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Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

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Declarations of competing interests

In the past 5 years, SN has been an investigator on untied education grants from Indivior, unrelated to the current work. SN has provided training to health care professionals on identifying and treating codeine dependence for which her institution has received payment from Indivior. DL has received speaking honoraria from the following: Astra Zeneca, Indivior, Janssen-Cilag, Lundbeck, Servier and Shire, and has participated on Advisory Boards for Indivior and Lundbeck.

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Abstract

Introduction and aims: Extramedical use of, and associated harms with pharmaceutical opioids are common. Analysis of coded ambulance clinical records provides a unique opportunity to examine a national population-level indicator of relative harms. This protocol describes an observational study with three aims: (1) To compare supply-adjusted rates of pharmaceutical opioid-related ambulance attendances for, buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol; (2) to compare presentation characteristics for these commonly used pharmaceutical opioids; and (3) to describe the context surrounding ambulance presentations related to oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a more recent 'atypical' opioid on the Australian market, with fewer studies that have directly examined signals of extramedical use.

Method: Trained coders extract data from clinical records for ambulance presentations relating to extramedical use of commonly used pharmaceutical opioids. This data forms the basis of a large, national database that captures alcohol and drug related harms. Supply adjusted rates of presentations will be examined using Poisson regression and multinomial logistic regression will be used to compare severity and other characteristics of attendances relating to different pharmaceutical opioids. Tapentadol-related and oxycodone-related cases will be qualitatively examined to understand the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables.

Ethics and dissemination: Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Findings will be submitted for peer review in 2019. The understanding of risk-profiles in real-world settings is of international public health importance. The analysis and publication of findings from this national dataset of clinical records will provide one of the most nuanced analyses to date of relative harms across nine pharmaceutical opioids over a seven-year period.

Keywords: pharmaceutical opioids, ambulance attendance, extramedical use, overdose, oxycodone, tapentadol

Article summary

- There are few studies which examine the relative harms associated with different pharmaceutical opioids
- This study will provide one of the most nuanced analyses to date of relative harms across nine pharmaceutical opioids across a seven-year period.

Strengths and limitations

- Strengths of this study include use of coded pharmaceutical opioid-related ambulance attendance data as validated population-level indicator of opioid-related harm such as extramedical use and overdose to inform risk profiles in real-world settings
- We will compare the supply-adjusted rates and characteristics of ambulance attendances with commonly used pharmaceutical opioids
- Limitations include the use of administrative data, and a lack of toxicological data to confirm substances taken

Introduction

Recently, the world's attention has focused on the rapidly escalating opioid-related deaths occurring in North America and other high-income countries (1). This has put into sharp focus the need to understand the risk profiles associated with different pharmaceutical opioids.

The number and potency of available pharmaceutical opioids has increased rapidly over the past decades. Morphine, a selective mu-opioid agonist, was isolated more than 200 years ago (2). Following this, analogues such as diamorphine and codeine were developed. Later, semi-synthetic opioids such as oxycodone (a full agonist at the mu-opioid receptor) and buprenorphine (a partial agonist at the mu-opioid receptor (with activity at delta and kappa) (3) were isolated. In addition, newer 'atypical' opioids such as tramadol and tapentadol exert their analgesic effects via opioid and non-opioid mechanisms (4). Tramadol, a lower potency mu opioid receptor agonist with a more potent metabolite, also selectively inhibits noradrenalin and serotonin uptake (5, 6). Tapentadol is another synthetic opioid, structurally similar to tramadol, with mu-opioid receptor agonism and inhibition of noradrenaline reuptake (7).

A United States (US) study of severe adverse events (SAEs) found a positive linear relationship between opioid potency and SAE rate, with the highest rate observed with hydromorphone (8.02 SAEs/100 kg), and the lowest rate with tapentadol (0.27 SAE/100 kg) (8). This suggests that harms related to opioids may not be equal, though replication studies outside the US are needed.

Abuse liability studies also find differences between prescribed opioids. Differences in the strength of reinforcing or subjective effects between tramadol, oxycodone, codeine have been found (9). Subjective effects of oxycodone appeared greater than codeine, though all opioids examined were reinforcing, particularly at higher doses (9). A separate study examined ratings of 'I feel high', and the amount that people were willing to pay for a drug varying by opioid type (10). Defined doses of diamorphine, morphine, and oxycodone had higher ratings than buprenorphine and fentanyl (10). In this study, oxycodone produced robust reinforcing effects, consistent with systematic review of nine studies that oxycodone had a higher abuse liability relative to other opioids (11).

Although abuse liability may vary in controlled laboratory studies, opioid use in real-world settings can vary as a function of cost, availability and other contextual factors (12). For this reason, pharmacovigilance studies are important to monitor for signals of extramedical use in real-world settings. Further, signals of extramedical use may only appear after trials, as those likely to use opioid

extramedically are often excluded from these studies, so data from diverse populations is important (13).

Sentinel surveillance aims to assess nonmedical use and harms with opioids such as oxycodone and morphine (14). For newer opioids, or opioids infrequently used by sentinel study populations, population level studies can more completely assess for signals of extramedical use (15). One population level indicator of opioid-related harm is ambulance attendances. These data are recognised as a valuable data source for identifying population level signals of harm (16). In Australia, the clinical records of ambulance attendances related to extramedical use of pharmaceuticals (i.e. use outside a medical context, or in a higher dose than prescribed) are coded by trained research assistants. These data can inform the risk profile with different pharmaceutical opioids (17), and has been used to monitor harms related to quetiapine and pregabalin (18, 19). These data can determine if unintended harms such as extramedical use and overdose are emerging, and provide information on the frequency, severity and context of presentations.

As such, this paper outlines the design of a study that aims to conduct a detailed examination of ambulance attendances related to pharmaceutical opioids, and test the hypothesis that the context and frequency of harms with different opioids will vary by opioid type. We write this protocol to maximize transparency (20, 21). The study is supported by an untied educational grant by Seqirus, who make Palexia® (tapentadol) and Tramal® (tramadol). The funders have no role in the design, conduct, analysis and interpretation of the study and its findings. As has been highlighted by others in the field (22), prospectively publishing study protocols with primary aims and related analysis plans assist in establishing independence around the study design, providing transparency, and ensuring a commitment to publishing study findings regardless of the outcome (21).

Methods

Study aims

This study has three aims:

1) Compare the supply-adjusted rates of ambulance attendances across commonly used pharmaceutical opioids (buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol).
2) Compare presentation characteristics for these nine opioids.
3) Describe the context surrounding ambulance presentations related to two opioids: oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a newer opioid with fewer studies describing extramedical use.

We will answer the following research questions:

1. Do the supply-adjusted rates of ambulance presentations differ by opioid potency?
2. Does the severity of presentation (as measured by presenting Glasgow Coma Scale, GCS) or other characteristics vary by opioid type?
3. Are there differences in the context surrounding ambulance presentations related to extramedical use of oxycodone and tapentadol?

Study design and setting

Data come from ambulance attendances in Victoria; a state which comprises approximately 26% of Australia's population (23), supplemented by national ambulance data. The Victorian dataset provides complete coverage across the study period (June 2013 until September 2018, excluding 3 months of missing data October - December 2014, due to industrial action). Coded electronic patient care records (ePCR) provide information on acute harms arising from extramedical pharmaceutical use, thus allowing comparison of attendance characteristics across multiple opioids.

We will examine data from the National Ambo Project from Queensland, New South Wales, Australian Capital Territory, Northern Territory and Tasmania to determine if Victorian trends are comparable to national trends. National data is available in quarterly 'snap-shot months' (Table 1) and are screened and coded using the same procedures and coders as the Victorian data.

Pharmaceutical opioid sales data

We will estimate the amount of each opioid supplied using monthly sales data (IQVIA third party access program). The total amount of each opioid will be calculated by jurisdiction in mg, converted into Oral Morphine Equivalents (OME) (24), and used to calculate a supply-adjusted rate of attendances.

Ambulance attendance data

Ambulance data are collected as part of the Ambo Project, a collaboration between Turning Point, Monash University and Ambulance Victoria (AV). Methods for the Ambo Project have been previously described (e.g. (18, 19)) and are outlined below.

Data includes electronic patient care records (ePCR), computer aided dispatch notes, and clinical details associated with the attendance that provide part of the patient care record (e.g. records of respiration rate and GCS). Primary filtering based on over-inclusive keyword searches identifies

attendances with involvement of alcohol, other drugs, or mental health symptomology. This filtered dataset is provided to Turning Point where data cleaning, validation, and coding of the ePCR is performed by a specialist team of research assistants. A systematic and validated coding system captures information from the ePCR. The core criterion used in determining the involvement of a substance is: "Is it reasonable to attribute the immediate or recent (not merely chronic) over- or inappropriate (i.e. extramedical) ingestion of the substance or medication as significantly contributing to the reason for the ambulance attendance?", as determined through examination of the clinical notes. As such, this dataset captures information on acute, not chronic, harms.

For this study, ambulance attendances where extramedical pharmaceutical opioid use was identified as a significant contributor to an attendance will be included. This dataset excludes cases of solely therapeutic use. Pharmaceutical opioid-related attendances include those where; a person prescribed opioids consumed medication more often or in higher than recommended amounts; a person consumed opioids not prescribed to them, or if opioids were consumed with a combination of other substances that contributed to the ambulance attendance. The inclusion criteria mean that extramedical opioid use must significantly contribute to the attendance, however other drugs or substances may have also been over- or inappropriately consumed, and the extramedical opioid use may not be the primary or only reason for the ambulance attending. These criteria differentiate Ambo Project data from adverse event reporting from the Therapeutic Goods Administration (TGA) Database of Adverse Event (AE) Notifications (25), which captures spontaneous AEs from prescribed medications. Spontaneous AE reporting can effectively identify serious harms with prescribed medicines, though is recognised to miss the vast majority of AEs (26).

Other associated factors such as alcohol and other drug use, mental health symptoms, and self-harm are also coded. All illicit drug use is coded, regardless of quantity. Current mental health symptomology is coded rather than mental health diagnosis as paramedics do not screen or assess mental illness diagnoses during an ambulance attendance.

These methods are consistent across other jurisdictions, which collect quarterly data as part of the National Ambo Project, with the exception that ambulance services in Tasmania, Australian Capital Territory, and the Northern Territory provide all data and do not undertake primary filtering.

