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Characteristics and circumstances of heroin and pharmaceutical opioid overdose deaths: Comparison across opioids

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ABSTRACT

Background: Although much is known about the correlates of heroin overdose, less is known about pharmaceutical opioid (PO) overdose. This study aimed to examine correlates of opioid overdose deaths by opioid and compare correlates between opioids.

Methods: Analysis of opioid overdose deaths in Australia between 2000–2015, extracted from the National Coronial Information System (NCIS). The NCIS is an online database of deaths reportable to the coroner, and contains coroner's findings, autopsy and toxicology reports. Deaths were categorized into mutually exclusive groups: 1) Heroin deaths; and 2) PO deaths (excluding heroin). PO deaths were examined by individual opioid.

Results: There were 10,795 opioid overdose deaths over the study period. Relative to deaths occurring in major cities, deaths in regional/remote areas had 15.2 (95 % CI: 11.5–20.2) times the risk of being attributed to pharmaceutical fentanyl than heroin. Relative to deaths among people without a recorded history of chronic pain, deaths among people with a recorded history of chronic pain had a 1.9–10.7-fold increased risk of the death being attributed to POs than heroin. Deaths among people with a recorded history of substance use problems where the opioid was injected prior to death had 7.2 and 1.7 times the risk of being attributed to methadone and pharmaceutical fentanyl (respectively) than heroin.

Conclusions: Findings suggest the need to: educate PO consumers about the risks of overdose at the time of prescribing; increase coverage and engagement in opioid dependence treatment (particularly in regional/remote areas); and increase uptake of take-home naloxone to reduce opioid overdose mortality.

1. Introduction

The number of opioid overdose deaths has increased over the past two decades in many countries (Martins et al., 2015) and especially markedly in North America (Ciccarone, 2017; Fischer et al., 2016, 2018; Hedegaard et al., 2017). Increases in opioid overdose deaths have also been observed across Europe (European Monitoring Centre for Drugs and Drug Addiction, 2018a) and Australia (Roxburgh et al., 2017b).

Risk factors identified for heroin overdose include: injecting drug use, opioid dependence, being male, and not currently receiving treatment for drug dependence (Caudarella et al., 2016; Darke et al., 2011; Mathers et al., 2013; Stoove et al., 2009). Although opioid agonist treatment (e.g. methadone) is generally protective against fatal overdose (Sordo et al., 2017), certain periods such as the first two weeks of treatment carry an increased risk of overdose (Degenhardt et al., 2009; Sordo et al., 2017). Increased retention in opioid agonist treatment also appears to be important in protecting against overdose (Ma et al., 2018). Conversely, there is a strong association between extra-medical use of methadone and methadone overdose death (Jones et al., 2016; Van Hout et al., 2018).

Risk factors associated with overdose from pharmaceutical opioids (POs) primarily used to treat pain (e.g. morphine and oxycodone) have been investigated, focusing on opioid dose (Bohnert et al., 2016; Gomes et al., 2011; Gwira Baumblatt et al., 2014; Zedler et al., 2014), and each opioid's pharmacological properties.

Previous research clearly shows a complex relationship between dose and overdose risk, with many other mediating factors (including pain severity, comorbid mental health problems, and opioid tolerance) likely to be involved (Campbell et al., 2015; Turner and Liang, 2015).

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Methadone deaths, for instance, can occur at low doses during treatment induction for opioid dependence (Sordo et al., 2017).

Opioids differ in potency and liposolubility which may contribute to differential risk in relation to overdose. For example, fentanyl is highly potent and is associated with greater overdose risk than heroin (Latimer et al., 2016), and greater risk compared to other POs (Fox et al., 2018; Zedler et al., 2018). Heroin has been associated with greater overdose risk than oxycodone (Roxburgh et al., 2017a). The liposolubility of different opioids (and hence the rate at which they cross the blood brain barrier) also influences overdose risk (Karch, 2009). Opioids with higher liposolubility (e.g. fentanyl and heroin) (Poyhia and Seppala, 1994; Stanley, 2014) cross the blood brain barrier more rapidly and can produce more rapid and severe respiratory depression. While smaller amounts of more potent opioids may produce fatal effects, there are many factors which can influence an individual's overdose risk.

Aspects related to the nature of opioid use are also associated with overdose. Injecting use and opioid dependence are strong risk factors for overdose (Bohnert et al., 2012; Hser et al., 2017; Zedler et al., 2018), as is extra-medical use of POs (Hall et al., 2008; Lanier et al., 2012; Larance et al., 2011; Yang et al., 2015). In addition, polypharmacy with central nervous system depressants is commonly implicated in opioid overdose, with benzodiazepines and alcohol featuring prominently (Darke, 2011; Fox et al., 2018). Finally, comorbid clinical characteristics such as mental health (Brady et al., 2017; Turner and Liang, 2015; Zedler et al., 2018) and chronic pain (Dilokthornsakul et al., 2016; Zedler et al., 2018; Brady et al., 2017; Dilokthornsakul et al., 2016; Cheatle, 2011; Madadi et al., 2013; Wilcox et al., 2004) are also associated with an increased rate of overdose.

