (heroin) is formed (19). A number of different synthetic structural and functional derivatives of morphine have been manufactured over the years in an attempt to derive similar analgesic effects but without the adverse features of morphine (20). Synthetic opioid drugs include a large group of compounds derived from a known precursor drug, including morphine derived (e.g. oxycodone),

thebaine derived (e.g. buprenorphine), piperidines (e.g. pethidine and fentanyl) and phenylpropylamines (e.g. methadone) (20).

The safe and effective use of long-term opioid analgesic drugs for the management of chronic non-cancer pain requires skills and knowledge in both the areas of opioid prescribing, as well as the assessment and management of the risks associated with opioid abuse, dependence and diversion (1, 18, 21, 22). The link between the misuse or non-medical use of opioid analgesic drugs before transitioning to heroin use has now also been well recognised (23-27). The long-term use of opioid analgesics is complicated because they often provide inadequate long-term pain control while being associated with high rates of adverse events, as well as an overall failure to improve function or quality of life in the majority of patients (1, 18, 28). Paradoxically, the long-term use of opioid drugs has been linked to the development of an opioid-induced abnormal pain sensitivity. This results in both opioid tolerance as well as a pro-nociceptive process that may contribute to the decrease in efficacy of opioid drugs, in addition to contributing to both physical and psychological drug dependence (21). The use of either heroin, or the non-medical use of opioid analgesic drugs appears in-part to depend on the availability of these drugs. In different regions of Australia where heroin is not readily available, it has been reported that the non-medical use of opioid analgesics is higher (29-31). This pattern is also consistent with Emergency Medical Service calls for opioid-related presentations, where the majority of heroin overdose events in Victoria, Australia, were demonstrated to have occurred in metropolitan Melbourne, while opioid analgesic-related presentations occurred at a higher rate in regional Victoria (16).

Initiation and consequences of heroin use

There are a number of individual and family risk factors that have been consistently identified as being associated with people who use and become dependent on heroin. The reasons for initiation of heroin use in the first place are variable, but females who use heroin commonly report mistreatment as a child including sexual abuse, emotional abuse and neglect, as well as being initially introduced to heroin by

their partner, boyfriend or spouse (32). The pattern of drug initiation in young people also commonly follows the order of initial alcohol and tobacco use, followed thereafter by cannabis use and then followed by other illicit drugs including heroin (7). In generalised terms, a typical dependent heroin user tends to be an adult who uses heroin on a daily basis, is commonly unemployed and engaged in criminal activities or sex work to fund their heroin use, is generally in poor health and is likely to have experienced repeated drug overdoses (33).

It has been estimated that heroin use is associated with an approximately six-times greater risk of premature death compared with the general age-matched population, where drug overdose is the leading cause of death (15, 17). In addition to the risk of overdose, people who use heroin are also at risk of other adverse health outcomes as a consequence of unsafe injecting practices including HIV, hepatitis B and hepatitis C infections (7). Additionally, mental health problems as well as suicidal thoughts and behaviours appear to be a significant issue for people who use heroin (34-37). A number of risk factors have been identified as being associated with an increased risk of fatal heroin overdose including; a history of non-fatal overdose, being of older age, having a longer heroin using history, injecting as a route of administration, HIV serostatus and multiple concurrent drug use especially with the concomitant use of benzodiazepines, alcohol and other opioid analgesic drugs (10, 15, 38, 39). Premature death from overdose and injecting-related infectious disease are however less likely among individuals who smoke rather than inject heroin (40). In Australia, people who die from heroin overdose tend to be predominantly male, aged in their thirties, as well as mostly in a private residence and alone when they die (10).

Acute heroin toxicity

Intravenous heroin, even in non-toxic doses, has been demonstrated to produce profound respiratory depression that results in a significant reduction in oxygen saturation shortly after administration (41-44). Acute heroin toxicity or overdose occurs when the dose of heroin administered exceeds the current opioid tolerance

level of the individual. Heroin overdose is associated with opioid-induced ventilatory impairment that can lead to hypoxia and hypercapnia secondary to central nervous system depression, the loss of airway reflexes, and respiratory failure (45, 46). The risk of overdose is additionally associated with a number of other parameters including individual pharmacokinetic factors, health status, underlying comorbidities, the environmental context and the concomitant use of other drugs (42, 47, 48). A major challenge with heroin use is that the chronic or repeated use of opioid drugs including heroin, is strongly associated with the development of drug tolerance. The development of drug tolerance is believed to occur through a complex neuroadaptive mechanism, primarily associated with desensitisation and the down-regulation of opioid receptors (21). In opioid-tolerant individuals, this means that there is a requirement to consistently increase the dose of heroin administered in order to maintain the same desired physiological response, or equipotent effects. The requirement to increase the dose of heroin administered adds to the complexity of drug administration for dependent users, and this dose variation may result in an excess amount of drug being administered causing an overdose.

Non-fatal heroin overdose appears to be a relatively common occurrence among users of this drug. In contrast to this, fatal heroin overdose has been shown to be relatively uncommon with estimates of approximately 3.1% of all heroin overdose events resulting in death (49). In a heroin overdose, opioid-induced loss of supraglottic airway muscle tone may contribute to airway obstruction, while decreased consciousness and blunted reflexes may also increase the risk of pulmonary aspiration and an inhibition of the ability to self-correct airway obstruction (45). Heroin overdose is a dynamic illness where individuals may deteriorate rapidly and death may occur within minutes after administration as a result of respiratory impairment. Rapid and significant deterioration may be exacerbated by patient comorbidities, the concomitant use of other opioid drugs or CNS depressants, pulmonary aspiration or positional asphyxia (42, 47, 48). Conversely, in some cases there may be a longer period of unresponsiveness and significant hypoxia lasting up to several hours prior to death. If left untreated, a

heroin overdose can follow the clinical trajectory of leading to the development of hypoxic brain injury, cardiac arrest and death.

Identifying contributors for heroin overdose and heroin-related death

Heroin overdose most commonly occurs in long-term, dependent users rather than young, novice and naïve or non-tolerant individuals (50). Street-level heroin is subject to variability in both the quality and quantity of heroin, and it has been postulated that the variability of street-level heroin may directly contribute to overdose. Certainly, regular users of heroin believe that variation in the purity of purchased street-level heroin is a major direct contributor to overdose (12). Fluctuations in heroin purity have been reported to be moderately correlated with heroin-related overdose fatalities in Australia (51). This is however contrasted by a number of other studies that found no correlation between increased variance in heroin purity and heroin-related emergencies or heroin-related deaths (52-55). Given the overall conflicting findings between these studies, fluctuation in the purity of street-level heroin has been currently suggested to have only a moderate influence for heroin-overdose (56). Given the logical and yet unresolved nature of this relationship, this is an area that requires further research.

Changes in the behaviour and environment of people who use heroin may also contribute to an increased risk of overdose. These factors, in addition to changes in personal and social support situations as well as the adoption of high-risk injecting behaviours, have all been reported to be associated with an increased likelihood of heroin overdose (57, 58). Previous non-fatal overdose has additionally been reported to increase the risk of subsequent non-fatal heroin overdose (59, 60). For people who use heroin, it appears that there is a substantially increased risk of premature death as a result of a fatal heroin overdose after experiencing a non-fatal heroin overdose, with that risk elevated to a greater extent with multiple non-fatal overdose events (38). Opportunities for intervention appear to be especially important within the first month after a non-fatal heroin overdose, where it has been reported that the risk of death from a subsequent overdose is 10 times greater

during this timeframe (61). Emergency presentations for mental health crisis, deliberate self-harm and previous suicide attempts may also be important factors that increase the risk of subsequent fatal heroin overdose in this population (34, 35, 62, 63).

A major challenge in identifying both contributors to overdose and also opportunities for intervention to reduce the risk of heroin-related deaths centres around the accurate understanding of the extent of this problem. The medico-legal investigation of heroin-related deaths can be complex and the demonstration of heroin use in toxicity-related deaths can be challenging. Following administration, heroin (diacetylmorphine) is rapidly converted to 6-acetylmorphine (6-AM) and then to morphine (64-68). Population pharmacokinetic studies have demonstrated that following administration, both heroin and 6-AM are unable to be detected in the circulating plasma following a period of time greater than 10-40 minutes, and greater than 2-3 hours respectively (66). Because of the extremely short elimination half-life of heroin after administration, the detection of 6-AM in blood or urine is considered sufficient evidence to reasonably demonstrate recent heroin use (64, 69). The detection of 6-AM in heroin-related death cases can however be elusive because of the relatively short elimination half-life and the rapid conversion of 6-AM to morphine shortly after administration (70). 6-AM has additionally been shown to demonstrate significant postmortem redistribution, to be unstable and to spontaneously hydrolyse in human postmortem toxicology samples, as well as poor stability in different storage conditions including in frozen toxicological samples (71-73).

Heroin-death investigation can be additionally challenging because toxicological analysis may not be feasible at all, and most cases are complicated by multiple substance use (64, 74-78). These challenges contribute to the underreporting of heroin-related deaths. In fact, data from the United States where incomplete death certification for opioid-related deaths was examined and corrected resulted in a 20-35% greater number of heroin-related death cases than originally reported (79). Issues with death certification and reporting have additionally been demonstrated to

impact on trend analysis of both heroin and opioid-related deaths, and this has a direct impact on our ability to provide targeted public health interventions (80, 81).

1.2 Overall research aims

The purpose of this research was to improve our understanding of a number of unresolved clinical and forensic issues associated with heroin toxicity and heroin-related deaths.

The specific aims of this research were:

1. To accurately define and describe deaths involving heroin for improved public health and reporting purposes.
2. To identify contributors to acute heroin toxicity as well as opportunities for intervention in order to reduce heroin-related deaths.
3. To examine the safety and efficacy of acute heroin overdose management in the out-of-hospital environment.

1.3 Outline and structure of thesis

In order to address these aims, three broad sub-studies that investigated different aspects of heroin-toxicity were investigated. The three sub-studies were:

- **Defining heroin-related deaths.**

This chapter investigated the current decision making and evidence used in the attribution of a death to heroin or not, as well as opportunities for improved consistency and transparency in this area. This chapter additionally investigated the impact of inconsistencies in certification and reporting of heroin-related deaths, as well as other factors that may contribute to the underreporting of heroin-related deaths.

- **The potential impact of fluctuations in street-level heroin for overdose.**

This chapter investigated variation in the dose of heroin contained in the most common street-level presentation of heroin and the direct potential contribution that this may to overdose.

- **The safety and efficacy of out-of-hospital clinical management of overdose.**

This chapter investigated the safety of the treatment and non-transportation to hospital of people who have experienced a non-fatal overdose. This chapter additionally investigated the impact and challenges associated with take-home naloxone for reducing heroin-overdose deaths.

Each of the three broad sub-studies used both different data sources as well as different investigation techniques in order to address existing knowledge gaps in each of these areas.

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Chapter 2:

Defining heroin-related deaths

2.1 Chapter introduction

As outlined in the review provided in **Chapter 1**, heroin-related deaths are a significant public health issue and in order to understand the causes or contributors to this problem, we need to understand the extent of the problem. This is also a fundamental step in order to consider targeted interventions in order to reduce heroin-related mortality. As outlined previously, the medico-legal investigation of heroin-related deaths can be challenging. The complexity of heroin death investigation can be contributed to by the lack of toxicological analysis in some cases, variability in the detection of heroin-specific metabolites, and the involvement of multiple substance use. During the medico-legal investigation process, an opinion is made by a forensic pathologist in relation to the most likely and reasonable cause of death based on the findings at autopsy, interpretation of available toxicological findings as well as the correlation of scene investigation and decedent history.

Chapter 2 presents an investigation and analysis of the current variability in the decision making and evidence used in the determination of whether a death is attributed to heroin or not as well as the overall impact of that variability or uncertainty in attribution and reporting of heroin-related deaths. **Publication 1** provides the first analysis of the current evidence and criteria used in the attribution of a death to heroin or not, in a cohort of forensic pathologists and forensic toxicologists. This publication also provides a consistent set of criteria or model that can be used to improve the consistency and transparency of the attribution of a death to heroin or not. The variability in heroin-related death attribution were also assessed in-practice by a detailed examination of the evidence and attribution to heroin or not is a cohort of cases that were considered reasonably attributable to heroin using this model. **Publication 2** provides an investigation and analysis of heroin-related death reporting. This publication provides an investigation of the impact that variability in the attribution, the manner in which the death was certified as well as the subsequent variability in classification and coding of these death has on the overall number of heroin-related deaths reported.

2.2 Publication 1

The attribution of a death to heroin: A model to help improve the consistent and transparent classification and reporting of heroin-related deaths.

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The attribution of a death to heroin: A model to help improve the consistent and transparent classification and reporting of heroin-related deaths

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ABSTRACT

Introduction: Accurate attribution of heroin-related deaths, as well as the differentiation from other opioid analgesic-related deaths, is essential from a public health perspective. Heroin-related deaths involve a number of complexities where heroin-specific or non-specific metabolites and indicators (6-acetylmorphine [6-AM], morphine, and codeine) may or may not be detected. The aims of this study were therefore to develop a model for improved consistency in the attribution of heroin-related deaths and to determine areas of variation in the current decision-making processes.

Methods: A model was developed using different toxicological indicators of heroin use (6-AM, morphine to codeine ratio (M:C) or morphine alone) along with investigative evidence of heroin use (circumstances, scene and clinical findings) which were used to assign a weighted score. The combined scores for the toxicological and investigative evidence were used to determine the relative strength of association for the death being attributable to heroin according to three categories: suspected; likely; or strong. An expert panel was convened to validate the model and a series of test cases were provided to a cohort of forensic toxicologists and pathologists in order to identify sources of variation in decision-making within this group. The model was also evaluated for sensitivity and specificity by reviewing potential heroin-related cases and examining the evidence associated with the attribution of these cases to heroin or not.

Results and Discussion: Across all potential heroin-related death cases, the use of this model enabled a greater level of consistency in the attribution of death to heroin, especially in cases where 6-AM was not detected. The largest amount of variation in the attribution of a death to heroin was observed with potential intoxication-related deaths and in toxicity cases where a M:C ratio only was reported, even more than when no toxicological evidence was available. The reviewed cases highlighted the same variation in the attribution of a death to heroin, including a large number of cases that were attributed to morphine where 6-AM was not detected.

Conclusion: This model provides a useful tool for improved accuracy and consistency in the differentiation, attribution and reporting of heroin-related deaths. Previously challenging cases where death occurred after a significant period of time and either no 6-AM was detected or no samples were taken, are able to be captured using this model.

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1. Introduction

The medico-legal investigation of deaths involving drugs can be complex and recommendations have been published to guide the investigation, diagnosis and certification of overdose deaths related to opioid drugs in order to improve accuracy of death reporting [1]. Heroin-related death investigation can be particularly challenging because of variability in the detection of heroin-specific metabolites, toxicological analysis may not be feasible at all, and most cases are complicated by multiple substance use [2–7]. Following administration, heroin (diacetylmorphine) is rapidly converted to 6-acetylmorphine (6-AM) and then to morphine [2,8–11]. Because of the extremely short elimination half-life of heroin, it is widely accepted that the detection of 6-AM in blood or urine is considered sufficient evidence to reasonably demonstrate recent heroin use [1,2]. Indeed, population pharmacokinetic studies have demonstrated that heroin and 6-AM are unable to be detected in the circulating plasma following a period of greater than 10–40 min, and greater than 2–3 h, respectively, following heroin administration [9]. However, the detection of 6-AM in heroin-related death cases can be elusive because of the relatively short elimination half-life and conversion of 6-AM to morphine [12]. Differences in the elimination half-life and clearance of heroin, 6-AM and morphine result in significant variation in the detection of these compounds in overdose-related death cases making the medico-legal investigation of these deaths complex.

The detection of 6-AM in postmortem toxicology samples is also complicated by the instability of this compound. The detection of 6-AM is compromised in cases where the individual is not discovered for a prolonged period of time or following a delay in toxicological sampling, as a result of postmortem redistribution and spontaneous hydrolysis of 6-AM associated with a substantial reduction in detectable levels following a relatively short postmortem interval. 6-AM has also been shown in human postmortem toxicology samples to be unstable and spontaneously hydrolyse, demonstrate significant postmortem redistribution as well as poor stability in different storage conditions including in frozen toxicological samples [13–15].

Forensic pathologists are required to offer an opinion as to what can be reasonably determined as the cause of death from the available evidence, including opinions from forensic toxicologists based on postmortem drug testing and/or analysis of drug paraphernalia or exhibits analysis. Currently there is no consistent approach to the determination and attribution of heroin related deaths, with varying interpretation and acceptance of heroin-specific and non-specific toxicological evidence in suspected heroin-related death cases. Alternate evidence such as morphine to codeine ratios as a strong marker for illicit heroin use have been reported; however until recently there has been little published evidence of the use and wider acceptance of this evidence in death attribution [16]. Similarly, the interpretation and use of investigative evidence surrounding heroin-related deaths, such as scene findings and history of use, is inconsistent and unstandardized.

The collective challenges associated with the interpretation of heroin toxicity data have resulted in the underreporting of deaths associated with heroin and often the misclassification of these deaths as morphine-related when heroin-specific markers such as 6-AM are not detected [17]. It has also been reported that non-specific death certification has resulted in a significant underestimation of many drug-related deaths including those involving heroin as well as those involving opioid analgesics more broadly [18]. Furthermore, the contribution of drugs to a death may be overlooked when significant external injury or natural disease is also present [19].

In this study we aimed to produce a model that provides a consistent and transparent set of criteria to aid in reasonably classifying or attributing a death to heroin, despite variation in the available toxicological and investigative evidence using investigations and data routinely available in forensic practice. Additionally, we aimed to identify current areas of variation in the decision-making and determination of cause of death attribution with potential heroin-related cases through an exploratory study using a test group of forensic toxicologists and forensic pathologists. Finally, we aimed to validate and highlight the strengths of this model using coronial cases to identify trends in both the toxicological and investigative evidence as well as current attribution to heroin in a large cohort of heroin-related death cases.

2. Methods

For the purposes of attribution, in this study the broad classification of heroin-related deaths encompasses both heroin toxicity, or overdose-related deaths, as well as deaths that occurred as a result of impairment secondary to acute heroin intoxication. Acute toxicity-related deaths included deaths that were the result of acute heroin toxicity or the result of a secondary complication of acute heroin toxicity. Heroin intoxication-related deaths were those deaths that were reasonably attributed to acute heroin intoxication, where acute impairment would reasonably be considered to have contributed to death. A model was developed to reasonably attribute heroin to the cause of death that included different toxicological markers of heroin use (6-AM, morphine to codeine ratio (M:C) or morphine alone) along with investigative evidence of heroin use (circumstances, scene, clinical and pathological findings). Consistent with the recommendations for the investigation, diagnosis and certification of deaths related to opioid drugs from another expert panel previously, the physical evidence of intravenous drug use or abuse, route of administration, source of the drug (prescription, illicit street purchase or diverted) and history which are considered important when determining how injury occurred and cause of death, were specifically included in this model [1]. The purpose of this model was to establish a standardized set of criteria, or evidence, for examination as well as an ability to quantify the strength of the evidence, in order to attribute a death to heroin using investigations and data routinely available in forensic practice. As part of this model we also assumed that analytical results are from an appropriately accredited or certified laboratory and that a typical level of quantitation (LOQ) for 6-AM, morphine and codeine would be 10 ng/mL (0.01 mg/L).

To develop the model, a heroin-related deaths expert panel was convened consisting of 14 representatives from the fields of forensic toxicology, forensic pathology, clinical practice and opioid-related or forensic research, all with relevant expertise. Weighting for each individual piece of toxicological or investigative evidence was assigned based on the consistency as well as presumptive discriminative ability of that evidence for a heroin-related death. The panel systematically reviewed the model, including the exclusion criteria; the toxicological and investigative evidence criteria and appropriate weightings; as well as the overall strength of association for heroin-related death attribution. Refinement of the model was conducted following user testing and feedback.

2.1. The model

Our model is underpinned by a weighted evidence score for both the toxicological and investigative evidence, with weighting applied according to the respective strength of the evidence to support attribution of heroin involvement in deaths. Final scores are then determined, based on the sum of these scores. A final

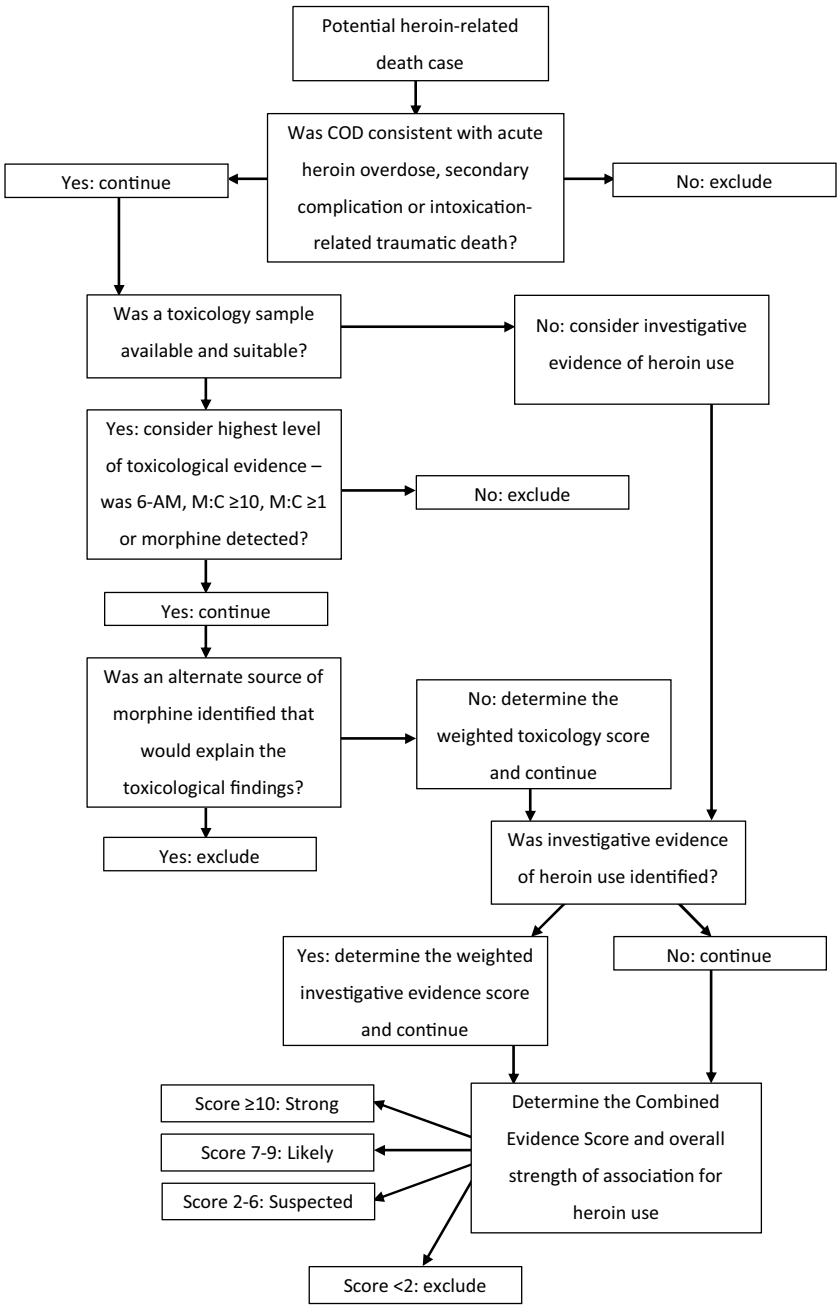

Fig. 1. Heroin-related death model flowchart.
Using this model, the toxicological and investigative evidence are evaluated in order to determine the strength of association of a death to be considered heroin-related or not. The toxicological evidence score (weighted score of the single highest toxicological evidence) in addition to the combined investigative evidence score (the sum of the weighted scores of all of the pieces of investigative evidence present) are used to determine the overall weighted evidence score and the relative strength of association of a death to heroin.
COD = cause of death, 6-AM = 6-acetylmorphine, M:C ≥ 10 = morphine to codeine ratio of 10 or greater, M:C ≥ 1 = morphine to codeine ratio of 1 or greater.

weighted evidence score is then used to determine the relative strength of association for a heroin-related death, being suspected; likely; or strong (Fig. 1). It must be emphasized however that this model is not designed as a screening tool in order to determine whether a death was drug-related or not. Instead, if a death has been determined to be related to or a complication of acute drug toxicity, then this model was designed to be used in order to determine whether or not the death could reasonably be attributed to heroin toxicity. The model was also developed to utilize typical available evidence rather than encompassing additional investigations, techniques or analysis that may be informative for heroin-related death investigation but that are not commonly reported in most laboratories or regions.