All substances related to the attendance are coded; including alcohol, illicit & pharmaceutical drugs. For this project, we will examine buprenorphine (as a single ingredient), codeine (codeine as a single ingredient, and in combination with paracetamol, or ibuprofen, or aspirin), fentanyl, morphine, oxycodone, oxycodone-naloxone, pethidine, tapentadol and tramadol. We will exclude opioids used as treatments for opioid dependence (methadone, buprenorphine-naloxone, or buprenorphine and a

single ingredient where indicated that it is for treatment of opioid dependence) as these represent a different clinical indication and specific treatment population.

Buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine and tramadol are routinely coded in the Ambo project database. Cases involving tapentadol are routinely coded in an 'other opioid' category. For this study 'tapentadol-related' cases will be identified and coded by reviewing all cases from June 2013 (aligned with tapentadol availability as a subsidised medicine in Australia), until September 2018. This is identical to the coding process used with other opioids, the only difference being that the cases will be coded retrospectively from 'other opioids' to 'tapentadol' where there is evidence of tapentadol involvement in the ePCR.

Aim 1 – supply-adjusted trends 2013-2018

Analysis of supply-adjusted trends will occur by quarterly aggregation of attendances in Victoria, by opioid group, with further aggregation to half-yearly if required to preserve cell sizes of at least five in the majority of cells. Where cell sizes of <5 occur, to preserve anonymity we will report average of all cells with 1-4 cases, rather than the number of cases in that cell. Units will be attendances per 100 000mg OME (24).

Aim 1 analysis plan

Prescription opioid-related ambulance attendances will be aggregated into 3 monthly periods corresponding to yearly quarters. Basic descriptive statistical analyses will be used to explore these attendances in Victoria, analyses include frequencies (number of attendances), proportions (demographics), and supply-adjusted rates.

Poisson regression will be used to assess trends in supply-adjusted rates for Victoria. Regression models will be fitted (one for each opioid), and adjusted for quarterly and yearly trends with the number of days per month used to offset the regression. Rates will be calculated for Victoria (where completed data are available), and compared with rates observed in other states for the time periods that data are available (Table 1). Due to industrial action, September 2014 contains partially complete data (26 out of 30 days). Supply data for this month will be weighted to represent the average supply for the proportion of days provided for September, with the offset variable representing the total number of days where data has been supplied.

The intention is to assess trends within each opioid where the opioid has been solely indicated, as well as a 'multiple opioid' category representing cases where multiple opioids have been indicated.

However, where this is not possible due to small case numbers, trends will be assessed using all cases in which the opioid has been indicated (sole use and multiple opioids).

Aim 2 – characteristics of attendances

For this analysis, opioid-related attendances will be analysed by opioid type listed above, by characteristics as per Table 2.

Aim 2 analysis plan

Multinomial logistic regression will be used to analyse characteristics of opioid-related attendances by opioid type. Opioid type (sole use of each opioid and multiple opioid use) will be used as the dependant variable, with each category being compared to morphine as mid-potency opioid, regressed on each characteristic separately. If the number of morphine cases is insufficient to allow use as a reference category then oxycodone will become the reference category. Each model will be adjusted for using a collapsed state variable (where jurisdictions with expected fewer cases such as the Australian Capital Territory and Northern Territory will be aggregated into an 'other states' category). When considering GCS as a proxy for severity, the model will be further adjusted for age, gender, concurrent alcohol use, concurrent illicit drug use (excluding heroin), concurrent heroin use, and concurrent non-opioid pharmaceutical use. All other models will be further adjusted for age, gender and other substance use (as an aggregated variable of concurrent alcohol use, illicit drug use, heroin, and non-opioid pharmaceutical misuse). Results will be reported as odds ratios. Comparison between states will be analysed through an interaction between state and characteristic.

Aim 3 – qualitative analysis of contexts of oxycodone and tapentadol-related attendances

Detail from the free-text fields from the ePCR will be utilised to establish a more complete picture of the ambulance attendance. These data are subject to rigorous coding by a highly trained team of coders using well-established and tested coding frameworks for existing fields, however additional uncoded data are available in these free-text fields are rarely used for qualitative analyses. Some studies have used text-based information to explore specific phenomena in further detail, such as intentional and unintentional injury (27) and heroin overdose (28).

We will use text-based case descriptions of oxycodone-related and tapentadol-related cases. These will be qualitatively examined in order to provide insight into the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables. We will compare tapentadol-related cases (with tapentadol being a newer 'atypical' opioid with a suggested lower rate of associated adverse events (8) and less non-medical use (29)), to oxycodone-related attendances, as oxycodone is the predominant opioid-analgesic prescribed in Australia (30) and has a

well-recognised abuse liability (11). We will consider the details of circumstances surrounding the presentation including details provided on the role and effect of the opioid used.

Aim 3 analysis plan

Qualitative coding will occur in two stages. First, an initial group of randomly selected cases (estimated n=30-40 until saturation has occurred) will be examined by two researchers to independently determine a coding framework. The researchers will negotiate a consensus framework, then code the remaining cases using this agreed upon framework. The project team will convene regularly to discuss coding techniques as they develop as well as emerging themes. A 10% sample of cases will be checked by a third researcher to confirm coding consistency, with further cases reviewed if inconsistencies are identified.

We will examine an equal number of tapentadol- and oxycodone-related cases, based on the number of cases identified for tapentadol (the less frequently used opioid). We will use a random number generator via Excel to randomly select an equal size number of oxycodone-related cases for qualitative comparison (i.e. the same number of cases as in the tapentadol-related case group), and perform the same analyses for oxycodone-related presentations. To ensure that selected oxycodone cases represent all oxycodone cases the sub-group of oxycodone-related attendances will be selected by weighted random sampling, with weightings on the basis of sex, age group, jursidiction and if the attendance was related to self-harm. Cases involving both tapentadol and oxycodone will be considered as a separate group.

In addition to qualitative analysis, multinomial regression will be used to analyse coded variables representing different aspects of attendance context surrounding three mutually exclusive groups: (1) tapentadol-related cases, (2) oxycodone-related cases, and (3) cases that are related to the concomitant use of tapentadol and oxycodone (i.e. considered-related to both opioids). Results will be reported as odds ratios.

All quantitative analysis for aims 1-3 will be conducted in STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP), with p values less than 0.05 considered significant. Qualitative data will be managed and analysed using nVivo 12.0 (31), but any subsequent quantitative analyses conducted using STATA as above.

Handling known or expected missing data

Where there are missing data for the characteristics of attendances, we will report the available sample size for each variable. To enable calculation of rates for each quarter with potentially identifiable cases (cell size 1-4), we will impute a value representing the mean for all potentially

identifiable cases. This will preserve the total number of cases without compromising privacy of individuals.

There are three months of missing Victorian data due to industrial action (October – December 2014) with partial missing data (4 days) for September 2014. For these months, to enable calculation of rates (Aim 1), we will impute values based on data from September – December in the previous and following year (2013 and 2015). In a planned sensitivity analysis, we will compare results using imputed data to results excluding missing data and report any differences observed.

Ethics and dissemination

Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Consistent with the ethics approval, cells of <5 will not be reported, though zeroes will be preserved. Due to the sensitivity and potentially identifiable nature of the data line item data is not available for sharing, consistent with the ethics approval.

We will present project findings at relevant scientific conferences. We plan to submit findings for publication as two peer-reviewed journal articles. One article will incorporate the quantitative analysis (aim 1 and 2) and one paper report the qualitative analysis (aim 3). We will report findings in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, an extension of the STROBE statement for reporting items specific to observational studies using routinely collected health data (32).

Discussion

Strengths and limitations

Recommendations for methods for pharmacovigilance studies identified a number of important features, depending on the aims of the study and the methods employed (16). These include the prospective publication of a study protocol including a detailed statistical analysis plan, transparency around study funding and publication in open-access journals. This study will conform to these requirements.

This study has several strengths. Firstly, coded ambulance data captures a broader range of outcomes and a wider population of people with extramedical pharmaceutical opioid use than may be captured in abuse liability studies, clinical trials, or spontaneous AE reporting systems.

Secondly, this study's population level database accurately codes detailed information about each attendance. This level of detail can provide important insights into harms related to substance use (17-19, 33-35). This study will represent an extension of these studies to provide a detailed analysis of rates and characteristics of harms related with widely used pharmaceutical opioids, and is strengthened by the use of population level supply data to calculate supply-adjusted rates. Finally, the study will be first to provide detailed context around circumstances of pharmaceutical opioid related ambulance attendances, utilising coding of qualitative data.

There are limitations in the use of data collected for operational purposes, similar to with hospital inpatient and emergency department data. There is potential for biases to exist in collection and coding, and incomplete or inconsistent recording of variables. Substance involvement is determined from patient-provided information, others at the scene, or paramedic's clinical assessment, not from toxicological testing. Other clinical details (e.g. mental health symptoms) are also determined in this way.

Rates of ambulance attendances are calculated based on sales data. Due to frequent ordering and limited capacity for controlled drug storage at the community pharmacy level, sales closely approximate supply. Use of sales data addresses limitations with publicly funded prescription data, which omits privately purchased prescriptions and over-the-counter medications and therefore is an incomplete measure of community opioid supply. Finally, as this is a naturalistic study, we cannot know if different patient populations are more likely to receive a given opioid. As such, there may be unmeasured confounders. Randomised trials can address this limitation; however, patients who use opioids extramedically are usually excluded from trials.

Data statement

To protect privacy and confidentiality, data from the Ambo Project are provided to Turning Point under strict conditions for the storage, retention and use of the data. The current approval permits storage of the data at one site, Turning Point, with any analysis to be undertaken onsite, no data to be removed, and no dissemination of unit level data. Researchers wishing to undertake additional analyses of the data are invited to contact Turning Point as the data custodians.

Conclusion

This will be the first detailed study to compare coded ambulance ePCR as a population level indicator of prescription opioid-related harm. These data will complement ongoing studies examining extramedical use of tapentadol in sentinel populations of people who use drugs, and data from poisons information centres (36). The data in this study represent all acute presentations in community settings where extramedical use of a pharmaceutical opioid analgesic is considered related to the ambulance attendance. This unique dataset has national reach and demonstrated consistency and completeness over multiple years. It will provide one of the most complete analyses of relative harms due to extramedical use for a range of pharmaceutical opioids to date. The study will add to our knowledge, and lead to a more nuanced understanding of whether different pharmaceutical opioids are associated with different harms.

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Author statement

SN conceptualised the study and drafted the initial design, with input from RC and DS. CW and MM provided input on the data analysis plan. All authors contributed the drafting of the protocol manuscript and revisions.