Research to date has largely focused on individual risk factors, such as extra-medical use (Bohnert et al., 2016; Gwira Baumblatt et al., 2014; Yang et al., 2015), clinical characteristics (Bohnert et al., 2012; Lanier et al., 2012), or risks relating to the specific opioid (Fox et al., 2018). Studies investigating multiple risk factors (Madadi et al., 2013; Zedler et al., 2018) have not reported risks by opioid (Madadi et al., 2013) and no study has modelled multiple risk factors while comparing heroin and PO overdose deaths.

Previously we have examined temporal trends in rates of heroin and PO deaths over time, and rates of PO deaths relative to the amount of opioids dispensed (per million oral morphine equivalents) annually (Roxburgh et al., 2017b). Findings showed an increase in PO deaths over time, particularly for pharmaceutical fentanyl (Roxburgh et al., 2017b). In this paper, we examine characteristics of people who died from opioid overdose across a number of clinical domains. Given that the majority of opioid overdose deaths in Australia are now attributed to POs (Roxburgh et al., 2018a, b), understanding how PO deaths differ from heroin deaths may provide important opportunities for clinical intervention.

1.1. Aims

1 To examine correlates of heroin and PO overdose deaths, including demographic and clinical characteristics, and nature of opioid use; and
2 To compare characteristics of people who died from opioid overdose according to the opioid to which the coroner attributed the death.

2. Methods

2.1. Data extraction from the National Coronial Information System

Deaths were extracted from the National Coronial Information System (NCIS), a national online database in Australia that covers all states and territories. All deaths attributable to an opioid overdose, as determined by a coroner, were extracted for inclusion in this study. Deaths are referred to a coroner in Australia in instances where the death is unexpected, due to an accident or injury, or the person died in an unnatural way. Drug-related deaths are defined as being an unnatural cause of death.

Keyword searches were conducted by individual opioid on the Medical Cause of Death fields, as well as the investigative reports (described below). Search strategies are described elsewhere (Roxburgh et al., 2018b). All categories of intent (accidental, intentional and undetermined) were extracted as assigned by the coroner. Deaths where opioids were detected in post-mortem toxicology, but the underlying cause was attributed to another cause (e.g. motor vehicle accident), were excluded. Accordingly, these deaths are those where an opioid overdose, either alone or in combination with other substances, was considered to be the underlying cause of death.

The NCIS contains investigative reports (police, autopsy and coroners' findings) that describe the circumstances of the death, and decedent's history. Police reports describe the scene of death and include medical history obtained from general practitioners and interviews with next of kin/witnesses where possible. Autopsy reports are prepared by forensic pathologists, and reports on the cause of death are prepared by a coroner.

2.2. Categorization of deaths by individual opioid

Deaths were categorized into mutually exclusive groups: 1) deaths that were attributed to illicit opioids (i.e. heroin deaths[1]) either alone, or in combination with POs – hereafter referred to as heroin deaths; and 2) deaths attributed to POs[2] only.

It can be difficult to distinguish between deaths due to codeine, heroin and morphine because they share common metabolites. Earlier work (Roxburgh et al., 2017b, b) describes the methods developed to identify these deaths as accurately as possible. There was a small proportion (7 %, n = 729) of deaths in this study where there was insufficient information to determine if they were attributable to heroin, morphine or codeine overdose. We have categorized these as 'undetermined opioid deaths.' For completeness we have included these deaths in the analysis and results, however, we do not interpret these findings in further detail.

PO deaths were further separated into; 1) buprenorphine only; 2) codeine only; 3) pharmaceutical fentanyl only[3] ; 4) methadone only; 5) morphine only; 6) multiple pharmaceutical opioids; 7) oxycodone only; and 8) tramadol only. This allowed for statistical comparison of independent groups. Table 1 outlines the definitions of each group. While deaths attributed to buprenorphine only (N = 41) were modelled statistically for completeness, we have not interpreted these findings further.

2.3. Measures of correlates

Demographic correlates assessed included: age, gender, and geographic location. These variables are included as standard data items in the NCIS. Postcode where the death occurred was converted to remoteness area in accordance with the Australian Standard Geographic Classification (ASGC) and classified as major city or regional/remote (Australian Bureau of Statistics, 2011).