2.1.1. Exclusion criteria

Casesare not reasonably considered to be acute heroin-related deaths if any one of three exclusion criteria is present:

1. The death was not reasonably attributed to acute heroin toxicity, a secondary complication of heroin overdose or as a direct result of heroin intoxication but rather heroin use was coincidental to death.

2. There was no 6-AM or morphine detected in blood or urine toxicology samples where these samples were available and suitable.
3. There was another identifiable and likely source of morphine that is consistent with the toxicological and investigative evidence apart from heroin (e.g. prescribed morphine or evidence of diverted morphine found at the scene).

In relation to the third exclusion criteria, in cases where 6-AM is not detected, the detection of impurities associated with the illicit manufacture of heroin such as papaverine, noscapine and thebaine, or their metabolites, may assist investigators in identifying illicit heroin rather than morphine directly where the source of detected morphine in unclear [20–22].

2.1.2. Toxicological evidence

Heroin toxicity may result in death that occurs within minutes after administration as a result of respiratory impairment, where decreased consciousness and blunted reflexes may increase the risk of pulmonary aspiration and an inhibition of the ability to self-correct airway obstruction [23]. Conversely, there may be a longer period of unresponsiveness and significant hypoxia lasting up to several hours prior to death or where death may be significantly protracted and result from secondary complications or protracted following resuscitation and admission to hospital. The variability in either rapid or delayed death has a direct impact on the metabolism and clearance of heroin as well as the ability to reasonably demonstrate heroin as the cause of death in drug toxicity-related cases [12]. Because of the variability in death following acute toxicity that will result in variability in the location of heroin metabolites associated with acute toxicity, for this model the detection of heroin metabolites in either blood or urine was not differentiated in terms of assigned weighted toxicological scores.

Given the strength of evidence for heroin use when 6-AM is detected in either blood or urine, this was assigned the highest toxicological evidence weighting of 10. In this model free morphine and free codeine were considered in blood samples or total morphine and total codeine in urine samples which was consistent with previous findings [5]. A high threshold standard of morphine to codeine ratio of 10 or more was set and assigned a toxicological evidence weighting of 8. A more modest M:C ratio of one was assigned a toxicological evidence weighting of 6, while cases where morphine, but not codeine, was detected, were assigned a lower toxicological evidence weighting of 4. In any case where 6-AM is not detected, an alternate source of morphine (apart from heroin) and codeine must be considered using the investigative evidence. Cases where no toxicological samples were available were not specifically excluded because toxicological data must be interpreted in the context of the circumstances surrounding death, the history or the decedent, the scene of the death and the autopsy findings [1]. In this model cases where no suitable or representative toxicological samples were available were assigned a toxicological evidence weighting of 0 in order to allow for sufficient investigative evidence that may support the attribution of a death to heroin. Where the toxicological evidence may meet more than one evidence criteria, the single highest evidence score alone is used in determining the overall strength of association (Table 1).

The toxicological analysis of tissue samples and alternative matrices (such as brain, liver, vitreous, hair etc.) for drug concentrations were not included in this model because of the interpretation challenges associated with these samples and because tissue samples and alternative matrices are not routinely analyzed in potential drug-toxicity cases in many regions. Similarly, morphine glucuronide metabolites may provide important information in potential heroin toxicity-related cases however because they are not reported in many laboratories routinely, they were not included in this model. Specific morphine concentrations have also not been specified in this model because of the difficulties in interpreting these levels in heroin-related deaths primarily because of differences in opioid-tolerance or naivety in individuals. Heroin toxicity may also be exacerbated by comorbidities, the concomitant use of other opioid drugs or CNS depressants, pulmonary aspiration, or positional asphyxia resulting in death at lower morphine concentrations. These factors invariably contribute to an overlap between what may be considered toxic and non-toxic morphine concentrations in heroin-related deaths and therefore no specific minimum or maximum morphine concentrations were detailed in this model.

Table 1
Toxicological evidence and associated weighted scores.

Toxicological evidence	Weighted score
6-AM detected in blood or urine samples	10
Morphine and codeine detected (M:C $\geq$ 10)	8
Morphine and codeine detected (M:C $\geq$ 1)	6
Morphine detected in blood or urine samples	4

2.1.3. Investigative evidence

The investigative evidence is comprised of a combination of criteria that alone are not definitive evidence of heroin use, however in combination and along with the toxicological evidence, may strongly support evidence of heroin use. The highest weighted investigative evidence score of 6 in this model was assigned in cases where a decedent was witnessed to have purchased or used heroin, or where they had self-reported use to a witness, prior to death. Clinical findings consistent with a heroin overdose diagnosed by a suitably qualified clinician either at the scene of the overdose, or in a hospital environment (e.g. clinical presentation consistent with opioid-induced ventilatory impairment [23,24] or response to naloxone administration), were assigned an investigative evidence weighting of 4. The discovery of drug paraphernalia consistent with heroin use (e.g. syringe, spoon, tourniquet) present at the scene was assigned a weighted evidence score of 2. In this model, peri-mortem intravenous access not associated with medical intervention and a known history of heroin use were each assigned an investigative weighted score of 1. Hair analysis may also be used to provide retrospective information regarding drug use or exposure and help identify a history of heroin use, particularly when the decedent's history is not known or there is dispute about the history of heroin use (Table 2).

2.1.4. Strength of association

In order to determine the whether or not a death could reasonably be attributed to heroin (causal or contributory), the strength of association is based on the combination of toxicological and investigative evidence. The final weighted evidence score is derived from the addition of (a) the single highest toxicological evidence score with (b) the combined investigative evidence score. This final weighted evidence score is then used to determine the relative strength of association for the death being attributable to heroin (Table 3).

The Weighted Evidence Score = (*a*) The Toxicological Evidence Score + (*b*) The Combined Investigative Evidence Score

where

(*a*) *The Toxicological Evidence Score* = The weighted score of the single highest toxicological evidence.

(*b*) *The Combined Investigative Evidence Score* = $\sum$ All of the associated weighted scores of all of the individual pieces of investigative evidence.

Table 2
Investigative evidence and associated weighted scores.

Investigative evidence	Weighted score
Witnessed or stated to have purchased or used heroin	6
Clinical findings consistent with heroin overdose	4
Drug paraphernalia consistent with heroin use present on the individual or at the scene	2
Evidence of peri-mortem IV access on postmortem examination	1
Known history of heroin use	1

Table 3
Strength of association for heroin-related deaths based on weighted toxicological and investigative evidence scores.

Strength of association	Weighted evidence score
Strong	10 or greater
Likely	7–9
Suspected	2–6

2.2. Current decision making for heroin-related death attribution

In order to test the usability of this heroin-related deaths model and compare the attribution results to existing decision making processes for overdose-related deaths, a group of 15 forensic toxicologists and seven forensic pathologists were provided with a series of randomized test cases. The test cases included 11 suspected drug toxicity-related deaths where all of the cases were fictitious, but largely based on typical heroin-related deaths seen in Victorian coronial cases.

The fictitious heroin toxicity-related death test cases included:

- Three cases where 6-AM was detected in either blood or urine;
- Two cases with a high morphine to codeine ratio (M:C ratio $\geq$ 10);
- Two cases with a morphine to codeine ratio of one (M:C ratio $\geq$ 1);
- One case where no toxicological evidence was available but with strong supportive investigative evidence;
- Two cases where an alternate source of morphine was identified; and
- One case where neither 6-AM nor morphine was detected in blood or urine samples but where the decedent had a history of heroin use.

A summary of the police report of circumstances, the toxicological report, the pathology report and coronial findings, were provided for each test case. Respondents were asked to determine if the case should be considered heroin-related or not based on the developed model; and then comment on whether they would have considered the case to be heroin-related or not without using the model and based on their current decision making processes. Respondents were provided the opportunity to provide comments regarding the reason for any discrepancy between their existing decision-making about a case and the model. The agreement for inclusion or exclusion as a heroin-related death from all respondents were collated and described. Responses returned as unsure for inclusion were classified as an exclusion for the purposes of this study.

2.3. Evaluation of the model and identified variation in decision making

In order to evaluate the model outlined in this study for both sensitivity and specificity, a review of potential heroin-related death cases over a two-year period was conducted where the developed model was used to determine deaths that could reasonably be attributed to heroin. Existing attribution of death for the identified potential heroin-related death cohort using the model was additionally examined in order to compare the current attribution of death to heroin, morphine or other drug toxicity as well as the evidence associated with the attribution of these cases. Areas of inconsistency in the attribution of deaths to heroin in this cohort were further compared to the identified variation in decision making for potential heroin-related deaths identified in the test group exploratory study. For the purposes of this study, regardless of whether heroin was mentioned in any of the reports associated with a case, a death was considered to have been attributed to either heroin or morphine if that drug was specifically stated in either the final cause of death or as an object (Primary or Secondary) that caused death.

2.3.1. The National Coronial Information System

Potential heroin-related death cases for this study were identified using the National Coronial Information System (NCIS) where cases typically contained an autopsy and toxicological report, a police narrative of the incident and circumstances around the time of death, as well as the coronial finding.

2.3.2. Search criteria for potential heroin-related death cases

Given the potential for heroin-related deaths to vary in their reporting and attribution of death, particularly when 6-AM is not detected, potential heroin-related death cases in this study were identified using a broad strategy. The search strategy was designed to capture all cases that are currently classified as heroin-related, cases that may be classified as morphine-related, or have a generic drug toxicity classification. A search of the NCIS for closed cases in the state of Victoria, Australia, between 01/01/2012 and 31/12/2013 was conducted using the following criteria:

- Heroin listed in the cause of death 1a, 1b, 1c, 2 or 3.
- An object search for heroin alone, in combination with any other drugs and heroin as a keyword search in the object field.
- A keyword search for heroin in the police report, the pathology report and coronial findings.
- A toxicology report keyword search for heroin, heroin and morphine or morphine.

The examination of cases over two-year period was chosen for this study in order to allow for the finalization of investigation and reporting of these cases, which can be protracted. The cases identified in each of the NCIS search strategies were assessed for relevance and inclusion in this study following the detailed review of the toxicological report, the autopsy report, the police narrative of the circumstances surrounding death and the coronial findings for each case where available. Duplicate results arising from the different search criteria were also identified and removed.

2.4. Ethics

This project was approved by the Victorian Institute of Forensic Medicine Research Advisory Committee (RAC 030/14) and the

Department of Justice and Regulation, Human Research Ethics Committee (CF/15/2853).

3. Results

3.1. Decision making for heroin-related death attribution using the fictitious test cases

For the user testing cohort, of the 22 invited participants a response rate of 59% (n = 13) was achieved consisting of seven forensic toxicologists and six forensic pathologists. The area of highest consistency across all respondents related to the exclusion of two potential cases where an identified alternate and likely source of morphine was present. Similarly, all respondents excluded an additional potential case where, despite a past history of heroin use, there was insufficient evidence to determine that the death was heroin-related. The test cases considered to be heroin-related as well as the percentage agreement for inclusion and comparison between using the model or not, are presented in Table 4.

The test cases where 6-AM was reported demonstrated the highest level of agreement on the attribution of death to heroin, being 100% using the model and between 85% and 100% without the model. The test cases where 6-AM was not reported but rather where a M:C ratio of ≥10 or a M:C ratio ≥1 was reported as the highest level of toxicological evidence demonstrated the most amount of variation and the lowest level of agreement. Both with and without the model, where responses ranged from 54% to 77% respectively. The reason for exclusion and 'unsure' in many of these cases when not using the model appeared to be as a direct result of 6-AM not being detected on toxicological analysis, regardless of the M:C ratio or investigative evidence indicative of heroin use. The majority of respondents stated that they considered the cases to be either morphine toxicity or mixed drug toxicity (morphine and codeine).

An apparent misunderstanding in relation to the exclusion criteria resulted in a lower level of agreement using the model than without for the one test case involving a suspected drug toxicity-related death where no toxicological evidence was available. These results subsequently resulted in the modification of the flowchart to clarify the application of the exclusion criteria and the assessment of cases where no toxicological samples are available for analysis.

These results highlight that when not using the model, cases where 6-AM is detected are predominantly attributed to heroin as the cause of death though there is still some variation in the attribution of deaths with even this level of evidence to heroin. These results also indicate that investigative evidence indicative of heroin use is generally well accepted within this user cohort, even in the absence of supportive toxicological evidence. The greatest amount of variation in the attribution of death to heroin without the model appeared to be in cases where indicative but not definitive markers of heroin use, such as a morphine alone or a M:C ratio of ≥1 are detected. The use of our model resulted in what was improved attribution consistency in cases where 6-AM is not detected and consideration of alternate toxicological evidence together with other investigative evidence of heroin use is required.

3.2. Evaluation of the model

3.2.1. Identified heroin-related death cases

Using the broad NCIS search criteria there were 9060 cases that were identified and reviewed. During the assessment of the identified potential cases, 6850 cases were excluded because the cause of death was not considered consistent with acute heroin toxicity, a known secondary complication of heroin overdose or as a direct result of heroin intoxication. A further 1941 cases were excluded because neither 6-AM nor morphine was detected in the available and suitable blood or urine samples. Additionally, 26 cases were excluded because another source of morphine was identified. Conversely, there were seven cases included in this study where no toxicological evidence was available as a result of a delayed death and a delay in sampling following resuscitation and subsequent hospital admission prior to death.

A total of 243 cases were considered to be reasonably attributed to heroin after assessment using the standardized criteria and model outlined in this study. Using the strength of association scale there were: 197 cases with a strong strength of association; 34 cases with a likely strength of association and 12 cases with a suspected strength of association for heroin. There were 235 heroin toxicity-related deaths identified in addition to eight heroin intoxication-related traumatic deaths. For the eight heroin intoxication-related traumatic deaths identified and included in this study, three of the deaths related to drowning, one case involved a pedestrian struck and killed by a vehicle and there were four fatal vehicle collision. In all of the fatal vehicle collision cases, the decedent was the driver of the vehicle and most involved single vehicle crashes into stationary objects.

3.2.2. Cause of death attribution

The attribution of death to heroin in either the cause of death or as an object that caused death for the 243 cases included in this study was determined and presented in Table 5. For the

Table 4
Number of respondents in the exploratory study attributing fictitious drug toxicity-related death test cases to heroin.

Case number	Strength of association	Attribution of death to heroin	
		Using the model Agreement for inclusion % (n)	Not using the model Agreement for inclusion % (n)
Test cases where 6-AM was reported			
1	Strong	100% (n = 13)	92% (n = 12)
2	Strong	100% (n = 13)	100% (n = 13)
3	Strong	100% (n = 13)	85% (n = 11)
Test cases with a M:C ratio as the highest toxicological evidence			
4	Strong	100% (n = 13)	69% (n = 9)
5	Strong	100% (n = 13)	77% (n = 10)
6	Strong	92% (n = 12)	77% (n = 10)
7	Likely	85% (n = 11)	54% (n = 7)
Heroin-related death attribution with no toxicological samples			
8	Likely	62% (n = 8)	85% (n = 11)

Table 5
Attribution of potential heroin-related death cases.

Classification of group based on heroin attribution (COD or object)	Number of cases (% overall cases)
Heroin toxicity attribution	180 (74%)
Both heroin and morphine toxicity attribution	11 (5%)
Morphine or other opioid toxicity attribution	39 (16%)
Generic drug toxicity with neither heroin nor morphine attribution	5 (2%)
Intoxication-related traumatic deaths	8 (3%)
Total	243

235 potential heroin drug toxicity-related death cases identified in this study, the attribution to heroin, morphine or multiple drug toxicity was specifically determined. Results revealed that the vast majority of the identified deaths were attributed specifically to heroin but importantly, that there were also a large number of these deaths attributed to morphine and a smaller proportion of attributed to both heroin and morphine. Additionally, for the eight heroin intoxication-related traumatic deaths, there were two drowning cases and one fatal motor vehicle crash case that were specifically attributed to heroin, three cases that were attributed to morphine rather than heroin and the remaining two cases described in generic drug-toxicity only.

3.2.3. Toxicological evidence of heroin use

For the 243 heroin-related death cases identified in this study, the highest level of toxicological evidence of heroin use was determined (Table 6). For the 235 heroin toxicity-related death cases, 6-AM was detected in 74% of cases overall with the majority of these cases attributed directly to heroin. There were in fact only eight cases (5%) attributed directly to heroin where 6-AM was not detected and a toxicological sample was available for analysis. There was, however, variation in the attribution of a death to heroin even when 6-AM was detected, including seven cases that were attributed to both heroin and morphine toxicity despite no evidence identified of an alternate primary source of morphine apart from heroin use. Furthermore, 6-AM was detected in three toxicity-related deaths that were attributed to morphine or other opioid toxicity and not heroin.

For the 235 heroin toxicity-related death cases, a M:C $\geq$ 1 was detected as the highest level of toxicological evidence in 15% of cases with the majority of these cases attributed to morphine, other opioid toxicity or generic drug toxicity. The detection of morphine alone or both morphine and codeine with a M:C $<$ 1 was detected in a further 11% (n = 27) of drug toxicity cases that were able to be captured using this model despite the atypical toxicological profile. This cohort included two cases where it was reported that codeine was concomitantly used in addition to heroin resulting in a higher codeine to morphine ratio.

3.2.4. Investigative evidence of heroin use

For the 243 heroin-related death cases identified in this study, the different investigative evidence criteria of heroin use were determined (Table 7). The highest weighted investigative evidence of heroin use for the purposes of this model was determined to be where the decedent was witnessed or stated to have purchased or used heroin immediately prior to death. This criterion was identified in only 21% of cases and this finding was also associated with an increased likelihood of detecting 6-AM in the toxicological analysis as well as the attribution of the death to heroin (n = 46). There was however variation in the weighting or consideration of this evidence, where four cases were attributed to morphine but not heroin despite the decedent being witnessed or stating that they had purchased or used heroin immediately prior to an overdose-related death. Clinical findings consistent with heroin overdose was assigned the second highest weighted investigative evidence score in this model however there were no cases identified in this study that met this criteria. In contrast to this, the most consistent investigative evidence finding within this cohort was a known history of heroin use identified and reported in 88% of cases. Evidence of drug paraphernalia consistent with heroin use, and evidence of peri-mortem IV access not through medical intervention, were also commonly reported in 67% and 61% of cases, respectively.

Table 6
Highest level of toxicological evidence of heroin use determined in the identified heroin-related death cases.

Heroin attribution group	6-AM	M:C $\geq$ 10	M:C $\geq$ 1	Morphine only	Toxicology not available	Total
Heroin toxicity	165	1	6	1	7	180
Both heroin and morphine toxicity	7	1	3	0	0	11
Morphine or other opioid toxicity	3	2	21	13	0	39
Generic drug toxicity	0	0	2	3	0	5
Intoxication-related traumatic deaths	5	0	1	2	0	8
Total	180	4	33	19	7	

Table 7
Investigative evidence of heroin use determined in heroin-toxicity related death cases.

Investigative evidence	Number of cases (%)
Witnessed or stated to have purchased or used heroin	50 (21%)
Clinical findings consistent with heroin overdose	0 (0%)
Drug paraphernalia consistent with heroin use present on the individual or at the scene	158 (67%)
Evidence of peri-mortem IV access on postmortem examination	144 (61%)
Known history of heroin use	206 (88%)

4. Discussion

The accurate attribution of heroin involvement in suspected drug toxicity-related deaths can be extremely challenging. As demonstrated by this study, this is partly because the unique markers of heroin use can be difficult to detect, are not detected in all cases, and are affected by the time interval between heroin administration and death, which is multifactorial and extremely variable. We developed a new model to help with the reasonable and consistent attribution of heroin involvement in acute drug toxicity-related deaths as well heroin intoxication-related deaths that encompassed the use of both toxicological and investigative evidence. We also identified common areas of variation in the determination and the decision-making processes for potential heroin-related death cases, particularly when 6-AM is not detected. This variation in decision making was consistent with the variation observed in the attribution of a death to heroin in the actual cases identified in this study. These findings indicated a reliance on 6-AM detection for the consistent attribution of a death to heroin, the limited use of toxicological markers such as morphine and codeine as evidence of heroin use, and that the use of a model improves the consistency of attribution of heroin-related deaths. The significance of our findings are further highlighted by the variation in both the toxicological and investigative evidence identified in this study and the rationale for a set of consistent criteria to reasonably attribute a death to heroin.

4.1. The detection and reliance of 6-AM in forensic toxicology samples

The results of this study demonstrate that toxicological evidence and particularly 6-AM detection is critical in the decision-making associated with the attribution of a death to heroin. The detection of 6-AM in blood or urine is considered sufficient evidence to reasonably demonstrate recent heroin use [1,2]. As a marker of heroin use, 6-AM is definitive when detected and yet also problematic as a single threshold standard because of the many cases where it may not be detected, as demonstrated in this study. In cases with even a slightly prolonged interval between the administration of heroin and death, 6-AM may not be present in either blood or urine samples as a result of extensive and rapid metabolism or elimination from the body [8,9]. Given this and the rapid metabolism of 6-AM to morphine following administration, it is appropriate to adopt a position where heroin use can still be reasonably inferred in the absence of 6-AM using other toxicological evidence in addition to any investigative evidence. Furthermore, results from this study demonstrated that there were seven cases that were specifically attributed to heroin toxicity as a result of overwhelming evidence of heroin use despite no appropriate toxicological data as a result of delayed sampling following admission to hospital. This emphasizes the point that a death can reasonably be attributed to heroin after consideration of the findings at autopsy, the interpretation of any available toxicological evidence, decedent history as well as both scene findings and evidence of intravenous drug use rather than reliance on toxicological data and particularly the detection or not of 6-AM alone.

