Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Victoria, Australia from 2013 to 2018

Suzanne Nielsen[1] (iD), Rose Crossin[1,2] (iD), Melissa Middleton[1], Tina Lam[1] (iD), James Wilson[2], Debbie Scott[1,2], Catherine Martin[3] (iD), Karen Smith[1,4,5,6] (iD) & Dan Lubman[1,2] (iD)

Monash Addiction Research Centre, Eastern Health Clinical School, Monash University, Frankston, Victoria, Australia,[1] Turning Point, Eastern Health and Eastern Health Clinical School, Monash University, Richmond, Victoria, Australia,[2] Biostatistical Unit, Public Health and Preventative Medicine, Monash University, Melbourne, Victoria, Australia,[3] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia,[4] Ambulance Victoria, Doncaster, Victoria, Australia[5] and Department of Community Emergency Health and Paramedic Practice, Monash University, Frankston, Victoria, Australia[6]

ABSTRACT

Background and aims Despite increases in opioid prescribing and related morbidity and mortality, few studies have comprehensively documented harms across opioid types. We examined a population-wide indicator of extramedical pharmaceutical opioid-related harm to determine if the supply-adjusted rates of ambulance presentations, the severity of presentations or other attendance characteristics differed by opioid type. **Design** Retrospective observational study of coded ambulance patient care records related to extramedical pharmaceutical opioid use, January 2013 to September 2018. **Setting** Australia **Cases** Primary analyses used Victorian data ($n = 9823$), with available data from other Australian jurisdictions ($n = 4338$) used to determine generalizability. **Measurements** We calculated supply-adjusted rates of attendances using Poisson regression, and used multinomial logistic regression to compare demographic, presentation severity, mental health, substance use and other characteristics of attendances associated with seven pharmaceutical opioids. **Findings** In Victoria, the highest rates of attendance [per 100 000 oral morphine equivalent mg (OME)] were for codeine (0.273/100 000) and oxycodone (0.113/100 000). The lowest rates were for fentanyl (0.019/100 000) and tapentadol (0.005/100 000). Oxycodone–naloxone rates (0.031/100 000) were lower than for oxycodone as a single ingredient (0.113/100 000). Fentanyl-related attendances were associated with the most severe characteristics, most likely to be an accidental overdose, most likely to have naloxone administered and least likely to be transferred to hospital. In contrast, codeine-related attendances were more likely to involve suicidal thoughts/behaviours, younger females and be transported to hospital. Supply-adjusted attendance rates for individual opioids were stable over time. Victorian states were broadly consistent with non-Victorian states. **Conclusions** In Australia, rates and characteristics of opioid-related harm vary by opioid type. Supply-adjusted ambulance attendance rates appear to be both stable over time and unaffected by large changes in supply.

Keywords Ambulance, extramedical use, opioid analgesic, overdose, oxycodone, tapentadol.

INTRODUCTION

The increasing use of pharmaceutical opioids is well documented in many high-income countries [1]. In the United States, 35% of all opioid-related deaths are attributed to pharmaceutical opioids, and the rate of pharmaceutical-opioid related deaths has risen more than threefold from 1.4/100 000 in 1999 to 5.2/100 000 in 2017 [2]. In Australia, mortality for all-opioids has almost doubled in the past decade from 3.8 to 6.6 deaths per 100 000, with 1045 opioid-related deaths in 2016, 70% of which were pharmaceutical opioid-related [3,4].

Pharmaceuticals opioids are often considered as a homogeneous group when their harms are reported. Most

opioids exert their analgesic effect through the mu-opioid receptor; however, opioids can differ in important ways, such as their potency as analgesics and pharmacokinetics [5]. One study examining rates of severe adverse events (SAEs) found a strong positive association with potency and SAEs [6]. Fentanyl is considered a high-potency opioid with rapid onset, high lipophilicity and short duration of action (30 minutes). Oxycodone and morphine are examples of medium-potency opioids with a slower onset (30–60 minutes) and longer duration of action (3–4 hours) [7,8]. Codeine, tramadol and tapentadol are examples of lower-potency opioids [5]. Tramadol and tapentadol are sometimes called 'atypical opioids', as their mu-opioid effects are combined with serotonin and/or noradrenaline re-uptake pharmacological actions [9–11].

Abuse liability also differs between opioids. For example, oxycodone has a consistently robust abuse liability profile [12]. In contrast, codeine is relatively less reinforcing [13]. Contextual factors such as cost and availability also affect propensity for extramedical use and harms; therefore, studies in real-world settings are important [14].

Sentinel surveillance studies can identify harms associated with different opioids (e.g. the National Illicit Drug Reporting System [15]), although these studies often target specific subpopulations of interest rather than the general population and are less useful for newer or less commonly used opioids. Mortality data can also provide an indication of relative harms; however, reporting can have up to a 3-year delay, and deaths are a relatively lower-frequency event. Finally, reporting systems that capture spontaneous adverse events are important, although these systems are known to be subject to under-reporting and selective reporting bias [16].

Ambulance attendance data have the potential to provide population-level data and address many of these limitations. Ambulance services are near-universal in Australia, with state-wide responsibility for service delivery. Paramedics are often the first or only health professionals that directly observe the scene (e.g. medicine packets, bystander accounts), providing unique and valuable information. A well-established programme of research (the National Ambulance Surveillance System) has developed a validated method of coding paramedic clinical records associated with substance use-related ambulance attendances [17].

