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Trends in heroin and pharmaceutical opioid overdose deaths in Australia

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ABSTRACT

Background: There has been international concern over the rise in fatal pharmaceutical opioid overdose rates, driven by increased opioid analgesic prescribing. The current study aimed to examine trends in opioid overdose deaths by: 1) opioid type (heroin and pharmaceutical opioids); and 2) age, gender, and intent of the death assigned by the coroner.

Methods: Analysis of data from the National Coronial Information System (NCIS) of opioid overdose deaths occurring between 2001 and 2012.

Results: Deaths occurred predominantly (98%) among Australians aged 15–74 years. Approximately two-thirds of the decedents (68%) were male. The heroin overdose death rate remains unchanged over the period; these were more likely to occur among males. Pharmaceutical opioid overdose deaths increased during the study period (from 21.9 per million population in 2001–36.2), and in 2012 they occurred at 2.5 times the incident rate of heroin overdose deaths. Increases in pharmaceutical opioid deaths were largely driven by accidental overdoses. They were more likely to occur among males than females, and highest among Australians aged 45–54 years. Rates of fentanyl deaths in particular showed an increase over the study period (from a very small number at the beginning of the period) but in 2012 rates of morphine deaths were higher than those for oxycodone, fentanyl and tramadol.

Conclusions: Given the increase in rates of pharmaceutical opioid overdose deaths, it is imperative to implement strategies to reduce pharmaceutical opioid-related mortality, including more restrictive prescribing practices and increasing access to treatment for opioid dependence.

1. Introduction

Research has found that among illicit drugs the opioids make the largest contribution to the global burden of disease (Degenhardt et al., 2013). This is largely because of the substantial contribution that opioids make to premature mortality from fatal opioid overdoses, liver and cardiovascular disease, motor vehicle accidents, homicide and assault (Degenhardt et al., 2011).

In the United States and parts of Canada, the type of opioid predominantly involved in overdose deaths shifted from heroin in the 1990s to pharmaceutical opioids by 2002 (Paulozzi et al., 2006; Fischer and Rehm, 2011; Fischer et al., 2012; Rudd et al., 2016). Several factors have driven this trend. Firstly, pharmaceutical opioid prescribing has increased dramatically in both the United States and Canada (Bohnert et al., 2011, Valenstein et al., 2011Bohnert et al., 2011, Valenstein et al., 2011; Fischer and Rehm, 2011). Second, pharmaceutical opioid use has increased among people who use illicit drugs, with North American data showing that pharmaceutical opioid use among this group had surpassed that of heroin (Fischer and Keates 2012; Fischer et al., 2013).

There has been an almost four-fold increase in pharmaceutical opioid utilisation in Australia between 1990 and 2014 (Karanges et al., 2016). In 2013, codeine, oxycodone, and buprenorphine were the most commonly sold opioids (Degenhardt et al., 2016). Non-medical use of analgesics has increased over time, predominantly among Australians aged 30–49 years (Australian, 2014). Non-medical use of pharmaceutical opioids among people who inject drugs constitutes a minority of opioid use (ranging from 10% for fentanyl to 27% for morphine).

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Heroin continues to dominate as the opioid of choice (46%) and the opioid most prevalently injected (56%) (Stafford and Breen, 2016). Research among Australians prescribed pharmaceutical opioids for chronic non-cancer pain shows that significant minorities of this population meet criteria for lifetime (8.5%) and past year (4.7%) pharmaceutical opioid dependence, and that the consumption of higher doses is associated with higher odds of opioid dependence (Campbell et al., 2015). In addition, those consuming higher doses had considerably more complex profiles with respect to physical and mental health, and greater social disadvantage. These findings together indicate the emergence of problematic use of pharmaceutical opioids in Australia, and a broader public health burden with respect to reduced functioning and markers for increased risk of opioid overdose (Campbell et al., 2015). This paper examines fatal overdoses related to opioids within Australia. Given that heroin continues to be the predominant opioid used among people who inject drugs in Australia, the paper compares rates of fatal heroin and fatal pharmaceutical opioid overdose.

This paper documents trends in heroin and pharmaceutical opioid overdose deaths in Australia during the period 2001–2012. In particular, it examines differences in heroin and pharmaceutical opioid overdose deaths with respect to age, gender, and whether the death was assigned as intentional or accidental by the coroner.

1.1. Aims

1) To examine trends in opioid overdose deaths for the period 2001–2012, attributable to heroin and pharmaceutical opioids;.
2) To examine trends in rates of pharmaceutical opioid overdose deaths per 100,000 Oral Morphine Equivalent (OME) grams dispensed each year; and.
3) To examine trends in opioid overdose deaths by age, gender and intention (accidental, intentional, or not determined).