Our study shows that without a model or consistent set of criteria such as those in our model, the attribution of heroin involvement in drug toxicity deaths is inconsistent, even when 6-AM is detected in toxicological samples. Furthermore, our findings suggest that the reliance on 6-AM as the only toxicological marker for heroin use would likely result in the failure to capture approximately 25% of all heroin-related death cases.

4.2. Morphine and codeine as toxicological markers of heroin use

With the significant challenges associated with the use of 6-AM as the sole evidence of heroin use, alternative toxicological indicators including morphine and codeine must be considered as previously recommended [1]. We found that the acceptance of morphine and codeine as non-specific toxicological markers of heroin involvement varied in our sample, despite the presence of reasonable investigative evidence indicative of heroin use. The conversion of heroin to morphine provides what has been a long-standing challenge in forensic medicine in distinguishing between the detection of morphine as a metabolite from heroin or following the primary administration of morphine. In the illicit manufacture of heroin, an initial morphine mixture obtained from raw opium contains a number of different opium alkaloids, including codeine, which are then processed through an acetylation stage where diacetylmorphine (heroin) is formed [25]. Although not a metabolite of either heroin or morphine, codeine is a known common contaminant of street heroin and the combination of both morphine and codeine provide a signature pattern of illicit heroin use. Low concentrations of codeine have been reported in both blood or urine samples following the use of street heroin and a morphine to codeine ratio of one or greater has been reported as a consistent marker for illicit heroin use [1,4,5,16].

Primary codeine administration is however an added challenge associated with the interpretation of morphine and codeine toxicological analysis and must be considered with a M:C less than or close to parity. Codeine is always metabolized to morphine to some extent with variations in the CYP2D6 phenotype resulting in both poor and extensive metabolizers [26–32]. The conversion of codeine to morphine does make the interpretation of toxicological samples more challenging, particularly with ultra-rapid codeine metabolizers. In relation to this model however, the conversion of codeine to morphine should not result in a M:C ratio ≥ 1 when codeine is used in the absence of another source of morphine and would not change the weighted toxicological evidence scores or the incorrect attribution of a death to heroin. Practically, a very high index of suspicion should be applied in suspected drug toxicity cases where codeine may have been administered, where high codeine concentrations are detected or where the M:C is less than or close to parity. It must be emphasized that the concomitant use of both heroin and codeine does occur and there were two cases in the present study where this was observed.

The detection of either morphine, either alone or when codeine was also detected, produced great uncertainty in suspected heroin-related death cases, often leading to attribution of death to morphine toxicity. For heroin-related deaths morphine detection should in-fact be expected as it is both a precursor compound in the illicit manufacture of heroin, and also a metabolite of heroin following administration [25]. Indeed, morphine plasma concentrations have been demonstrated to peak between 2–45 min following heroin administration and have an elimination half-life of approximately three hours [8]. Although with some variation in the timings reported, other studies have also demonstrated similar findings and relationships for the detection, metabolism and clearance of heroin, 6-AM and morphine from the circulating plasma [9,10]. Unlike 6-AM, morphine as well as codeine demonstrate both greater chemical stability and reduced post-mortem redistribution making the detection of these markers generally more reliably than 6-AM in heroin toxicity-related death cases [13,15,33]. We also found this pattern in the toxicological findings for the heroin-related death cases identified in this study. Postmortem redistribution and stability of 6-AM, morphine and codeine are important considerations when interpreting the detected concentrations of these compounds in the context of each individual case, particularly in the setting of a protracted

postmortem interval or delayed toxicological sampling. Allowance for consideration of the likelihood of detection of these compounds and situations where 6-AM may specifically not be detected are facilitated using the model presented in this study which is important for the accurate capturing of cases that may have been subject to significant postmortem redistribution.

4.3. Using a standardized model for the consistent and transparent attribution of heroin-related deaths

One of the most striking results from this study was the difference in the attribution of deaths to heroin when our model was not used. The importance of this was further highlighted by the variation in both the toxicological markers and investigative evidence of heroin use identified in this study. Variation in decision-making and the justification for the adoption of a particular position is common in clinical practice, and this is no different in forensic medicine. This study however revealed the range of variation in the decision-making and attribution in suspected heroin-related deaths, especially when 6-AM is not detected in toxicological samples. This study demonstrated that the use of a model for the assessment and determination of heroin-related deaths improved the consistency of attribution as well as exclusion across a wide range of potential heroin-related cases. Based on the number of potential heroin-related deaths currently attributed to morphine in this study, we conclude that using a consistent set of criteria such as this model may result in a higher number of reported heroin-related deaths. This is similar to a previous study which reported that the use of a consistent set of criteria resulted in the re-classification and a 43% increase in the number of deaths attributed to heroin where those deaths had previously been attributed to either morphine or codeine toxicity [17].

While positive identification of markers such as 6-AM used for the determination of heroin-related deaths are definitive, heroin use can be reasonably inferred using other metabolic and indicative markers, such as morphine and codeine, as well as investigative evidence as previously recommended [1]. An algorithm used to differentiate heroin-related overdose deaths, even when 6-AM is not detected, was recently reported and well accepted because of the transparency and consistency in classification and reporting [16]. The model proposed in the present study complements this algorithm, but further enables the capture of potential heroin-related deaths where:

1. No toxicological evidence is available;
2. Cases where morphine but not codeine is detected;
3. Cases where the M:C ratio may be less than one, particularly in cases where both heroin and codeine were concomitantly used; and
4. Cases where heroin-intoxication reasonably and likely significantly contributed to death rather than overdose-related deaths only.

Similar to the use of other algorithms in this domain, our model is designed to support the consistent use of both toxicological and investigative evidence for interpretation and formulation of an opinion where heroin may have been involved. This is particularly relevant in heroin-related deaths where the toxicological evidence must be interpreted in the context of the other clinical or pathological findings in order to arrive at the most logical clinical conclusion, not necessarily what can be definitively proven beyond all doubt. Although this clinical interpretation and opinion may conflict with forensic toxicology in a strictly scientific approach, it is similar to a cause of death determination ascribed to other deaths where definitive clinical evidence, identified anatomical abnormalities or biochemical markers may not be present. The model presented here may help provide a holistic view of the evidence and circumstances surrounding death, providing a step towards a more informed and accurate opinion to be formed. This model also enables the standardization of the investigative evidence used in order to improve consistency and transparency of the decision making process. Furthermore, the proposed model enables investigators to quantify the strength of the evidence for heroin use using both toxicological and investigative evidence.

Trends in opioid analgesic and heroin-related deaths have important implications for informing public health policy and prevention initiatives in order to reduce the misuse and diversion of prescription medications, or community-based initiatives to reduce heroin-related deaths. Underestimating the rate of heroin-related deaths in a community may result in inadequate allocation of resources to address the issue. Improved reporting of heroin-related deaths therefore has the potential to reduce the number of these preventable fatalities currently underreported due to non-specific death certification [18]. The accurate, transparent and consistent reporting of opioid-related deaths as well as the differentiation and reasonable attribution of deaths to heroin rather than opioid analgesics, particularly morphine, is a fundamental step in this process. The current model was designed to provide a set of criteria for the reasonable attribution of a death to heroin, whether in the setting of multiple drug use or heroin use alone. It is hoped that the current model provides a tool for the recognition of heroin use that may have contributed to a death and a cause of death description be recorded that appropriately reflects heroin and other contributory drugs that may have been used concomitantly. Consistent with the expert panel recommendations for the investigation, diagnosis and certification of deaths related to opioid drugs, we would also support cause of death certification whereby the generic names of all of the drugs believed responsible for causing death are listed [1]. Using this model, where sufficient evidence of heroin use exists then we would also recommend that heroin be specifically included instead of morphine, codeine or generic opioid toxicity where there was no evidence of another source of these drugs apart from heroin use. Ultimately we hope that using this model will provide far more accurate and consistent determination of deaths associated with heroin use either alone or in the setting of multiple drug use.

The exploratory study using the test group of forensic toxicologists and forensic pathologists enabled the identification of common areas of inconsistency in the decision making of deaths that may be considered heroin-related, despite a small cohort of participants in this group. Importantly, with the subsequent comparison of these areas of inconsistency to the evidence and actual attribution for forensic cases of a very large sample size ($n = 9060$) we were able to demonstrate the same variation in the evidence used and subsequent attribution of a death to heroin. The consistency of these findings highlights the current variation in the decision making in potential heroin-related death cases and the requirement for the utilization of a standardized set of criteria or model to improve the consistency and accuracy of heroin-related death attribution.

4.4. Limitations

Limitations with the decision making and attribution component of this study centre around the small size of the user-testing cohort, and the provision of summary reports rather than more detailed reports typically available to them. In reality, much more information would be available to the participants in order to make an informed opinion about the attribution and cause of death. Despite this, the brief summary of information enabled insight into the different decision making, weighting and determination of the

sample group of forensic toxicologists and forensic pathologists based on the toxicological and investigative evidence presented.

We also acknowledge that there was the potential for introduced bias with the user testing participants as a result of asking participants to review the test cases using the model prior to determining the attribution outcome that they would have derived themselves based on their own internal judgement or decision making processes. Any bias in this instance would have increased the agreement in decision making rather than decreased the agreement in attribution of a test case to heroin using the model or not. Therefore, the disparity demonstrated between the attribution of deaths to heroin when our model was not used compared to current decision making processes and the improvement in consistency of attribution as well as exclusion across a wide range of potential heroin-related cases would not be diminished because of this potential bias at all.

Refinement of our model and particularly the flowchart following user testing and feedback is a further limitation of this study. It is likely that the percentage agreement for the attribution of a death to heroin using the model for the test cases would have been higher because of the changes reflected in the current model description and flowchart. The attribution of a death to heroin without the model would not have been affected by this.

5. Conclusion

The determination of opioid-related deaths and the differentiation of heroin is a challenge in forensic medicine. Given the rapid metabolism of 6-AM to morphine, heroin use can still be reasonably inferred using other toxicological evidence in addition to related investigative evidence. Using a model that encompassed a weighted scale and drawing on toxicological and investigative evidence criteria that are uniquely, commonly or often associated with heroin use, it was possible to demonstrate consistent and reasonable attribution of deaths to heroin. Our model provides an important first step in improving the accuracy and consistency in the differentiation, attribution and reporting of heroin-related deaths.

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Declaration of interest

PD has received untied educational grants from Reckit Benkiser and Gilead Sciences for work unrelated to this study. No other authors declare any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence this work.

Authors contribution

All authors contributed to the preparation of the manuscript and have approved the final manuscript.

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2.3 Publication 2

Issues in the classification and reporting of heroin-related deaths.

Publication Title

Issues in the classification and reporting of heroin-related deaths.

Authors and affiliations

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Abstract

The aim of this study was to investigate the extent of variability in reporting of heroin-related deaths in Victoria, Australia. An additional aim was to identify opportunities to improve the accuracy and consistency of heroin-related death reporting by examining variability in the attribution, death certification, classification and coding of heroin-related death cases. Methods. Heroin-related deaths in the state of Victoria, Australia over a two-year period (2012 – 2013) were examined using the National Coronial Information System (NCIS) as well as data from the Australian Institute of Health and Welfare (AIHW) and Australian Bureau of Statistics (ABS). Differences in the number of deaths reported as well as the classification and coding assigned to the identified heroin-related death cases were investigated by cross-referencing these datasets and by examining the assigned ICD-10 codes. Results and Discussion. There were a total of 243 heroin-related deaths identified through the NCIS in comparison to statistics from the AIHW where 165 heroin-related deaths were reported and assigned the heroin-specific ICD-10 code of T40.1. Results demonstrated that 40% of all the missed heroin-related death cases resulted from either the attribution of the death to morphine toxicity or with non-specific drug toxicity certification. A further 30% of the missed heroin-related death cases occurred where the cases had been attributed to heroin but there were irregularities in death certification. A further 24% of the missed heroin-related death cases occurred as a result of late initial registration of these deaths to the Registry of Births, Deaths and Marriages, and where these cases were then not assessed by the ABS for classification and coding purposes. Conclusion. This study demonstrated that in Victoria, Australia, the number of heroin-related deaths are underreported by 47% compared to the number of deaths currently identified by the ABS and reported by the AIHW.

Keywords

Heroin toxicity; Opioid toxicity; Attribution of death; Death certification; Surveillance

Introduction

Morbidity and mortality resulting from the overdose of opioid drugs including heroin, oxycodone, fentanyl, methadone and codeine represents a significant public health issue with an estimated 70 000 to 100 000 people dying from opioid overdose around the world each year [1-6]. More broadly, the non-medical use of prescription and illicit opioids, especially heroin, is particularly prevalent in North America, Oceania, Eastern Europe and South Eastern Europe [7, 8]. Trends in heroin and opioid analgesic drug-related deaths more broadly have important implications for informing public health policy and prevention initiatives. The accurate, transparent and consistent reporting of heroin-related deaths is fundamental to these processes. Improved classification, coding and reporting of heroin-related deaths therefore has the potential to facilitate a greater understanding of the extent of this problem and to enable the appropriate allocation of funding and resources to address these related but also distinctly different issues.

The medico-legal investigation of deaths involving drugs can be complex and recommendations have been published to guide the investigation, diagnosis and certification of overdose deaths related to opioid drugs in order to improve accuracy of death reporting [9]. Variability in death certification has been reported to have resulted in a significant underestimation of heroin-related deaths as well as many other drug-related deaths more broadly [10]. Heroin-related death investigation can be particularly challenging because of variability in the detection of heroin-specific metabolites, toxicological analysis may not be feasible at all, and most cases are complicated by multiple substance use [11-16]. The challenges associated with the interpretation of toxicity data in heroin-related death cases have also resulted in the misclassification of heroin-related deaths as being morphine-related when heroin-specific toxicological markers such as 6-acetylmorphine (6-AM) are not detected, which further contributes to the underreporting of these deaths [17].

The aim of this study was to investigate the extent of variability in reporting of heroin-related deaths in Victoria, Australia. An additional aim was to identify

opportunities to improve the accuracy and consistency of heroin-related death reporting by examining variability in the attribution, death certification, classification and coding of heroin-related death cases.

Methods

In Australia, cases are reported to the coroner in all unexpected, accidental or suspicious deaths, as well as those where the cause of death is unknown with the processed represented in Figure 1. Reportable deaths are initially referred to the coroner for medico-legal death investigation, as well as initial registration of the death with the local State Registry of Births, Deaths and Marriages. Initial registration of a death is provided to the Australian Bureau of Statistics (ABS) by the Registry of Births, Deaths and Marriages. Following a coronial investigation and formal cause of death finding, the certified cause of death for cases is provided through the National Coronial Information System (NCIS). Based on the information available about a death from the Registry of Births, Deaths and Marriages and the NCIS, cause of death classification and coding will be assigned by ABS mortality coders in accordance with the International Classification of Disease, 10th revision (ICD-10). Following processing and coding, the ABS compile and report aggregate statistical data on deaths in Australia to provide to the Australian Institute of Health and Welfare (AIHW). Because the timeframes associated with the coronial investigation process in some cases, the cause of death classification and coding assigned by the ABS mortality coders is subject to a revision process. Cases where coronial investigations are open at the time of initial coding are revised when further information becomes available on the NCIS. ABS mortality data are deemed preliminary when first published, revised when published the following year and considered final when published after the second year.

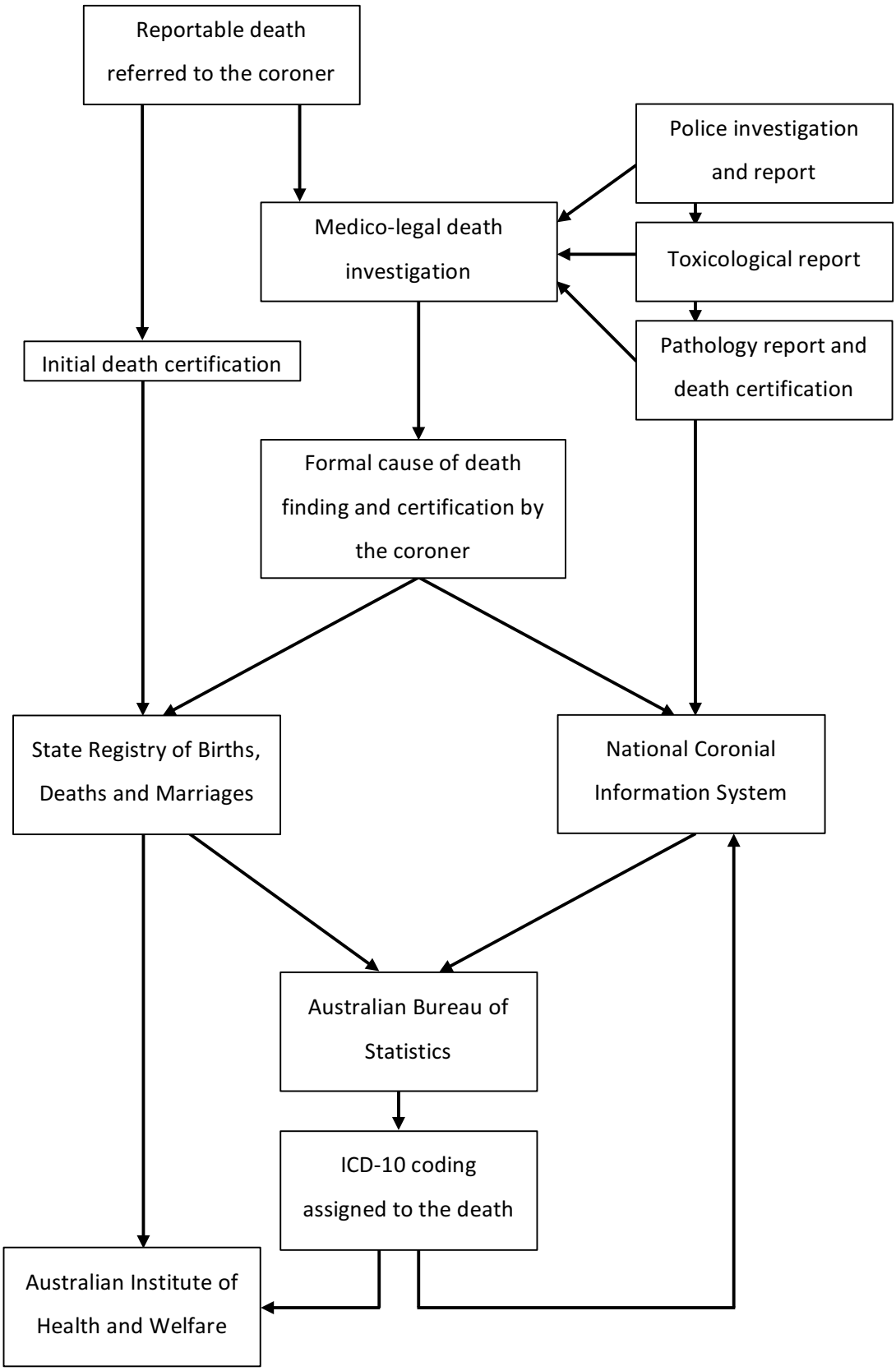

Figure 1 – Australian reportable death investigation, coding and reporting system

Heroin-related deaths and study period

Heroin-related deaths that occurred in the state of Victoria, Australia over a two-year period in 2012 and 2013 were examined for the purposes of this study. This timeframe and jurisdiction were chosen in order to control for as many variables in classification and reporting as possible. Examining 2012 and 2013 data allowed for the finalization of investigation and reporting of cases by the coroner, which can sometimes take some years, particularly if other persons may have contributed to their deaths. In this study, the broad classification of heroin-related deaths encompassed both heroin toxicity or overdose-related deaths, as well as deaths that occurred as a result of impairment and misadventure secondary to acute heroin intoxication.

Heroin-related deaths identified through the NCIS

As a baseline measure for this study, heroin-related death cases were identified using the NCIS. Cases in the NCIS typically contained an autopsy and toxicological report, a police narrative of the incident and circumstances around the time of death, as well as the coronial finding. Given the potential for heroin-related deaths to vary in both attribution and reporting, particularly when 6-AM is not detected, a previously described search strategy and inclusion criteria were used to identify heroin-related deaths [18]. The strength of evidence to support the attribution of death to heroin was assessed using different toxicological markers of heroin use (6-AM, morphine to codeine ratio (M:C) or morphine alone) along with investigative evidence of heroin use (circumstances, scene, clinical and pathological findings).

Heroin-related deaths from the AIHW and ABS

Data from the Australian Institute of Health and Welfare (AIHW) for heroin-related deaths that occurred in the state of Victoria, Australia, for the same period were used for comparison purposes because this data is commonly used for public health surveillance and government reporting purposes. Data was derived from the AIHW National Mortality Database where cause of death unit record file data are provided to the AIHW by the Australian Coordinating Registry which is governed by the

Registries of Births, Deaths and Marriages. ICD-10 coded cause of death data for the AIHW registered cases are provided by the ABS which includes ICD-10 codes assigned for the underlying and associated cause of death. For the purposes of this study, a death was considered to have been identified as heroin-related by the ABS mortality coders if it was assigned the ICD-10 code T40.1 (associated cause) which specifies that the death involved heroin.

Heroin-related deaths were included for both open and closed cases where:

- The death was registered in Victoria, Australia, and not based on the usual residential location of the deceased.
- The date of occurrence of death within the study period was used rather than the date of registration of the death.
- Heroin-related deaths were identified using the following ICD-10 codes (underlying cause):
    - X42 and X44 with T40.1 (accidental poisoning)
    - X62 and X64 with T40.1 (intentional self-poisoning)
    - X85 with T40.1 (assault by drugs)
    - Y12 and Y14, with T40.1 (poisoning with undetermined intent)
    - F11 and F19 with T40.1 (mental and behavioural code) for deaths prior to 2013.

Published secondary reports that encompassed heroin-related deaths over the same two-year study period that utilised data primarily derived from the NCIS, ABS or AIHW were additionally identified and compared. Variation in the number of reported heroin-related death cases in these secondary reports were investigated in order to identify the causes of the variation, including whether the timing or interpretation of the mortality data were contributing factors.

Identified causes of variation in the classification and coding of heroin-related deaths

Comparison of heroin-related death cases identified through the NCIS with those reported through the AIHW and ABS was conducted in order to identify the cause and extent of any variation with the preceding classification and coding process. Cases from the NCIS as well as those reported through the AIHW and ABS were cross-referenced by examining the ICD-10 codes assigned for both the underlying and associated cause of death. Cases that were identified through the NCIS search and that were assigned the heroin-specific ICD-10 code of T40.1 (associated cause) but not reported as heroin-related deaths in the AIHW and ABS data were examined in detail in order to identify the classification and coding assigned to these cases as well as possible causes for these cases being missed or misclassified.