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Table 1. Summary of data availability across jurisdictions

State / Territory	Notes on data available^
ACT	All cases coded one month per quarter from March 2015 until December 2017
NSW	All cases coded one month per quarter from March 2015 until December 2017
NT	All cases coded one month per quarter from March 2016 until December 2017
QLD	All cases coded one month per quarter from March 2015 until December 2016
TAS	All cases coded one month per quarter from March 2014, until December 2017
VIC	All cases coded from January 2012 till September 2018
WA & SA	Data not yet available

^ We will conduct a comparison on supply-adjusted rates of attendance for Victoria and other states utilising periods of time where corresponding data are available.

Table 2. Variables and response options to be examined in association with pharmaceutical opioid-related ambulance attendances

Variable	Response options
Presenting Glasgow Coma Scale (GCS)	3 (non-responsive), 4-12 (moderate-severe impairment), 13-15 (minor-no impairment)
Presenting respiratory rate (breaths per minute)	<6, 6-12, >12
Transport to hospital	Not transported, transported
Naloxone administered: not stated, yes	Not states, yes
Naloxone response: not effective, effective	Not effectives, effective
Sex of patient	Male, female, other/unspecified
Age of patient	12-54, 55-65 (nearing retirement age) and 65+^
Socio-economic status based on residential postcode	Quintile 1-5 based on SEIFA-IRSD 201s, IRSD 2016 (30)
Concurrent alcohol involvement	Not stated, alcohol involved but no evidence of intoxication, alcohol intoxication∞
Concurrent heroin involvement	Not stated, present
Concurrent illicit drug use (excluding heroin)	based on the presence of at least one of the illicit drugs coded for; meth(amphetamine), cannabis, synthetic cannabinoids, emerging psychoactive substances, cocaine, MDMA, GHB, ketamine, LSD, psilocybin, inhalant, illicit drug other or unspecified)
Concurrent non-opioid extramedical pharmaceutical use	not stated, present (based on the presence of at least one of the pharmaceutical groups coded for; non-opioid analgesics, benzodiazepines, anti-depressants, anti-psychotics, anti-convulsants, opioid-dependence treatments, pharmaceutical stimulants, other medication)
Co-morbid mental health symptoms	not stated, present (based on the presence of at least one of; symptoms of anxiety, depression, psychosis, social / emotional distress, symptoms associated with disorders with clinical evidence, and mental health unspecified)
Co-morbid suicidal thoughts or behaviours	Not stated, present (based on the presence of at least one of; suicidal ideation, suicide ats, suicide attempt)
Co-morbid non-suicidal self-injury	Not stated, present (based on the presence of at least one of; threat of non-suicidal self-injury, non-suicidal self-is, non-suicidal self-injury)
Accidental overdose	Not stated, yes
Unknown intent overdose#	Not stated, yes
Past history of psychiatric issues	Not stated, present (based on the presence of at least one of; past history of mood disorder, psychosis, suicidal ideation, suicide attempt, alcohol and other drug misuse)

^based on previous age categories used in studies of opioid use for pain (27). We will exclude cases where age is reported to be less than 12 due to the unclear intention of use in children of this age, consistent with previous research (28, 29)
#(where information provided in the patient care records by the paramedic means that the coding team cannot determine if the overdose was accidental or if there was suicidal intent)
∞The involvement of alcohol is coded as 'alcohol involved' and 'alcohol intoxication'. Attendances where the person has consumed alcohol, but the paramedic notes do not clearly indicate alcohol intoxication are coded as 'alcohol involved' and 'alcohol intoxication is a subset of 'alcohol involved'. The default code is for 'alcohol involved' unless the paramedic notes provide clear evidence of alcohol intoxication.

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Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

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Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

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Declarations of competing interests

In the past 5 years, SN has been an investigator on untied education grants from Indivior, unrelated to the current work. SN has provided training to health care professionals on identifying and treating codeine dependence for which her institution has received payment from Indivior. DL has received speaking honoraria from the following: Astra Zeneca, Indivior, Janssen-Cilag, Lundbeck, Servier and Shire, and has participated on Advisory Boards for Indivior and Lundbeck.

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Abstract

Introduction and aims: Extramedical use of, and associated harms with pharmaceutical opioids are common. Analysis of coded ambulance clinical records provides a unique opportunity to examine a national population-level indicator of relative harms. This protocol describes an observational study with three aims: (1) To compare supply-adjusted rates of pharmaceutical opioid-related ambulance attendances for, buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol; (2) to compare presentation characteristics for these commonly used pharmaceutical opioids; and (3) to describe the context surrounding ambulance presentations related to oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a more recent 'atypical' opioid on the Australian market, with fewer studies that have directly examined signals of extramedical use.

Method: Trained coders extract data from clinical records for ambulance presentations relating to extramedical use of commonly used pharmaceutical opioids. This data forms the basis of a large, national database that captures alcohol and drug related harms. Supply adjusted rates of presentations will be examined using Poisson regression and multinomial logistic regression will be used to compare severity and other characteristics of attendances relating to different pharmaceutical opioids. Tapentadol-related and oxycodone-related cases will be qualitatively examined to understand the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables.

Ethics and dissemination: Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Findings will be submitted for peer review in 2019. The understanding of risk-profiles in real-world settings is of international public health importance. The analysis and publication of findings from this national dataset of clinical records will provide one of the most nuanced analyses to date of relative harms across nine pharmaceutical opioids over a seven-year period.

Keywords: pharmaceutical opioids, ambulance attendance, extramedical use, overdose, oxycodone, tapentadol

Article summary

Strengths and limitations

- Strengths of this study include use of coded pharmaceutical opioid-related ambulance attendance data as validated population-level indicator of opioid-related harm such as extramedical use and overdose to inform risk profiles in real-world settings
- We will compare the supply-adjusted rates and characteristics of ambulance attendances with commonly used pharmaceutical opioids
- Limitations include the use of administrative data, and a lack of toxicological data to confirm substances taken

Introduction

Recently, the world's attention has focused on the rapidly escalating opioid-related deaths occurring in North America and other high-income countries (1). This has put into sharp focus the need to understand the risk profiles associated with different pharmaceutical opioids.

The number and potency of available pharmaceutical opioids has increased rapidly over the past decades. Morphine, a selective mu-opioid agonist, was isolated more than 200 years ago (2). Following this, analogues such as diamorphine and codeine were developed. Later, semi-synthetic opioids such as oxycodone (a full agonist at the mu-opioid receptor) and buprenorphine (a partial agonist at the mu-opioid receptor (with activity at delta and kappa) (3) were isolated. In addition, newer 'atypical' opioids such as tramadol and tapentadol exert their analgesic effects via opioid and non-opioid mechanisms (4). Tramadol, a lower potency mu opioid receptor agonist with a more potent metabolite, also selectively inhibits noradrenalin and serotonin uptake (5, 6). Tapentadol is another synthetic opioid, structurally similar to tramadol, with mu-opioid receptor agonism and inhibition of noradrenaline reuptake (7).

A United States (US) study of severe adverse events (SAEs) found a positive linear relationship between opioid potency and SAE rate, with the highest rate observed with hydromorphone (8.02 SAEs/100 kg), and the lowest rate with tapentadol (0.27 SAE/100 kg) (8). This suggests that harms related to opioids may not be equal, though replication studies outside the US are needed.

Abuse liability studies also find differences between prescribed opioids. Differences in the strength of reinforcing or subjective effects between tramadol, oxycodone, codeine have been found (9). Subjective effects of oxycodone appeared greater than codeine, though all opioids examined were reinforcing, particularly at higher doses (9). A separate study examined ratings of 'I feel high', and the amount that people were willing to pay for a drug varying by opioid type (10). Defined doses of diamorphine, morphine, and oxycodone had higher ratings than buprenorphine and fentanyl (10). In this study, oxycodone produced robust reinforcing effects, consistent with systematic review of nine studies that oxycodone had a higher abuse liability relative to other opioids (11).

Although abuse liability may vary in controlled laboratory studies, opioid use in real-world settings can vary as a function of cost, availability and other contextual factors (12). For this reason, pharmacovigilance studies are important to monitor for signals of extramedical use in real-world settings. Further, signals of extramedical use may only appear after trials, as those likely to use opioid

extramedically are often excluded from these studies, so data from diverse populations is important (13).

Sentinel surveillance aims to assess nonmedical use and harms with opioids such as oxycodone and morphine (14). For newer opioids, or opioids infrequently used by sentinel study populations, population level studies can more completely assess for signals of extramedical use (15). One population level indicator of opioid-related harm is ambulance attendances. These data are recognised as a valuable data source for identifying population level signals of harm (16). In Australia, the clinical records of ambulance attendances related to extramedical use of pharmaceuticals (i.e. use outside a medical context, or in a higher dose than prescribed) are coded by trained research assistants. These data can inform the risk profile with different pharmaceutical opioids (17), and has been used to monitor harms related to quetiapine and pregabalin (18, 19). These data can determine if unintended harms such as extramedical use and overdose are emerging, and provide information on the frequency, severity and context of presentations.

As such, this paper outlines the design of a study that aims to conduct a detailed examination of ambulance attendances related to pharmaceutical opioids, and test the hypothesis that the context and frequency of harms with different opioids will vary by opioid type. We write this protocol to maximize transparency (20, 21). The study is supported by an untied educational grant by Seqirus, who make Palexia® (tapentadol) and Tramal® (tramadol). The funders have no role in the design, conduct, analysis and interpretation of the study and its findings. As has been highlighted by others in the field (22), prospectively publishing study protocols with primary aims and related analysis plans assist in establishing independence around the study design, providing transparency, and ensuring a commitment to publishing study findings regardless of the outcome (21).

Methods

Study aims

This study has three aims:

1) Compare the supply-adjusted rates of ambulance attendances across commonly used pharmaceutical opioids (buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol).
2) Compare presentation characteristics for these nine opioids.
3) Describe the context surrounding ambulance presentations related to two opioids: oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a newer opioid with fewer studies describing extramedical use.

We will answer the following research questions:

1. Do the supply-adjusted rates of ambulance presentations differ by opioid potency?
2. Does the severity of presentation (as measured by presenting Glasgow Coma Scale, GCS) or other characteristics vary by opioid type?
3. Are there differences in the context surrounding ambulance presentations related to extramedical use of oxycodone and tapentadol?