The remaining measures were derived from examination of the NCIS

[1] Illicit opioid deaths attributed to illicit fentanyl preparations and other illicit opioid analogues were not detected in these data at the time the study was conducted.

[2] Pharmaceutical opioids refer to opioids that are registered for medical use in Australia. With the exception of heroin, a prohibited substance in Australia, the remaining opioids studied in this paper are pharmaceutical opioids.

[3] Data collected from investigative reports indicated that all fentanyl deaths reported in this study related to pharmaceutical fentanyl, and occurred as a result of injecting fentanyl extracted from transdermal patches, or use of transdermal patches applied to the skin. There were no reports of transmucosal administration or chewing of fentanyl patches.

Table 1
Definitions of opioid overdose death categories.

Category of opioid deaths	Definition
Heroin deaths*	Overdose deaths attributed to illicit (heroin) opioids either alone, or in combination with other pharmaceutical opioids.
Pharmaceutical opioid (PO) deaths*	Overdose deaths attributed to pharmaceutical opioids only, excluding heroin.
Undetermined opioid deaths*	Overdose deaths where there was insufficient information to determine if they were attributable to heroin, morphine or codeine.
Sub-categories of Pharmaceutical opioid deaths*	
Buprenorphine only	Overdose deaths attributed to buprenorphine – only opioid detected
Codeine only	Overdose deaths attributed to codeine - only opioid detected
Fentanyl only	Overdose deaths attributed to fentanyl - only opioid detected.
Methadone only	Overdose deaths attributed to methadone – only opioid detected.
Morphine only	Overdose deaths attributed to morphine - only opioid detected.
Multiple opioids	Overdose deaths attributed to multiple pharmaceutical opioids
Oxycodone only	Overdose deaths attributed to oxycodone - only opioid detected
Tramadol only	Overdose deaths attributed to tramadol - only opioid detected

* All of these groups are mutually exclusive.

investigative (toxicology, autopsy and coroner's findings) reports.

Clinical correlates examined included a recorded history of: 1) injecting drug use; 2) substance use problems; 3) mental health problems; and 4) chronic pain problems.

History of injecting drug use was coded where there was mention in the investigative reports of injecting drug use, syringes located at the death scene, or evidence on the decedent's body of intravenous access (excluding medical intervention). *History of substance use problems* was coded where there was mention of problematic drug use in the investigative reports. Some examples include mention of: long-term heroin use, chronic injecting use, a history of 'drug abuse', a history of 'abuse' of prescription medication, buying prescription opioids illicitly, attendance for drug/alcohol treatment, treatment for drug dependence, (including mention of opioid agonist treatments – i.e. methadone or buprenorphine). *Mental health problems* were coded if there was mention of a diagnosis of a mental health condition (e.g. depression, bipolar, personality disorder, post-traumatic stress disorder, schizophrenia, anxiety), or treatment with a mental health professional/counselling service for a mental health problem. *Chronic pain problems* were coded where there was mention of a history of chronic injuries, accidents, or chronic (cancer and non-cancer) pain.

Nature of opioid use included recorded mentions of: 1) whether the opioid was injected prior to death; 2) if the opioid was prescribed to the decedent; and 3) whether alcohol or benzodiazepines were detected in post-mortem toxicology and reported by the coroner as contributing to the death.

Opioid injected prior to death was coded where there was mention in investigative reports of recent intravenous access (excluding medical intervention), needles and/or syringes being located on/near the body, or eye-witness reports that the decedent had injected prior to death. *Opioid prescribed* was coded where prescriptions/medications were found with the decedent's name, or a treating practitioner confirmed the decedent was prescribed medication. *Alcohol/benzodiazepines contributing* was coded where toxicology and coroner's reports, or the medical cause of death, listed alcohol or benzodiazepines as contributing to the death.

Geographic location was coded as major city/regional and remote (0,1). All other correlates were coded as not recorded/recorded (0,1).

2.4. Data analysis

Analyses were conducted using SAS version 9.4 (SAS Institute Inc, 2016). Demographic and clinical correlates, and nature of opioid use are presented descriptively. Multinomial logistic regression was used to calculate unadjusted and adjusted relative risk ratios (RRRs) and 95 % confidence intervals (95 % CI) for correlates of deaths according to the opioid to which the coroner attributed the death.

Opioid prescribed was excluded from the multivariable analysis as codeine was available on prescription as well as over the counter in Australia at the time of the study (Therapeutic Goods Administration, 2017). This resulted in missing data in a large proportion of codeine deaths (Roxburgh et al., 2015).