Death certification and attribution of a death to heroin

Variation in the attribution of a death to heroin and the manner in which a death is certified were examined in detail in order to determine the extent that these factors may have played in the missed or misclassified deaths. For the purposes of this study, heroin-related deaths were categorized as being identified and attributed to heroin, both heroin and morphine, morphine, other drugs generically but specifically not heroin or morphine, and misadventure-related intoxication deaths. A death was considered to have been attributed to heroin where heroin was specifically detailed either alone or in combination with other drugs in either the Cause of Death (1a, 1b, 1c, 2 or 3) or as an Object (Primary or Secondary) that caused death.

Statistics

All graphs were produced as well as analyses conducted using SPSS for Mac version 23.

Ethics

This project was approved by the Victorian Institute of Forensic Medicine Research Advisory Committee (RAC 030/14) and the Department of Justice and Regulation, Human Research Ethics Committee (CF/15/2853).

Results

The number of heroin-related death cases reported

Heroin-related deaths identified through the NCIS

A total of 9060 potential heroin-related death cases were identified, reviewed and assessed for inclusion over the 2-year period. Using standardized criteria and model previously described, a total of 243 cases were considered to be reasonably attributed to heroin after assessment including 180 where the heroin-specific toxicological marker 6-AM was detected. From the 243 heroin-related deaths identified overall, there were 235 heroin toxicity-related deaths as well as eight deaths due to misadventure as a result of heroin intoxication.

Heroin-related deaths from the AIHW and ABS

By comparison, statistics returned from the AIHW revealed 165 deaths over the study period that where assigned the heroin-specific ICD-10 code of T40.1 (associated cause) by the ABS mortality coders. Overall there were therefore 78 fewer heroin-related death cases in Victoria over the study period reported in the AIHW data compared to the 243 heroin-related death cases identified overall.

Heroin-related deaths from secondary reports

The Australia's Annual Overdose Report 2016 was identified as a published secondary report that encompassed heroin-related deaths over the same study period and where this report was compiled using data from ABS [19]. For 2012 and 2013 there were a total of 220 heroin-related deaths reported Australia wide, and this report included heroin-related deaths that occurred in Victoria. The number of heroin-related death cases identified using the NCIS search, reported heroin-related deaths from the AIHW and ABS as well as Australia's Annual Overdose Report 2016 are presented in Figure 2.

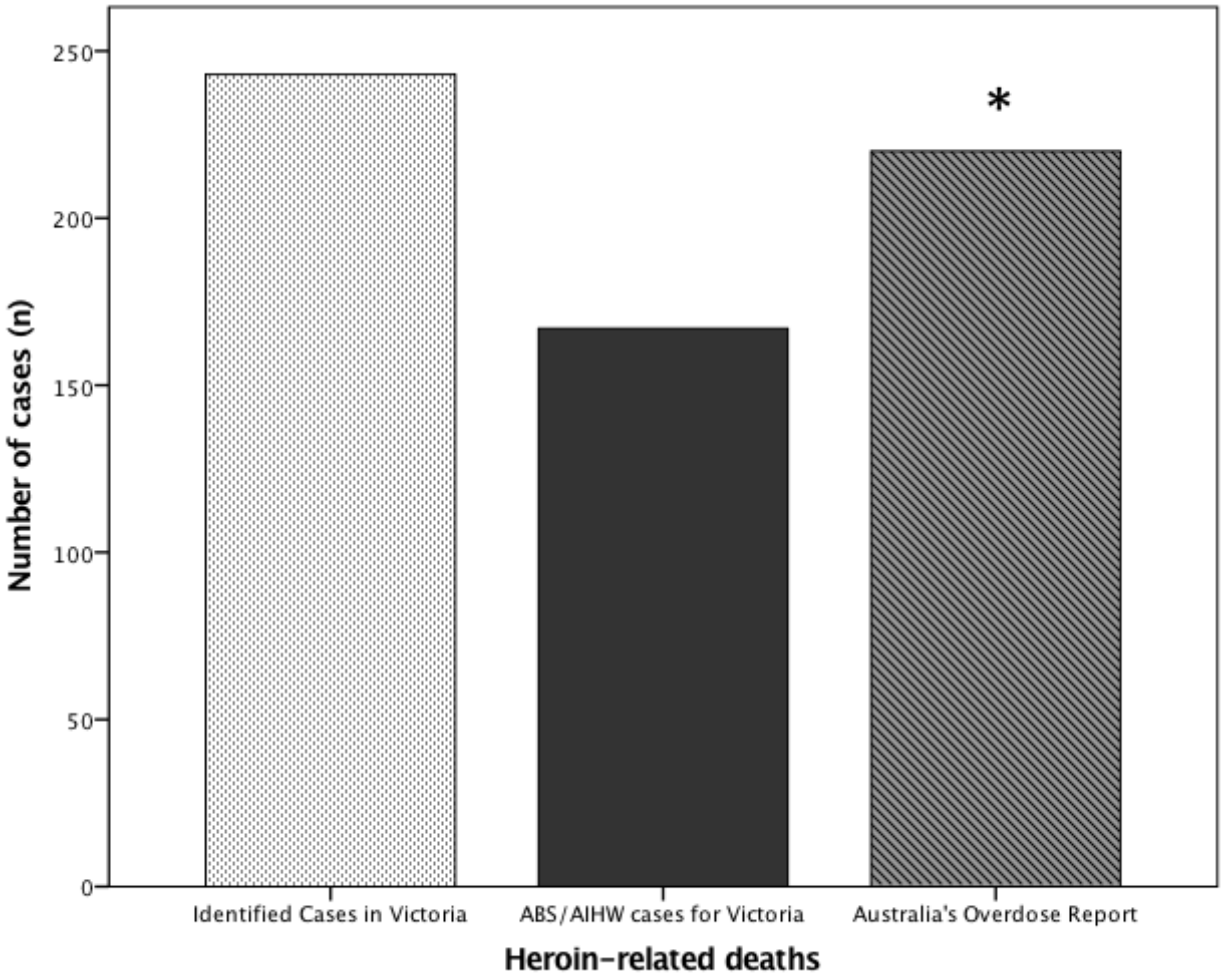

Figure 2 – Heroin-related deaths for Victoria reported in 2012 and 2013

Over the study period in Victoria there were 243 identified heroin-related death cases identified compared to 165 heroin-related death cases in Victoria reported by the AIHW and 220 heroin-related deaths across Australia reported in Australia's Overdose Report 2016 over the same period. *National data reported.

Discrepancies in the assigned classification and coding of heroin-related deaths

Comparison of the cases assigned the heroin-specific ICD-10 code of T40.1.

The assigned ICD-10 codes for the 243 heroin-related death cases identified through the NCIS search were reviewed in order to examine the cases that had not been assigned the heroin-specific ICD-10 code of T40.1. Examination of the underlying and associated ICD-10 codes assigned for the 243-identified heroin-related death cases revealed that only 161 of these cases were assigned the heroin-specific T40.1 ICD-10 code. There were an additional four cases that were assigned the heroin-specific T40.1 ICD-10 code that were excluded based on the cause of death criteria for this study. These results revealed that there were an additional 82 heroin-related death cases over the study period that had not been assigned the heroin-specific ICD-10 code of T40.1 and therefore not captured in the AIHW and ABS data.

Variation in the ICD-10 coding assigned to the identified heroin-related death cases

The ICD-10 codes assigned for the underlying cause of death to the heroin-related death cases identified through the NCIS were examined with the cases classified as being heroin-related and assigned the heroin-specific associated cause of death ICD-10 code of T40.1 (Table 1). Comparison of the data revealed that there were cases that should have been identified and coded as heroin-related but were not. This included three cases where heroin was specifically listed in the cause of death field that were assigned the generic opioid ICD-10 designation T40.2 and not the heroin specific ICD-10 code of T40.1. The largest discrepancy in the classification and coding of heroin-related deaths between the two cohorts however, occurred in cases that were classified and coded as ‘accidental poisoning with other and unspecified drugs’ (ICD-10 code X44) and cases that were assigned an alternate underlying ICD-10 code, where 20 heroin-related death cases were missed from the AIHW data. Because the majority of missed or misclassified cases were coded as being related to ‘unspecified’ and ‘other drug’ classifications, the contribution of variation in the attribution and cause of death certification of these cases was examined in detail.

Comparison between the NCIS as well as the AIHW and ABS datasets also revealed that there were 20 cases that were not misclassified, but rather were not assigned any ICD-10 coding at all for either the underlying or associated cause of death. Protracted time for closure of these cases was investigated as a possible cause. There was a median duration of 15.5 months (IQR of 6 months) with a range between 10 months to 30 months from the date of death until the date that the case was closed. Hence protracted medico-legal investigation and closure times associated with these cases was not the cause of the coding irregularity. Instead it was most reasonably attributed to a delay in the initial reporting of these cases resulting in them not being assessed for classification and coding by the ABS.

Variation in heroin attribution or cause of death certification

The 243-identified heroin-related death cases from the NCIS search were categorized by the primary attribution to heroin or not and the manner in which the death was certified (Table 2). The number of cases within each category coded with the heroin-specific ICD-10 code of T40.1 were also examined. From the 243-identified heroin-related death cases, there were 180 deaths that were considered to be specifically attributed to heroin toxicity and an additional 11 cases that were considered to be attributed to both heroin and morphine toxicity. Despite the 191 cases being specifically attributed to either heroin alone, or where heroin was described in combination with other contributory drugs, only 154 (81%) of the these cases were classified and coded as being heroin-related. There were 44 drug toxicity-related cases that were not specifically attributed to heroin in the cause of death certification and only five (11%) of these cases were identified and coded with the heroin-specific ICD-10 code of T40.1. There were also eight heroin intoxication-related misadventure deaths where only two (25%) of these cases were specifically attributed to heroin in the cause of death certification.

Table 1 – Identified and AIHW reported heroin-related deaths in Victoria by ICD-10 code (underlying cause).

ICD-10 code (underlying cause)	Description	Heroin-related death cases (n)	
		AIHW cases	Identified cases
F11	Mental & behavioural disorders due to use of opioids	1	3
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	75	79
X44	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	69	98
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	0	0
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	6	6
Y12	Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent	4	5
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent	10	12
Other	Other ICD-10 code assigned for underlying cause of death		20
Nil	No ICD-10 code returned		20
Total		**165**	**243**

Data revealed that there were 37 heroin-attributed toxicity cases that were missed as being subsequent coded as being heroin-related because of inconsistencies in the manner that the cause of death was described. These included:

- 11 cases were the cause of death was certified in generic terms only, such as ‘mixed drug toxicity’ or ‘combined drug toxicity’. In these cases, the drugs determined to be contributory to the toxicity death were listed in the Object (Primary or Secondary) that caused death field only.
- Cases where morphine was listed in the cause of death field and then heroin, but not morphine, was listed as an object that caused death.
- Eight cases where the cause of death certification started with the listing of either a secondary or medical complication, such as ‘hypoxic brain injury’, followed by the description of this occurring in the setting of heroin use or toxicity.

Table 2 – The heroin-specific T40.1 ICD-10 code for cases based on the cause of death classification.

Classification of group based on certification and heroin attribution (COD or object)	Number of identified cases identified through NCIS search	Number of cases (%) from AIHW data with heroin ICD-10 code (T40.1) attributed
Heroin toxicity attribution	180	146 (81%)
Both heroin and morphine toxicity attribution	11	8 (73%)
Morphine or other opioid toxicity attribution	39	5 (13%)
Generic drug toxicity with neither heroin nor morphine attribution	5	0 (0%)
Misadventure-related heroin intoxication deaths	8	2 (25%)
Total	**243**	**161 (66%)**

Discussion

Heroin use is associated with an increased risk of premature death [20-24]. The accurate reporting of heroin-related deaths is important so that the extent of the issue can be clearly understood. In Australia, the reporting of heroin-related deaths has a number of processes before the generation of statistical outputs for public health and government reporting purposes. This study demonstrated that from a single cohort of 243 heroin-related deaths identified in Victoria over a two-year study period, variation in each of these processes resulted in a large number of these deaths not being captured for these purposes. Significantly, this study demonstrated that the actual number of heroin-related deaths for Victoria over the study period was 47% greater than the 165 deaths currently reported by the AIHW and ABS data. Subsequent variability in the interpretation and reporting of these deaths was then demonstrated to occur in a secondary report derived from the ABS data over the study period, further highlighting some of the challenges and need for both accurate and consistent reporting of these deaths. An important outcome of the current study has been the identification of the extent of underreporting of heroin-related deaths and the additional identification of key areas to improve the accuracy and consistency of heroin-related death reporting.

Data from the current study demonstrated that 40% of all the missed heroin-related death cases resulted from either the attribution of the death to morphine toxicity or with non-specific drug toxicity certification. Non-specific death certification has been demonstrated to significantly contribute to the underreporting of both opioid as well as drug deaths more broadly [10]. Similar findings to those of this study have been reported from the United States where the re-examination of unintentional drug overdose deaths resulted in a 43% increase in the number of heroin-related deaths that were previously missed as a result of the attribution to either morphine or codeine toxicity, as well as variation in cause of death reporting for these cases [17]. The accurate attribution of the contributory drugs in toxicity-related deaths is fundamental from a public health perspective so that extent and contributors to the problem can be identified. Data from the current study demonstrated that there was

both an underreporting of the number of heroin-related deaths as well as an over-reporting of morphine-related deaths that occurred over the study period. The use of a consistent set of criteria for the medico-legal death investigation of potential heroin-related deaths is important to address this issue. Previous studies have demonstrated a reliance on 6-AM detection, the limited use of alternate toxicological markers such as morphine and codeine as evidence of heroin use, and that the use of a model improves the consistency of heroin-related death attribution [18, 25].

The manner in which death is certified was demonstrated to impact on the subsequent classification, coding and reporting of deaths in general and even if a death had been attributed to heroin. Data from this study demonstrated that 30% of the heroin-related death cases that were missed occurred where the cases that had been attributed to heroin but where these cases were associated with irregularities in death certification. The heroin-attributed deaths that were underreported most commonly occurred in cases were the death certification involved either: the cause of death was reported in generic terms only and the drugs including heroin that were considered contributory were reported as an object that caused death; or where for the cause of death description started with the listing of either a secondary or medical complication. This aspect of the findings of this study are also consistent with data from the United States where incomplete death certification for opioid-related deaths was examined and corrected data resulted in a 20-35% greater number of heroin-related deaths than reported [26]. Issues with death certification and mortality reporting have additionally been demonstrated to impact on our understanding of trends of heroin and opioid-related deaths which then directly impacts the targeting of public health interventions [27, 28]. The results from this study demonstrate the importance of both specificity and consistency in the certification of both toxicity and heroin-related deaths in order to improve the accuracy of reporting for both surveillance and public health purposes.
In order to improve the consistency in the classification and coding of heroin-related deaths, all of the drugs believed responsible for death should be attributed and specifically listed in the Cause of Death field for death certification. This is consistent

with broader recommendations for the investigation, diagnosis and certification of deaths related to opioid drugs [9].

The findings from this study also revealed that almost one-quarter (24%) of all of the missed heroin-related death cases were never assessed for classification or coding by the ABS. It was demonstrated that these cases did not involve miscoding or a coding error, nor a protracted time taken for these cases to be closed. Instead, these cases were missed as a result of late initial registration of these deaths to the Registry of Births, Deaths and Marriages, where as a result of this they were then not assessed by the ABS for classification and coding purposes or included in the AIHW reported data.

Limitations

A limitation of the current study is associated with the extrapolation of the findings of this study to more recent data. Since the 2012 and 2013 period investigated in the current study, there have been changes to the ABS revisions process. Prior to these changes to the revisions process only the underlying cause of death was revised, however associated cause of death toxicity codes are also now revised if more information becomes available.

Conclusion

The accurate and consistent reporting of heroin-related deaths is both challenging and also essential for both public health and surveillance purposes. This study demonstrated that in Victoria, Australia, the number of heroin-related deaths are underreported by 47% compared to the number of deaths currently identified by the ABS and reported by the AIHW. The late initial registration of heroin-related deaths to the Registry of Births, Deaths and Marriages, non-specific drug attribution and generic death certification as well as attribution of the drug-toxicity death to morphine instead of heroin were the cause of the majority of the missed heroin-related death cases. Data from this study also demonstrated that a large number of

cases that been attributed to heroin were also missed as a result of irregularities in the cause of death certification for these cases.

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Contribution

All authors contributed to the preparation of the manuscript and have approved the final manuscript.

Conflict of interest declaration

No other authors declare any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence this work.

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Chapter 3:

The potential impact of fluctuations in street-level heroin for overdose

3.1 Chapter introduction

As outlined in the review provided in **Chapter 1** as well as the data provided in **Chapter 2**, the vast majority of heroin-related deaths occur as a direct result of acute drug toxicity or overdose. A number of factors including health status, underlying comorbidities, the environmental context as well as the concomitant use of other drugs have been identified as risk factors for overdose. The link between variability in the purity of street-level heroin and overdose has not been established because of conflicting findings from previous studies, despite regular heroin users reporting that they believe it is a major direct contributor to overdose.

A heroin overdose occurs when the dose of heroin administered exceeds the current opioid tolerance level of the individual. **Chapter 3** and **Publication 3** present the first investigation of the dose of heroin contained in street-level heroin samples in order to determine the standard or anticipated dose of heroin that may be expected by users. This publication also provides an examination of the quality and quantity of street-level heroin and an analysis of the extent of variability in the dose of heroin that users of this drug may experience despite purchasing the same amount or presentation on the street.

3.2 Publication 3

Determining the effective dose of street-level heroin: a new way to consider fluctuations in heroin purity, mass and potential contribution to overdose.

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Determining the effective dose of street-level heroin: A new way to consider fluctuations in heroin purity, mass and potential contribution to overdose

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ABSTRACT

Background & Aims: Heroin use is associated with a disproportionately high level of morbidity and mortality with most deaths attributable to drug overdose. Aggregate heroin purity data has been used to examine the relationship between overdose and variability in street-level heroin, however heroin purity data alone may not be the most appropriate nor a sensitive enough measurement tool for this assessment. The aim of this study was to measure the variability in effective dose of street-level heroin seizures, accounting for variation in both purity and mass, and determine the proportion of samples with higher than expected effective dose that would not be detected using a purity-only measure.
Methods: Data on Victorian heroin seizures ≤150 mg in mass made between 01/01/2012 and 31/12/2013 were obtained from the Victoria Police Forensic Services Department. The effective dose of heroin in each sample was determined by multiplying the mass and purity variables. Effective dose outlier samples were considered as those containing either greater than 1.5–2 times or >2 times the median effective dose of heroin for the sample data.
Results: The 983 street-level heroin samples of ≤150 mg had a median mass of 92 mg (IQR of 43 mg), a median purity of 13% (range 3.6%–80.9%) and a median effective dose of 12.0 mg of heroin (IQR 6.6 mg; range 0.4 mg–111 mg). Approximately one in 13 samples (8%) and one in 17 samples (6%) contained between 1.5–2 times and >2 times the median effective dose of heroin respectively.
Conclusion: The effective dose of heroin is a more appropriate measure than purity to identify outlier samples that containing larger than expected doses of heroin compared to typical doses that may be expected by users. Together with other identified risk factors, fluctuation in the effective dose of heroin contained in street-level samples may contribute to the potential for overdose.

1. Introduction

Heroin use is associated with significant morbidity and mortality [1–4]. It is estimated that people who use heroin are up to six times more likely to die prematurely compared with the general age-matched population, with most of this excess mortality attributable to drug overdose [4,5]. The chronic or repeated use of heroin, like other opioid drugs, is associated with the development of opioid tolerance. For individuals this means that increasing doses are required to achieve equipotent analgesic or hedonistic effects [6]. An opioid dose that is in excess of the individual's current opioid tolerance level may lead to acute toxicity, but the risk of overdose is also related to a number of other parameters including individual pharmacokinetic factors, health status, underlying comorbidities, the environmental context and

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the concomitant use of other drugs [7–9]. Variation in the opioid tolerance of an individual as well as the large number of risk factors for overdose result in challenges for our understanding and defining a lethal heroin dose, including an overlap between non-toxic and toxic blood morphine concentrations associated with heroin use [10,11].

An important question that is still unresolved is whether the amount of heroin contained in street-level purchases may drive overdose. The contribution and relationship of variation in the content and amount of heroin contained in street-level heroin presentation to other known risk factors that may contribute to heroin overdose is not yet clearly understood. This is especially pertinent where the amount of heroin exceeds the anticipated amount for that presentation and this exceeds the opioid tolerance of the individual. Illicit heroin is typically purchased in street-level units that are based on mass [12]. It is well known that street-level presentations are subject to variability in both quality and quantity to the point where regular users of this drug believe that variation in the purity of purchased heroin is a major direct contributor to overdose [1]. In Australia, the price and average purity of seized heroin demonstrates regional variation and fluctuations [13]. Examination of street-level heroin in Victoria over the period 2006–2014 indicates a stable and relatively low average purity overall (approximately 15%), though with a small number of high-purity outliers [13–15]. Although small, fluctuations in heroin purity have been shown to have a moderate correlation to heroin-related overdose fatalities in Australia [16]; however a number of other studies from other regions have found no correlation between increased variance in heroin purity and heroin-related emergencies or heroin-related deaths [17–20]. Given these conflicting findings, fluctuation in the purity of street-level heroin is currently considered to have only a moderate influence on the rate of heroin-overdose, in comparison to other factors such as the concomitant use of CNS depressants [21].

Attempts to examine the relationship of variation in street-level heroin presentation and overdose have so far focused on fluctuations in aggregate heroin purity over time. A potential reason for the conflicting and inconclusive previous findings may actually centre around the question of whether the use of heroin purity data alone is not the most appropriate measurement tool for this assessment. The previous use of heroin purity measurement alone, rather than consideration of the variation in both purity and mass in street-level heroin samples together may have contributed to the conflicting previous findings. Heroin purity has been used to describe the strength or dose of street-level heroin but this extrapolation from the purity data of a sample is only appropriate when the masses of the samples are consistent. For example, a sample with a higher purity but lower mass may contain a lower dose of heroin than a sample with lower purity and a higher mass. Heroin purity alone does also not enable an accurate measure of the contribution of other drugs and adulterants in street-level heroin, including other opioid drugs, which may contribute to the equivalent effective opioid dose contained in a sample.

Street-level heroin is purchased in typical quantities based on mass (e.g. a 'cap', 'quarter gram', 'half-gram' or 'gram' of heroin) and in typical presentations for each mass, however these purchases may vary in both quality due to often unknown purity, and mass due to imprecise measurement. The aim of this study was to examine both the sample mass and purity of individual street-level seizures, in order to quantify the actual effective dose of heroin commonly contained within these samples. We then used this measure of effective dose to determine the variability of heroin contained within these street-level samples, including the proportion of samples that contained a larger dose than would typically be expected by users of this drug.