2. Methods

2.1. National coronial information system

We extracted data on opioid overdose deaths from the National Coronial Information System. This is an online database that records all deaths referred to the coroner. Deaths are referred to a coroner in Australia where they are unexpected, due to an accident or injury, or the person died in an unnatural way. The NCIS includes records of deaths that occur in hospital following an overdose. Drug related deaths are defined as being an unnatural cause of death. The data contain results of toxicology analyses, pathology analyses, police reports, and findings made by the coroner (Degenhardt and Dietze, 2005). The NCIS has previously been used to answer various research questions including analysis of particular types of death, deaths among particular populations, intentional deaths, and circumstances involved (Bugeja et al., 2016). We obtained ethics approval to access and report on these data from the University of New South Wales Human Research Ethics Committee HC 13081.

2.2. Nature of overdose deaths

We categorised opioid overdose deaths into 3 categories: 1) heroin overdose deaths (which included both deaths attributed to heroin overdose alone and deaths attributed to a combination of heroin and pharmaceutical opioids); 2) pharmaceutical opioid overdose deaths in which heroin was not involved; and 3) heroin/morphine overdose deaths, where there was insufficient information to determine if the death was due to heroin or morphine overdose. With respect to the heroin overdose deaths, methadone (used to treat opioid dependence) was the pharmaceutical opioid most commonly identified among deaths involving a combination of heroin and pharmaceutical opioids. We categorised heroin deaths, with or without pharmaceutical opioids as deaths that involved the presence of an illicit opioid (i.e., heroin).

We only included deaths where an opioid overdose, either in combination with other substances or opioids alone, was considered to be the underlying cause of death, that is, drug overdose initiated the train of events that led directly to death (World Health Organization, 2016). We defined heroin overdose deaths as deaths where heroin toxicity was determined by the coroner to be the underlying cause of death. Pharmaceutical opioid overdose deaths were similarly defined as deaths in which toxicity due to pharmaceutical opioids was determined by the coroner to be the underlying cause of death.

Pharmaceutical opioid deaths were further categorised by opioid type (e.g., methadone, fentanyl, etc.), where the coroner concluded that the deaths were due to toxicity of these opioids. We did not include deaths in which the presence of heroin or pharmaceutical opioids was recorded in the toxicology, but the coroner did not consider them to have contributed to the death.

2.3. Intent of death

We summarised the role of intent in the death as assigned by the coroner into three categories; 1) accidental, where there was no information to suggest that the decedent intended on taking their own life; 2) intentional, where there was information that the decedent deliberately took their own life; and 3) not determined, where intent was assigned by the coroner to one of the following categories; ‘unlikely to be known’, ‘not determined’ or was left blank.

2.4. Rates of death in the population

We restricted our analysis to cases aged between 15 and 74 years as 98% of opioid overdose deaths occurred within this age range. We calculated death rates per million population aged 15–74 using Australian Bureau of Statistics estimates of the resident population of Australia as at June each year as the denominator (Australian Bureau of Statistics, 2012).

2.5. Rates of death in relation to pharmaceutical opioid utilisation

We calculated rates of opioid deaths per 100,000 Oral Morphine Equivalent (OME) grams dispensed in each year, in order to examine and compare overdose deaths for morphine, oxycodone, fentanyl and tramadol in relation to their utilisation levels in the community. To do this, we obtained dispensing records for opioids subsidised through the Australian Pharmaceutical Benefits Scheme (PBS) and Repatriation Schedule of Pharmaceutical Benefits (RPBS) from the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee (Karanges et al., 2016). These data include records of all opioid prescriptions dispensed under the PBS and RPBS as well as estimates of non-subsidised under co-payment and private prescriptions (obtained from a sample of approximately 370 community pharmacies). For further information on data parameters please refer to Mellish et al. (2015). Dispensed quantities of each opioid were summed and converted to OME grams in line with previously published work (Nielsen et al., 2016; Drug Utilisation Sub-Committee (DUSC), 2014). Expressing utilisation of each of the opioids in OME grams enabled us to take into account the differences in potencies of each of these opioids and in turn, compare rates of death between different opioids and examine trends over time.

We did not calculate rates of opioid deaths per 100,000 OME grams for methadone or buprenorphine as we did not have data on the use of these medicines for opioid dependence treatment. This would have resulted in under-estimating use of these opioids. Similarly, we did not calculate rates for codeine, because approximately 40% of codeine used in Australia in 2013 was sold over the counter, without prescription (Gisev et al., 2016). Codeine use, therefore, was not fully represented in

dispensing records.