Study design and setting

Data come from ambulance attendances in Victoria; a state which comprises approximately 26% of Australia's population (23), supplemented by national ambulance data. The Victorian dataset provides complete coverage across the study period (June 2013 until September 2018, excluding 3 months of missing data October - December 2014, due to industrial action). Coded electronic patient care records (ePCR) provide information on acute harms arising from extramedical pharmaceutical use, thus allowing comparison of attendance characteristics across multiple opioids.

We will examine data from the National Ambo Project from Queensland, New South Wales, Australian Capital Territory, Northern Territory and Tasmania to determine if Victorian trends are comparable to national trends. National data is available in quarterly 'snap-shot months' (Table 1) and are screened and coded using the same procedures and coders as the Victorian data. See Figure 1 for an overview of data sources and study processes. We will aim to complete case identification by March 2017, with analyses planned for March-April 2019.

Pharmaceutical opioid sales data

We will estimate the amount of each opioid supplied using monthly sales data (IQVIA third party access program). The total amount of each opioid will be calculated by jurisdiction in mg, converted into Oral Morphine Equivalents (OME) (24), and used to calculate a supply-adjusted rate of attendances, consistent with previous studies of pharmaceutical opioid related harm that have adjusted for supply using similar methods (8, 25).

Ambulance attendance data

Ambulance data are collected as part of the Ambo Project, a collaboration between Turning Point, Monash University and Ambulance Victoria (AV). Methods for the Ambo Project have been previously described (e.g. (18, 19)) and are outlined below.

Data includes electronic patient care records (ePCR), computer aided dispatch notes, and clinical details associated with the attendance that provide part of the patient care record (e.g. records of respiration rate and GCS). Primary filtering based on over-inclusive keyword searches identifies attendances with involvement of alcohol, other drugs, or mental health symptomology. This filtered dataset is provided to Turning Point where data cleaning, validation, and coding of the ePCR is performed by a specialist team of research assistants. Details on research assistant training, and interrater review processes are contained in Supplementary files (Appendix A). A systematic and validated coding system captures information from the ePCR. The core criterion used in determining the involvement of a substance is: “Is it reasonable to attribute the immediate or recent (not merely chronic) over- or inappropriate (i.e. extramedical) ingestion of the substance or medication as significantly contributing to the reason for the ambulance attendance?", as determined through examination of the clinical notes. As such, this dataset captures information on acute, not chronic, harms.

For this study, ambulance attendances where extramedical pharmaceutical opioid use was identified as a significant contributor to an attendance will be included. This dataset excludes cases of solely therapeutic use. Pharmaceutical opioid-related attendances include those where; a person prescribed opioids consumed medication more often or in higher than recommended amounts; a person consumed opioids not prescribed to them, or if opioids were consumed with a combination of other substances that contributed to the ambulance attendance. The inclusion criteria mean that extramedical opioid use must significantly contribute to the attendance, however other drugs or substances may have also been over- or inappropriately consumed and the extramedical opioid use may not be the primary or only reason for the ambulance attending. These criteria differentiate Ambo Project data from adverse event reporting from the Therapeutic Goods Administration (TGA) Database of Adverse Event (AE) Notifications (26), which captures spontaneous AEs from prescribed medications. Spontaneous AE reporting can effectively identify serious harms with prescribed medicines, though is recognised to miss the vast majority of AEs (27).

Other associated factors such as alcohol and other drug use, mental health symptoms, and self-harm are also coded. All illicit drug use is coded regardless of quantity. Current mental health symptomology is coded rather than mental health diagnosis as paramedics do not screen or assess mental illness diagnoses during an ambulance attendance.

These methods are consistent across other jurisdictions, which collect quarterly data as part of the National Ambo Project, with the exception that ambulance services in Tasmania, Australian Capital Territory, and the Northern Territory provide all data and do not undertake primary filtering.

All substances related to the attendance are coded; including alcohol, illicit & pharmaceutical drugs. For this project, we will examine buprenorphine (as a single ingredient), codeine (codeine as a single ingredient, and in combination with paracetamol, or ibuprofen, or aspirin), fentanyl, morphine, oxycodone, oxycodone-naloxone, pethidine, tapentadol and tramadol. We will exclude opioids used as treatments for opioid dependence (methadone, buprenorphine-naloxone, or buprenorphine and a single ingredient where indicated that it is for treatment of opioid dependence) as these represent a different clinical indication and specific treatment population.

Buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine and tramadol are routinely coded in the Ambo project database. Cases involving tapentadol are routinely coded in an 'other opioid' category. For this study 'tapentadol-related' cases will be identified and coded by reviewing all cases from June 2013 (aligned with tapentadol availability as a subsidised medicine in Australia), until September 2018. This is identical to the coding process used with other opioids, the only difference being that the cases will be coded retrospectively from 'other opioids' to 'tapentadol' where there is evidence of tapentadol involvement in the ePCR.

Aim 1 – supply-adjusted trends 2013-2018

Analysis of supply-adjusted trends will occur by quarterly aggregation of attendances in Victoria, by opioid group, with further aggregation to half-yearly if required to preserve cell sizes of at least five in the majority of cells. Where cell sizes of <5 occur, to preserve anonymity we will report average of all cells with 1-4 cases, rather than the number of cases in that cell. Units will be attendances per 100 000mg OME (24).

Aim 1 analysis plan

Prescription opioid-related ambulance attendances will be aggregated into 3 monthly periods corresponding to yearly quarters. Basic descriptive statistical analyses will be used to explore these attendances in Victoria, analyses include frequencies (number of attendances), proportions (demographics), and supply-adjusted rates.

Poisson regression will be used to assess trends in supply-adjusted rates for Victoria. Regression models will be fitted (one for each opioid), and adjusted for quarterly and yearly trends with the number of days per month used to offset the regression. Rates will be calculated for Victoria (where completed data are available), and compared with rates observed in other states for the time periods that data are available (Table 1). Due to industrial action, September 2014 contains partially complete data (26 out of 30 days). Supply data for this month will be weighted to represent the average supply

for the proportion of days provided for September, with the offset variable representing the total number of days where data has been supplied.

The intention is to assess trends within each opioid where the opioid has been solely indicated, as well as a 'multiple opioid' category representing cases where multiple opioids have been indicated. However, where this is not possible due to small case numbers, trends will be assessed using all cases in which the opioid has been indicated (sole use and multiple opioids).

Aim 2 – characteristics of attendances

For this analysis, opioid-related attendances will be analysed by opioid type listed above, by characteristics as per Table 2 (additional details on variables are contained in Appendix B).

Aim 2 analysis plan

Multinomial logistic regression will be used to analyse characteristics of opioid-related attendances by opioid type. Opioid type (sole use of each opioid and multiple opioid use) will be used as the dependant variable, with each category being compared to morphine as mid-potency opioid, regressed on each characteristic separately. If the number of morphine cases is insufficient to allow use as a reference category then oxycodone will become the reference category. Each model will be adjusted for using a collapsed state variable (where jurisdictions with expected fewer cases such as the Australian Capital Territory and Northern Territory will be aggregated into an 'other states' category). When considering GCS as a proxy for severity, the model will be further adjusted for age, gender, concurrent alcohol use, concurrent illicit drug use (excluding heroin), concurrent heroin use, and concurrent non-opioid pharmaceutical use. All other models will be further adjusted for age, gender and other substance use (as an aggregated variable of concurrent alcohol use, illicit drug use, heroin, and non-opioid pharmaceutical misuse). Results will be reported as odds ratios. Comparison between states will be analysed through an interaction between state and characteristic.

Aim 3 – qualitative analysis of contexts of oxycodone and tapentadol-related attendances

Detail from the free-text fields from the ePCR will be utilised to establish a more complete picture of the ambulance attendance. These data are subject to rigorous coding by a highly trained team of coders using well-established and tested coding frameworks for existing fields, however additional uncoded data are available in these free-text fields are rarely used for qualitative analyses. Some studies have used text-based information to explore specific phenomena in further detail, such as intentional and unintentional injury (28) and heroin overdose (29).

We will use text-based case descriptions of oxycodone-related and tapentadol-related cases. These will be qualitatively examined in order to provide insight into the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables. We will compare tapentadol-related cases (with tapentadol being a newer 'atypical' opioid with a suggested lower rate of associated adverse events (8) and less non-medical use (30)), to oxycodone-related attendances, as oxycodone is the predominant opioid-analgesic prescribed in Australia (31) and has a well-recognised abuse liability (11). We will consider the details of circumstances surrounding the presentation including details provided on the role and effect of the opioid used.

Aim 3 analysis plan

Qualitative coding will occur in two stages. First, an initial group of randomly selected cases (estimated n=30-40 until saturation has occurred) will be examined by two researchers to independently determine a coding framework. The researchers will negotiate a consensus framework, then code the remaining cases using this agreed upon framework. The project team will convene regularly to discuss coding techniques as they develop as well as emerging themes. A 10% sample of cases will be checked by a third researcher to confirm coding consistency, with further cases reviewed if inconsistencies are identified.

We will examine an equal number of tapentadol- and oxycodone-related cases, based on the number of cases identified for tapentadol (the less frequently used opioid). We will use a random number generator via Excel to randomly select an equal size number of oxycodone-related cases for qualitative comparison (i.e. the same number of cases as in the tapentadol-related case group), and perform the same analyses for oxycodone-related presentations. To ensure that selected oxycodone cases represent all oxycodone cases the sub-group of oxycodone-related attendances will be selected by weighted random sampling, with weightings on the basis of sex, age group, jurisdiction and if the attendance was related to self-harm. Cases involving both tapentadol and oxycodone will be considered as a separate group.

In addition to qualitative analysis, multinomial regression will be used to analyse coded variables representing different aspects of attendance context surrounding three mutually exclusive groups: (1) tapentadol-related cases, (2) oxycodone-related cases, and (3) cases that are related to the concomitant use of tapentadol and oxycodone (i.e. considered-related to both opioids). Results will be reported as odds ratios.

All quantitative analysis for aims 1-3 will be conducted in STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP), with p values less than 0.05 considered

significant. Qualitative data will be managed and analysed using nVivo 12.0 (32), but any subsequent quantitative analyses conducted using STATA as above.

Handling known or expected missing data

Where there are missing data for the characteristics of attendances, we will report the available sample size for each variable. To enable calculation of rates for each quarter with potentially identifiable cases (cell size 1-4), we will impute a value representing the mean for all potentially identifiable cases. This will preserve the total number of cases without compromising privacy of individuals.