3. Results

A total of 10,795 opioid overdose deaths were identified between 2000 and 2015. Just over half were attributed to POs. One-third were attributed to heroin overdose, either alone (n = 3352 - 92 %), or in combination with another PO (n = 297 – 8 %; predominantly methadone – n = 205) (Table 2). The remaining deaths were 'undetermined opioid deaths'. PO deaths were largely attributed to methadone only, multiple opioids, oxycodone only, morphine only, and codeine only (Table 3).

Those who overdosed on heroin were typically younger (median 34 years) than those who overdosed on POs only (with the exception of pharmaceutical fentanyl) (Tables 2 and 3). A recorded history of injecting drug use was evident in 90 % of heroin (Table 2), 63 % of pharmaceutical fentanyl, and 55 % of methadone deaths (Table 3). Opioids were prescribed in 59 % of tramadol and 53 % of oxycodone deaths. Fewer than half of the remaining PO deaths had a record of an opioid being prescribed prior to death (Table 3).

History of injecting drug use was excluded from the multivariable analysis as it was highly correlated with *opioid injected* ($r = 0.759$, $p < .001$). In the adjusted model (Table 4), relative to deaths among females, deaths among males had 0.38-0.71 times the risk of being attributed to a PO (with the exception of pharmaceutical fentanyl) than heroin. This difference was particularly evident for overdose deaths attributed to codeine (aRRR: 0.38, 95 % CI: 0.31-0.46) and multiple opioids (aRRR: 0.48, 95 % CI: 0.40-0.58).

Relative to deaths that occurred in major cities, deaths occurring in regional/remote areas had 5.96–15.25 times the risk of being attributed to a PO than heroin, particularly fentanyl (e.g. aRRR for fentanyl: 15.25, 95 % CI: 11.50–20.23).

Relative to deaths without a recorded history of chronic pain problems, deaths with a recorded history of these conditions had increased relative risk of being attributed to a PO than heroin, particularly multiple opioids (aRRR: 9.40; 95 % CI: 7.34–12.02) and oxycodone (aRRR: 10.71; 95 % CI: 8.37–13.71).

An interaction between substance use problems and whether the opioid was injected prior to death was observed in the multivariable model.

Relative to those without a recorded history of substance use problems, deaths with a history of substance use problems (irrespective of whether the opioid was injected prior to death) generally had a decreased risk of being attributed to a PO than heroin (with the exception of pharmaceutical fentanyl and methadone). Deaths with a recorded

Table 2
Correlates of opioid overdose deaths - descriptive analysis.

	Total Opioid Deaths		Heroin Deaths		Undetermined opioid deaths		PO deaths	
Characteristic	N	%	N	%	N	%	N	%
	10,795	100	3648	34	729	7	6418	59
Gender (Male)	7431	69	2994	82	533	71	3904	61
Median age yrs range	39	14-98	34	14-77	38	16-90	43	14-98
14-34 years	3902	36	1891	52	279	38	1732	27
35-44 years	3105	29	1105	30	229	31	1771	27
45-54 years	2285	21	520	14	163	22	1602	25
55 and over	1490	14	130	4	58	8	1302	20
Major City	8210	76	3371	93	553	76	4286	67
Regional/Remote	2545	24	265	7	176	24	2106	33
Mental health problems documented	4423	41	1088	30	242	33	3093	48
Chronic pain conditions documented	2441	23	125	3	50	7	2266	35
Substance use problems documented	6136	57	2844	78	348	48	2944	46
History of injecting drug use	5743	53	3278	90	358	49	2107	33
Opioid prescribed	N/A		N/A	N/A	61	8	2537	39
Opioid injected	4931	46	3215	88	304	42	1422	22
Alcohol contributory factor	2296	21	834	23	160	22	1302	20
Benzodiazepines contributory factor	4098	38	1019	28	220	30	2859	45
Intent								
Accidental	7442	69	3146	86	522	71	3774	59
Intentional	1729	16	200	6	78	11	1451	23
Undetermined	1624	15	302	8	129	18	1193	18

history of substance use problems (relative to deaths without this history) had 0.47 (where the opioid had not been injected prior to death), and 1.72 (where the opioid had been injected) times the risk of being attributed to pharmaceutical fentanyl than heroin. Relative to deaths without a recorded history of substance use problems, deaths with this history had 1.66 (where the opioid had not been injected prior to death), and 7.19 times (where the opioid had been injected) the risk of being attributed to methadone than heroin. (Table 4).

Relative to deaths that were determined by the coroner to be accidental, those determined to be intentional deaths had an increased risk of being attributed to POs (with the exception of pharmaceutical fentanyl and methadone) than heroin, particularly codeine (aRRR:5.59, 95 % CI: 4.28, 7.29).

Relative to deaths where benzodiazepines were not deemed to be a contributory factor, deaths involving benzodiazepines had an increased risk of being attributed to POs (with the exception of pharmaceutical fentanyl) than heroin. This was most pronounced for multiple opioids (aRRR: 4.86, 95 % CI: 4.00–5.90). The contribution of alcohol varied across the groups.