2. Methods

2.1. Data sources

All seizures of heroin in Victoria between 01/01/2012 and 31/12/2013 that were analyzed by the Drug Sciences Group of the Victoria Police Forensic Services Department were assessed for inclusion in this study. Samples were analyzed using gas chromatography–mass spectrometry (GC–MS) for the identification of different compounds with a typical level of detection (LOD) of 5mcg/mL (0.005 mg/mL). Heroin, which was typically in the HCl form, was then quantified using gas chromatography (GC) with a level of quantitation (LOQ) of 0.43 mg/mL. The characteristics of each sample including the presentation (form), packaging, other drugs that were detected in the sample, purity of heroin quantification, number of packages (where multiple packages were seized) and total mass were recorded in a database managed by the Drug Sciences Group. For this study, where multiple packages were seized and recorded, the mass equal to the individual package was determined and each package was considered an individual sample. For the purposes of this study, one common street-level dose of heroin (typically termed a 'cap', 'point' or 'rock' referring to approximately 0.1 g, hereafter referred to as a cap) was selected for investigation because it was both a common presentation and considered a representative unit that in most instances would be unlikely to be further divided or adulterated. We restricted the mass range for a cap of heroin to be any sample equal or less than 150 mg (0.15 g) in mass, with samples greater than 150 mg considered to be more likely associated with larger typical purchases such as quarter or half grams. In the case of multiple package seizures, samples were also included where the mass for each sample was calculated to be less than or equal to 150 mg.

2.2. Heroin dose calculation

The effective dose of heroin (g) for each cap was calculated by multiplying the purity (%) by the mass (g) of each sample. Samples were excluded from analysis where either mass or purity data were not available.

2.3. Correlation between mass, purity and effective dose of heroin

Separate scatterplots were produced for heroin purity versus seizure sample mass and effective dose of heroin versus seizure sample mass. Because an increase in street-level sample mass should be associated with an increase in the effective dose of heroin if purity is stable, a linear regression was performed to determine the percentage of variance in effective dose of heroin that was explained by sample mass. A further linear regression was performed that additionally included physical presentation (form) as an independent variable, to determine its significance.

2.4. Identification and classification of samples containing excessive heroin doses

For each sample, we determined its purity relative to the median purity of all caps (for example 1.2 times the median purity). Similarly, we determined the effective dose of the sample relative to the median effective dose of all caps. Based on the magnitude of drug administered above what was anticipated, planned or expected, and based on routine clinical practice associated with bolus dose morphine administration for the purposes of this study the following conservative dose classifications were used:

- Within the standard range — samples with an effective dose of heroin less than 1.5 times the median heroin dose.

- Greater than 1.5 times the median dose — samples with an effective dose of heroin that was greater than or equal to 1.5 times the median heroin dose, but less than twice the median heroin dose.
- Greater than 2 times the median dose — samples with an effective dose of heroin greater than or equal to twice the median dose.

Samples were also further characterized by the presentation of the seized heroin sample, typically being a cigarette foil, a small plastic bag or a balloon.

2.5. Statistical analysis

Descriptive statistics were used to describe samples within the cap range, including the distribution of mass, purity and median effective dose of heroin for this street-level purchase size. All graphs were produced as well as analyses conducted using SPSS for Mac version 23, where statistical significance was considered at $p < 0.05$.

3. Results

There were 983 heroin samples included in this study where the samples were determined to be of less than or equal to 150 mg in mass. This included 313 samples where the sample was seized as an individual item and 670 samples that were derived from 135 separate seizures of multiple samples (range 2–32 multiple samples). More than half of samples were presented in a cigarette foil (59%, n = 576), with a plastic bag (24%, n = 239) or balloon (14%, n = 134) also common packaging presentations. A small number of samples had either an unknown or atypical presentation (3%, n = 34).

3.1. Mass of seized heroin samples

The distribution of the mass of the samples considered showed a left-skewed distribution around a median of 92 mg in mass and an IQR of 43 mg (Fig. 1).

3.2. Composition and purity of the seized heroin samples

Most samples were in the form of compressed powder (83%), with granular powder (8%) and amorphous powder (8%) the next most common presentations. Heroin purity data were available for 961 of the samples and the overall or aggregate median purity was determined to be 12.8% (IQR = 3.4%), ranging from 3.6% to 80.9% (Fig. 2). The detected drugs, adulterants and contaminants in the seized heroin samples are presented in Table 1. By definition heroin was detected in all of the included samples. Other opiates that were commonly detected included acetylcodeine in 81% of cases (n = 792), 6-acetylmorphine (6-AM) in 68% of cases (n = 672) and morphine in 14% of cases (n = 137). Papavarine and noscapine which may be used as markers for illicit heroin in toxicological samples, were only detected in 0.7% (n = 7) and 0.1% (n = 1) of samples within this study, respectively. Stimulants were also commonly detected in the samples with caffeine detected in 39% of cases (n = 385) and amphetamine derivatives in 10% of samples (n = 98). A range of other different and diverse classes of drugs were also detected including dimethylsulfone (DMS) in 46% of cases (n = 451) and paracetamol in 14% of cases (n = 141). A number of different sugars or artificial sweeteners were also commonly detected as diluents, with xylitol the most common and detected in 81% of samples (n = 797).

3.3. Variation in sample mass, purity and effective dose

The heroin caps demonstrated variation in both mass and purity, as shown in Fig. 3. Variation in heroin purity was apparent at both the higher and lower mass ranges of the caps. Outliers were observed among the samples including high purity samples across the mass spectrum, as well as higher mass samples with moderate purity that contained a high amount of heroin or a large effective dose. Caps with high purity and low mass or low purity and high mass were observed to result in a similar effective dose of heroin. Conversely, caps with the same purity but different mass were observed to result in different effective doses of heroin. Fig. 4 shows that the median effective dose of heroin was 12.0 mg of (IQR 6.6 mg) and skewed towards the right. The effective dose of heroin varied between 0.4 mg and 111 mg of heroin.

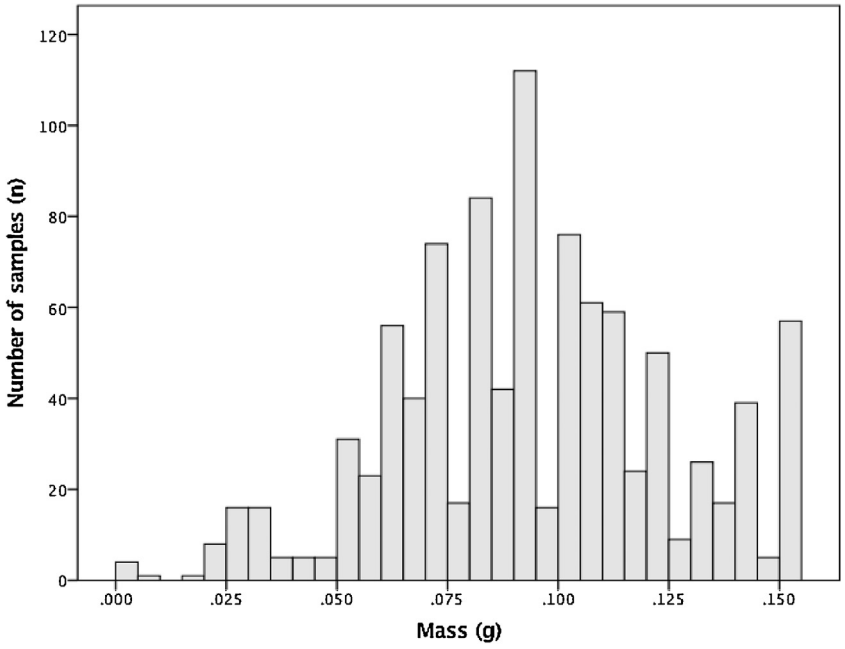

Fig. 1. Street-level 'cap' of heroin distribution by mass.

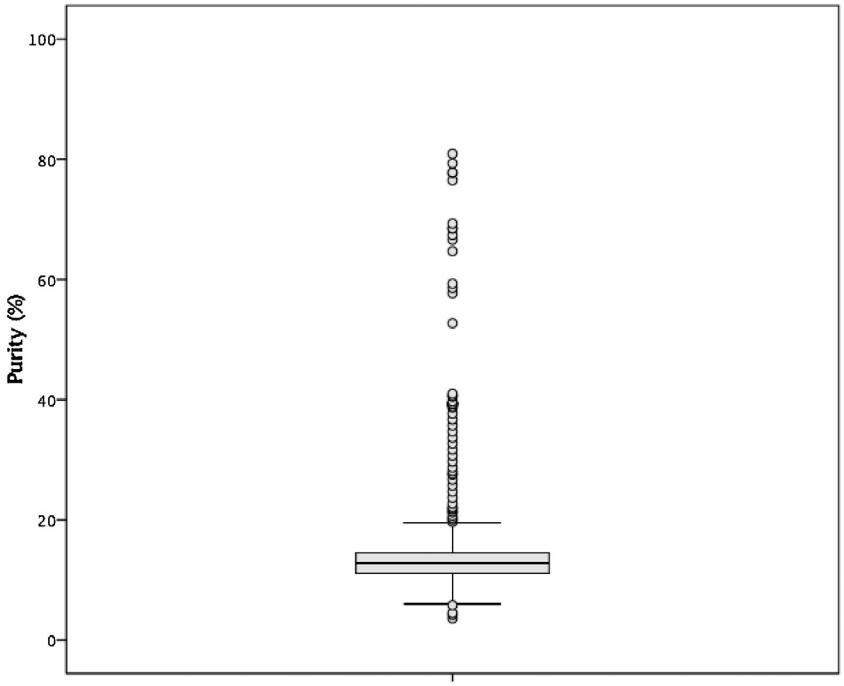

Fig. 2. Boxplot of heroin purity in street-level cap samples.

Table 1
Drugs, adulterants and contaminants detected in seized heroin samples.

Drug, adulterant or contaminant	Number (%)
Diacetylmorphine (heroin)	983 (100%)
Acetylcodeine	792 (81%)
6-Acetylmorphine (6-AM)	672 (68%)
Morphine	137 (14%)
Codeine	23 (2%)
Papaverine	7 (0.7%)
Noscapine	1 (0.1%)
Caffeine	385 (39%)
Methylamphetamine	70 (7%)
Dimethylamphetamine	26 (3%)
alpha-Pyrrolidinovalerophenone (alpha-PVP)	21 (2%)
3,4-Methylenedioxypyrovalerone (MDPV)	3 (0.3%)
3,4-Methylenedioxy-*N*-methylamphetamine (MDMA)	2 (0.2%)
Cocaine	2 (0.2%)
Dimethylsulfone (DMS) also known as methylsulfonylmethane (MSM)	451 (46%)
Paracetamol	141 (14%)
Methorphan	10 (1%)
Lignocaine	5 (0.5%)
Methylone	4 (0.4%)
Phenylimidothiazole	1 (0.1%)
Pyrovalerone	1 (0.1%)
Nicotinamide	1 (0.1%)
Xylitol	797 (81%)
Glucose or sucrose	56 (6%)
Sorbitol	52 (5%)

There was a positive association between increased mass of seized heroin and increased effective dose of heroin as would be expected (Fig. 5). The strength of the correlation between mass and the effective dose of heroin was moderate with an *r*-value of 0.536, p-value <0.001. Simple linear regression analysis demonstrated that mass has a statistically significant effect on the effective dose of heroin (p-value <0.001) but only accounted for 29% ($R^2 = 0.288$) of the effective heroin dose variance. The intercept and beta coefficient for mass were determined from the regression to be −3.770 mg and 187.75 mg (95% CI 169.02–206.48 mg) respectively. The residual plot and normality plot for this model are not shown. Multiple linear regression analysis showed no significant associations between the physical form of heroin presentation and the effective dose of heroin. The mass was again determined to have a statistically significant correlation with the effective dose of heroin, with a similar regression coefficient to the simple linear regression analysis (184.20 mg, 95% CI 166.11–202.30, p-value <0.001). This model accounted for 34% (adjusted $R^2 = 0.336$) of the effective heroin dose variance, which was only a small improvement over the simple linear regression analysis. This data demonstrated that an increase in mass is associated with an increase in the effective dose, but that it accounted for less than half of the variability in the effective dose of heroin in the cap samples. Therefore, more than half of the variability in the effective dose of heroin was not directly related to mass.

Table 2 shows that doses outside of the normal range were observed across all package types. Plastic bag presentation had the highest proportion of samples with excessive effective heroin dose (31% overall) and the highest number of samples in the higher dose category of greater than twice the median dose of heroin (n = 47, 21%).

4. Discussion

Mass and purity of individual heroin samples were both assessed to better calculate the effective dose of heroin contained within common street-level seizures. Data from this study showed that dose of heroin contained within most cap samples were clustered around the median, but significant outliers were observed across all of the different packaging presentations. A number of previous studies have demonstrated no correlation between fluctuation in heroin purity and heroin-related emergencies or heroin-related deaths [17–20]. Results from this study suggest that this may be due to consideration of aggregate purity data, rather than consideration of the effective dose of heroin contained within street-level samples and the extent of the variability in these samples compared to the standard dose that may be expected by users. Importantly, this study showed that

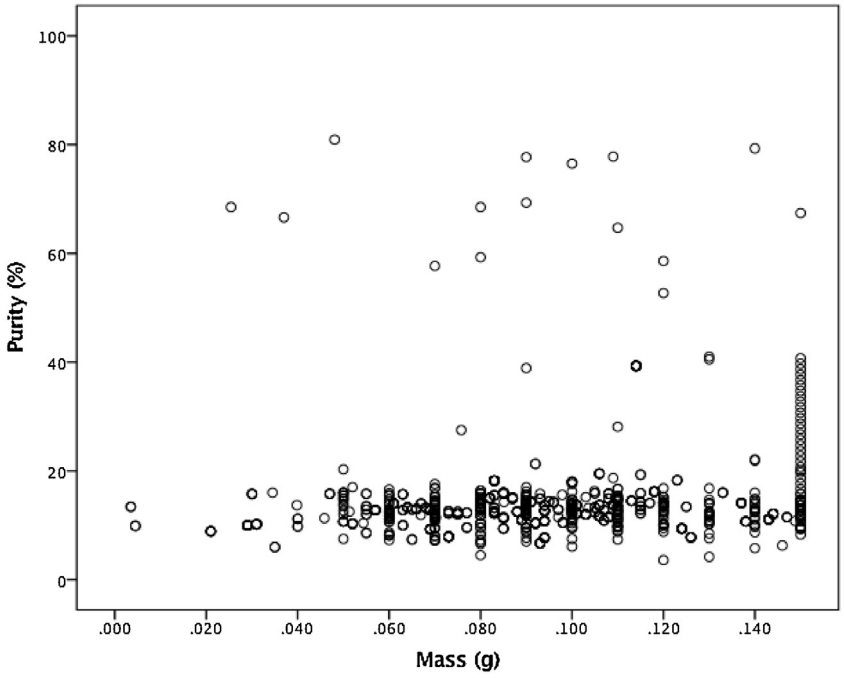

Fig. 3. Heroin purity versus seizure sample mass scatterplot.

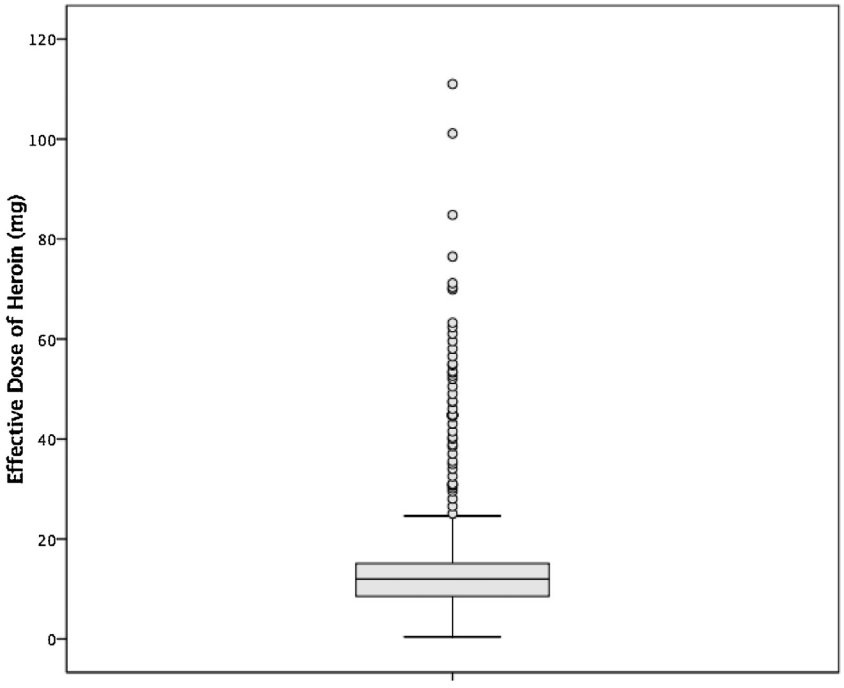

Fig. 4. Boxplot of the effective dose of heroin contained in street-level 'cap' samples.

purity alone is a poor measure of the amount of heroin contained in samples, where it was demonstrated that samples with the same purity can contain large differences in the effective dose of heroin. Furthermore, this study also demonstrated that use of aggregate purity data alone does not capture the extent of variability in street-level samples because it is not the most appropriate, nor a sensitive enough measurement tool.

Examination of the effective dose of heroin in the street-level cap presentation has enabled insight into the contribution of variability associated with both the quality and quantity of street-level heroin. Data from this study demonstrated outlier cap samples contain large doses of heroin that may exceed the amount of heroin expected by a user and their current opioid tolerance level. The direct relationship of a user receiving a higher than anticipated effective heroin dose to overdose was not established in this study, but examination of the anticipated effective dose and variability including high-dose outliers may provide significant insight for future research. Additional research is required to determine whether changes to typical sources, presentation and location of purchase for regular users

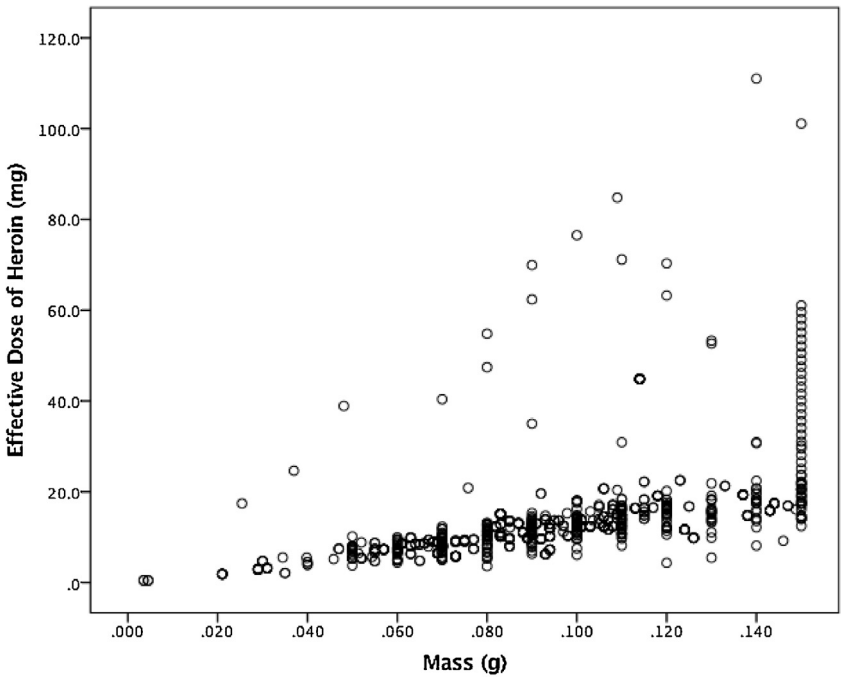

Fig. 5. Effective heroin dose versus sample seizure mass scatterplot.

Table 2
Effective dose classification for the different packaging presentations.

Effective dose of heroin	Cigarette foil	Plastic bag	Balloon	Other or unknown	Total (%)
Within the standard range	530 (93%)	158 (70%)	114 (86%)	22 (71%)	**824 (86%)**
Greater than 1.5 times the median dose (≥18 mg – 23.9 mg)	31 (5%)	22 (10%)	18 (14%)	7 (23%)	**78 (8%)**
Greater than 2 times the median dose (≥24 mg)	10 (2%)	47 (21%)	0 (0%)	2 (6%)	**59 (6%)**
Total	**571**	**227**	**132**	**31**	**961**

of the cap street-level presentation may expose them to a greater risk of overdose because of fluctuations in the effective dose of heroin. The typical amount of heroin and the extent of variability in street-level presentations across different geographical regions, as well as analysis of larger mass street-level presentations that would be more commonly used by individuals with a higher opioid tolerance also require further investigation. This data may contribute to our understanding of the reason that heroin overdose commonly occurs in long-term, dependent users rather than young, novice and naïve or non-tolerant individuals [22].

The impact of variability in the dose of heroin contained in street-level samples and the potential contribution to overdose in long-term, dependent heroin users is highlighted by the significantly reduced risk of overdose-related mortality with opioid substitution therapy. Pharmaceutical or prescribed heroin may in-part be safer than illicit heroin because the dose of heroin administered is known. Trials of prescribed heroin for dependent users who do not respond to standard treatments have now been reported from a number of different regions [23–29]. A Cochrane systematic review of the outcomes of these studies, as well as a subsequent systematic review and meta-analysis of supervised injectable heroin studies demonstrated no significant difference in mortality associated with prescribed or pharmaceutical heroin compared to methadone treatment groups [30,31]. This is important because opioid substitution treatment with methadone has been consistently demonstrated to be associated with a significantly decreased risk of premature death for dependent users, compared to the use of illicit heroin outside of the high-risk transition periods [32]. Further research is needed in this area.

Analysis of the composition of street-level heroin in this study revealed a wide range of contaminants, adulterants and other drugs. Interestingly, the high purity heroin samples identified in this study were unlikely to be the result of prescribed pharmaceutical heroin that has been diverted because supervised injectable heroin programs are yet to be trialed in Australia. Morphine is a precursor compound used in the illicit manufacture of heroin, where an initial morphine mixture obtained from raw opium contains a number of different opium alkaloids, including codeine, which are then processed through an acetylation stage where diacetylmorphine (heroin) is formed [33]. Therefore, it was not surprising that both morphine and 6-acetylmorphine as well as acetylcodeine were detected in a large proportion of samples, though quantification of these compounds was not available for this study. This data supports other studies where both morphine and codeine detection in toxicological samples has been reported to provide a consistent marker for illicit heroin use [34–38]. Papaverine and noscapine have also been reported as markers that may be used in toxicological analysis for the identification of illicit heroin use [39,40]. Data from this study however revealed that these markers may have limited use for the detection of illicit heroin in Victoria, Australia, as papaverine and noscapine were detected in less than 1% of street-level cap samples of heroin seizures, respectively. This finding was consistent with previous illicit street sample data from Sydney, Australia [41]. These results highlight the differences in composition of street-level heroin in

Australia compared to heroin commonly found in Europe over the same time period, and this includes the lower level of adulteration with caffeine and paracetamol but a greater extent of diluents such as xylitol [42].