There are three months of missing Victorian data due to industrial action (October – December 2014) with partial missing data (4 days) for September 2014. For these months, to enable calculation of rates (Aim 1), we will impute values based on data from September – December in the previous and following year (2013 and 2015). In a planned sensitivity analysis, we will compare results using imputed data to results excluding missing data and report any differences observed.

Ethics and dissemination

Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Consistent with the ethics approval, cells of <5 will not be reported, though zeroes will be preserved. Due to the sensitivity and potentially identifiable nature of the data line item data is not available for sharing, consistent with the ethics approval.

We will present project findings at relevant scientific conferences. We plan to submit findings for publication as two peer-reviewed journal articles. One article will incorporate the quantitative analysis (aim 1 and 2) and one paper report the qualitative analysis (aim 3). We will report findings in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, an extension of the STROBE statement for reporting items specific to observational studies using routinely collected health data (33).

Patient and public involvement

Interpretation of the findings and dissemination will be informed by people with lived experience through contact with consumer organisations such as the Association of Participating Service Users.

Discussion

Strengths and limitations

Recommendations for methods for pharmacovigilance studies identified a number of important features, depending on the aims of the study and the methods employed (16). These include the prospective publication of a study protocol including a detailed statistical analysis plan, transparency around study funding and publication in open-access journals. This study will conform to these requirements.

This study has several strengths. Firstly, coded ambulance data captures a broader range of outcomes and a wider population of people with extramedical pharmaceutical opioid use than may be captured in abuse liability studies, clinical trials, or spontaneous AE reporting systems.

Secondly, this study's population level database accurately codes detailed information about each attendance. This level of detail can provide important insights into harms related to substance use (17-19, 34-36). This study will represent an extension of these studies to provide a detailed analysis of rates and characteristics of harms related with widely used pharmaceutical opioids, and is strengthened by the use of population level supply data to calculate supply-adjusted rates. Finally, the study will be first to provide detailed context around circumstances of pharmaceutical opioid related ambulance attendances, utilising coding of qualitative data.

There are limitations in the use of data collected for operational purposes, similar to with hospital inpatient and emergency department data. There is potential for biases to exist in collection and coding, and incomplete or inconsistent recording of variables. Substance involvement is determined from patient-provided information, others at the scene, or paramedic's clinical assessment, not from toxicological testing. Other clinical details (e.g. mental health symptoms) are also determined in this way.

Rates of ambulance attendances are calculated based on sales data. Due to frequent ordering and limited capacity for controlled drug storage at the community pharmacy level, sales closely approximate supply. Use of sales data addresses limitations with publicly funded prescription data, which omits privately purchased prescriptions and over-the-counter medications and therefore is an incomplete measure of community opioid supply. Finally, as this is a naturalistic study, we cannot know if different patient populations are more likely to receive a given opioid. As such, there may be

unmeasured confounders. Randomised trials can address this limitation; however, patients who use opioids extramedically are usually excluded from trials.

Data statement

To protect privacy and confidentiality, data from the Ambo Project are provided to Turning Point under strict conditions for the storage, retention and use of the data. The current approval permits storage of the data at one site, Turning Point, with any analysis to be undertaken onsite, no data to be removed, and no dissemination of unit level data. Researchers wishing to undertake additional analyses of the data are invited to contact Turning Point as the data custodians.

Conclusion

This will be the first detailed study to compare coded ambulance ePCR as a population level indicator of prescription opioid-related harm. These data will complement ongoing studies examining extramedical use of tapentadol in sentinel populations of people who use drugs, and data from poisons information centres (37). The data in this study represent all acute presentations in community settings where extramedical use of a pharmaceutical opioid analgesic is considered related to the ambulance attendance. This unique dataset has national reach and demonstrated consistency and completeness over multiple years. It will provide one of the most complete analyses of relative harms due to extramedical use for a range of pharmaceutical opioids to date. The study will add to our knowledge, and lead to a more nuanced understanding of whether different pharmaceutical opioids are associated with different harms.

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Author statement

Suzanne Nielsen (SN) initially conceptualised the study and drafted the initial design, with input from Rose Crossin (RC), Debbie Scott (DS) and James Wilson (JW). Cathy Martin (CM) and Melissa Middleton (MM) provided input on, and drafted the statistical analysis plan. SN, RC, DS, JW, Tina Lam (TL), Karen Smith (KS) and Dan Lubman (DL) contributed the drafting of the protocol manuscript and revisions of the protocol. KS, DL and DS lead the broader Victorian Ambo Project and the National Ambo project from which the data is drawn and provided detailed technical advice relating to procedures from that study to inform the development of this study and analysis of the data.

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Table 1. Summary of data availability across jurisdictions

State / Territory	Notes on data available^
ACT	All cases coded one month per quarter from March 2015 until December 2017
NSW	All cases coded one month per quarter from March 2015 until December 2017
NT	All cases coded one month per quarter from March 2016 until December 2017
QLD	All cases coded one month per quarter from March 2015 until December 2016
TAS	All cases coded one month per quarter from March 2014, until December 2017
VIC	All cases coded from January 2012 till September 2018
WA & SA	Data not yet available

^ We will conduct a comparison on supply-adjusted rates of attendance for Victoria and other states utilising periods of time where corresponding data are available.

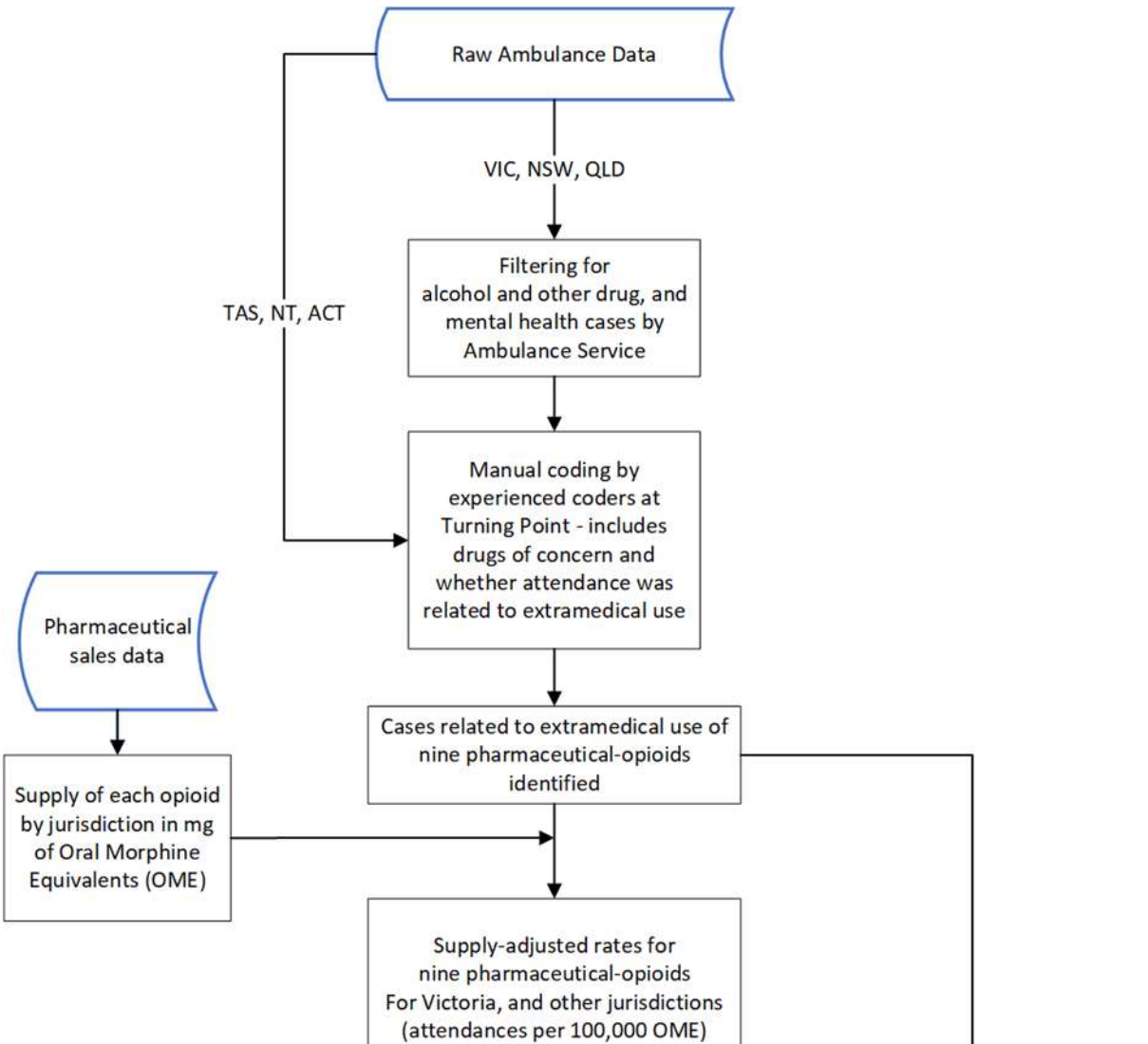
Table 2. Variables and response options to be examined in association with pharmaceutical opioid-related ambulance attendances

Variable	Response options
Presenting Glasgow Coma Scale (GCS)	3 (non-responsive), 4-12 (moderate-severe impairment), 13-15 (minor-no impairment)
Presenting respiratory rate (breaths per minute)	<6, 6-12, >12
Transport to hospital	Not transported, transported
Naloxone administered: not stated, yes	Not states, yes
Naloxone response: not effective, effective	Not effectives, effective
Sex of patient	Male, female, other/unspecified
Age of patient	12-34, 35-54, 55-65 (nearing retirement age) and 65+^
Socio-economic status based on residential postcode	Quintile 1-5 based on SEIFA-IRSD 201s, IRSD 2016 (30)
Concurrent alcohol involvement	Not stated, alcohol involved but no evidence of intoxication, alcohol intoxication∞
Concurrent heroin involvement	Not stated, present
Concurrent illicit drug use (excluding heroin)	based on the presence of at least one of the illicit drugs coded for; meth(amphetamine), cannabis, synthetic cannabinoids, emerging psychoactive substances, cocaine, MDMA, GHB, ketamine, LSD, psilocybin, inhalant, illicit drug other or unspecified)
Concurrent non-opioid extramedical pharmaceutical use	not stated, present (based on the presence of at least one of the pharmaceutical groups coded for; non-opioid analgesics, benzodiazepines, anti-depressants, anti-psychotics, anti-convulsants, opioid-dependence treatments, pharmaceutical stimulants, other medication)
Co-morbid mental health symptoms	not stated, present (based on the presence of at least one of; symptoms of anxiety, depression, psychosis, social / emotional distress, symptoms associated with disorders with clinical evidence, and mental health unspecified)
Co-morbid suicidal thoughts or behaviours	Not stated, present (based on the presence of at least one of; suicidal ideation, suicide attempt)
Co-morbid non-suicidal self-injury	Not stated, present (based on the presence of at least one of; threat of non-suicidal self-injury, non-suicidal self-is, non-suicidal self-injury)
Accidental overdose	Not stated, yes
Unknown intent overdose#	Not stated, yes
Past history of psychiatric issues	Not stated, present (based on the presence of at least one of; past history of mood disorder, psychosis, suicidal ideation, suicide attempt, alcohol and other drug misuse)

^based on previous age categories used in studies of opioid use for pain (38). We will exclude cases where age is reported to be less than 12 due to the unclear intention of use in children of this age, consistent with previous research (39, 40).
#(where information provided in the patient care records by the paramedic means that the coding team cannot determine if the overdose was accidental or if there was suicidal intent)
∞The involvement of alcohol is coded as 'alcohol involved' and 'alcohol intoxication'. Attendances where the person has consumed alcohol, but the paramedic notes do not clearly indicate alcohol intoxication are coded as 'alcohol involved' and 'alcohol intoxication is a subset of 'alcohol involved'. The default code is for 'alcohol involved' unless the paramedic notes provide clear evidence of alcohol intoxication.