4. Discussion

This paper investigated the characteristics and circumstances of opioid overdose deaths and potential differences between opioids. Several differences were evident in the nature of deaths attributed to heroin and POs (with the exception of pharmaceutical fentanyl). Deaths among young males, particularly those with substance use problems that had injected the opioid prior to death, were associated with increased relative risk of being attributed to heroin than PO deaths. Deaths occurring in major cities also had an increased relative risk of being attributed to heroin than POs. In contrast, deaths occurring in regional/remote had an increased relative risk of being attributed to a PO, particularly pharmaceutical fentanyl. Deaths with a recorded history of mental health, chronic pain, and benzodiazepines as a contributory factor, and deaths determined to be intentional, all had an increased relative risk of being attributed to POs than heroin.

There were also important differences across individual POs. Pharmaceutical fentanyl deaths (56 %) were more common in regional/remote areas than heroin deaths (7 %). These findings are consistent with research showing higher rates of pharmaceutical fentanyl utilisation in regional/remote areas of Australia (Gisev et al., 2018). Higher availability of pharmaceutical fentanyl in these locations may potentially lead to increased diversion and extra medical use, a finding documented in North America (Keyes et al., 2014; Paulozzi et al., 2006). Only one-third of the pharmaceutical fentanyl deaths had evidence of fentanyl being prescribed to the person prior to death. It is therefore possible that diverted pharmaceutical fentanyl played a role in some of these deaths.

Comparing findings for fentanyl deaths to international trends, much of the recent increase in opioid overdose deaths in North America has been driven by illicitly manufactured fentanyl. Deaths attributed to illicitly manufactured fentanyl now outnumber heroin in North America (Ciccarone, 2017; Fischer et al., 2018; Hedegaard et al., 2017; Young et al., 2015). Deaths from illicitly manufactured fentanyl have also occurred in parts of Europe (European Monitoring Centre for Drugs and Drug Addiction, 2018b). There is not yet evidence that illicitly manufactured fentanyl deaths, or deaths attributed to fentanyl-laced heroin, have occurred in large numbers in Australia (Moss et al., 2017; Rodda et al., 2017).

One of the most commonly reported predictors of overdose, recorded history of substance use problems (Brady et al., 2017), was highly prevalent among all opioid overdose deaths in our study. Substance use problems were prevalent among heroin, pharmaceutical fentanyl and methadone deaths, particularly among decedents who had injected the opioid prior to death. This suggests that extra-medical use appears to be a factor in both the pharmaceutical fentanyl and methadone deaths. Nonetheless, almost one-third of the deaths attributed to other POs also had substance use problems recorded.

The findings from this study have important implications. Mental health and chronic pain problems, and deaths that were intentional, differentiated the PO deaths from heroin deaths, which has implications for clinical practice. High rates of mental health problems have been documented among chronic pain patients (Scott et al., 2010). There is a complex relationship between mental health, chronic pain and overdose, with mental health problems being associated with a higher likelihood of being prescribed an opioid (Davis et al., 2017), and at higher doses. Assessment and early intervention for mental health problems and suicide risk among patients presenting for chronic pain treatment is essential prior to prescribing opioids, particularly given the intersect between chronic pain, mental health and suicide (Oquendo and Volkow, 2018). Assessment of substance use problems among chronic pain patients is also important, given their high rate of occurrence in this population (Campbell et al., 2015; Tang and Crane, 2006). Finally, education about the risk of overdose is critical at the time of

Table 3
Correlates of pharmaceutical opioid overdose deaths by individual opioid - descriptive analysis.