The aim of this study was to compare the rates and characteristics of pharmaceutical opioid-related ambulance attendances.

Specifically, we questioned:

1 Do the supply-adjusted rates of ambulance presentations differ by opioid type?
2 Does the severity of presentation or other attendance characteristics differ by opioid type?

METHODS

The study's research questions, methods and analysis plan were published a priori [17], and reported in compliance with The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement (Supporting information, Table S1).

Study design and setting

We used ambulance attendance data from January 2013 to September 2018. The primary analysis represent data from the state of Victoria, which comprises approximately 26% of the Australian population (5.7 million residents in 2013 and 6.5 million in 2018) [18]. To determine generalizability, we compared our continuous data set of Victorian pharmaceutical opioid attendances with data from 'snapshot months' from the other jurisdictions [Queensland, New South Wales (NSW), Australian Capital Territory (ACT), Northern Territory and Tasmania]. Snapshot data were available for the months March, June, September and December for 2015–17 [17]. Data for Western Australia and South Australia are not yet available for analysis.

Ambulance attendance data

Data are from the previously described [19,20] National Ambulance Surveillance System [21]. Briefly, electronic patient care records (ePCR), computer-aided dispatch and other clinical details are provided to Turning Point for data cleaning, validation and coding by specialist research assistants using a systematic and validated coding method [17].

Cases where the recent extramedical (i.e. over- or inappropriate) use of a pharmaceutical drug is assessed to have significantly contributed to the reason for the ambulance attendance are identified from the ePCR. Substance involvement and other associated factors including clinical presentation, mental health symptoms and self-harm are coded.

For this study, all ambulance attendances involving extramedical use of buprenorphine, codeine, fentanyl, oxycodone, oxycodone–naloxone, morphine, pethidine, tramadol and tapentadol were included. Seven of these are routinely coded. Codeine is coded under four different variables (codeine, codeine + aspirin, codeine + ibuprofen, codeine + paracetamol), so a single aggregated variable was created. Tapentadol is coded as an 'other opioid'. Therefore, to identify tapentadol-related attendances, 'other opioid' attendances were searched using keywords (see Supporting information, Table S2 for the comprehensive search strategy).

We excluded attendances related to opioid agonist treatment (for opioid dependence), as these represent a

specific clinical population and indication. Further, we excluded attendances with individuals aged < 12 years (*n* = 32), due to unclear intention of use in children [22,23]. Deaths were not excluded, but are not quantified due to data-capture inconsistencies.

Sales data

To calculate a supply-adjusted rate of attendances, we used sales data (IQVIA third-party access program). We calculated the total amount of each opioid supplied per month in milligrams (mg), converted to oral morphine equivalents (OME) [24]. OME is a widely used measure to quantify population-level opioid use, with advantages over defined daily doses [25].

Variables

The primary independent variable was opioid type. We assessed trends within each opioid where a single opioid was involved, as well as a 'multiple opioid' category (i.e. more than one of the opioids examined as part of the study contributed to the attendance). Outcome variables and covariates describe the context and characteristics of the attendances (Supporting information, Table S3). These include the Glasgow Coma Scale (GCS) as a measure of medical severity; respiration rate; transport to hospital; naloxone administration; naloxone response; age; sex; socio-economic status based on residential postcode [26]; concurrent alcohol use, illicit drug use excluding heroin, heroin use and non-opioid pharmaceutical involvement; comorbid mental health, suicidal thoughts or behaviours or non-suicidal self-injury; and accidental overdose, unknown intent overdose or past psychiatric history.

Statistical analysis

Analyses were planned a priori [17].

Rates of attendances per 100 000 mg of opioid supplied

Attendances were aggregated into 3-monthly periods. Regression (Poisson) models were fitted for each opioid. Temporal variations were explored and were apparent only for codeine, so were not adjusted for the final models. Estimates are presented as incidence rate ratios (IRRs) and represents the estimated rate ratio associated with a 1-year increase. Monthly rates were calculated for Victoria, and compared with other states for corresponding time-periods as a sensitivity analysis.

Characteristics of attendances

Multinomial logistic regression was used to analyse characteristics of opioid-related attendances by opioid type. Each attendance characteristic was regressed separately with opioid type as the dependent variable; morphine, a mid-potency opioid considered the standard reference for calculating opioid doses, was the reference category.

When considering severity of presentations (measured with GCS), the model was adjusted for age, sex (as male/female only), concurrent alcohol use, concurrent illicit drug use (excluding heroin), concurrent heroin use and concurrent non-opioid pharmaceutical use. All other models were adjusted for age, sex and other substance use (as an aggregated variable of concurrent alcohol use, illicit drug use, heroin and non-opioid pharmaceutical misuse). Deaths were not excluded, but are not separately reported due to small cell sizes. State location (Victoria or 'other jurisdictions') was assessed as an effect modifier when case numbers allowed.

All analyses were undertaken in Stata (StataCorp 2013), with *P*-values less than 0.05 considered significant, with no correction for multiple testing [27].

Missing data

Missing data were minimal (< 5%, Supporting information, Table S4). For data missing due to industrial action, we ran planned sensitivity analysis using imputed data.