Central nervous system (CNS) stimulant drugs including caffeine and amphetamine derivatives were also commonly detected in the street-level heroin samples in this study. The adulteration of street-level heroin with CNS stimulant drugs provides an additional challenge associated with determining the likely or potential adverse drug reactions associated with an effective heroin or equivalent opioid dose primarily. Other adulterant drugs including CNS depressants also complicate the risk of heroin use when attempting to predict outcomes and adverse reactions associated with a specific opioid dose because of their potential for influencing the risk of toxicity. With methylamphetamine detected in 70 of the illicit heroin sample it must also be considered that with the increased risk of overdose and death within the heroin user cohort, increased reported rates of drug-related deaths where methylamphetamine was reported may actually be heroin-related deaths [46].

4.1. Limitations

The seizure data used in this study does not constitute a random sample of street preparations across the state of Victoria and may be systematically biased by police operations. However, the overall purity of heroin samples used for this study was consistent with other published data and the study time period and location were not considered unusual or associated with excessive fluctuations in the availability, price or purity of heroin [12,14].

The extent that opioid and other contaminants contribute to the pharmacological effects of street-level heroin purchases of the type sampled in this study is currently unknown. For example, other opioid drugs were not detected in the samples analyzed in this study likely because of the study time period where recent reports have indicated the addition of fentanyl in street-level heroin that may contribute to an increased risk of overdose [43–45]. One way of examining this issue in relation to the presence of other opioids either substituted for, or in addition to heroin in street-level samples would be to determine an opioid equivalence dose for all of the opioid compounds. An opioid equivalent dose would provide a more accurate measure of the fluctuation in effective dose that results from the variation and contribution of all opioids involved. However, effects other drugs such as stimulants and the effect of drug combinations and overall health would need further examination and consideration of alternative models of interaction.

Chemical analysis of the illicit heroin prepared for administration would provide more precise data in relation to linking fluctuations in street-level heroin to overdose. This is because of inter-user variation in the preparation of illicit heroin where factors such as total volume, concentration, dose and insoluble particles administered can also vary. Presuming that each user is consistent in their preparation method, this study demonstrated that they may end up administering quite different amounts or doses of heroin compared to what they would normally expect. Therefore, street-level heroin seizure data still provides valuable insight into the variability of street-level heroin that may be experienced by a user, though chemical analysis of the illicit drugs prepared for administration would provide a more precise measurement of the dose of heroin administered.

5. Conclusion

Heroin overdose is a significant problem and although a number of identified risk factors for heroin overdose are known, the role of fluctuations in the quality, quantity and composition of street-level heroin remains unclear. This was the first study to describe fluctuations in both the purity and mass of street-level heroin together in order to determine the effective dose of heroin contained within cap samples and identify outlier samples that contain large doses of heroin. One in 13 samples contained greater than 1.5 times the median effective dose of heroin, while one in 17 samples contained greater than twice the median effective dose of heroin than may be expected by users for this presentation. Further research is required to determine any specific relationship between these high heroin dose outliers directly with overdose, although determining the effective dose of heroin is a more appropriate measurement tool in order to understand the contribution of contaminants and adulterants that may also contribute to toxicity.

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Contribution

All authors contributed to the preparation of the manuscript and have approved the final manuscript.

Conflict of interest declaration

No other authors declare any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence this work.

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Chapter 4:

The safety and efficacy of the out-of-hospital clinical management of heroin overdose

4.1 Chapter introduction

As outlined in the review provided in **Chapter 1**, non-fatal heroin overdose appears to be a relatively common occurrence among users of this drug, with fatal overdose occurring in only a small proportion of overdose events or cases. **Chapter 4** presents an investigation and analysis of the out-of-hospital management of non-fatal heroin overdose by linking the detailed information about the cohort of heroin-related death cases identified in **Chapter 2**, with Emergency Medical Service (EMS) data for each of the decedents where available.

Ambulance Victoria (AV) is the statewide EMS for Victoria and the linkage of coronial with EMS data for Victoria provides a clearer understanding of the circumstances, type and frequency of clinical presentations to EMS for decedents prior to the fatal heroin-related outcome. In Victoria, patients commonly refuse transport to hospital by EMS for observation following a non-fatal heroin overdose, including cases where naloxone is administered to achieve acute overdose reversal. Because most heroin overdose events occur in the out-of-hospital environment and where most harm-reduction strategies or interventions are also based in the community, the detailed examination of both out-of-hospital clinical and coronial data through data linkage provides an important insight into the safety and efficacy of these interventions. A detailed description of the data linkage process is provided in **Appendix A**.

Publication 4 provides an investigation into the safety of the treatment of non-fatal overdose in the out-of-hospital environment. This publication provides a unique perspective on this issue by examining the cohort of heroin-related deaths and then determining whether death was attributable to the last episode of care by paramedics for a non-fatal overdose. This was the first study to investigate the safety of this practice whether naloxone was administered or not as part of the clinical management of the overdose event, as well as where death may have occurred as a result of heroin-intoxicated misadventure following the acute overdose management by paramedics. **Publication 5** provides a detailed investigation of the circumstances at the time the fatal heroin overdose events in order to determine the

potential for timely and meaningful intervention by a bystander or witness in order to avert the fatal outcome if naloxone had been available. This publication provides an examination of the potential impact as well as challenges that Take-Home Naloxone may have had in reducing the number of fatal heroin overdose cases over the two-year study period.

4.2 Publication 4

Catch and release: evaluating the safety of non-fatal heroin overdose management in the out-of-hospital environment.

CLINICAL TOXICOLOGY
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CLINICAL RESEARCH

Catch and release: evaluating the safety of non-fatal heroin overdose management in the out-of-hospital environment

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ABSTRACT

Background: The aim of this study was to investigate the safety of the management of non-fatal heroin overdose in the out-of-hospital environment; irrespective of whether or not naloxone had been administered. Heroin toxicity-related deaths as well as heroin intoxication-related traumatic deaths following patient-initiated refusal of transport were investigated.

Methods: Heroin-related deaths in the state of Victoria, Australia between 1 January 2012 and 31 December 2013 were investigated and data linkage to pre-hospital Emergency Medical Services performed, in order to identify whether the death was related to the last episode of care by paramedics. The number of non-fatal heroin overdose events over the study period were also examined.

Results and discussion: There were a total of 3921 heroin-related attendances by paramedics during the study period, including 2455 cases that involved treatment but where the patient was not transported to hospital. There were also 243 heroin-related deaths identified over the study period and 93% ($n = 225$) of those cases were matched with Ambulance Victoria electronic patient care records. Data linkage revealed 31 heroin-related deaths where there had been a recent presentation with a non-fatal heroin overdose to paramedics; however, none of these deaths were related to that episode of care, including for 11 individuals that were treated on scene by paramedics but not transported to the hospital.

Conclusions: This study demonstrated that the treatment of uncomplicated heroin overdose in the out-of-hospital environment was safe in terms of mortality, irrespective of whether or not naloxone had been administered. In all of the non-fatal heroin toxicity cases attended by paramedics, whether or not transported to hospital, death occurred as a result of a subsequent and unrelated heroin overdose.

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Introduction

Heroin overdose is a major public health concern and the leading cause of death for people who use heroin [1,2]. Non-fatal heroin overdose is a far more common occurrence than fatal heroin overdose, with only 3.1% of all heroin overdose events in Australia resulting in death [3]. A recent report from a medically supervised injecting center in Sydney, Australia revealed an overdose rate of 12.7 heroin overdoses per 1000 injections, or on average, one overdose for every 80 injections of heroin [4]. Heroin overdose is a problem because it is associated with the rapid onset of opioid-induced ventilatory impairment that can lead to hypoxia and hypercapnia secondary to central nervous system depression, the loss of airway reflexes, respiratory failure and pulmonary aspiration [5–10].

Naloxone is a competitive-reversible, non-selective antagonist with high affinity for the opioid receptor, which is effective for treating opioid overdose, including heroin [11]. Rebound toxicity can occur because of its short half-life and duration of action compared to heroin and other opioid drugs. Other risks include the induction of acute withdrawal symptoms in opioid-dependent individuals and, uncommonly, complications of catecholamine release including cardiac arrhythmias and acute pulmonary edema [12–14]. Despite the physiological significance of a heroin overdose, studies have demonstrated that prolonged observation greater than one hour or hospital admission following naloxone administration is not usually required [15–17]. This appears to be the case where patients have normal mentation, normal vital signs, are able to ambulate and have no features of opioid intoxication.

In the clinical setting, initial ventilatory support and the correction of physiological derangements associated with overdose can result in an improvement in the conscious state of patients to the point where they may refuse further treatment, including naloxone administration. In fact, it was recently reported that only 20% of heroin overdoses in a medically supervised injecting center in Sydney, Australia were administered naloxone where airway management and

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oxygen administration failed to improve consciousness [4]. The management of a heroin overdose can be complex and even the dose of naloxone administered by clinicians has also been shown to depend on key clinical features associated with the overdose [18]. Paramedics and other emergency medical service providers commonly treat heroin overdose cases in the out-of-hospital environment and this is often followed by the patient-initiated refusal of transport to the hospital. The safety of this practice has been investigated by a number of studies but is not yet clearly understood because of some of the challenges and limitations associated with these studies [19–25].

Heroin death investigation can be complex, contributed to by the lack of toxicological analysis in some cases, variability in the detection of heroin-specific metabolites, and the involvement of multiple substance [26–31]. A significant challenge associated with previous studies relates to the variability and underreporting of a large number of deaths associated with heroin, with the common misclassification of these deaths as being morphine or codeine toxicity-related or because of non-specific death certification [32,33]. The extent of the underreporting of heroin-related death cases compromises the ability of previous studies to accurately evaluate the safety of non-fatal heroin overdose management as a result of the missing heroin-related death data. Another limitation of previous studies has been the restricted focus of the investigations to suspected heroin overdose cases only where naloxone had been administered. Lastly, previous studies did not investigate the linkage of any deaths that may have directly resulted from impairment and misadventure associated with heroin intoxication following a refusal of transport to the hospital.

The aim of this study was to investigate the safety of the common "catch and release" practice, or the management of non-fatal heroin overdose in the out-of-hospital environment by starting with the accurate identification of heroin-related deaths in the first instance. Through the detailed forensic investigation associated with these deaths and data linkage, the safety of non-fatal heroin overdose management was investigated. The safety of this practice was investigated irrespective of whether or not naloxone had been administered, and where death may have occurred as a result of toxicity directly or impairment and misadventure following patient-initiated refusal of transport.

Methods

Heroin-related deaths over a two-year period from 1 January 2012 to 31 December 2013 in the state of Victoria, Australia were investigated for this study. To provide context, the number of non-fatal heroin overdose events that presented to pre-hospital Emergency Medical Services (EMS) in Victoria over the study period were also examined. Heroin-related death cases were first identified and then forensically investigated, including data linkage to pre-hospital EMS in Victoria, in order to identify whether the death was related to the last episode of care by paramedics. Because the time interval between heroin administration, toxicity-related complications and death is multifactorial and extremely variable, the timeframe from non-fatal heroin toxicity-related presentation to EMS and either death or the documented date of death may also be variable and protracted. For this study, heroin-related deaths that occurred within one month of the last presentation to EMS for a non-fatal overdose were investigated.

Heroin-related presentation to paramedics

Ambulance Victoria (AV) is the statewide EMS for Victoria. Details of heroin-related emergency cases attended by paramedics in Victoria are recorded as an electronic Patient Care Record (ePCR) which is migrated with Computer Aided Dispatch data into the AV data warehouse.

Potential alcohol and drug-related cases are extracted monthly by AV and provided electronically to Turning Point. Turning Point is a national addiction treatment center that is affiliated with both the Monash University Eastern Clinical School as well as Eastern Health to provide treatment, research and education for addiction and related issues. Cases are reviewed, coded and then entered into a database as part of a long-standing collaborative project for the surveillance of alcohol and drug-related presentations to paramedics in Victoria. The attribution of paramedic attendance to specific drugs or substances is based on the documented clinical findings by paramedics, patient self-report as well as other information provided at the scene [34]. Turning Point coders manually review all cases in order to accurately extract and validate relevant alcohol and drug-related presentations. Although not definitive without toxicological testing, overdose cases were classified as being heroin-related following a positive response to naloxone administration and where there was no indication that the overdose resulted from another opioid, such as morphine or methadone. Cases were also attributed to heroin where naloxone was not administered but where heroin use was established as a result of the clinical findings by paramedics and information from the patient or witnesses at the scene. All of the coded data for alcohol and drug-related presentations are validated for auditing and quality control purposes.

Heroin-related deaths

Heroin toxicity, or overdose-related deaths, were the primary focus of this study in order to assess any direct link with the last overdose presentation to paramedics. Deaths that occurred as a result of misadventure and impairment secondary to acute heroin intoxication were also investigated for the purposes of this study. Heroin-related death investigation is associated with a number of challenges including primarily the differentiation between morphine detection from heroin metabolism or as a result of the primary administration of morphine.

Heroin (diacetylmorphine) is rapidly converted to 6-acetylmorphine (6-AM) and then to morphine soon after administration [26,35–38]. Pharmacokinetic differences for heroin, 6-AM and morphine result in significant variation in the clearance rate and detection of these compounds in

overdose-related death cases. Population pharmacokinetic studies have demonstrated that heroin and 6-AM are unable to be detected in the circulating plasma following a period of greater than 10–40 min, and greater than 2–3 h, respectively, following heroin administration [36]. These differences are exacerbated by variability in the time interval between the administration of heroin and death, including where death is protracted or following resuscitation and hospital admission. In cases with even a slightly prolonged interval between heroin administration and death, 6-AM may not be detected in either blood or urine samples because of extensive and rapid metabolism or elimination from the body [35,36]. Furthermore, differences in the postmortem redistribution and stability of these compounds add to the complexity of heroin-related death investigation. In particular, where 6-AM has been shown in human postmortem toxicology samples to be unstable and spontaneously hydrolyse, demonstrate significant postmortem redistribution as well as poor stability in different storage conditions including in frozen toxicological samples [39–41]. These factors have contributed to the underreporting of a large number of heroin-related deaths including variability in the attribution and reporting of these deaths as either morphine or codeine toxicity or documented as non-specific certification associated with multiple drug toxicity [32,33]. A previously described model was used to determine the strength of evidence to support the attribution of death to heroin based on different toxicological markers of heroin use [6-AM, morphine to codeine ratio (M:C) or morphine alone] along with investigative evidence of heroin use (circumstances, scene, clinical and pathological findings) [42].

In Australia, cases are reported to the coroner in all unexpected, accidental or suspicious deaths, as well as those where the cause of death is unknown. Heroin-related death cases for this study were identified using the National Coronial Information System (NCIS) where cases typically contained an autopsy and toxicological report, a police narrative of the incident and circumstances around the time of death, as well as the coronial finding. Given the potential for heroin-related deaths to vary in their reporting and attribution of death, particularly when 6-AM is not detected, heroin-related death cases in this study were identified using a broad strategy. The search strategy was designed to capture all cases that are currently classified as heroin-related, cases that may be classified as morphine-related, or have a generic drug toxicity classification. A search of the NCIS for closed cases in the state of Victoria, Australia, between 1 January 2012 and 31 December 2013 was conducted using the following criteria:

- Heroin listed in the Cause of Death 1a, 1b, 1c, 2 or 3.
- An object search for heroin alone, in combination with any other drugs and heroin as a keyword search in the object field.
- A keyword search for heroin in the police report, the pathology report and coronial findings.
- A toxicology report keyword search for heroin, heroin and morphine or morphine alone.

The examination of cases over a two-year period was chosen for this study in order to allow for the finalization of investigation and reporting of these cases, which can sometimes take years, particularly if other persons may be involved. The cases identified in each of the NCIS search strategies were assessed for relevance and inclusion in this study following the detailed review of the toxicological report, the autopsy report, the police narrative of the circumstances surrounding death and the coronial findings for each case, where available. Duplicate results arising from the different search criteria were identified and removed.

Data linkage

For this study, identified heroin-related death cases from the NCIS were linked to the AV data for all prior case presentation to paramedics in Victoria prior to death for each of the decedents. Probabilistic data linkage using specific identifying information of the decedents to the AV database included: first name, surname, alias, date of birth, age, gender, residential address, location or address of the incident/death and date of death. All heroin-related presentations to AV for each of the decedents in the month prior to death were examined. The autopsy and toxicological report, police narrative as well as the coronial findings for each case was cross referenced with the AV Patient Care Record in order to determine whether the death was related to the last episode of care by paramedics. Information related to the last non-fatal heroin-related presentation to paramedics including whether or not naloxone was administered, as well as transportation to the hospital, were investigated and reported. Where a patient was declared deceased by paramedics either on initial presentation or following resuscitation attempts, this presentation was excluded for the purposes of this study.

Ethics

Ethical approval for the heroin-related presentations from Ambulance Victoria and Turning Point was obtained from the Eastern Health Human Research Ethics Committee (E122/0809). The project was also approved by the Ambulance Victoria Research Governance Committee.

Ethical approval for NCIS access and the heroin-related death data as well as data linkage was obtained by the Victorian Institute of Forensic Medicine Research Advisory Committee (RAC 030/14) and the Department of Justice and Regulation, Human Research Ethics Committee (CF/15/2853). The data linkage aspect of this project was also approved by the Coroners Court of Victoria and the Ambulance Victoria Research Governance Committee.

Results

Heroin-related attendances by paramedics

There was a total of 3921 heroin-related attendances by paramedics in Victoria, Australia, during the study period. Of the total number of heroin-related presentations, there were

2455 cases (63% overall), where the patient was clinically treated but not transported to the hospital by paramedics. The treatment and not the transport group comprised of 1632 cases (66%) where naloxone was administered as well as a further 823 cases (34%), where naloxone was not administered (Figure 1). In contrast to this, there were also 1466 heroin-related presentations (37% overall) where the patient was transported to the hospital by paramedics following clinical assessment and management including 507 (35%) cases where naloxone was administered as well as a further 959 cases (65%) where naloxone was not administered and was specifically withheld.

Heroin-related deaths

A total of 9060 potential heroin-related death cases were identified, reviewed and assessed for inclusion based on the weighting of toxicological and investigative evidence. Using the standardized criteria and the model previously described, a total of 243 cases were considered to be reasonably attributed to heroin after the assessment. Through probabilistic data linkage, 93% ($n = 225$) of the identified heroin-related death cases were able to be matched with Ambulance Victoria electronic patient care records. From the 243 heroin-related deaths identified there were 235 fatal heroin overdose cases. There were also eight heroin intoxication-related traumatic deaths where three of the deaths involved drowning, one case involved a pedestrian struck and killed by a vehicle, and four involved fatal vehicle collisions. In all of the fatal vehicle collision cases, the decedent was the driver of the vehicle and most involved single vehicle crashes into stationary objects.

Last episode of care by paramedics before death

Investigation of the last presentation or episode of care by paramedics before death revealed that there were 31 individuals with a heroin toxicity-related presentation as their final episode of care in the month of preceding death. Forensic investigations into the 31 cases where the last episode of care by paramedics was heroin toxicity revealed that there were 20 cases that were transported to hospital by paramedics while only 11 cases that were not transported to hospital (Table 1). For the 11 cases that were not transported to the hospital, it was revealed that the decedents died of a separate heroin-related overdose that was unrelated to the last presentation or episode of care by paramedics. This included one instance where death occurred as a result of subsequent heroin use within a 24-hour period.

Investigations into the 16 heroin toxicity cases attended by paramedics in the week prior to death that were transported to the hospital revealed that seven of these cases involved resuscitation at the scene, subsequent transportation and admission to hospital where the death occurred either one day ($n = 1$), two days ($n = 3$) or three days ($n = 3$) following admission, typically to an Intensive Care Unit (ICU). Investigations into the remaining nine cases revealed that the individuals died as a result of a separate heroin-related overdose that was unrelated to the last episode of care by paramedics and hospital presentation following

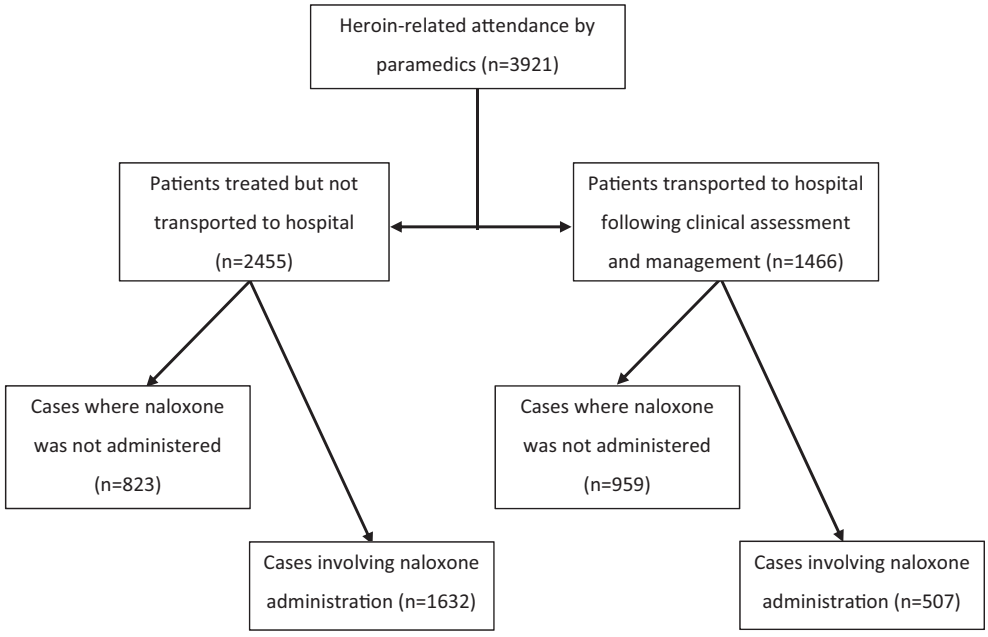

Figure 1. Heroin presentation to paramedics.

Table 1. Heroin toxicity-related final presentation to paramedics prior to death.

Presentation	Transported to hospital	Not transported to hospital
Within one month prior to death	20	11
Within one week prior to death	16	2
Within 24 h prior to death	3	1

transportation. This included three cases where the decedents self-discharged from hospital and death occurred within a 24-hour period as a result of the separate heroin-related overdose.

Discussion

Heroin use is associated with significant morbidity and an increased risk of premature mortality [1,2,43–45]. This study investigated questions about the safety of the treatment of non-fatal heroin overdose in the out-of-hospital environment. It is important to understand whether current clinical practice involving the "catch and release" of patients experiencing a non-fatal heroin overdose is safe and does not contribute to harms associated with this already vulnerable population. We found that there were 2455 acute heroin-related presentations to paramedics during the two-year study period that were clinically managed in the out-of-hospital environment by paramedics. However, through forensic investigation, we were able to determine that none of the 243 heroin-related deaths identified within the study period were attributable to the last episode of care that involved treatment and non-transportation to the hospital. The accurate attribution of heroin involvement in suspected drug toxicity-related deaths can be extremely challenging where it has been demonstrated that heroin-related deaths had been underreported by 43% with a large number of these deaths incorrectly attributed to morphine or codeine toxicity [32]. Significantly, the previous issues related to the variability and underreporting of heroin-related deaths that were a challenge of previous studies in this area were mitigated in the current study. This study involved the examination of all fatal heroin overdose cases that were treated with naloxone but not transported to the hospital, and whether the subsequent death that occurred was directly related to rebound toxicity or another adverse event related to the last episode of care.