2.6. Data analysis

We conducted analyses using SAS version 9.4. We modelled rates for trends in; 1) heroin and pharmaceutical opioid overdose deaths; 2) overdose deaths by opioid type; 3) overdose deaths by gender; and 4) overdose deaths by intent using negative binomial regression where there was over-dispersion, and Poisson regression where there was not (Coxe et al., 2009). Separate regression models, including interaction terms, assessed differences in trends of opioid overdose deaths over time by; 1) opioid type; 2) age; 3) gender; and 4) intent of the overdose. Finally, we modelled the differences in rates in 2012, across all of these measures. We model trends in deaths between 2001 and 2012, as at the time of data analyses, substantial minorities of the cases beyond these years remained open.

3. Results

There were a total of 8547 opioid overdose deaths identified during the period 2001–2012 among Australians aged 15–74 years. Approximately one-third (34% − n = 2895) were categorised as heroin overdose deaths. In 9% (n = 277) of heroin deaths, the presence of a pharmaceutical opioid (predominantly methadone) was also recorded. Just over half (58% n = 4963) of all deaths were categorised as pharmaceutical opioid overdose deaths, and the remaining 8% (n = 689) were categorised as heroin/morphine overdose deaths.

3.1. Trends in opioid overdose deaths

There was no significant change in rates of heroin overdose deaths between 2001 (13.2 per million population; 95% CI: 11.4, 15.2) and 2012 (14.5 per million population; 95% CI: 12.7, 16.4) (p = 0.09) (Fig. 1; Table A1.2). In contrast, rates of pharmaceutical opioid overdose deaths increased significantly during this time (from 21.9 per million population; 95% CI: 19.5, 24.4 in 2001–36.2 per million population; 95% CI: 33.5, 39.2 in 2012) by an average of approximately 6% (95% CI: 4.8, 7.1) each year (p < 0.0001; Fig. 1; Table A1.2). Trends in rates of pharmaceutical opioid overdose deaths were significantly different to trends in rates of heroin overdose deaths (p = 0.01). In 2012, rates of pharmaceutical opioid deaths were significantly higher, occurring at 2.5 times the incident rate of heroin deaths (p = 0.01). (Fig. 1; Table A1.2).

3.2. Pharmaceutical opioid overdose deaths by opioid type

3.2.1. Rates per million population

Rates of fentanyl, oxycodone, and methadone deaths all increased significantly between 2001 and 2012, by an average of approximately 40% (95% CI: 32.2, 48.4) (p < 0.0001), 16% (95% CI: 13.8, 18.3) (p < 0.0001), and 3% (95% CI: 1.5, 5.0) (p = 0.0002) each year respectively (Fig. 2a; Table A2.1A). Although the rate of deaths due to fentanyl in 2001 was lower (0.35 per million population; 95% CI: 0.1, 0.8) than deaths due to morphine (10.97; 95% CI: 9.3, 12.8), methadone (9.43; 95% CI: 7.9, 11.2), codeine (6.5; 95% CI: 5.2, 8.0) and oxycodone (1.89; 95% CI: 1.2, 2.7), a significant increase in fentanyl related deaths was observed over the study period.

3.2.2. Rates per 100,000 OME grams dispensed

Rates of morphine, oxycodone, tramadol and fentanyl deaths per 100,000 OME grams dispensed are presented in Fig. 2b and Table A2.22. The rates of fentanyl deaths per 100,000 OME grams dispensed increased significantly between 2002 and 2012, by an average rate increase of 31% (95% CI: 20.7, 31.8) each year (p < 0.0001) (Fig. 2b; Table A2.22). Conversely, tramadol deaths per 100,000 OME grams declined on average by approximately 5% (95% CI: 1.6, 9.5) each year (p = 0.005). There was no change over time in morphine or oxycodone deaths per 100,000 OME grams. The trend in rates of oxycodone deaths per 100,000 OME grams was significantly different to the trends in rates of fentanyl and tramadol deaths per 100,000 OME grams (p < 0.0001). There were no differences in trends in rates of oxycodone deaths per 100,000 OME grams versus morphine deaths per 100,000 OME grams (p = 0.74). In 2012, rates of morphine deaths per 100,000 OME grams were 1.7 times the incident rate of oxycodone deaths (p = 0.01), 2.2 times the incident rate of fentanyl deaths (p = 0.0006), and 5.4 times the incident rate of tramadol deaths per 100,000 OME grams (p < 0.0001).

3.3. Opioid overdose deaths by age

Rates of heroin deaths among 35–44, and 45–54 year olds increased significantly between 2001 and 2012. Conversely, they declined significantly among the youngest age group (15–24 year olds) (Fig. A1.1).