Changes from planned analyses

Due to low numbers of attendances with buprenorphine and pethidine (≤ 5 in total over the study period), we were unable to explore presentation characteristics or calculate quarterly rates, although these opioids contributed to the multiple opioid category when involved in other attendances.

Ethics committee approval

This project was approved by the Eastern Health Human Research Ethics Committee (E122–0809). Cells with *n* < 5 are not reported to preserve confidentiality, per conditions of approval.

RESULTS

We identified 9823 opioid-related ambulance attendances in Victoria across the almost 6-year study period, with a further 4338 captured in NSW, ACT, Northern Territory, Queensland and Tasmania during the relevant 'snapshot' months. Codeine and oxycodone were the most prevalent opioids, representing 67% of cases combined. Overall, 9.7% of cases involved multiple opioids.

Aim 1—supply-adjusted trends

The supply-adjusted ambulance attendances rate was highest for codeine [0.273/100 000 mg OME, 95% confidence interval (CI) = 0.261–0.285] and lowest for

tapentadol (0.005/100 000 mg OME, 95% CI = 0.003–0.007) (Table 1, Fig. 1). Supporting information, Fig. S1 depicts the raw attendance and supply data used to calculate the supply-adjusted rates.

The Poisson regression estimates show that the mean monthly attendance rates for Victoria were stable over time (Table 1). The mean monthly supply-adjusted rates for each year (Table 2) were generally consistent with the Poisson regression findings, with the exception of oxycodone. The supply-adjusted oxycodone rate was stable from 2014 to 2017. However, the rates in the first and last years examined fall outside the 95% CI for the overall study period, indicating an increase in supply-adjusted oxycodone attendance rates over that time.

Results using multiply imputed data were consistent with findings from the primary analysis (Supporting information, Table S5). Results for quarterly snapshot months from states outside Victoria were broadly consistent with patterns observed with the complete Victorian data set for the Poisson regression, with larger confidence intervals representing the greater uncertainty involved in using snapshot months with fewer cases (Supporting information, Table S6). However, the rates for fentanyl and morphine appeared higher outside Victoria, with the most noticeable difference seen for morphine, with a significantly higher estimated monthly rate.

Aim 2—characteristics of attendances

Attendance characteristics are presented for each opioid in Supporting information, Table S7, and relative to morphine in Table 3. We report differences from the reference opioid (morphine) below.

As case severity (measured with GCS) increased, fentanyl was more likely to be involved as a sole opioid. The opposite association was seen for oxycodone, oxycodone–naloxone, codeine, tramadol and multiple opioid attendances. The largest change occurred for oxycodone–naloxone, in which attendances with minor–no impairment, compared to non-responsive attendances, were more likely to be oxycodone–naloxone-related rather than morphine-related [odds ratio (OR) = 9.55, 95% CI = 4.03–

Table 1 Supply adjusted trends for Victoria from January 2013 to September 2018.

	Frequency n (%)	Incidence rate ratio[a]	95% Confidence interval	P-value	Mean supply-adjusted Rate[b]	95% Confidence interval
Codeine						
Sole opioid	3936 (87.5%)	1.03	0.83–1.27	0.804	0.273	0.261–0.285
Multiple opioid	561 (12.5%)	1.09	0.62–1.94	0.760	0.040	0.035–0.044
Fentanyl						
Sole opioid	242 (83.5%)	1.07	0.47–2.44	0.875	0.019	0.016–0.021
Multiple opioid	48 (16.5%)	0.90	0.15–5.55	0.910	0.004	0.002–0.005
Morphine						
Sole opioid	474 (82.0%)	1.04	0.63–1.71	0.883	0.050	0.046–0.055
Multiple opioid	104 (18.0%)	1.10	0.38–3.22	0.857	0.011	0.009–0.014
Oxycodone						
Sole opioid	2791 (79.1%)	1.09	0.78–1.53	0.610	0.113	0.107–0.120
Multiple opioid	738 (20.9%)	1.16	0.59–2.28	0.678	0.030	0.027–0.033
Oxycodone–naloxone						
Sole opioid	434 (64.1%)	1.11	0.56–2.20	0.773	0.031	0.027–0.036
Multiple opioid	243 (35.9%)	1.22	0.45–3.34	0.698	0.016	0.014–0.018
Tapentadol						
Sole opioid	48 (73.8%)	1.39	0.14–13.73	0.781	0.005	0.003–0.007
Multiple opioid	17 (26.2%)	1.15	0.05–24.84	0.931	0.002	0.001–0.003
Sole opioid(2014–18)[c]	48 (73.8%)	1.11	0.06–20.02	0.944	0.006	0.004–0.008
Multiple opioid(2014–18)[c]	17 (26.2%)	0.79	0.01–59.90	0.916	0.003	0.013–0.004
Tramadol						
Sole opioid	902 (74.7%)	1.06	0.63–1.80	0.821	0.045	0.041–0.049
Multiple opioid	306 (25.3%)	1.04	0.42–2.56	0.937	0.015	0.013–0.017
Multiple opioids	992 (10.1%)	1.15	0.84–1.59	0.381	0.135	0.108–0.163