The findings of this study close an important knowledge gap in our understanding of the safety of the management of patients experiencing a heroin overdose in the out-of-hospital environment. Heroin overdose is a dynamic illness where adverse effects may be exacerbated by patient comorbidities, health status, the environmental context and the concomitant use of other opioid or CNS depressant drugs [8,46,47]. This study comprehensively examined outcomes associated with heroin overdose cases treated with naloxone in addition to the large number of cases where naloxone was not administered and there is also a risk of subsequent toxicity following refusal of transport to the hospital. Deaths that occurred from misadventure as a result of heroin intoxication and impairment following refusal of transport to the hospital were also included in this study in order to capture all of the associated mortality outcomes following non-fatal heroin overdose management by clinicians in the out-of-hospital environment. These findings are important for a range of different clinical settings including paramedics and other emergency medical service personnel, the management of patients in safe injecting rooms, for clinicians providing advice about patients during custody, as well as issues associated with the increase in the distribution of naloxone in the community.

The data from this study revealed that a large number of patients ($n = 1466$) with presentations associated with acute heroin toxicity and associated complications were transported to the hospital for further assessment or management. Furthermore, 65% of these patients ($n = 959$) were not administered naloxone for various clinical reasons. It has been reported previously that clinicians accurately identify patients at risk of deterioration and adverse events following naloxone administration for suspected opioid overdose [15]. With the vast majority of patients ($n = 2455$) experiencing a heroin overdose safely managed by paramedics in the out-of-hospital environment, it remains unclear the specific reasons that a large number of patients were also transported to the hospital. It would seem reasonable to suggest that the patients that were transported may have presented with significant physiological compromise or complications associated with, or secondary to, acute heroin toxicity. We know from previous studies that patients who present with lower levels of consciousness and lower respiratory rates tend to require more aggressive clinical management, particularly where other drugs including alcohol are concomitantly used [18].

An important consideration of the findings of this study involves the current climate where synthetic opioids, including fentanyl, may be entirely used or sold in place of heroin. Fentanyl is highly potent, approximately 50–100 times more potent than morphine, has a fast onset of action and a narrow therapeutic window leading to the rapid onset toxic effects [48]. The adulteration of heroin with fentanyl has had a major impact on the number of opioid-related deaths in some areas and provided an additional challenge for healthcare providers in the safe and effective management of overdose cases [49,50]. Furthermore, novel synthetic opioids (NSOs) that include fentanyl analogs (acetylfentanyl, butyrylfentanyl, furanylfentanyl, para-fluoroisobutyrylfentanyl, beta-hydroxythiofentanyl and carfentanil) as well as structurally distinct opioid receptor agonist compounds (U-447700 and MT-45) have also emerged in fatal overdose cases [51–53]. The NSOs are particularly concerning because there is little up to date information about the biological effects of these drugs and the mechanism or degree to which these compounds produce significant toxicological effects is largely unknown [54,55]. The effectiveness of naloxone as an antagonist for treating overdose cases involving these NSOs is also largely unknown in humans. The required dose of naloxone for the treatment of acute overdose is dependent on the potency and dose of the opioid agonist reports of higher doses of naloxone for toxicity cases involving fentanyl have been reported including the requirement of up to 12 mg of naloxone to be administered [56,57]. A challenge with these compounds is also the variability in potency with some compounds equipotent to fentanyl, while carfentanil e.g., is far more potent and approximately 10,000 times more potent than morphine [51,55]. The adulteration of heroin with synthetic opioids including fentanyl analogs would likely contribute to more aggressive clinical management of toxicity-related cases where larger doses of naloxone may be required to achieve overdose reversal [50].

Data from this study indicate that an "uncomplicated" heroin overdose does not require transportation to the hospital for observation or admission and that this practice is safe in terms of mortality. Extrapolating the physiological and clinical criteria from previous reports, we would suggest that "uncomplicated" heroin overdose is where:

- Overdose reversal is achieved, which is particularly important in the setting of heroin adulterated with fentanyl;
- The patient is awake and alert;
- The patient has no compromise of vital signs; and
- The patient exhibits no signs of pulmonary complications.

Based on data from the present study as well as previous reports, it appears that it is safe to manage these patients in the out-of-hospital environment either following naloxone administration or not [15–17]. A caveat to these findings is that where an overdose involved NSOs, then it would not be considered uncomplicated. Importantly, there were no identified cases involving NSOs in the current study and because of the largely unknown duration of action of these compounds, the safety of the "catch and release" practice for toxicity cases involving NSOs is unknown and requires further research.

Limitations

A limitation of the current study involves the likelihood that not all of the previous non-fatal heroin presentations to paramedics would have been identified and linked to the decedent. This is because it is likely that in some instances where paramedics attend heroin-related cases, the patient may refuse to give a name and details, provide false details or a nickname because of the illicit nature of this activity. That said, we were able to link 93% of decedents to the previous presentation to Ambulance Victoria in the preceding month prior to the death. A second limitation is that non-fatal heroin overdose where an ambulance was not called, was not captured. It is likely that a greater number of non-fatal heroin overdose events occurred in the community where an ambulance was not called and also possible that patients were transported by other means directly to the hospital. A final limitation of the current study was that complication that may have required medical intervention or hospital admission following non-fatal heroin overdose management in the out-of-hospital environment but that did not result in the death were not captured. Additional treatment by EMS following non-fatal heroin overdose would have been captured, however, not direct presentation to the hospital or treatment by other healthcare providers and further research is required in this area.

Conclusions

Paramedics and other emergency medical service providers commonly treat heroin overdose cases in the out-of-hospital environment. Despite heroin overdose being a significant clinical event, many patients' self-initiate refusal of transport to the hospital for observation and further assessment. This study demonstrated that the treatment of uncomplicated heroin overdose in the out-of-hospital environment is safe in terms of mortality, where none of the 243 heroin-related deaths were attributable to the treatment but non-transportation of a patient following a heroin overdose. This study investigated the direct link between heroin-related deaths and the last episode of care by paramedics for non-fatal heroin overdose, irrespective of whether or not naloxone had been administered. In all of the non-fatal heroin toxicity cases attended by paramedics, whether transported to hospital or not, death occurred as a result of a subsequent and unrelated heroin overdose.

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No potential conflict of interest was reported by the authors.

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4.3 Publication 5

Challenges with take-home naloxone in reducing heroin mortality: a review of fatal heroin overdose cases in Victoria, Australia.

CLINICAL TOXICOLOGY
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CLINICAL RESEARCH

Challenges with take-home naloxone in reducing heroin mortality: a review of fatal heroin overdose cases in Victoria, Australia

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ABSTRACT

Aim: Take-home naloxone (THN) programs have been implemented in order to reduce the number of heroin-overdose deaths. Because of recent legislative changes in Australia, there is a provision for a greater distribution of naloxone in the community, however, the potential impact of these changes for reduced heroin mortality remains unclear. The aim of this study was to examine the characteristics of the entire cohort of fatal heroin overdose cases and assess whether there was an opportunity for bystander intervention had naloxone been available at the location and time of each of the fatal overdose events to potentially avert the fatal outcome in these cases.

Methods: The circumstances related to the fatal overdose event for the cohort of heroin-overdose deaths in the state of Victoria, Australia between 1 January 2012 and 31 December 2013 were investigated. Coronial data were investigated for all cases and data linkage was performed to additionally investigate the Emergency Medical Services information about the circumstances of the fatal heroin overdose event for each of the decedents.

Results and Discussion: There were 235 fatal heroin overdose cases identified over the study period. Data revealed that the majority of fatal heroin overdose cases occurred at a private residence ($n = 186$, 79%) and where the decedent was also alone at the time of the fatal overdose event ($n = 192$, 83%). There were only 38 cases (17%) where the decedent was with someone else or there was a witness to the overdose event, and in half of these cases the witness was significantly impaired, incapacitated or asleep at the time of the fatal heroin overdose. There were 19 fatal heroin overdose cases (8%) identified where there was the potential for appropriate and timely intervention by a bystander or witness.

Conclusion: This study demonstrated that THN introduction alone could have led to a very modest reduction in the number of fatal heroin overdose cases over the study period. A lack of supervision or a witness to provide meaningful and timely intervention was evident in most of the fatal heroin overdose cases.

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Heroin toxicity; heroin overdose; naloxone; take-home naloxone

Introduction

Drug overdose is the leading cause of death for people who use heroin and it has been estimated that heroin use is associated with a six-times greater risk of premature death compared with the general age-matched population [1,2]. Heroin overdose is associated with opioid-induced ventilatory impairment that can lead to hypoxia and hypercapnia secondary to central nervous system depression, the loss of airway reflexes, and respiratory failure [3,4]. Naloxone is a non-selective, competitive-reversible antagonist with high affinity for the opioid receptors and is effective in reversing the symptoms associated with opioid overdose symptoms, including heroin [5]. The morbidity and mortality associated with heroin use prompted calls for the increased availability of naloxone including take-home naloxone (THN) programs to complement the existing harm-reduction strategies [6–11]. In response to this, programs that facilitated access to naloxone for peer administration in the setting of a heroin overdose were introduced in a number of regions across Australia [12]. The distribution and access to naloxone were, however, limited because it was still scheduled as a prescription-only medication, though this was eventually changed to enable purchase over the counter in 2016 [13]. What remains unclear, however, is whether the increased availability and community distribution of naloxone alone will likely have a significant impact in reducing the number of fatal heroin overdose cases in the entire population of people who use heroin in this region.

From a clinical perspective, heroin overdose management typically involves basic supportive care including ventilatory support as well as the administration of naloxone where clinically indicated. Heroin overdose is a dynamic illness where individuals may deteriorate rapidly and death may occur within minutes after administration as a result of cardiorespiratory collapse. Rapid and significant deterioration may

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be exacerbated by patient comorbidities, the concomitant use of other opioid drugs or CNS depressants, pulmonary aspiration or positional asphyxia [14–16]. Even non-toxic doses of intravenous heroin have been demonstrated to produce profound respiratory depression including a significant reduction in oxygen saturation shortly after administration [14,17–19]. Opioid-induced loss of supraglottic airway muscle tone may contribute to airway obstruction, while decreased consciousness and blunted reflexes may also increase the risk of pulmonary aspiration and an inhibition of the ability to self-correct airway obstruction [3]. Conversely, in some cases, there may be a longer period of unresponsiveness and significant hypoxia lasting up to several hours prior to death. If left untreated, a heroin overdose can follow the clinical trajectory leading to the development of hypoxic brain injury, cardiac arrest and death. The concomitant use of other central nervous system active drugs, including benzodiazepines, will often exacerbate this risk. In this context, there is a "window of opportunity" for intervention in a heroin overdose by witnesses, peers or medically trained staff, at the time of the overdose event which may include naloxone administration.

The majority of heroin overdose events, however, do not result in death. In Australia, the number of fatal heroin overdose cases has been reported at between 4.1 and 6% compared to the number of non-fatal heroin overdose cases managed by paramedics [20,21]. Modelling based on the number of fatal to non-fatal heroin overdose events together with the number of times naloxone has been administered to reverse an opioid overdose has been used to estimate the impact of THN on overdose mortality [22–24]. Practically speaking, however, it remains difficult to differentiate between cases where naloxone administration may have averted a fatal outcome, or cases that were likely to be non-fatal anyway. In areas where THN programs have been implemented, measuring the impact of these interventions based on gross changes in heroin-related mortality data are challenging to interpret because of the typically rising trajectory of opioid-deaths in these areas, and where determining an appropriate control group can also be challenging [25,26]. Furthermore, the impact of THN programs may be greater in specific high-risk populations following relative periods of abstinence than in the entire population of people who use heroin. The impact of THN programs in a recent prison-release population have been investigated, and this includes the reporting of a 36% reduction in the proportion of opioid-related deaths that occurred in the four-week period following release from prison [27,28].

The aim of this study was to examine the characteristics of the entire cohort of fatal heroin overdose cases in Victoria, Australia and assess whether there was an opportunity for bystander intervention if naloxone had been available at the location and time of each of the fatal overdose events to potentially avert the fatal outcome in these cases. The potential for meaningful and timely intervention in fatal heroin overdose cases can then be used to determine the potential impact that the greater availability of naloxone may have in reducing the number of heroin-related deaths.

Methods

Heroin-related deaths over a two-year period from 1 January 2012 to 31 December 2013 in the state of Victoria, Australia were investigated for this study. This timeframe corresponded with the crossover point for the beginning of the first THN programs in Victoria in August 2013 [29]. This study period was also examined in order to allow the finalization of investigation and reporting of the heroin-related death cases, which can sometimes take years, particularly if other persons may be involved.

Heroin-related deaths

In Australia, cases are reported to the coroner in all unexpected, accidental or suspicious deaths, as well as those where the cause of death is unknown. Heroin-related death cases for this study were identified using the National Coronial Information System (NCIS) where cases typically contained an autopsy and toxicological report, a police narrative of the incident and circumstances around the time of death, as well as the coronial finding. Toxicological analysis was performed for all common drugs and poisons. A previously described model was used to determine the strength of evidence to support the attribution of death to heroin based on different toxicological markers of heroin use (6 am, morphine to codeine ratio (M:C) or morphine alone) along with investigative evidence of heroin use (circumstances, scene, clinical and pathological findings) [30]. A search of the NCIS for closed cases in the state of Victoria, Australia, between 01 January 2012 and 31 December 2013 was conducted. The cases identified in each of the NCIS search strategies were assessed for relevance and inclusion in this study following the detailed review of the toxicological report, the autopsy report, the police narrative of the circumstances surrounding death and the coronial findings for each case, where available. Duplicate results arising from the different search criteria were identified and removed.

Fatal overdose event investigation

For this study, the autopsy and toxicological report, police narrative as well as the coronial findings for each case were cross referenced with the Ambulance Victoria (AV) Patient Care Record where available, in order to investigate all of the circumstances related to the fatal overdose event. Probabilistic data linkage was used to link the AV data and the fatal overdose event for each of the decedents using specific identifying information including first name, surname, alias, date of birth, age, gender, residential address, location or address of the incident/death and date of death. The location of the fatal overdose event, whether it was witnessed and whether Emergency Medical Services (EMS) were called were investigated. Information about the scene, bystanders and whether resuscitation was performed in each of the fatal heroin overdose cases was also investigated. The timing of the emergency response, information about the scene and clinical findings as well as interventions by

paramedics were also investigated where EMS were called for the fatal overdose event for the decedents.

Ethics

Ethical approval for NCIS access and the heroin-related death data as well as data linkage was obtained by the Victorian Institute of Forensic Medicine Research Advisory Committee (RAC 030/14) and the Department of Justice and Regulation, Human Research Ethics Committee (CF/15/2853). The data linkage aspect of this project was also approved by the Coroners Court of Victoria and the Ambulance Victoria Research Governance Committees.

Results

Heroin-related deaths

A total of 9060 potential heroin-related death cases were identified, reviewed and assessed for inclusion based on the weighting of both the toxicological and investigative evidence for each case. Using the standardized criteria and model previously described, a total of 243 cases were considered to be reasonably attributed to heroin after final assessment [30]. From these deaths, there were 235 fatal heroin overdose cases identified as well as 8 misadventure-related deaths that occurred as a result of heroin intoxication. Of the 235 fatal heroin overdose cases, the majority of the decedents were male ($n = 194$, 83%). The median age of decedents was 37 years (IQR of 13) with a range between 19 and 67 years of age. The vast majority of the fatal heroin overdose cases ($n = 206$, 88%) occurred in Metropolitan Melbourne, with only a small number ($n = 29$, 12%) occurring in Regional Victoria.

Within the entire cohort of fatal heroin overdose cases, 8% of these decedents ($n = 19$) were identified as being at a high risk of mortality because of change in their circumstances. This included nine decedents who experienced a fatal heroin overdose within a four-week period following recent prison release. Eight of the decedents experienced a fatal heroin overdose within the first two weeks following prison release and this included three decedents who died from a fatal heroin overdose within 48 hours after release. Additionally, there were eight decedents identified who experienced a fatal heroin overdose within a four-week period after leaving an abstinence-orientated drug treatment and detoxification program, as well as a further two fatal heroin overdose cases that occurred following a recent hospital discharge.

Fatal overdose event

The coronial reports, police narrative of the incident and circumstances around the time of death as well as the linked electronic patient care records from Ambulance Victoria for the fatal heroin overdose were investigated. Data revealed that the majority of fatal heroin overdose cases occurred at a private residence ($n = 186$, 79%). The next most common locations for fatal heroin overdose cases were in a public place or facility ($n = 15$, 6%) or in a private vehicle ($n = 13$, 6%), with a range of different locations for the remaining cases (Table 1).

Table 1. Location of fatal heroin overdose event occurrence.

Location of overdose event	Number of cases, *n* (%)
At a private residence	186 (79%)
Public places or facilities	15 (6%)
Private vehicles	13 (6%)
Medical or residential care facility	5 (2%)
Hotel or motel	4 (2%)
Shopping centres or stores	4 (2%)
Work	3 (1%)
Unable to be determined	5 (2%)
Total	235 (100%)

The potential for intervention with naloxone by a bystander or witness at the time of the overdose was assessed in 230 of the fatal heroin overdose cases, where information about the circumstances at the time of the overdose event were unable to be determined in five of the cases. Investigation revealed that there were 192 cases (83%) overall where the decedent was alone at the time of the fatal overdose event (Figure 1). In contrast to this, there were 38 cases (17%) overall where the decedent was with someone else, or there was someone else present to witness the overdose event. However, in half of these cases ($n = 19$), the witness was significantly impaired or incapacitated, commonly because of heroin use at the same time, or was asleep at the time of the fatal heroin overdose. Therefore, there were 19 fatal heroin overdose cases (8%) identified where there was the potential for appropriate and timely intervention by a bystander or witness.

Investigation of the fatal overdose event revealed that the resuscitation was not always attempted, particularly in fatal overdose events that were not witnessed. Calls to EMS for heroin overdose events by bystanders and witnesses in Victoria commonly occur and it was recently reported that there were a total of 3921 heroin-related attendances by paramedics in this region over the two-year study period [21]. However, investigation and data linkage revealed that EMS were called to only 68% ($n = 159$) of the fatal heroin overdose cases. The unwitnessed overdose cases made up all but four of the cases where EMS were not called and it is possible that this may have been because the person was clearly deceased at the time they were discovered.

Additional investigations of the 19 witnessed overdose cases where there was the potential for intervention revealed that appropriate intervention was not attempted in seven of these cases by the designated witness or partner at the time of the overdose. Specifically, there were two cases where the witness to the overdose did not attempt resuscitation at all but rather drove the decedent directly to hospital before resuscitation was attempted by hospital staff. There was also another case where the witness drove the decedent to another location before resuscitation was attempted by persons at that location and EMS called. Two separate cases were also identified where there was a significant delay in resuscitation attempts or EMS being called following the

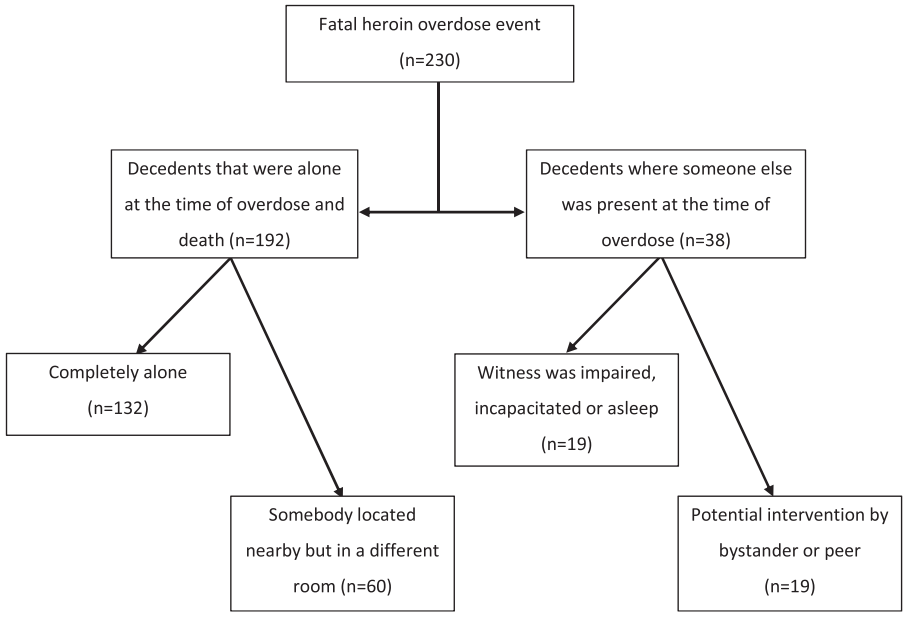

Figure 1. Potential for intervention at the time of the fatal heroin overdose.

witnessed overdose. There were also two cases in this cohort where the overdose occurred in a public place and a passing bystander attempted resuscitation and called EMS because the partner of the decedent was also unconscious at the scene.

Discussion

Despite a range of public health initiatives and harm-reduction strategies, a large number of deaths occur each year as a direct result of heroin use and overdose. Through the detailed forensic investigation of the cohort of heroin-related deaths, this study demonstrated that the vast majority of fatal heroin overdose cases occurred where the decedent was at home and alone at the time of the fatal overdose event. This finding is consistent with previously reported data for fatal heroin overdose cases, including where a potential witness may be physically segregated from the decedent at the time of the overdose event [31–33]. Significantly, this study also demonstrated that in half of the fatal overdose cases where there was a witness or peer located with the decedent at the time of the overdose, they did not have the capacity to provide resuscitation or to administer naloxone because they were incapacitated, unconscious or asleep. These findings highlight two central principles for THN to reduce heroin-related deaths: that naloxone must be available at the location of the overdose; and that there must be a witness or bystander present at the time of the overdose who can provide both timely and meaningful intervention.

An assumption of this study was that naloxone was available to be administered at the time and location of the overdose event. Practically, however, in order to facilitate adequate reach or distribution of naloxone, it has been suggested that THN should be provided or prescribed to at-risk individuals with the aim of approximately 20 times the number of THN-kits distributed as there are opiate-related deaths [26]. This study demonstrated that the wider distribution and greater availability of naloxone alone would not have led to a large reduction in the number of fatal heroin overdose cases in Victoria over the study period. This is principally because in the vast majority of fatal heroin overdose cases the decedent was either alone, or the witness was incapable of providing meaningful and timely intervention. Self-reported studies from heroin users that encompassed both fatal and non-fatal heroin overdose events have previously indicated that witnesses are commonly present and could intervene in most heroin overdose cases [34,35]. Taken together, these findings indicate that it may be more likely that non-fatal heroin overdose events are more likely to be witnessed than fatal overdose cases. There was a very modest 8% of fatal overdose cases identified in the present study where there was the potential for naloxone to be administered by a bystander or witness, and where this may have changed the fatal outcome. Interestingly, this finding is similar to the modelled impact of naloxone distribution in the general population of people who use heroin reported previously, where it was suggested that THN would result in a 6.1% reduction in mortality [36]. Although only a proportion of the cohort of heroin overdose deaths, data from the current study also indicate that the targeting of high-risk populations for THN may also be warranted. Specifically, this would include individuals recently released from prison as well as those individuals leaving abstinence-orientated drug treatment and detoxification programs.