	Total PO deaths		Methadone only		Fentanyl Only		Morphine Only		Multiple Opioids		Oxycodone Only		Tramadol Only		Codeine Only		Buprenorphine Only	
Characteristic	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	6418	59	1573	24	267	4	1000	15	1190	18	1092	17	335	5	921	14	40	< 1
Gender (Male)	3904	61	1119	71	203	76	612	61	644	54	687	63	184	55	422	46	33	83
Median age yrs range	43	14-98	38	14-75	40	17-79	47	15-98	44	14-92	44	15-90	47	14-88	46	14-93	30	18-56
14-34 years	1732	27	597	38	83	31	231	23	284	24	262	24	67	20	182	20	26	65
35-44 years	1771	27	507	32	92	35	218	22	343	29	291	27	82	25	226	25	12	29
45-54 years	1602	25	356	23	58	22	238	24	333	28	282	26	83	25	251	27	NP	NP
55 and over	1302	20	112	7	31	12	312	31	228	19	253	23	103	30	261	28	NP	NP
Major City	4286	67	1152	73	116	44	612	61	769	65	739	68	221	66	645	70	32	80
Regional/Remote	2106	33	405	26	150	56	386	39	419	35	351	32	114	34	275	30	6	15
Mental health problems documented	3093	48	622	39	104	39	459	46	615	52	575	53	176	53	525	57	17	42
Chronic pain conditions documented	2266	35	204	13	87	33	411	41	570	48	529	48	160	48	304	33	NP	NP
Substance use problems documented	2944	46	1070	68	161	60	340	34	560	47	413	38	97	29	271	29	32	80
History of injecting drug use	2107	33	864	55	167	63	291	29	363	31	302	28	36	11	56	6	28	70
Opioid prescribed	2537	39	641	41	88	33	465	46	494	41	573	53	199	59	N/A	N/A	8	20
Opioid injected	1422	22	494	31	154	58	251	25	254	21	228	21	10	3	8	< 1	13	32
Alcohol contributory factor	1302	20	232	15	34	13	156	16	238	20	338	31	47	14	243	26	14	35
Benzodiazepines contributory factor	2859	45	624	40	66	25	311	31	781	66	476	44	107	32	471	51	23	58
Intent																		
Accidental	3774	59	1190	76	189	71	542	54	748	63	589	54	155	46	328	36	33	83
Intentional	1451	23	124	8	25	9	248	25	256	21	300	27	109	33	388	42	NP	NP
Undetermined	1193	18	259	16	53	20	210	21	186	16	203	19	71	21	205	22	NP	NP

NP – not published due to small numbers.

Table 4
Correlates of opioid overdose deaths – multivariable analysis.

Characteristic	Methadone only vs Heroin (ref) aRRR (95% CI)	Fentanyl Only vs Heroin (ref) aRRR (95% CI)	Morphine Only vs Heroin (ref) aRRR (95% CI)	Multiple Opioids vs Heroin (ref) aRRR (95% CI)	Oxycodone Only vs Heroin (ref) aRRR (95% CI)	Tramadol Only vs Heroin (ref) aRRR (95% CI)	Codeine Only vs Heroin (ref) aRRR (95% CI)
Gender (Male)	**0.71 (0.60, 0.84)**	0.90 (0.65, 1.23)	**0.64 (0.53, 0.77)**	**0.48 (0.40, 0.58)**	**0.68 (0.56, 0.82)**	**0.57 (0.44, 0.74)**	**0.38 (0.31, 0.46)**
Age							
15–34 years	REF	REF	REF	REF	REF	REF	REF
35–44 years	1.26 (1.07, 1.49)	1.47 (1.06, 2.03)	1.14 (0.91, 1.42)	1.39 (1.13, 1.71)	1.21 (0.98, 1.49)	1.30 (0.91, 1.87)	**1.32 (1.03, 1.70)**
45–54 years	1.50 (1.24, 1.83)	1.66 (1.14, 2.42)	**1.86 (1.47, 2.36)**	1.92 (1.53, 2.42)	**1.62 (1.28, 2.05)**	**1.69 (1.17, 2.45)**	**1.86 (1.43, 2.42)**
55 and over	1.04 (0.76, 1.42)	1.95 (1.18, 3.21)	**3.89 (2.87, 5.28)**	2.36 (1.72, 3.24)	**2.43 (1.78, 3.32)**	**2.88 (1.90, 4.36)**	**2.89 (2.08, 4.02)**
Major city	REF	REF	REF	REF	REF	REF	REF
Regional/remote	4.61 (3.82, 5.56)	15.25 (11.50, 20.23)	**7.89 (6.44, 9.67)**	**7.19 (5.87, 8.81)**	**5.96 (4.85, 7.33)**	**6.70 (5.04, 8.91)**	**5.72 (4.56, 7.17)**
Mental health problems documented	**1.23 (1.06, 1.42)**	**1.47 (1.11, 1.94)**	**1.62 (1.35, 1.93)**	**1.45 (1.22, 1.72)**	**1.78 (1.50, 2.12)**	**1.78 (1.37, 2.32)**	**1.86 (1.53, 2.25)**
Chronic pain conditions documented	**1.90 (1.47, 2.46)**	**7.34 (5.22, 10.33)**	**7.30 (5.68, 9.38)**	**9.40 (7.34, 12.02)**	**10.71 (8.37, 13.71)**	**8.06 (5.88, 11.04)**	**4.16 (3.18, 5.43)**
Substance use problems*Opioid not injected#	**1.66 (1.31, 2.10)**	**0.47 (0.28, 0.79)**	**0.48 (0.36, 0.64)**	0.84 (0.65, 1.09)	**0.61 (0.47, 0.80)**	0.73 (0.52, 1.02)	**0.75 (0.58, 0.98)**
Substance use problems*Opioid injected	**7.19 (4.01, 12.90)**	**1.72 (1.04, 2.93)**	**0.64 (0.46, 0.89)**	1.13 (0.75, 1.70)	**0.69 (0.48, 0.97)**	0.81 (0.17, 3.88)	0.32 (0.07, 1.35)
Alcohol contributed	**0.53 (0.44, 0.64)**	**0.56 (0.38, 0.82)**	**0.76 (0.61, 0.95)**	0.87 (0.71, 1.07)	**1.77 (1.46, 2.13)**	**0.68 (0.48, 0.96)**	**1.39 (1.12, 1.73)**
Benzodiazepines contributed	**1.74 (1.50, 2.02)**	0.94 (0.69, 1.28)	**1.44 (1.20, 1.72)**	**5.38 (4.53, 6.40)**	**2.13 (1.79, 2.54)**	**1.44 (1.10, 1.89)**	**3.12 (2.58, 3.78)**
Intent							
AccidentalAccidental	REF	REF	REF	REF	REF	REF	REF
IntentionalIntentional	0.90 (0.68, 1.18)	1.27 (0.79, 2.05)	**2.62 (2.02, 3.40)**	**2.31 (1.78, 2.99)**	**3.16 (2.45, 4.07)**	**3.44 (2.46, 4.81)**	**5.59 (4.28, 7.29)**
UndeterminedUndetermined	**1.31 (1.06, 1.62)**	**1.65 (1.15, 2.37)**	**1.92 (1.51, 2.43)**	**1.39 (1.09, 1.77)**	**1.85 (1.45, 2.34)**	**2.02 (1.44, 2.83)**	**2.88 (2.23, 3.73)**