[a]Rate is per 100 000 mg oral morphine equivalents (OME), per year increase, generated through Poisson regression; [b]rate is based off monthly estimates over whole study period; [c]due to low sales volume and no attendances related to tapentadol in 2013, overall trends are also presented 2014–18 only, resulting in slightly higher rates.
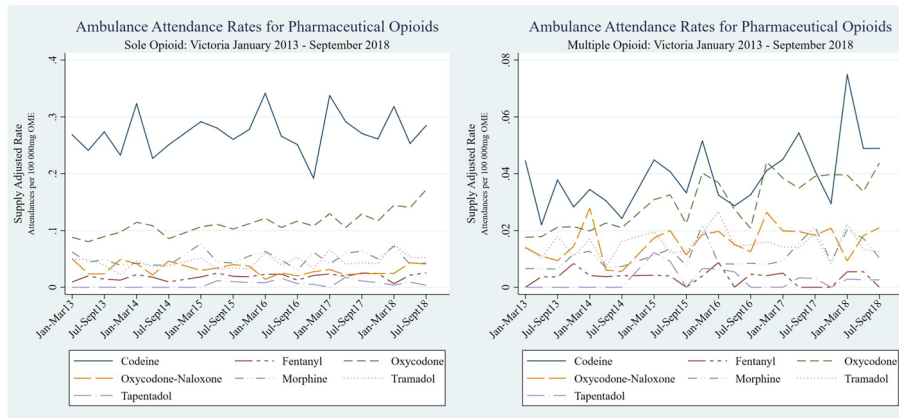
Figure 1 Rates of supply-adjusted pharmaceutical opioid related ambulance attendances (Victoria only). [Colour figure can be viewed at wileyonlinelibrary.com]

22.6); $P < 0.001$]. The same pattern was seen with a lower magnitude of effect for oxycodone-only attendances (OR = 2.06, 95% CI = 1.45–2.91; $P < 0.001$). Similarly, attendances with a normal respiration rate ($\geq$ 12 breaths/minute) were less likely to be fentanyl-related compared with morphine-related (OR= 0.14, 95% CI = 0.08–0.23; $P < 0.001$).

Compared with morphine-related attendances, fentanyl, oxycodone, codeine, tramadol and multiple opioid-related attendances were associated with younger patients. Codeine and tramadol were less likely to involve a patient aged > 65, compared with those aged 12–34 years (codeine: OR = 0.15, 95% CI = 0.11–0.22; $P < 0.001$; tramadol: OR = 0.19, 95% CI = 0.12–0.30; $P < 0.001$). This age effect was less pronounced for stronger opioids (fentanyl: OR = 0.41, 95% CI= 0.23–0.71, $P = 0.002$; oxycodone OR = 0.45, 95% CI = 0.32–0.63, $P < 0.001$) and multiple opioids (OR = 0.45, 95% CI = 0.30–0.66, $P < 0.001$). Relative to morphine, attendances for other opioids (with the exception of fentanyl) were approximately two to three times higher for females than males. For socio-economic status, for opioids other than fentanyl, it appeared that greater socio-economic advantage was associated with greater odds of an attendance.

Attendances related to codeine, tramadol or multiple opioids were more likely to be transported to hospital. Attendances in which naloxone was administered were more likely to involve fentanyl (OR = 3.97, 95% CI = 2.77–5.69, $P < 0.001$) and less likely to involve any other opioid or a combination of opioids when compared to morphine. The only opioid that differed from morphine in response to naloxone was oxycodone–naloxone, where response was less likely (OR = 0.17, 95% CI = 0.04–0.67; $P = 0.012$).

In terms of other substance use, codeine-related attendances were more likely to involve alcohol compared to morphine-related cases. For most opioids (excluding fentanyl and tapentadol), concurrent heroin or illicit drug use

was less likely to be reported. Similarly, extramedical non-opioid pharmaceutical use was more likely with opioids other than morphine (excluding fentanyl), with this being most likely with tapentadol (OR = 3.66, 95% CI = 1.42–9.44; $P = 0.007$).

Mental health symptoms were less likely to be reported with fentanyl (OR = 0.39, 95% CI = 0.22–0.70, $P = 0.001$) and more likely with codeine (OR = 1.42, 95% CI = 1.08–1.86; $P = 0.011$) and oxycodone–naloxone (OR = 1.42, 95% CI = 1.01–2.02, $P = 0.046$), compared to morphine-related attendances. Conversely, when compared to morphine, history of psychiatric issues was more likely with all opioids other than fentanyl.

Codeine-related attendances were more likely to involve comorbid suicidal ideation (OR = 4.46, 95% CI = 3.52–5.66; $P < 0.001$) and less likely to involve an accidental overdose compared with morphine-related attendances (OR = 0.38, 95% CI = 0.28–0.52; $P < 0.001$). Accidental overdose-related attendances were most commonly fentanyl-related (OR = 2.89, 95% CI = 1.97–4.24; $P < 0.001$). Unknown intent-related attendances were more commonly associated with fentanyl (OR = 1.73, 95% CI = 1.60–2.63; $P = 0.010$), codeine (OR = 1.43, 95% CI = 1.07–1.92; $P = 0.016$) and less likely for oxycodone–naloxone (OR = 0.62, 95% CI = 0.40–0.97; $P = 0.038$) when compared to morphine.