With the exception of the youngest age group (15–24 year olds among whom rates remained stable), rates of pharmaceutical opioid deaths increased significantly across all age groups. In 2012, rates of pharmaceutical opioid deaths were significantly higher (p < 0.0001) among the 45–54 year olds than rates among all other age groups (Fig. A1.2).

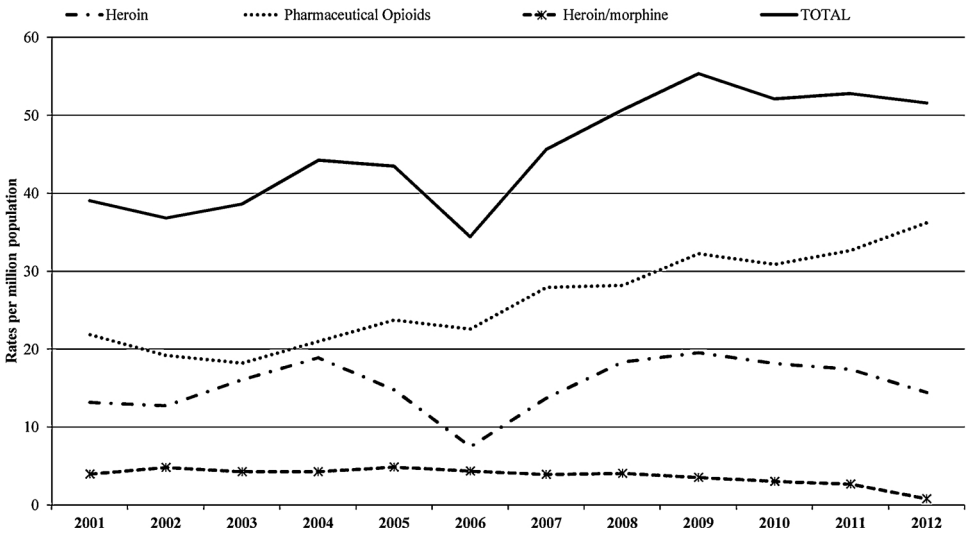

Fig. 1. Rates per million population 15–74 years, heroin, pharmaceutical opioid and heroin/morphine overdose deaths, 2001–2012.
NB: The Heroin/morphine category refers to deaths where there was not enough information to determine whether the death was due to heroin or morphine.