Figure Captions:

Figure 1- Overview of study processes and data sources (VIC = Victoria, NSW = New South Wales, QLD = Queensland, TAS = Tasmania, ACT = Australian Capital Territory, NT = Northern Territory)



Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

Supplementary materials

Appendix A. Description of coder training and inter-rated reliability processes

Research Assistants undertake extensive and ongoing training to ensure coding is consistent. To assist with this, coding guides are utilised that detail categories, the process of classification, provide examples of typical attendance types, and examples of uncommon attendance types. When a new Research Assistant commences, they are first trained by senior researchers, and then paired with multiple experienced Research Assistants on a rotating basis, until they and their senior coding partner are confident of coding consistency. Senior researchers review attendances coded by new Research Assistants to ensure inter- and intra-coder reliability. In addition to training upon appointment, all Research Assistants participate in monthly ongoing training. This training covers issues like complex cases or the introduction of new variables. This training is completed with workshops and "dummy case exercises".

On a day-to-day basis, if Research Assistants are not confident in coding a specific attendance, the attendance is escalated to a senior researcher for review (<1% of attendances). These review cases then feed into regular workshops, which are also used to identify common coding issues, and disseminate coding clarifications on an ongoing basis.

To maintain inter-coder validation, inter-rater review audits are completed by a senior researcher. These are used as a personal learning tool for Research Assistants, and to identify common issues that may need to be addressed across the coding team. As an example of inter-coder validation, results of the most recent coding audit are described below: A maximum of 90 previously coded attendances per Research Assistant were extracted, from the Victoria Quarter 1, 2017 dataset. The 90 attendances met 26 criteria for case-classification. Each Research Assistant then re-coded a random selection of attendances for which they were not the original coder. At that time, there were 23 individual Research Assistants, and the attendances they re-coded came from an average of 9±3 (mean±standard deviation) other Research Assistants. A total of 1,718 attendances were re-coded, which meant 221,622 AOD variables were re-coded, of which only 470 differences were identified (i.e. 0.2% of variables). Differences were systematically identified, and reviewed by a senior researcher for personalised feedback to each Research Assistant and then followed up with systemic team training.

Appendix B. Description of variables to be examined in association with pharmaceutical opioid-related ambulance attendances

Variable	Description	Transformations/ intended aggregations and final response options used for analyses	Data source
Presenting Glasgow Coma Scale (GCS)	The Glasgow Coma Scale [1] is a 13 point (range 3-15) scale that assesses injured patients' level of consciousness. The GCS's overall reliability is adequate [2], and it is used by prehospital and hospital staff in most English speaking countries and most of Europe [3].	Response Options: 3 (non-responsive), 4-8 (severe impairment), 9-12 (moderate impairment)), 13-15 (minor-no impairment), consistent with previous research with substance-related attendances [4, 5]. This study further isolated the "non-responsive" group (GCS=3) who would not have responded at all, to any of the three components of eye, verbal and motor response to external stimuli.	GCS score is assessed and directly entered into the ePCR by trained paramedics.
Presenting respiratory rate (breaths per minute)	There are not clearly defined standard grouping for respiration rate. However, the normal adult respiration rate is generally considered 12-20 breaths per minute [6], and high doses of opioids depress ventilation [7]. The dispatch protocols from the ambulance systems involved in this study class less than 6 breaths a minute as ineffective breathing.	Grouped into three response Options: <6, 6-12, >12	Respiration rate is assessed and directly entered into the ePCR by trained paramedics.
Transport to hospital	Transport outcome relating to attendance	Response Options: Not transported, transported	Outcome of attendance directly entered into the ePCR as a binary variable by trained paramedics and validated by trained coders after reviewing free-text fields.
Naloxone administered: not stated, yes	Naloxone is an opioid antagonist that reverses the effects of opioid overdose [7].	Response Options: Not stated, yes	Binary variable in ePCR, entered by trained paramedic and validated by trained coders after free-text fields.

Naloxone response: not effective, effective		Response Options: Not effective, effective	Binary variable entered by trained paramedic and validated by coders checking free text field on clinical descriptions e.g. GCS ~3 returning to GCS ~15.
Sex of patient	Sex is coded into male, female and non-binary options, however states vary on how they to record non-binary gender. Coders validate and re-code gender as male, female, and other/unknown.	For these analyses response options are coded as: Male (0), female (1), other/unknown (9), missing (.) All patients regardless of sex included in analyses related to Aim 1 (rates) and Aim 3 (context of presentation). Those with unknown sex will be included in the analyses for Aim 2, with missing data quantified.	Four options in the ePCR entered by paramedics, missing data may be coded based on information in free-text.
Age of patient	Our categories were based on previous age categories used in studies of opioid use for pain which were <55, 55-65 and 65+ [8] to enable comparison. In Australia, most overdoses occur in adults with the peak age category in 35-44 [9] and increases observed in older age categories. For this reason we have split those aged from 12 -54 into two categories, 12-34 and 35-55, to enable comparison with national overdose trends. Smaller age groups are not possible due to low rates in younger adults leading to potential censoring of cells. We will exclude cases where age is reported to be less than 12 due to the unclear intention of use in children of this age, consistent with previous research [10, 11].	Response Options: 12-34, 35-54, 55-65 (nearing retirement age) and 65+	DOB is entered by paramedic, missing data may be coded based on information in free-text.

Socio-economic status based on residential postcode	The Socio-Economic Indexes for Areas (SEIFA) ranks geographic areas according to relative socio-economic advantage and disadvantage [12, 13]. The SEIFA is one of the most commonly used measures for socioeconomic status in Australia, and it has been updated every 10 years with Census data since 1986 [14]. Lower scores indicate more disadvantaged areas and higher scores indicate more advantaged areas.	Response Options: Quintile 1-5. At Turning Point, the postcode from the EPCR is linked to the Australian Bureau of Statistics' (ABS) database of SEIFA ranks by postcode (2016), and then these ranks were allocated into quintiles specific to each state.	Postcode is entered by paramedic
Concurrent alcohol involvement	Concurrent alcohol use is captured because the simultaneous use of multiple depressant drugs (e.g. opioids, alcohol and heroin) increase the risk of overdose [15].	Response Options: Not stated, alcohol involved but no evidence of intoxication, alcohol intoxication. The involvement of alcohol is coded as 'alcohol involved' and 'alcohol intoxication'. Attendances where the person has consumed alcohol, but the paramedic notes do not clearly indicate alcohol intoxication are coded as 'alcohol involved', and 'alcohol intoxication' is a subset of 'alcohol involved'. The default code is for 'alcohol involved' unless the paramedic notes provide clear evidence of alcohol intoxication. For this study, these cases were recoded into exclusive categories – not stated, alcohol involved but no evidence of intoxication and alcohol intoxication.	Coders extract information about alcohol involvement from free-text fields as 'not stated' or 'alcohol involved'. There is a subcategory of 'intoxication' under 'alcohol involved'.

Concurrent heroin involvement	Response Options: Not stated, present	Analysed as binary coded variable.	Coders extract information about heroin involvement from free-text fields and code.
Concurrent illicit drug use (excluding heroin)	Response Options: Not stated, present (based on the presence of at least one of the illicit drugs coded for; meth(amphetamine), cannabis, synthetic cannabinoids, emerging psychoactive substances, cocaine, MDMA, GHB, ketamine, LSD, psilocybin, inhalant, illicit drug other or unspecified)	Not stated/ present if any one of the illicit substances listed are reported as being used in the ePCR	Coders extract information about illicit drug involvement from free-text fields and code.
Concurrent non-opioid extramedical pharmaceutical use	Response Options: Not stated, extramedical use present (based on the presence of at least one of the pharmaceutical groups coded for; non-opioid analgesics, benzodiazepines, anti-depressants, anti-psychotics, anti-convulsants, opioid-dependence treatments, pharmaceutical stimulants, other medication)	Not stated/ present if any one of the pharmaceutical drugs listed are reported in the ePCR	Coders extract information about extramedical use of pharmaceutical drugs from free-text fields and code.
Co-morbid mental health symptoms	Response Options: Not stated, present (based on the presence of at least one of; symptoms of anxiety, depression, psychosis, social / emotional distress, symptoms associated with disorders with clinical evidence, and mental health unspecified). Symptomology is reported rather than diagnoses, as paramedics do not diagnose mental illness.	Recorded as binary option of not stated/ present if any one co-morbid symptoms listed are reported in the ePCR	Coders extract information from free-text fields and code.
Co-morbid suicidal thoughts or behaviours	Response Options: Not stated, present (based on the presence of at least one of; suicidal ideation, suicide, suicide attempt)	Recorded as binary option of not stated/ present if any one co-morbid suicidal thoughts or behaviours listed are reported in the ePCR	Coders extract information from free-text fields and code.
Co-morbid non-suicidal self-injury	Response Options: Not stated, present (based on the presence of at least one of;	Recorded as binary variable of not stated or present based on either threat of non-suicidal	Coders extract information from free-text fields and code.

	threat of non-suicidal self-injury, non-suicidal self-injury)	self-injury or non-suicidal self-injury documented in the ePCR	
Unintentional alcohol and other drug overdose	Where information provided in the patient care records by the paramedic suggests that the person did not intend to die (though they may have intended to take the substance). Overdose (also referred to as *AOD poisoning*) determined using GCS < 9 or 10x dose (for pharmaceuticals), however must also be evidence available to suggest poisoning was unintentional to be coded as yes.	Recorded as binary variable of not stated, yes	Coders extract information from free-text fields and code.
Undetermined intent overdose	Where information provided in the patient care records by the paramedic means that the coding team cannot determine if the overdose was unintentional (also referred to as *'accidental'*) or if there was suicidal intent.	Response Options: Not stated, yes	Coders extract information from free-text fields and code.
Past history of psychiatric issues	Response Options: Not stated, present (based on the presence of at least one of; past history of mood disorder (including anxiety, depression, PTSD, Bipolar and OCD), psychosis, suicidal ideation, suicide attempt, alcohol and other drug misuse).	Response Options: Not stated, present	Coders extract information from free-text fields and code.