When comparing Victorian results to the remaining states, there were too few attendances for tapentadol, oxycodone–naloxone and fentanyl outside Victoria to enable a comparison of characteristics. The effect of most characteristics remained the same across the states. GCS, age, alcohol involvement, unknown intent and past psychiatric history were the only characteristics in which the magnitude of effect changed, but the direction did not (data not presented). Non-suicidal self-injury in codeine-related cases and naloxone response in oxycodone–naloxone-related cases become inconclusive outside Victoria. Overall,

Table 2 Estimated supply-adjusted rates for each opioid in Victoria, from 2013 to 2018.

| Opioid | Mean monthly supply-adjusted rate (per 100 000 mg oral morphine equivalents)[a] | | | | | |
Year	2013	2014[b]	2015	2016	2017	2018[b]
Codeine						
Sole	0.256 (0.227–0.285)	0.267 (0.224–0.309)	0.278 (0.253–0.303)	0.264 (0.221–0.308)	0.291 (0.265–0.316)	0.285 (0.255–0.315)
Multiple	0.033 (0.024–0.042)	0.030 (0.022–0.038)	0.043 (0.033–0.052)	0.033 (0.028–0.039)	0.042 (0.032–0.053)	0.058 (0.040–0.077)
Fentanyl						
Sole	0.014 (0.010–0.018)	0.016 (0.007–0.026)	0.020 (0.014–0.025)	0.020 (0.015–0.025)	0.023 (0.014–0.032)	0.018 (0.009–0.027)
Multiple	0.004 (0.001–0.006)	0.004 (0.001–0.008)	0.004 (0.001–0.008)	0.005 (0.000–0.009)	0.001 (−0.000–0.002)	0.004 (0.001–0.008)
Morphine						
Sole	0.049 (0.040–0.057)	0.040 (0.025–0.056)	0.055 (0.041–0.062)	0.051 (0.039–0.062)	0.054 (0.039–0.068)	0.052 (0.038–0.066)
Multiple	0.009 (0.005–0.013)	0.009 (0.003–0.016)	0.013 (0.007–0.019)	0.008 (0.004–0.012)	0.015 (0.007–0.022)	0.015 (0.005–0.024)
Oxycodone						
Sole	0.089 (0.080–0.099)	0.103 (0.088–0.117)	0.108 (0.100–0.117)	0.113 (0.103–0.123)	0.120 (0.109–0.131)	0.152 (0.126–0.178)
Multiple	0.020 (0.016–0.023)	0.021 (0.018–0.025)	0.031 (0.025–0.038)	0.032 (0.026–0.039)	0.038 (0.030–0.045)	0.039 (0.029–0.050)
Oxycodone–naloxone						
Sole	0.036 (0.020–0.053)	0.037 (0.028–0.042)	0.035 (0.028–0.042)	0.022 (0.015–0.028)	0.025 (0.019–0.032)	0.036 (0.022–0.050)
Multiple	0.011 (0.004–0.018)	0.014 (0.005–0.023)	0.017 (0.011–0.022)	0.018 (0.014–0.023)	0.020 (0.016–0.024)	0.016 (0.009–0.023)
Tapentadol						
Sole	0	0	0.004 (0.000–0.008)	0.008 (0.002–0.013)	0.009 (0.003–0.015)	0.007 (0.003–0.012)
Multiple	0	0	0.005 (−0.000–0.010)	0.003 (−0.000–0.006)	0.002 (0.000–0.004)	0.004 (0.001–0.007)
Tramadol						
Sole	0.040 (0.030–0.050)	0.040 (0.031–0.049)	0.038 (0.030–0.046)	0.047 (0.036–0.057)	0.048 (0.035–0.061)	0.060 (0.046–0.075)
Multiple	0.013 (0.009–0.018)	0.014 (0.008–0.019)	0.016 (0.010–0.022)	0.018 (0.013–0.023)	0.014 (0.010–0.017)	0.016 (0.012–0.021)
Multiple Opioids	0.092 (0.082–0.103)	0.099 (0.075–0.123)	0.133 (0.105–0.160)	0.121 (0.101–0.142)	0.207 (0.052–0.363)	0.156 (0.121–0.191)

[a]95% Confidence interval presented in brackets; [b]Estimates calculated using 9-months of the year, reflecting available data.

Table 3 Regression estimates from multinomial logistic regression for each characteristic.[a]