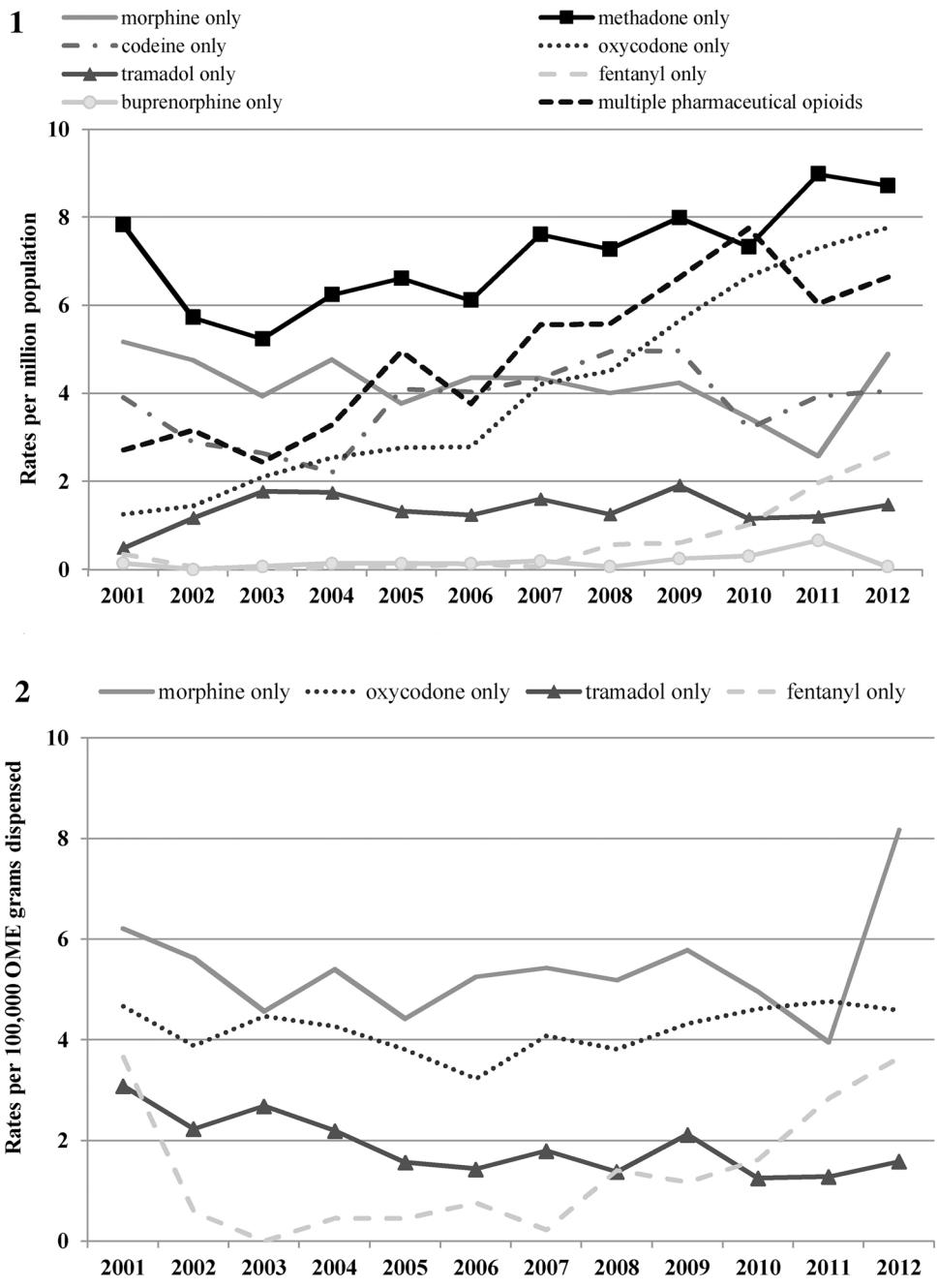

Fig. 2. Pharmaceutical opioid overdose deaths by opioid type, 2001–2012. (a) Rates per million population 2001–2012. (b) Deaths per 100,000 OME grams by opioid type 2001–2012.

3.4. Opioid overdose deaths by gender

There were no significant changes over time in heroin deaths among males ($p = 0.07$) or females ($p = 0.7$) (Fig. A2.1). Rates of heroin deaths were significantly higher among males than females across all years from 2001 to 2012 ($p < 0.0001$). In 2012, rates of heroin deaths among males were 4.6 times the incident rate of heroin deaths among females.

Rates of pharmaceutical opioid deaths were also significantly higher among males than females for the entire period ($p < 0.0001$), and increased significantly between 2001 and 2012 ($p < 0.0001$; Fig. A2.2). Pharmaceutical opioid deaths among females also increased significantly ($p < 0.0001$; Fig. A2.2). In 2012, rates of pharmaceutical opioid deaths among males were 1.6 times the incident rate of pharmaceutical opioid deaths among females.

3.5. Intent of death assigned by the coroner

Rates of pharmaceutical opioid overdose deaths where the coroner assigned intent as accidental increased significantly by an average of 7% (95% CI: 5.7, 9.1) each year between 2001 and 2012 ($p < 0.0001$; Fig. 3b; Table A5.2A), while those assigned as intentional remained stable. Rates of pharmaceutical opioid overdose deaths assigned as intentional were significantly higher than rates of heroin overdose deaths assigned as intentional across the entire period ($p < 0.0001$) (Fig. 3a,b; Table A5.1A; Table A5.2A).

4. Discussion

Rates of pharmaceutical opioid overdose deaths increased in Australia by approximately 1.6 times the rate recorded in 2001 (21.87 per million) to 36.27 in 2012. These deaths were more likely to occur among males than females, and among Australians aged 45–54 years.