prescribing pharmaceutical opioids.

Consistent with previous national and international studies (Lalic et al., 2018; Pham et al., 2018), substantial proportions of the PO deaths recorded benzodiazepines as contributing to the death, despite prescribing guidelines suggesting that clinicians avoid prescribing benzodiazepines and opioids concurrently (Dowell et al., 2016; Royal Australasian College of Physicians, 2009). More judicious prescribing for this group is warranted, particularly avoiding co-prescribing benzodiazepines.

The relatively high rates of injecting recorded for the pharmaceutical fentanyl deaths is concerning. Fentanyl is higher in potency and liposolubility, relative to other pharmaceutical opioids (Therapeutic Guidelines Limited, 2015), and is more rapidly available when injected (Karch, 2009). Further, extraction of pharmaceutical fentanyl from patches for injection is imprecise, with little control over the dose, further increasing the risk of overdose (Firestone et al., 2009). Continued education about the risks involved when fentanyl is injected is critical.

Substance use problems, although more common among heroin, pharmaceutical fentanyl and methadone deaths, were also prevalent among the other PO deaths, indicating the need for several strategies targeting both medical and extra-medical use of POs. These include: assessment of substance use problems prior to prescribing; close monitoring of the development of problematic patterns of opioid use among those being treated with pharmaceutical opioids for chronic pain; and increased coverage, engagement and retention in opioid dependence treatment in Australia. Engagement and retention in treatment have both been identified as protective factors for opioid overdose among people who are being treated for opioid dependence (Sordo et al., 2017). Some Australians being treated for chronic pain are experiencing problems with their PO use (Campbell et al., 2015), however, they comprise a very small proportion of those accessing treatment for opioid dependence (Nielsen et al., 2011). Australian research has shown that unmet demand for opioid dependence treatment is higher in regional/remote areas than major cities (Holliday et al., 2013; Nielsen et al., 2015). Increased resourcing of treatment in these areas may reduce the disproportionate number of fentanyl deaths in these locations.

Australian research has also shown that increasing opioid overdose deaths (Roxburgh et al., 2017b) are occurring alongside increased opioid prescribing (Karanges et al., 2016). While more judicious prescribing of POs may be warranted, this needs to be balanced with the need to ensure continuity of care for those patients who require continued access to these medications and providing access to opioid agonist treatment as appropriate. Prescription drug monitoring programs (PDMPs) are important mechanisms to encourage the judicious prescribing of POs. Two jurisdictions in Australia currently have operational PDMPs, with plans for the implementation of a national system currently underway.

Finally, increasing awareness, and uptake, of take-home naloxone, now available over the counter in Australia (Therapeutic Goods Administration, 2015), is important. More than 26,000 overdoses between 1996 and 2014 were successfully reversed in the United States with naloxone (Wheeler et al., 2015). Health care professionals have an important role to play in encouraging patients they consider to be at high risk for overdose to obtain take-home naloxone. Evaluation of the uptake, use, and outcomes of take-home naloxone programs in Australia will be important. Naloxone is a life-saving treatment, and one strategy that should be readily accessible in order to reduce opioid overdose mortality.