	n	Codeine OR	Codeine 95% CI	Fentanyl OR	Fentanyl 95% CI	Oxycodone OR	Oxycodone 95% CI	Oxycodone–naloxone OR	Oxycodone–naloxone 95% CI
Glasgow Coma Scale[d]	9665								
Non-responsive		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Severe impairment		2.66	1.40–5.02	0.83	0.40–1.72	1.41	0.76–2.63	4.48	1.42–14.20
Moderate impairment		2.81	1.65–4.79	0.56	0.29–1.06	1.84	1.11–3.06	4.48	1.59–12.63
Minor–no impairment		4.53	3.12–6.59	0.19	0.13–0.29	2.06	1.45–2.91	9.55	4.03–22.60
Age (years)[e]	14073								
12–34		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
35–54		0.39	0.30–0.49	0.79	0.65–1.14	0.60	0.47–0.77	1.04	0.74–1.44
55–65		0.24	0.17–0.33	0.49	0.29–0.83	0.40	0.29–0.55	0.96	0.63–1.47
>65		0.15	0.11–0.22	0.41	0.23–0.71	0.45	0.32–0.63	1.16	0.74–1.80
Sex[f]	14073								
Male		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female		2.99	2.45–3.65	0.79	0.57–1.10	2.10	1.71–2.56	1.89	1.45–2.47
Respiration rate[c]	9467								
<6		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
6–12		5.89	3.15–11.02	0.36	0.21–0.61	1.72	1.06–2.77	3.69	1.23–11.08
>12		13.08	7.20–23.76	0.14	0.08–0.23	2.13	1.37–3.32	7.63	2.65–21.94
Transport to hospital[b,c]	14073	2.63	1.99–3.47	0.50	0.35–0.72	1.20	0.92–1.56	1.37	0.93–1.99
Naloxone administered[b,c]	14073	0.12	0.08–0.17	3.97	2.77–5.69	0.59	0.44–0.78	0.16	0.09–0.30
Naloxone response[b,c]	557	1.11	0.41–3.03	2.51	0.86–7.33	1.12	0.53–2.38	0.17	0.04–0.67
SEIFA quintile[c]	9412								
1 (greatest disadvantage)		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
2		0.92	0.70–1.20	1.09	0.70–1.68	0.98	0.75–1.19	0.94	0.65–1.36
3		2.91	2.00–4.24	1.47	0.81–2.64	2.62	1.79–2.94	2.83	1.80–4.43
4		1.39	1.03–1.87	1.08	0.66–1.76	1.43	1.06–1.93	1.03	0.69–1.55
5 (least disadvantage)		2.03	1.46–2.83	1.54	0.92–2.57	1.49	1.07–2.09	1.13	0.73–1.77
Alcohol involvement[c]	14073								
Not stated		Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Alcohol involved, no intoxication		1.45	1.00–2.09	1.33	0.70–2.49	1.32	0.91–1.84	0.69	0.42–1.13
Alcohol intoxication		1.72	1.28–2.32	0.62	0.33–1.16	1.29	0.96–1.74	0.74	0.50–1.10
Heroin involvement[b,c]	9785	0.06	0.03–0.10	0.75	0.33–1.73	0.14	0.08–0.23	0.47	0.25–0.88
Illicit drug use[b,c]	14073	0.19	0.13–0.26	0.54	0.28–1.04	0.36	0.26–0.50	0.22	0.13–0.39
Non–opioid extramedical pharmaceutical use[b,c]	14073	1.63	1.27–2.10	0.67	0.42–1.08	1.72	1.33–2.22	3.15	2.20–4.52
Comorbid mental health symptoms[b,c]	14073	1.42	1.08–1.86	0.39	0.22–0.70	1.23	0.94–1.62	1.42	1.01–2.02

Table 3. (Continued)

	n	Codeine		Fentanyl		Oxycodone		Oxycodone–naloxone	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Comorbid suicidal thoughts or behaviours[b,c]	14 073	4.46	3.52–5.66	0.22	0.12–0.42	2.57	2.02–3.26	2.67	1.98–3.61
Comorbid non-suicidal self-injury[b,c]	9785	2.28	0.92–5.65	0.70	0.13–3.63	1.42	0.56–3.60	1.50	0.47–4.78
Accidental overdose[b,c]	14 073	0.38	0.28–0.52	2.89	1.97–4.24	0.41	0.30–0.57	0.26	0.14–0.47
Unknown intent overdose[b,c]	14 073	1.43	1.07–1.92	1.73	1.60–2.63	1.26	0.93–1.69	0.62	0.40–0.97
Past history of psychiatric issues[b,c]	14 073	3.18	2.58–3.91	0.81	0.57–1.14	1.98	1.61–2.44	2.36	1.79–3.11

	Morphine		Tramadol		Tapentadol		Multiple Opioids	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Glasgow Coma Scale[d]								
Non-responsive	Ref		Ref		Ref		Ref	
Severe impairment			2.46	1.11–5.44	–	–	2.15	1.07–4.31
Moderate impairment			3.67	1.91–7.06	2.99	0.26–34.56	1.72	0.94–3.15
Minor–no impairment			3.96	2.41–6.51	5.96	0.80–44.33	2.17	1.43–3.31
Age (years)								
12–34	Ref		Ref		Ref		Ref	
35–54			0.48	0.37–0.63	0.83	0.41–1.70	0.64	0.49–0.84
55–64			0.28	0.19–0.40	0.42	0.13–1.32	0.47	0.33–0.67
> 65			0.19	0.12–0.30	1.09	0.43–2.76	0.45	0.30–0.66
Sex[f]								
Male	Ref		Ref		Ref		Ref	
Female			1.86	1.47–2.33	2.30	1.26–4.21	2.35	1.88–2.95
Respiration rate[c]								
< 6	Ref		Ref		Ref		Ref	
6–12			4.35	1.90–9.99	–	–	2.14	1.17–3.91
> 12			7.54	3.40–16.74	–	–	2.63	1.49–4.64
Transport to hospital[b,c]			1.42	1.03–1.96	2.82	0.85–9.35	2.21	1.57–3.12
Naloxone administered[b,c]			0.17	0.10–0.27	0.12	0.02–0.90	0.59	0.42–0.83
Naloxone response[b,c]			0.53	0.16–1.84	–	–	0.70	0.29–1.64
SEIFA quintile[c]								
1 (greatest disadvantage)	Ref		Ref		Ref		Ref	