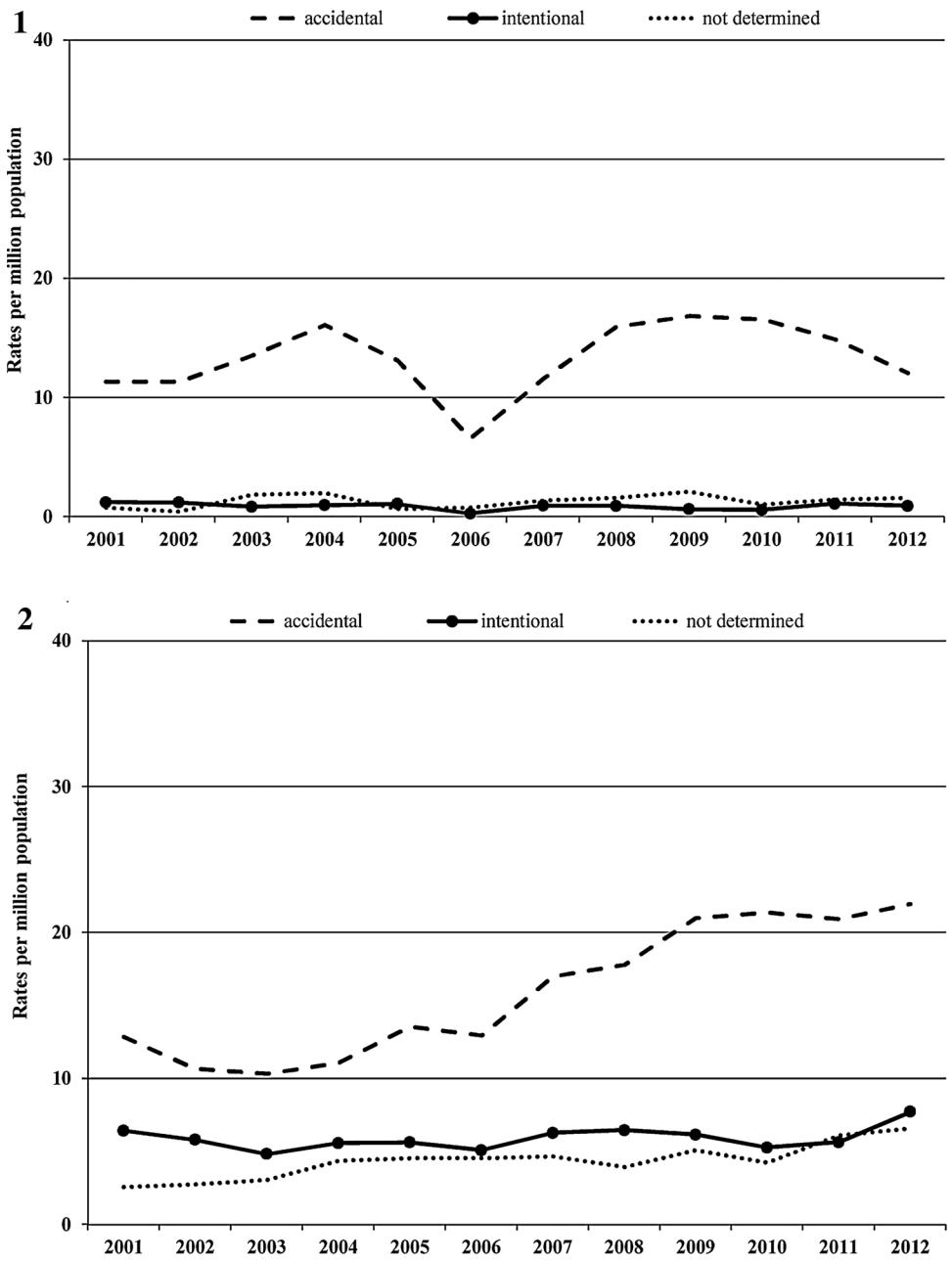

Fig. 3. Rates per million population heroin and pharmaceutical opioid overdose deaths (15–74 years) by intent, 2001–2012. (a) Heroin deaths. (b) Pharmaceutical opioid overdose deaths.

Despite the higher prevalence of pharmaceutical opioid overdose deaths among males, the increase in rates of these deaths was slightly higher among females (6% each year) than males (5% each year) over the period. Rates of heroin overdose deaths overall did not significantly change between 2001 and 2012. Heroin deaths were more likely to occur among males and among Australians aged 25–44 years. In 2012, rates of pharmaceutical opioid overdose deaths were 2.5 times the incident rate of heroin overdose deaths. In 2006, a reduction in heroin deaths was recorded, which was consistent with declines in a number of other heroin-related indicators (number and weight of seizures, and heroin users' reported availability and prevalence/frequency of use (ACS, 2007; Stafford and Breen, 2016). Increases in pharmaceutical opioid overdose deaths were largely driven by accidental overdose deaths. Intentional overdose deaths involving pharmaceutical opioids were significantly higher than intentional overdose deaths involving heroin.

Internationally, increases in pharmaceutical opioid overdose deaths have occurred within the context of increased prescribing of opioid analgesics (Paulozzi et al., 2006; Bohnert et al., 2011; Dart et al., 2015; Martins et al., 2015; Tjagvad et al., 2016). Global estimates show a doubling worldwide in the use of opioid analgesics between 2001 and 2013, largely driven by increased prescribing in North America, Western and Central Europe and Australia (Berterame et al., 2016). North America's rates of opioid analgesic utilisation are now more than double that of the European Union and Oceania (Fischer et al., 2012), and unsurprisingly, opioid overdose death rates in North America have remained higher (Rudd et al., 2016) than Australian rates presented here.

Our findings are largely consistent with international trends. Opioid overdose deaths among men outnumber those among women in many countries (Martins et al., 2015; Sampson et al., 2015). Interestingly, recent Australian estimates suggested that rates of oxycodone use (particularly 80 mg preparations) were twice as high in men than women, while fentanyl use was higher among women than men (particularly in their 70 s) (Hollingworth et al., 2015). Despite pharmaceutical opioid overdose deaths being higher among men, the rate of

deaths among women increased more rapidly than men.