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Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

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Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

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Declarations of competing interests

In the past 5 years, SN has been an investigator on untied education grants from Indivior, unrelated to the current work. SN has provided training to health care professionals on identifying and treating codeine dependence for which her institution has received payment from Indivior. DL has received speaking honoraria from the following: Astra Zeneca, Indivior, Janssen-Cilag, Lundbeck, Servier and Shire, and has participated on Advisory Boards for Indivior and Lundbeck.

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Abstract

Introduction and aims: Extramedical use of, and associated harms with pharmaceutical opioids are common. Analysis of coded ambulance clinical records provides a unique opportunity to examine a national population-level indicator of relative harms. This protocol describes an observational study with three aims: (1) To compare supply-adjusted rates of pharmaceutical opioid-related ambulance attendances for, buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol; (2) to compare presentation characteristics for these commonly used pharmaceutical opioids; and (3) to describe the context surrounding ambulance presentations related to oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a more recent 'atypical' opioid on the Australian market, with fewer studies that have directly examined signals of extramedical use.

Method: Trained coders extract data from clinical records for ambulance presentations relating to extramedical use of commonly used pharmaceutical opioids. This data forms the basis of a large, national database that captures alcohol and drug related harms. Supply adjusted rates of presentations will be examined using Poisson regression and multinomial logistic regression will be used to compare severity and other characteristics of attendances relating to different pharmaceutical opioids. Tapentadol-related and oxycodone-related cases will be qualitatively examined to understand the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables.

Ethics and dissemination: Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Findings will be submitted for peer review in 2019. The understanding of risk-profiles in real-world settings is of international public health importance. The analysis and publication of findings from this national dataset of clinical records will provide one of the most nuanced analyses to date of relative harms across nine pharmaceutical opioids over a seven-year period.

Keywords: pharmaceutical opioids, ambulance attendance, extramedical use, overdose, oxycodone, tapentadol

Strengths and limitations

- Strengths of this study include use of coded pharmaceutical opioid-related ambulance attendance data as validated population-level indicator of opioid-related harm such as extramedical use and overdose to inform risk profiles in real-world settings
- We will compare the supply-adjusted rates and characteristics of ambulance attendances with commonly used pharmaceutical opioids
- Limitations include the use of administrative data, and a lack of toxicological data to confirm substances taken

Introduction

Recently, the world's attention has focused on the rapidly escalating opioid-related deaths occurring in North America and other high-income countries (1). This has put into sharp focus the need to understand the risk profiles associated with different pharmaceutical opioids.

The number and potency of available pharmaceutical opioids has increased rapidly over the past decades. Morphine, a selective mu-opioid agonist, was isolated more than 200 years ago (2). Following this, analogues such as diamorphine and codeine were developed. Later, semi-synthetic opioids such as oxycodone (a full agonist at the mu-opioid receptor) and buprenorphine (a partial agonist at the mu-opioid receptor (with activity at delta and kappa) (3) were isolated. In addition, newer 'atypical' opioids such as tramadol and tapentadol exert their analgesic effects via opioid and non-opioid mechanisms (4). Tramadol, a lower potency mu opioid receptor agonist with a more potent metabolite, also selectively inhibits noradrenalin and serotonin uptake (5, 6). Tapentadol is another synthetic opioid, structurally similar to tramadol, with mu-opioid receptor agonism and inhibition of noradrenaline reuptake (7).

A United States (US) study of severe adverse events (SAEs) found a positive linear relationship between opioid potency and SAE rate, with the highest rate observed with hydromorphone (8.02 SAEs/100 kg), and the lowest rate with tapentadol (0.27 SAE/100 kg) (8). This suggests that harms related to opioids may not be equal, though replication studies outside the US are needed.

Abuse liability studies also find differences between prescribed opioids. Differences in the strength of reinforcing or subjective effects between tramadol, oxycodone, codeine have been found (9). Subjective effects of oxycodone appeared greater than codeine, though all opioids examined were reinforcing, particularly at higher doses (9). A separate study examined ratings of 'I feel high', and the amount that people were willing to pay for a drug varying by opioid type (10). Defined doses of diamorphine, morphine, and oxycodone had higher ratings than buprenorphine and fentanyl (10). In this study, oxycodone produced robust reinforcing effects, consistent with systematic review of nine studies that oxycodone had a higher abuse liability relative to other opioids (11).

Although abuse liability may vary in controlled laboratory studies, opioid use in real-world settings can vary as a function of cost, availability and other contextual factors (12). For this reason, pharmacovigilance studies are important to monitor for signals of extramedical use in real-world settings. Further, signals of extramedical use may only appear after trials, as those likely to use opioid

extramedically are often excluded from these studies, so data from diverse populations is important (13).

Sentinel surveillance aims to assess nonmedical use and harms with opioids such as oxycodone and morphine (14). For newer opioids, or opioids infrequently used by sentinel study populations, population level studies can more completely assess for signals of extramedical use (15). One population level indicator of opioid-related harm is ambulance attendances. These data are recognised as a valuable data source for identifying population level signals of harm (16). In Australia, the clinical records of ambulance attendances related to extramedical use of pharmaceuticals (i.e. use outside a medical context, or in a higher dose than prescribed) are coded by trained research assistants. These data can inform the risk profile with different pharmaceutical opioids (17), and has been used to monitor harms related to quetiapine and pregabalin (18, 19). These data can determine if unintended harms such as extramedical use and overdose are emerging, and provide information on the frequency, severity and context of presentations.

As such, this paper outlines the design of a study that aims to conduct a detailed examination of ambulance attendances related to pharmaceutical opioids, and test the hypothesis that the context and frequency of harms with different opioids will vary by opioid type. We write this protocol to maximize transparency (20, 21). The study is supported by an untied educational grant by Seqirus, who make Palexia® (tapentadol) and Tramal® (tramadol). The funders have no role in the design, conduct, analysis and interpretation of the study and its findings. As has been highlighted by others in the field (22), prospectively publishing study protocols with primary aims and related analysis plans assist in establishing independence around the study design, providing transparency, and ensuring a commitment to publishing study findings regardless of the outcome (21).

Methods

Study aims

This study has three aims:

1) Compare the supply-adjusted rates of ambulance attendances across commonly used pharmaceutical opioids (buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine, tramadol and tapentadol).
2) Compare presentation characteristics for these nine opioids.
3) Describe the context surrounding ambulance presentations related to two opioids: oxycodone, a widely used opioid with an established abuse liability, and tapentadol, a newer opioid with fewer studies describing extramedical use.

We will answer the following research questions:

1. Do the supply-adjusted rates of ambulance presentations differ by opioid potency?
2. Does the severity of presentation (as measured by presenting Glasgow Coma Scale, GCS) or other characteristics vary by opioid type?
3. Are there differences in the context surrounding ambulance presentations related to extramedical use of oxycodone and tapentadol?

Study design and setting

Data come from ambulance attendances in Victoria; a state which comprises approximately 26% of Australia's population (23), supplemented by national ambulance data. The Victorian dataset provides complete coverage across the study period (June 2013 until September 2018, excluding 3 months of missing data October - December 2014, due to industrial action). Coded electronic patient care records (ePCR) provide information on acute harms arising from extramedical pharmaceutical use, thus allowing comparison of attendance characteristics across multiple opioids.

We will examine data from the National Ambo Project from Queensland, New South Wales, Australian Capital Territory, Northern Territory and Tasmania to determine if Victorian trends are comparable to national trends. National data is available in quarterly 'snap-shot months' (Table 1) and are screened and coded using the same procedures and coders as the Victorian data. See Figure 1 for an overview of data sources and study processes. We will aim to complete case identification by March 2019, with analyses planned for March-April 2019.

Pharmaceutical opioid sales data

We will estimate the amount of each opioid supplied using monthly sales data (IQVIA third party access program). The total amount of each opioid will be calculated by jurisdiction in mg, converted into Oral Morphine Equivalents (OME) (24), and used to calculate a supply-adjusted rate of attendances, consistent with previous studies of pharmaceutical opioid related harm that have adjusted for supply using similar methods (8, 25).

Ambulance attendance data

Ambulance data are collected as part of the Ambo Project, a collaboration between Turning Point, Monash University and Ambulance Victoria (AV). Methods for the Ambo Project have been previously described (e.g. (18, 19)) and are outlined below.

Data includes electronic patient care records (ePCR), computer aided dispatch notes, and clinical details associated with the attendance that provide part of the patient care record (e.g. records of respiration rate and GCS). Primary filtering based on over-inclusive keyword searches identifies attendances with involvement of alcohol, other drugs, or mental health symptomology. This filtered dataset is provided to Turning Point where data cleaning, validation, and coding of the ePCR is performed by a specialist team of research assistants. Details on research assistant training, and interrater review processes are contained in Supplementary files (Appendix A). A systematic and validated coding system captures information from the ePCR. The core criterion used in determining the involvement of a substance is: “Is it reasonable to attribute the immediate or recent (not merely chronic) over- or inappropriate (i.e. extramedical) ingestion of the substance or medication as significantly contributing to the reason for the ambulance attendance?", as determined through examination of the clinical notes. As such, this dataset captures information on acute, not chronic, harms.