(Continues)

Table 3. (Continued)

	Morphine		Tramadol		Tapentadol		Multiple Opioids	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
2			0.92	0.67–1.28	0.83	0.31–2.22	0.94	0.68–1.29
3			**2.58**	**1.71–3.90**	**3.33**	**1.32–8.44**	**2.63**	**1.75–3.97**
4			1.39	0.99–1.95	1.45	0.58–3.66	**1.57**	**1.12–2.19**
5 (least disadvantage)			**1.48**	**1.01–2.16**	**2.56**	**1.05–6.24**	**1.58**	**1.09–2.29**
Alcohol involvement[c]								
Not stated	Ref	Ref	Ref		Ref		Ref	
Alcohol involved, no intoxication			1.11	0.74–1.68	1.77	0.72–4.34	1.02	0.68–1.52
Alcohol Intoxication			1.10	0.79–1.54	0.78	0.30–2.06	0.93	0.67–1.30
Heroin involvement[b,c]			**0.14**	**0.08–0.28**	–	–	**0.05**	**0.02–0.13**
Illicit drug use[b,c]			**0.30**	**0.20–0.44**	0.36	0.10–1.22	**0.20**	**0.13–0.31**
Non–opioid extramedical pharmaceutical use[b,c]			**2.30**	**1.71–3.09**	**3.66**	**1.42–9.44**	**3.14**	**2.33–4.22**
Comorbid mental health symptoms[b,c]			1.20	0.88–1.63	1.12	0.50–2.50	1.30	0.96–1.76
Comorbid suicidal thoughts or behaviours[b,c]			**2.76**	**2.12–3.59**	**3.80**	**2.04–7.07**	**3.51**	**2.70–4.56**
Comorbid non–suicidal self–injury[b,c]			1.86	0.70–4.97	–	–	1.60	0.59–4.32
Accidental overdose[b,c]			**0.48**	**0.32–0.71**	0.31	0.07–1.32	**0.50**	**0.34–0.73**
Unknown intent overdose[b,c]			1.26	0.90–1.75	0.31	0.07–1.30	1.35	0.98–1.87
Past history of psychiatric issues[b,c]			**1.95**	**1.54–2.48**	**3.35**	**1.76–6.39**	**2.40**	**1.90–3.04**

Bolded text indicates statistically significant differences. [a]Estimates are using national data unless specified otherwise; [b]reference category is no/not stated/not effective; [c]adjusted for age group, sex, concurrent alcohol, heroin, illicit drug and other pharmaceutical use; [d]adjusted for age group, sex, and concurrent other substance use; [d]adjusted for age group and concurrent other substance use; [f]adjusted for sex and concurrent other substance use; insufficient case numbers available for inclusion of state location as effect modifier, estimates produced using Victoria data only; [g]excluding heroin. OR = odds ratio; CI = confidence interval; SEIFA = Socio–Economic Indexes for Areas.

Victoria appeared representative of the 'snapshot' Australian states.

DISCUSSION

We examined more than 14 000 ambulance attendances related to extramedical pharmaceutical opioid use to determine if the rates and the severity of attendances differed by opioid type. There are three key findings. First, the rates of attendances differed by opioid, and this was not explained by potency. Different attendance rates were also observed for oxycodone and oxycodone–naloxone. Secondly, the supply-adjusted attendance rates were stable over time, and appeared unaffected by large changes in supply. Thirdly, severity and other attendance characteristics differed by opioid. We now explore these key findings in more detail.

When considering supply-adjusted rates for single-opioid attendances, the highest rate was for codeine (the lowest potency opioid examined), which was more than 50 times that of the lowest rate calculated observed with tapentadol. For buprenorphine (transdermal) and pethidine, attendances were rare (fewer than five each), so rates could not be calculated, although the limited number of cases is a finding in itself. This wide variation in supply-adjusted rates between opioids is contrasted with relative consistency in the supply-adjusted rate over time within individual opioid types, despite considerable changes in some supply volumes over the study period. For example, oxycodone supply volume reduced (~ 50%) from 2014 to 2018, and oxycodone–naloxone more than doubled during the same period. Tapentadol supply steadily increased from 2013, becoming the fourth most commonly supplied opioid in 2018. This consistency in supply-adjusted rates may suggest that harms relating to specific opioids are more closely linked to the opioids and less affected by context, such as changing patterns of use, greater experience prescribing or knowledge of harms. Low rates of attendees with tapentadol appear consistent with a lower abuse liability reported elsewhere [28,29].

The differences between oxycodone and oxycodone–naloxone attendance rates demonstrate that the opioid alone does not determine the rate of harm. The supply-adjusted rate of oxycodone–naloxone-related attendances was consistently one-third that of oxycodone throughout the study period. The exception to this appears to be in the final 12 months of the observation period, where rates of oxycodone-related harm increased, while supply reduced. Differences in demographic characteristics were also present, with oxycodone-related attendances being more likely to involve younger age groups compared with oxycodone–naloxone-related attendances, although females were over-represented in both groups. For socio-economic status, for opioids other than fentanyl rates seemed to decrease with disadvantage, and appears broadly consistent with other studies finding that opioid mortality is a concern among all socio-economic groups [30].