Age trends were also consistent with European data that show increases predominantly among older age groups (European Monitoring Centre for Drugs and Drug Addiction, 2016). Data from the United States show people aged 45–54 years have the highest rates of overdose death, for both heroin and pharmaceutical opioids (Calcaterra et al., 2013). Our findings showed that the greatest increase in rates of heroin (9% each year) and pharmaceutical opioid (10% each year) overdose deaths occurred among the 45–54 year age group.

Australian pharmaceutical opioid utilisation shows marked increases in dispensed amounts for oxycodone, tramadol and fentanyl (Karanges et al., 2016). Comparisons of pharmaceutical opioid deaths by opioid type according to levels of utilisation (i.e., rates of deaths per 100,000 OME grams) showed that only fentanyl deaths significantly increased between 2002 and 2012. That is, fentanyl deaths continued to increase after taking into account the amount and relative potency of each opioid dispensed in the community. In contrast, oxycodone deaths per 100,000 OME grams showed no change over time. These findings suggest that while trends in rates of oxycodone deaths track trends in increased prescribing, the increase in rates of fentanyl deaths appears to exceed the increased levels of prescribing. This may be indicative of extra-medical use. Also of note is that rates of morphine deaths per 100,000 OME grams in 2012 were significantly higher than rates of oxycodone, fentanyl, and tramadol deaths per 100,000 OME grams. There appears to be no obvious explanation for the increase in morphine deaths per 100,000 OME grams in 2012. The trend in these deaths is concerning, and warrants ongoing monitoring.

Our findings have important clinical, public health and research implications. Firstly, it is critical in reducing opioid related overdose deaths to reduce inappropriate use of pharmaceutical opioids without restricting access to timely and appropriate pain medication. Specifically, we need to reduce both the diversion of these medications and their use that is not in accordance with prescribing guidelines ('extra-medical' use) (Larance et al., 2011). Several strategies are required to address the very different needs of people who engage in extra-medical and diverted use of prescribed pharmaceutical opioids. One strategy for extra-medical use is to introduce more restrictive prescribing practices that include shorter times to review before providing further prescriptions, a comprehensive assessment of risk factors among patients presenting for pain treatment, and careful monitoring of problems associated with pharmaceutical opioids. A strategy for people using diverted pharmaceutical opioids is to increase access to treatment for opioid dependence. This will likely reduce the diversion and extra-medical use of pharmaceutical opioids. Increased treatment access can also address problematic pharmaceutical opioid use that develops during the medical treatment of pain.

Second, in reducing the likelihood of overdose it is critical to educate health professionals, consumers, and caregivers, about the risks of long-term opioid analgesic use (including dose escalation, dependence, and polydrug use). Evaluation of consumer education programs in the United States shows promise in reducing problematic pharmaceutical use and harms (Johnson et al., 2011; McCauley et al., 2013). Similar evaluations have not been conducted in Australia.

Third, the provision of naloxone (an opioid antagonist that reverses respiratory depression) over the counter (OTC) can reduce fatal opioid overdose. Naloxone has been an important harm reduction initiative in several countries including Italy and some jurisdictions in the United States. Legislation has recently been introduced in Australia to provide OTC naloxone, but this legislation remains to be fully implemented (Lenton et al., 2016). Any effects on opioid deaths from increased naloxone dispensing in Australia are unlikely to be apparent at such an early stage of the implementation of OTC naloxone sales.

It is worth noting that evaluations of these strategies to reduce pharmaceutical opioid prescribing, and related harms have shown mixed results (Haegerich et al., 2014). Restrictive prescribing has shown promise in the U.S., with benzodiazepine prescribing being significantly reduced in New York State (Weintraub et al., 1991). In the U.K., the introduction of supervised methadone dosing resulted in a substantial decline in methadone-related mortality (Strang et al., 2010). Evaluative research in this area has been limited in Australia because of the diversity of legislation across the states and territories. In order to improve the evidence base of what works, implementation of standardised clinical prescribing and education guidelines is critical (Haegerich et al., 2014). Naloxone dispensing has also shown promise in parts of the U.S. in reducing opioid-related mortality (Walley et al., 2013), however, it is too early to evaluate the impact of OTC naloxone provision in Australia. One strategy that has been evaluated in Australia is the introduction of tamper resistant formulations of oxycodone to reduce opioid use and related harms. This strategy did not appear to impact on population level opioid use or related harms (Larance et al.,in preparation).