As has been suggested previously, no single intervention is likely to eliminate the risk of heroin overdose or heroin-related deaths [34]. Data from this study suggest that any expectation of a dramatic decrease in the number of overdose deaths associated with THN programs alone in the general heroin-using population are unlikely, but rather would be more effective when used in conjunction with other education, training and harm-reduction strategies. It was demonstrated in this study that in the fatal heroin overdose cases

there was an inadequate peer or witness response to overdose, and in some cases a delay in calling EMS. These findings indicate that broader harm-reduction strategies including reinforcing safe injecting practices including to not inject alone, the training of peers in overdose recognition, the provision of basic life support and calling EMS may independently be associated with improved fatal overdose outcomes. Inadequate supervision and the provision of meaningful or timely intervention including naloxone administration were evident in most of the fatal heroin overdose cases in the present study. This data add weight to the call for supervised injecting facilities in Victoria in order to reduce heroin-overdose deaths, where the establishment of these facilities in other areas has also been demonstrated to be associated with a reduction in the overdose mortality rate in the surrounding region [37,38]. The provision of THN should also be considered as part of an intervention strategy for the management of non-fatal overdose cases, particularly in the current environment of novel synthetic opioids that are prevalent in some regions [23]. Lastly, in order to reduce heroin-related deaths, an important aspect of harm-reduction strategies to complement the provision of THN is the wider need to address the risk of overdose in the first place, including the personal, social and behavioural risks [39].

Limitations

A limitation of the current study is that it is possible that either a witness or additional witnesses were present but not identified as part of the paramedic documentation, police report or coronial investigation. In such cases, the heroin overdose was still unfortunately fatal and therefore if a witness was present but not identified, they were likely incapacitated, incapable or unwilling to provide appropriate and timely intervention. The outcomes of this study would therefore not reasonably be affected by these potential cases. An additional limitation of the current study relates to extrapolation of these findings. This study focused on fatal heroin-toxicity and the impact of THN for other opioid analgesic-related deaths was not examined, where the potential benefits in this cohort may be different and further research is required in this area. A final limitation of the current study was that it was not possible to use a more recent cohort and study period for this investigation.

Conclusion

Heroin-related deaths are a major public health concern and heroin overdose is the leading cause of death for people who use heroin. This study investigated the potential for meaningful and timely bystander intervention in fatal heroin overdose cases, including cases where if naloxone had been available to potentially avert the fatal outcome in these cases. This study demonstrated that the vast majority of fatal heroin overdose cases occurred where the decedent was at home and alone at the time of the fatal overdose event. Where the decedent was with someone else or there was someone else present to witness the overdose event, this study also demonstrated that in half of these cases the witness or peer did not have the capacity to provide resuscitation or to administer naloxone because they were incapacitated, unconscious or asleep. This study demonstrated that THN could have led to a modest reduction in the number of fatal heroin overdose cases in Victoria but might be more effective when used in conjunction with other education, training and harm-reduction strategies.

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Chapter 5: Conclusion

5.1 Overview and impact of findings

Heroin-related deaths are a significant public health concern. However, the extent of this problem as well as the impact of harm-reduction strategies designed to reduce heroin-related mortality are not clearly understood because the number of heroin-related deaths are often underreported or misclassified. Additionally, the safety of non-fatal heroin overdose interventions in the out-of-hospital environment for this population are also not clearly understood because of the issues associated with heroin-related death underreporting. The first aim of this research was to more accurately define and describe deaths involving heroin for improved public health and reporting purposes. **Chapter 2** directly addressed this aim. Investigation of heroin-related deaths in **Publication 1** demonstrated that the unique markers of heroin use such as 6-acetylmorphine (6-AM) are not detected in all cases, and are affected by the time interval between heroin administration and death, which is multifactorial and extremely variable. This publication demonstrated that the attribution of heroin involvement in drug toxicity deaths is inconsistent, even when 6-AM is detected in toxicological samples. A model was developed and validated to assist with the reasonable and consistent attribution of heroin involvement in acute drug toxicity-related deaths as well heroin intoxication-related deaths that encompassed the use of both toxicological and investigative evidence.

Similar to the use of other algorithms in this domain, the developed model in **Publication 1** was designed to support the consistent use of both toxicological and investigative evidence for interpretation and formulation of an opinion where heroin may have been involved. This is particularly relevant in suspected heroin-related deaths where the toxicological evidence must be interpreted in the context of the other clinical or pathological findings in order to arrive at the most logical clinical conclusion, not necessarily what can be definitively proven beyond all doubt. The developed model was designed to assist in providing a holistic view of the evidence and circumstances surrounding death, facilitating a more informed and accurate opinion to be formed. This publication and model enabled the standardisation of the investigative evidence used in order to improve consistency and transparency of the

decision-making process in the attribution of a death to heroin or not. The medico-legal investigation of potential heroin-related deaths can be challenging however, this publication and model allows investigators to quantify the strength of the evidence for heroin use in order to qualify their opinion about whether a death was reasonably attributed to heroin or not. This aspect of the research is significant in attempting to address a long-standing issue in forensic medicine and the accurate capture as well as differentiation of heroin versus morphine-related deaths.

The developed model in **Publication 1** was used to identify heroin-related deaths over a two-year period using the National Coronial Information System (NCIS). Investigation of heroin-related death reporting in **Publication 2** demonstrated the extent of underreporting of these cases. A total of 9060 potential cases were identified, reviewed and assessed based on the weighting of the evidence, with a total of 243 heroin-related death cases identified. By cross-referencing these cases with the Australian Institute of Health and Welfare (AIHW) and Australian Bureau of Statistics (ABS) for heroin-related death data over the same study period, it was demonstrated in **Publication 2** that the actual number of heroin-related deaths in Victoria, Australia, were underreported by 47%. This is an important finding that directly impacts on our understanding of the extent of this significant public health issue, including for the targeting of appropriate funding, interventions or harm-reduction strategies in order to reduce heroin mortality.

The current contributors and causes of the underreporting of these heroin-related deaths were additionally investigated. Findings from this publication also revealed that 40% of all the missed heroin-related death cases resulted from either the attribution of the death to morphine toxicity or with non-specific drug toxicity certification. A further 30% of the missed heroin-related death cases occurred where the cases had been attributed to heroin but there were irregularities in death certification. A final 24% of the missed heroin-related death cases occurred as a result of late initial registration of these deaths to the Registry of Births, Deaths and Marriages, and where these cases were then not assessed by the ABS for classification and coding purposes. The findings from both **Publication 1** and

Publication 2 have already been translated into practice, where the processes for mortality coding by the ABS has been changed as a result of this research as outlined in **Appendix B**.

The second aim of this research was to identify contributors to acute heroin toxicity as well as opportunities for intervention in order to reduce heroin-related mortality. **Chapter 3** addressed this aim. The relationship between the variability in street-level to an overdose risk has been a perplexing problem where most previous studies in this area have failed to demonstrate a direct relationship, despite this relationship seemingly having a logical connection and where regular heroin users believe that this relationship exists. Both **Chapter 3** and **Publication 3** investigated the variability in both quantity and quality of street-level heroin and the relation that this has on the effective dose of heroin contained in these samples.

Publication 3 was the first study to examine the dose of heroin contained in street-level samples, including both the common or typical dose of heroin contained in these samples as well as the proportion of samples that contained a larger dose of heroin than would have been expected by a user. Street-level heroin seizures of ≤150 mg in mass were analysed over a two-year study period by the Victoria Police Forensic Services Department allowing for the dose of heroin contained in these 'cap' presentations to be determined. There were 983 samples analysed and it was demonstrated the 'cap' samples had a median mass of 92 mg (IQR of 43mg), a median purity of 13 % (range 3.6 % to 80.9 %) and contained a median effective dose of 12.0 mg of heroin (IQR 6.6 mg; range 0.4 mg to 111 mg). This study revealed that 8% of samples between 1.5-2 times the median effective dose of heroin, while 6% of samples contained >2 times the typical dose of heroin that may be expected by users of this drug. Importantly, this research identified variation in the dose of heroin contained in street-level samples that had not previously been reported. This publication also highlighted that the impact and relationship between variation in street-level heroin and overdose needs to be reexamined. These findings are also important for heroin market monitoring and harm-reduction strategies associated with variation in the dose of heroin contained in street-level samples as well as

improving our understanding of the safety associated with opioid substitution therapies including methadone and pharmaceutical or prescribed heroin.

The third and final overall aim of this research was to examine the safety and efficacy of acute heroin overdose management in the out-of-hospital environment. **Chapter 4** directly addressed this aim. Specifically, **Publication 4** examined the safety of non-fatal heroin overdose management while **Publication 5** examined the efficacy and issues of Take Home Naloxone (THN) in reducing heroin-overdose deaths. The safety and efficacy of these respective interventions has not clearly been understood fundamentally because of the extent of underreporting of these deaths as highlighted in **Publication 2**. In both of the publications in **Chapter 4**, the heroin-related death cases identified in **Publication 1** were used and cases linked to Ambulance Victoria electronic patient care records using probabilistic data linkage.

The majority of heroin overdose cases are treated in the out-of-hospital environment, and the safety of the treatment of non-fatal heroin overdose in the out-of-hospital environment was investigated in **Publication 4**. There were 243 heroin-related deaths identified over the study period, with 93% (n=225) of these cases matched through probabilistic data linkage with Ambulance Victoria electronic patient care records. An important and unique aspect of this study was the investigation of the direct link between heroin-related deaths and the last episode of care by paramedics for non-fatal heroin overdose, irrespective of whether naloxone had been administered or not and where death may have occurred as a result of acute toxicity, or as a result of heroin intoxication-related misadventure. Data linkage revealed that there were 31 heroin-related deaths with a recent presentation for a non-fatal heroin overdose to paramedics in the month prior to death. Forensic investigation revealed that none of these deaths were related to that episode of care by paramedics, including for 11 individuals that were treated on scene by paramedics but not transported to hospital. In fact, in all of the 31 cases it was revealed that death occurred as a result of a subsequent and unrelated heroin overdose, whether the patient was transported to hospital or not at the time of their last non-fatal heroin overdose managed by paramedics.

Publication 4 demonstrated that the treatment of uncomplicated heroin overdose in the out-of-hospital environment is safe in terms of mortality, where none of the 243 heroin-related deaths were attributable to the treatment but non-transportation of a patient following a heroin overdose. The findings of this publication help to address important safety issues for the management of non-fatal heroin overdose in the community. Moreover, these findings are important for a range of different clinical settings including paramedics and other emergency medical service personnel, the management of patients in supervised injecting rooms, for clinicians providing advice about patients during custody, as well as for information associated with THN programs in the community.

The disproportionately high level of mortality associated with heroin together with heroin overdose being the leading cause of death in this population formed the basis of THN and other similar programs. There is a 'window of opportunity' for intervention in a heroin overdose by witnesses, peers or medically trained staff to provide meaningful intervention, including naloxone administration to reverse the effects of overdose. Various THN programs have been implemented to reduce the number of heroin-related deaths, however data demonstrating the impact of these programs is limited. Measuring the impact of these programs has been challenging and particularly differentiating the impact of naloxone administration between cases where naloxone administration may have averted a fatal outcome, or cases that were likely to be non-fatal anyway. The potential impact of THN in reducing heroin mortality was investigated in **Publication 5**.

Detailed investigation of the circumstances at the time of the fatal heroin overdose event for each of the decedents revealed that the majority of fatal heroin overdose cases occurred at a private residence (n=186, 79%) and where the decedent was also alone at the time of the fatal overdose event (n=192, 83%). There were only 38 cases (17%) where the decedent was with someone else or there was a witness to the overdose event, but in half of these cases the witness was significantly impaired, incapacitated or asleep at the time of the fatal heroin overdose. There were 19 fatal

heroin overdose cases (8%) identified where there was the potential for appropriate and timely intervention by a bystander or witness. This publication was the first to examine the potential for meaningful intervention by witnesses or bystanders with naloxone in order to have potentially changed the outcome in a cohort of heroin-overdose death cases. Importantly, **Publication 5** demonstrated that in the cohort of people who die as a result of heroin overdose, THN may have directly contributed to a modest reduction in these deaths. The effectiveness of THN in reducing heroin-overdose deaths is limited because most fatal overdose events were un-witnessed and where a witness or bystander was present, they were often not capable of providing early and meaningful intervention to avert the fatal outcome. The implications of these findings are important for targeting this cohort in order to understand the efficacy of this harm-reduction strategy in reducing heroin overdose-related mortality.

5.2 Overall strengths and limitations of the thesis

Overall, the research associated with this thesis has contributed a number of unique and valuable insights, however also has similar limitations to other research in this area. The strength of this thesis was primarily derived from the consideration of both scientific and clinical perspectives to the research problems. This was highlighted in **Publication 1** and **Publication 2** where both scientific and clinical data were used to develop a consistent set of criteria for the attribution of a death to heroin, and demonstrate the need for change based on a public health and reporting perspective. This is a long-standing challenge in forensic medicine and this thesis has enabled progress in this area using current data that is commonly collected or common analytical techniques.

The combined scientific and clinical perspectives also enabled when looking at the same data. This was highlighted in **Publication 3** where the application of fundamental clinical principles for drug administration, dosing and clinical toxicology enabled a completely unique perspective on the scientific data associated with

street-level heroin seizures and the potential contribution to overdose. Lastly, the out-of-hospital clinical perspective associated with this thesis also enabled the consideration of theoretical ideas for harm-reduction with an understanding of the real-life challenges associated with their implementation. This was highlighted in **Publication 4** and **Publication 5** where best-intentioned principles such as Take-Home Naloxone were tested from a practical clinical perspective and supported with scientific forensic data.

Overall, a major limitation of this thesis and the conclusions that can be drawn however centre around the fact that because heroin use is illegal and our understanding of the population of people who use heroin is limited in many respects. Long-term dependent users of heroin are commonly in poor health and overdose is also commonly associated with multiple drug use. These aspects provide significant confounding to the identification of other risk factors that may contribute to overdose such as in **Publication 3**. These factors also make clinical safety recommendations following a non-fatal overdose challenging such as in **Publication 4**, and the potential impact of harm-reduction strategies potentially quite variable such as in **Publication 5**. Because of our limited understanding of this population, many years of research, trials and interventions have demonstrated that there is no 'silver bullet' in terms of a harm-reduction strategies that will solve the problem of heroin overdose and death and this was highlighted in **Publication 5**.

Heroin toxicity and fatal heroin overdose is a significant and complex problem. Overall, a significant strength of this thesis involved the detailed examination and identification of all deaths that were reasonably attributed to heroin in Victoria over the study period. This well-defined outcome then formed the basis for other studies where the extent of underreporting, the safety of out-of-hospital management of non-fatal overdose and the potential impact of Take-Home Naloxone could be examined. This research has contributed to our understanding in this field of study overall and from a scientific, clinical and public health perspective.

5.3 Future research directions

The causes as well as extent of the underreporting of heroin-related deaths was investigated and reported in **Chapter 2**. Further research in this area is required in order to examine both the impact, as well as barriers to the adoption of such a model in order to improve the consistency and transparency of attribution and reporting of heroin-related deaths. The detailed investigation of heroin-related deaths also formed the basis of the investigation into the safety and efficacy of heroin overdose clinical management that was investigated in **Chapter 4**. The linkage of these cases with Emergency Medical Services (EMS) data for this chapter enabled the investigation of important and unresolved issues in this area. There are however additional research questions that could be investigated using this methodology. This includes the examination of the characteristics of non-fatal heroin overdose presentations to EMS to aid in the identification of individuals at high-risk of experiencing a fatal heroin overdose. Additional research in this area may also include examination of whether changes in behaviour of in individual and presentation to EMS including deliberate self-harm, acute mental heroin crisis as well as suicidal ideation or attempt may also precede a fatal heroin overdose.

The largest area of future research however centres around the fluctuations in the effective dose of heroin contained in street-level samples that was investigated and reported in **Chapter 3**. Further research is required to determine any specific relationship between the high heroin dose outliers that were identified directly with overdose. Previous research in this area that had focused on aggregate heroin purity data should be reexamined and the effective or equivalent dose of heroin contained in street-level samples used as the measure instead. Understanding this relationship is important for our understanding of all of the contributors and risks for heroin overdose and the reexamination of this relationship is fundamentally important. Street-level heroin market monitoring using the opioid equivalent dose as outlined in **Publication 3** may also help from a public health and overdose prevention strategy particular in areas where street-level heroin may be adulterated or entirely substituted with fentanyl, fentanyl derivatives or Novel Synthetic Opioids (NSO's)

and the equivalent opioid dose administered may exceed the typical dose expected by a user. Finally, the concurrent use of heroin with other central nervous system active drugs, and especially with the concomitant use of benzodiazepines, alcohol and other opioid analgesic drugs is associated with an increased risk of overdose and sudden death. This is an important aspect of heroin toxicity, especially in the context of the identified variation in the dose of heroin contained in street-level samples, and where heroin may be substituted or adulterated with other opioid compounds. This is an additional area that requires further investigation.

5.4 Concluding remarks

Heroin-related deaths are a significant public health problem and the research in this thesis has helped our understanding of the true extent of this problem by improving our understanding of the causes and scale of heroin-related death underreporting. Findings from the research in this thesis provide a unique and significant contribution to our understanding of this issue and add to the robust debate about the most meaningful way of reducing heroin-related mortality through examination of the efficacy and challenges of different harm-reduction strategies. Other aspects of heroin toxicity were also examined by the research in this thesis, including the potential contribution of variation in the quality and quantity of street-level heroin to overdose and the safety of non-fatal heroin overdose management in the community. The potential applicability of these findings are far-reaching and may inform public health policy, be used in clinical decision making in the field and also be used to improve the classification and reporting of heroin-related deaths in forensic medicine.

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Appendix A:

Probabilistic data linkage process

Data linkage

Ambulance Victoria (AV) is the statewide EMS for Victoria. As outlined in **Chapter 4**, Emergency Medical Service (EMS) data was linked for each of the heroin-related death cases identified in **Chapter 2** where available in order to assess the safety and efficacy of out-of-hospital interventions. An outline of the data linkage process was provided in **Publication 4** and **Publication 5**, however detailed to a greater extent in this appendix.

Heroin-related deaths identified and assigned unique identifiers

Heroin-related death cases were first identified through the National Coronial Information System (NCIS) using the criteria outlined in **Publication 1**. Details of the cases to be linked were then provided to the NCIS where a unique identifier (or linkage key) was assigned. For the purposes of data linkage, specific information was provided back to the research team from the NCIS with a unique identifier for each decedent that included: first name, surname, alias, date of birth, age, gender, residential address, location or address of the incident/death and date of death. No other information about the cause or circumstances of death for the decedents are provided with this data. The data linkage information for the decedents along with a unique identifier (or linkage key) was then shared through a secure data transfer process to AV by the research team for the purposes of identifying any prior presentations to AV within the three years preceding death.

Linkage fields for decedents provided to Ambulance Victoria to identify EMS presentations

The data linkage information and unique identifier for the decedents was provided to a nominated team at AV who were independent to the research team. Using the specific identifying information for each decedent, prior emergency presentation to EMS in Victoria for the three years prior to death was investigated. Details of all cases attended by paramedics in Victoria are recorded as an electronic Patient Care Record (ePCR) which is migrated with Computer Aided Dispatch data into the AV

data warehouse. Based on the decedent identifying information, probabilistic matching for EMS presentations for each decedent was then performed by the nominated team at AV. A search of the ePCR database is performed in order to match EMS cases within the study period for each decedent. A register of identified cases for each decedent are then compiled with the following information: case date, response time, scene time, case nature, case description (free text description), final assessment, past history or pre-existing conditions, vital sign survey (initial and final), secondary survey, clinical management (interventions), location type, others at scene and transport fields/variables. The unique identifier (or linkage key) for each decedent was merged with the specific information to be returned for the identified cases. All other case or identifying information for each record was removed.

EMS data from Ambulance Victoria provided to the research team for data linkage

The case data for all of the EMS case presentations over the study period are merged together with the unique identifier (or linkage key) for the decedents was then shared through a secure data transfer process to the research team by AV. Using the unique identifier for each decedent, the research team were then able to perform the data linkage between the coronial data and the EMS data for each case. During this process neither of the two individual data custodians or organisations had access to the other data in relation to any of the decedents, rather the two individual datasets were only linked when returned to the research team with the same unique identifier (or linkage key) from the different datasets for each of the decedents.

Following the data linkage by the research team, all data analysis was conducted using the de-identified information. Furthermore, all data from individual cases collected during the research was pooled with other related cases and analysed at an epidemiological level in order to identify patterns and trends at a population level. To further protect privacy, no individual case or potentially identifying

information was included in any published materials or presented work arising from this research.

Data linkage summary

A summary of the data linkage process is as follows:

1. Heroin-related death cases identified through the NCIS.
2. Identified cases assigned a unique identifier (or linkage key) together with linkage variables by the NCIS and returned to the research team.
3. The research team provide the linkage variables to AV through secure data exchange.
4. The nominated team at AV (separate to the research team) search for EMS cases or presentations for each decedent using the ePCR database.
5. Specific information for the identified EMS cases are merged with the unique identifier (or linkage key) for each decedent, with all other case or identifying information removed.
6. AV provide the EMS data for each unique identifier (or linkage key) to the research team through secure data exchange.
7. The research team merge the coronial and EMS data for each case using the same unique identifier for each of the decedents that was used for the two different datasets in order to perform the data linkage.
8. Data analysis performed with the linked data by the research team using only de-identified information, with no individual case or potentially identifying information included in any published materials or presented work.

Appendix B:

ABS Letter of research impact

Australian Bureau of Statistics

Brisbane Office
[redacted]

[redacted]

ABN 26 331 428 522

Attention: Academic Promotions Committee

To whom it may concern,

My name is Lauren Moran and I am the assistant director of the Health and Vital Statistics Section. My team is responsible for compiling and classifying all causes of death which are registered within Australia each year.

Over the last year, I have worked with Nathan Stam on understanding the potential under-reporting of deaths due to heroin in Australia. As part of this process the ABS Mortality team has worked to understand our role in a connected medical and civil registration system that works to identify and classify drug-related deaths. This improved understanding of our role allowed us to identify improvement areas for the classification and coding of heroin-related deaths in Australia.

Specifically, improvements have been implemented through the work with Nathan by:

- Enhancing our capture of current heroin-related deaths by applying a drug attribution model to cause of death coding processes;
- Enhancing our capture of heroin-related deaths over the last two years by applying the same attribution model to existing opiate deaths and;
- Enhancing our engagement with clients to communicate the issue of heroin-related deaths and efforts occurring to address this.

This project with Nathan has resulted in a more robust drug-related death dataset which will have benefits for researchers and policy formation.

Please contact me if further information is required.

Best Regards,

Lauren

Lauren Moran
Assistant Director, Health and Vital Statistics Section, Australian Bureau of Statistics
[redacted]