The apparent association between availability, formulation and harm is another important consideration. The highest rates of harm were observed with codeine. In Australia, codeine was available in compounded medications without a prescription for the majority of the study period, and as a lesser regulated (Schedule 4) prescription opioid when compounded with acetaminophen or ibuprofen. Sales data indicated that supply was approximately evenly split between the over-the-counter and prescribed codeine, with minimal supply as a restricted single-ingredient product [31]. It is possible that ease of access and the compounded ingredients (e.g. acetaminophen–codeine combinations) contributed to the harms observed. Notably, codeine-related attendances had four times higher odds of having suicidal intent documented and were less likely to represent accidental overdoses. Both codeine and tramadol-related attendances, the two lesser-restricted opioids in Australia, represented largely younger females with suicidal or self-injurious intent, consistent with international evidence [32]. This highlights that not all opioid-related harm can be addressed through measures aimed at accidental overdose.

Finally, although fentanyl-related attendance rates were low, particularly in Victoria, they were characterized by their medical severity, and were reflective of heroin overdoses with low consciousness, respiration, more males, higher rates of naloxone administration and low rates of transport to hospital [33]. This severity of attendances is consistent with other Australian data [34] and considerable opioid-related mortality attributed to the widespread fentanyl supply in North America [35]. In contrast to the cases here, fentanyl is more likely to be prescribed to older adults and to females [36]. In general, there was an over-representation of younger people despite most opioid prescriptions being for older adults [37]. With the exception of morphine and fentanyl-related attendances, both supply data and ambulance data show consistent over-representation of females [37], highlighting the need for female-specific research in this area.

Implications for policy

Policy attention has largely focused on accidental overdose, with relatively less focus on intentional harm. Future research may explore the role of regulation to address intentional self-harm. Reduced access to pharmaceuticals may reduce suicide by pharmaceutical self-poisoning, as well as suicide more generally [38,39]. Self-poisoning is a commonly reported modality for suicide attempts [40].

Implications for practice

Most clinical efforts to prevent opioid-related harm have focused on accidental overdose, such as via naloxone distribution programmes, patient education [41] and limiting higher-dose prescribing of opioids for chronic pain [42]. This work is important for stronger opioids (e.g. fentanyl), but may be less relevant to codeine and tramadol-related harms. Understanding the clinical context and contributors to intentional self-harm may inform such initiatives. Prescribers should also be aware of the distinctly different harm profiles with different opioids and opioid formulations, particularly as newer products are introduced.

Strengths and limitations

This paper has a number of strengths. This study is unique, in that it examines a range of harms related to extramedical use, extending existing work that has predominantly focused on overdose as an outcome. This work underscores the need to understand the role of suicide and self-harm in escalating opioid-related mortality [40,43]. As a sensitive and timely population-level indicator of harm, this work highlights the utility of coded ambulance attendances to monitor harms with new opioid formulations, and to evaluate policy changes intended to address opioid-related harm.

There are also limitations with these data. Toxicological results are not available to confirm the reported substances taken, although in many cases documented medical histories confirm patient self-report. The opioid source cannot be determined, thus the contribution of diversion to harm cannot be quantified. These administrative data were not primarily generated for research. The analysis of each attendance by trained coders results in a validated and reliable data set [17], although there are still limitations in the information provided by paramedic clinical notes, which are based on clinical observations, and information provided by patients and others at the scene. Supply-adjusted rates make assumptions around OME, although patterns observed with rates unadjusted for supply appear consistent, suggesting that correcting for underlying volume of supply is unlikely to have biased the result.

Some cases involved multiple opioids, so the contribution of individual opioids cannot be determined in these cases; however, as most cases involved a sole opioid, this lessens the risk that this would have affected our results. This analysis did not explore temporal trends in attendance characteristics, although future analysis to explore trends with oxycodone, where harms appeared to be increasing over time, are warranted. Finally, the low number of tapentadol-related attendances result in relatively wide confidence intervals concerning estimates for demographic characteristics. The lack of differences between tapentadol-

and morphine-related attendances may be due to sample size; future studies should revisit these comparisons when more data are available.

In conclusion, this study represents one of the most detailed population-level examinations of pharmaceutical opioid-related harm. We found distinct patterns of rates, types and severity of harms related to different opioids, even when comparing opioids of comparable clinical efficacy. These findings highlight the need to consider factors such as the opioid formulation, and the role of self-harm, to develop nuanced responses to pharmaceutical opioid-related harm.

Declaration of interests

Acknowledgements

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 RECORD Checklist of items - extended from the STROBE statement to include items that should be reported in observational studies using routinely collected health data.

Table S2 Search terms for tapentadol-related ambulance attendances.

Table S3 Variables and response options to be examined in association with pharmaceutical opioid-related ambulance attendances.

Table S4 Missing data.

Table S5 Poisson regression following multiple imputation (Victoria).

Table S6 Attendance rates for Queensland, New South Wales (NSW), Australian Capital Territory (ACT), Northern Territory, and Tasmania combined from snapshot months.

Table S7 Patient characteristics for pharmaceutical opioid-related ambulance attendances from January 2013 to September 2018 (Victoria only).

Figure S1a Raw ambulance attendance rates.

Figure S1b Raw opioid supply.