Finally, continued research is essential. The growth in opioid utilisation in Australia is in part due to several opioids (including buprenorphine, fentanyl and oxycodone) being registered to treat chronic non-cancer pain. Although rates of deaths for fentanyl relative to their use in the community are lower than other opioids, they have increased over time, suggesting that extra-medical use may be implicated. Ongoing monitoring of overdose deaths, and a better understanding of the context in which these deaths occur, is essential in developing policies to reduce opioid overdose deaths. Prescription drug monitoring programs (PDMP) have been successful in parts of the United States in reducing overdose deaths (Delcher et al., 2015). The only jurisdiction in Australia to have implemented a PDMP to date is Tasmania (Ogeil et al., 2016). It is an online system that allows medical practitioners access to prescription history for individuals, and only monitors Schedule 8 drugs (refer to Appendix Table A64 for the scheduling of opioids in Australia), and alprazolam. It is not mandatory for general practitioners and pharmacies to access the PDMP and there has been varied uptake of the system across services. While no formal evaluation of the program has been conducted, analysis of opioid sales data suggests there has been a shift towards prescribing weaker and less restricted opioids from schedule 8 opioids. Similar monitoring systems have yet to be implemented and evaluated at a national level in Australia (Ogeil et al., 2016).

4.1. Limitations

Our analysis only included deaths where opioid overdose was the underlying cause of death, which may underestimate the extent of opioid involvement in mortality rates in Australia. International research shows however (Degenhardt et al., 2010), that opioid overdose represents the largest contributory factor (70%) to all opioid-related mortality. Additionally Australian research has shown deaths where the underlying cause was not drug-related but opioids were involved comprise a minority (0.5% motor vehicle accidents, 1.3% other medical conditions) of these deaths (Jauncey et al., 2005)

We were unable to determine the rate of deaths for methadone, buprenorphine and codeine, relative to the extent of their use in the community. As such, we may have overestimated the increase in death rates due to these opioids. Furthermore, given that heroin is metabolised into morphine quite rapidly, it is likely that some morphine deaths are actually attributable to heroin. We tried to distinguish between morphine and heroin deaths where possible, through careful investigation of autopsy, findings and police reports, but in approximately 8% (n = 689) of the opioid overdose cases there was not enough information to decide whether these deaths should be coded as due to heroin or morphine. Accordingly, we reported these deaths as heroin/morphine deaths, but excluded them from statistical analyses.

The way intent of the death is ascribed by respective coroners may vary over time, which may influence trends.

Finally, although this study focuses on fatal overdose associated with opioids, it is important to acknowledge that opioid use is also

associated with a number of other harms. Previous work estimates that for every fatal overdose, there are 25–50 non-fatal overdoses, further highlighting the need for strategies to prevent both fatal and non-fatal harms related to opioid use (Darke et al., 2003).

5. Conclusions

There have been marked increases in rates of pharmaceutical opioid overdose deaths in Australia between 2001 and 2012, and these increases are largely being driven by accidental overdose. Death rates due to pharmaceutical opioid overdose were higher among males than females, but increases were slightly higher among females over the eleven year period. Pharmaceutical opioid overdose deaths were significantly higher than heroin deaths during the entire study period. Rates of fentanyl deaths per 100,000 OME grams showed marked increases, although these deaths started from a comparatively low rate. Notably, in 2012, rates of morphine deaths per 100,000 OME grams were significantly higher than those for oxycodone, fentanyl and tramadol.

A multifaceted response is therefore needed to minimise the harms associated with heroin and pharmaceutical opioid use and misuse. This includes: 1) restricting access to pharmaceutical opioids through careful assessment of risk, and shorter time to review patients; 2) early identification of problematic patterns of pharmaceutical opioid use; 3) increasing access to treatment for opioid (both heroin and pharmaceutical) dependence; and 4) ongoing harm reduction strategies such as naloxone provision and overdose awareness education.

Conflict of interest

SP is a member of the Drug Utilisation Sub-Committee of the Australian Pharmaceutical Benefits Advisory Committee (PBAC). The views presented are those of the authors and do not reflect those of the PBAC. **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.

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Contributors

AR developed the idea for the manuscript in discussion with **LD** and **WH**, conducted analyses and drafted the manuscript for comment. **WH** provided comment on successive drafts of the manuscript. **TD** provided direction and expertise on statistical analysis, as well as providing comment on successive drafts of the manuscript. **NG** analysed PBAC data to inform the deaths data and provided comment on successive drafts. **SP** provided PBAC data to allow for analysis of deaths in the context of opioid prescribing, and commented on the manuscript. **LB** provided comment on successive drafts. **LD** provided guidance on the overall content and focus of the manuscript, and commented on successive drafts. All authors approved the final manuscript before submission.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.07.018.

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