A multifaceted response to reduce opioid overdose deaths in Australia is crucial. The experience in United States shows that restricting pharmaceutical opioid prescribing in isolation created problems for a large group of opioid dependent people (Beletsky and Davis, 2017), pushing some to initiate illicit opioid use (Cicero et al., 2014; Compton et al., 2016). While there is undoubtedly a range of other complex economic and social factors implicated (Dasgupta et al., 2018),

the large numbers of illicitly manufactured fentanyl deaths, and the resurgence in heroin deaths in North America (Hedegaard et al., 2017), should serve as important warnings for Australia.

4.1. Strengths and limitations

A major strength of this study was the ability to investigate deaths due to pharmaceutical opioids (e.g. fentanyl, morphine, tramadol) separately, which is not possible using deaths data that are coded under the current ICD-10 coding system (World Health Organization, 2010).

Another major strength was the use of investigative reports. This allowed the collection of data about the circumstances of the death, including clinical correlates and the nature of opioid use, that provided important context on the risks associated with overdose deaths.

Limitations also need to be considered. Despite undertaking a systematic review of all available investigative reports, there were jurisdictional differences in the availability, quality and completeness of these reports. NCIS case attachment statistics as of 1 June 2017 show report availability differed by jurisdiction, ranging from 25 % for toxicology reports to 100 % of police reports (http://www.ncis.org.au/wp-content/uploads/2017/06/Document-Attachment-Statistics.pdf).
Given such variability, it is likely that the prevalence of diversion of opioids (with information on the opioid being prescribed not always available) has been overestimated. Conversely, the prevalence of mental health, substance use, and chronic pain problems among decedents has likely been underestimated. The underestimation of mental health problems among heroin decedents may be greater than for PO decedents because they may not have been in contact with medical services, and therefore associated reports would not be available in coronial records. The recording of details about prescribed medication and clinical background of the deceased as part of the coronial investigation is complex. This information is not always available, or may not be relevant to the investigation. Incompleteness of data on clinical characteristics is an inherent limitation of studies that rely on coronial data. Any estimates of these characteristics will be conservative. Previous research on the prevalence of mental health problems among heroin users (33–50%) (Darke, 2011) and in patients prescribed POs for chronic pain (50 %) (Campbell et al., 2016), however, shows remarkably similar findings to the current study (30 % - heroin deaths; 52 % - PO deaths).

This study did not include information on opioid dose (an important factor influencing overdose risk), or duration of opioid use (an important factor in the development of substance use problems). Pain severity was also not investigated in this study.

Finally, given the complexities in coronial processes, there is often a time lag between deaths and data being made available on the NCIS. Unfortunately, this may impact findings in relation to new and emerging opioids, such as illicitly manufactured fentanyl, and deaths related to these opioids.

4.2. Conclusions

This study offered unique findings on a range of characteristics associated with opioid overdose deaths according to the opioid to which the coroner attributed the death. Pharmaceutical fentanyl, heroin and methadone deaths were similar with respect to a recorded history of substance use problems, particularly in the context of the opioid being injected prior to death. There were also differences, with pharmaceutical fentanyl deaths more prevalent in regional/remote areas than heroin deaths. Recorded histories of mental health and chronic pain problems, and deaths determined to be intentional, were more prevalent among people who died as a result of PO overdose.

Strategies in responding to opioid overdose deaths include: education among those being prescribed POs about the risks of overdose; increasing coverage, engagement and retention in opioid dependence treatment, particularly in regional/remote areas in Australia; and increasing the uptake of take-home naloxone.

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Contributors

AR developed the idea for the manuscript in discussion with LD, conducted analyses and drafted the manuscript for comment. WH provided comment on successive drafts of the manuscript. NG provided guidance on analysis and interpretation of the results and assisted in drafting the revised version for submission. LD provided guidance on the overall content and focus of the manuscript, interpretation of the findings, and commented on successive drafts.

All authors have approved the final manuscript for submission.

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Declaration of Competing Interest

LD has received untied educational grants from Reckitt Benckiser/Indivior for post-marketing surveillance of buprenorphine-naloxone tablets and film in the treatment of opioid dependence in Australia, development of an opioid-related behaviour scale, and a study examining opioid substitution therapy among chronic non-cancer pain patients. **LD** has received untied educational grant funding from Mundipharma for post-marketing surveillance of Reformulated OxyContin® in Australia. **LD** has received an untied educational grant from Indivior to examine the safety of pharmaceutical opioids, and measures to improve patient safety. None of the companies listed had any knowledge or involvement in this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.06.035.

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