For this study, ambulance attendances where extramedical pharmaceutical opioid use was identified as a significant contributor to an attendance will be included. This dataset excludes cases of solely therapeutic use. Pharmaceutical opioid-related attendances include those where; a person prescribed opioids consumed medication more often or in higher than recommended amounts; a person consumed opioids not prescribed to them, or if opioids were consumed with a combination of other substances that contributed to the ambulance attendance. The inclusion criteria mean that extramedical opioid use must significantly contribute to the attendance, however other drugs or substances may have also been over- or inappropriately consumed and the extramedical opioid use may not be the primary or only reason for the ambulance attending. These criteria differentiate Ambo Project data from adverse event reporting from the Therapeutic Goods Administration (TGA) Database of Adverse Event (AE) Notifications (26), which captures spontaneous AEs from prescribed medications. Spontaneous AE reporting can effectively identify serious harms with prescribed medicines, though is recognised to miss the vast majority of AEs (27).

Other associated factors such as alcohol and other drug use, mental health symptoms, and self-harm are also coded. All illicit drug use is coded regardless of quantity. Current mental health symptomology is coded rather than mental health diagnosis as paramedics do not screen or assess mental illness diagnoses during an ambulance attendance.

These methods are consistent across other jurisdictions, which collect quarterly data as part of the National Ambo Project, with the exception that ambulance services in Tasmania, Australian Capital Territory, and the Northern Territory provide all data and do not undertake primary filtering.

All substances related to the attendance are coded; including alcohol, illicit & pharmaceutical drugs. For this project, we will examine buprenorphine (as a single ingredient), codeine (codeine as a single ingredient, and in combination with paracetamol, or ibuprofen, or aspirin), fentanyl, morphine, oxycodone, oxycodone-naloxone, pethidine, tapentadol and tramadol. We will exclude opioids used as treatments for opioid dependence (methadone, buprenorphine-naloxone, or buprenorphine and a single ingredient where indicated that it is for treatment of opioid dependence) as these represent a different clinical indication and specific treatment population.

Buprenorphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, morphine, pethidine and tramadol are routinely coded in the Ambo project database. Cases involving tapentadol are routinely coded in an 'other opioid' category. For this study 'tapentadol-related' cases will be identified and coded by reviewing all cases from June 2013 (aligned with tapentadol availability as a subsidised medicine in Australia), until September 2018. This is identical to the coding process used with other opioids, the only difference being that the cases will be coded retrospectively from 'other opioids' to 'tapentadol' where there is evidence of tapentadol involvement in the ePCR.

Aim 1 – supply-adjusted trends 2013-2018

Analysis of supply-adjusted trends will occur by quarterly aggregation of attendances in Victoria, by opioid group, with further aggregation to half-yearly if required to preserve cell sizes of at least five in the majority of cells. Where cell sizes of <5 occur, to preserve anonymity we will report average of all cells with 1-4 cases, rather than the number of cases in that cell. Units will be attendances per 100 000mg OME (24).

Aim 1 analysis plan

Prescription opioid-related ambulance attendances will be aggregated into 3 monthly periods corresponding to yearly quarters. Basic descriptive statistical analyses will be used to explore these attendances in Victoria, analyses include frequencies (number of attendances), proportions (demographics), and supply-adjusted rates.

Poisson regression will be used to assess trends in supply-adjusted rates for Victoria. Regression models will be fitted (one for each opioid), and adjusted for quarterly and yearly trends with the number of days per month used to offset the regression. Rates will be calculated for Victoria (where completed data are available), and compared with rates observed in other states for the time periods that data are available (Table 1). Due to industrial action, September 2014 contains partially complete data (26 out of 30 days). Supply data for this month will be weighted to represent the average supply

for the proportion of days provided for September, with the offset variable representing the total number of days where data has been supplied.

The intention is to assess trends within each opioid where the opioid has been solely indicated, as well as a 'multiple opioid' category representing cases where multiple opioids have been indicated. However, where this is not possible due to small case numbers, trends will be assessed using all cases in which the opioid has been indicated (sole use and multiple opioids).

Aim 2 – characteristics of attendances

For this analysis, opioid-related attendances will be analysed by opioid type listed above, by characteristics as per Table 2 (additional details on variables are contained in Appendix B).

Aim 2 analysis plan

Multinomial logistic regression will be used to analyse characteristics of opioid-related attendances by opioid type. Opioid type (sole use of each opioid and multiple opioid use) will be used as the dependant variable, with each category being compared to morphine as mid-potency opioid, regressed on each characteristic separately. If the number of morphine cases is insufficient to allow use as a reference category then oxycodone will become the reference category. Each model will be adjusted for using a collapsed state variable (where jurisdictions with expected fewer cases such as the Australian Capital Territory and Northern Territory will be aggregated into an 'other states' category). When considering GCS as a proxy for severity, the model will be further adjusted for age, gender, concurrent alcohol use, concurrent illicit drug use (excluding heroin), concurrent heroin use, and concurrent non-opioid pharmaceutical use. All other models will be further adjusted for age, gender and other substance use (as an aggregated variable of concurrent alcohol use, illicit drug use, heroin, and non-opioid pharmaceutical misuse). Results will be reported as odds ratios. Comparison between states will be analysed through an interaction between state and characteristic.

Aim 3 – qualitative analysis of contexts of oxycodone and tapentadol-related attendances

Detail from the free-text fields from the ePCR will be utilised to establish a more complete picture of the ambulance attendance. These data are subject to rigorous coding by a highly trained team of coders using well-established and tested coding frameworks for existing fields, however additional uncoded data are available in these free-text fields are rarely used for qualitative analyses. Some studies have used text-based information to explore specific phenomena in further detail, such as intentional and unintentional injury (28) and heroin overdose (29).

We will use text-based case descriptions of oxycodone-related and tapentadol-related cases. These will be qualitatively examined in order to provide insight into the situationally-specific contexts of the ambulance attendances outside of the characteristics captured in routinely coded variables. We will compare tapentadol-related cases (with tapentadol being a newer 'atypical' opioid with a suggested lower rate of associated adverse events (8) and less non-medical use (30)), to oxycodone-related attendances, as oxycodone is the predominant opioid-analgesic prescribed in Australia (31) and has a well-recognised abuse liability (11). We will consider the details of circumstances surrounding the presentation including details provided on the role and effect of the opioid used.

Aim 3 analysis plan

Qualitative coding will occur in two stages. First, an initial group of randomly selected cases (estimated n=30-40 until saturation has occurred) will be examined by two researchers to independently determine a coding framework. The researchers will negotiate a consensus framework, then code the remaining cases using this agreed upon framework. The project team will convene regularly to discuss coding techniques as they develop as well as emerging themes. A 10% sample of cases will be checked by a third researcher to confirm coding consistency, with further cases reviewed if inconsistencies are identified.

We will examine an equal number of tapentadol- and oxycodone-related cases, based on the number of cases identified for tapentadol (the less frequently used opioid). We will use a random number generator via Excel to randomly select an equal size number of oxycodone-related cases for qualitative comparison (i.e. the same number of cases as in the tapentadol-related case group), and perform the same analyses for oxycodone-related presentations. To ensure that selected oxycodone cases represent all oxycodone cases the sub-group of oxycodone-related attendances will be selected by weighted random sampling, with weightings on the basis of sex, age group, jursidiction and if the attendance was related to self-harm. Cases involving both tapentadol and oxycodone will be considered as a separate group.

In addition to qualitative analysis, multinomial regression will be used to analyse coded variables representing different aspects of attendance context surrounding three mutually exclusive groups: (1) tapentadol-related cases, (2) oxycodone-related cases, and (3) cases that are related to the concomitant use of tapentadol and oxycodone (i.e. considered-related to both opioids). Results will be reported as odds ratios.

All quantitative analysis for aims 1-3 will be conducted in STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP), with p values less than 0.05 considered

significant. Qualitative data will be managed and analysed using nVivo 12.0 (32), but any subsequent quantitative analyses conducted using STATA as above.

Handling known or expected missing data

Where there are missing data for the characteristics of attendances, we will report the available sample size for each variable. To enable calculation of rates for each quarter with potentially identifiable cases (cell size 1-4), we will impute a value representing the mean for all potentially identifiable cases. This will preserve the total number of cases without compromising privacy of individuals.

There are three months of missing Victorian data due to industrial action (October – December 2014) with partial missing data (4 days) for September 2014. For these months, to enable calculation of rates (Aim 1), we will impute values based on data from September – December in the previous and following year (2013 and 2015). In a planned sensitivity analysis, we will compare results using imputed data to results excluding missing data and report any differences observed.

Ethics and dissemination

Ethics approval related to analysis of ambulance attendance data was obtained from the Eastern Health Human Research Ethics Committee (E122 08-09), with an amendment specific to the qualitative analysis. Consistent with the ethics approval, cells of <5 will not be reported, though zeroes will be preserved. Due to the sensitivity and potentially identifiable nature of the data line item data is not available for sharing, consistent with the ethics approval.

We will present project findings at relevant scientific conferences. We plan to submit findings for publication as two peer-reviewed journal articles. One article will incorporate the quantitative analysis (aim 1 and 2) and one paper report the qualitative analysis (aim 3). We will report findings in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, an extension of the STROBE statement for reporting items specific to observational studies using routinely collected health data (33).

Patient and public involvement

Interpretation of the findings and dissemination will be informed by people with lived experience through contact with consumer organisations such as the Association of Participating Service Users.

Discussion

Strengths and limitations

Recommendations for methods for pharmacovigilance studies identified a number of important features, depending on the aims of the study and the methods employed (16). These include the prospective publication of a study protocol including a detailed statistical analysis plan, transparency around study funding and publication in open-access journals. This study will conform to these requirements.

This study has several strengths. Firstly, coded ambulance data captures a broader range of outcomes and a wider population of people with extramedical pharmaceutical opioid use than may be captured in abuse liability studies, clinical trials, or spontaneous AE reporting systems.

Secondly, this study's population level database accurately codes detailed information about each attendance. This level of detail can provide important insights into harms related to substance use (17-19, 34-36). This study will represent an extension of these studies to provide a detailed analysis of rates and characteristics of harms related with widely used pharmaceutical opioids, and is strengthened by the use of population level supply data to calculate supply-adjusted rates. Finally, the study will be first to provide detailed context around circumstances of pharmaceutical opioid related ambulance attendances, utilising coding of qualitative data.

There are limitations in the use of data collected for operational purposes, similar to with hospital inpatient and emergency department data. There is potential for biases to exist in collection and coding, and incomplete or inconsistent recording of variables. Substance involvement is determined from patient-provided information, others at the scene, or paramedic's clinical assessment, not from toxicological testing. Other clinical details (e.g. mental health symptoms) are also determined in this way.

Rates of ambulance attendances are calculated based on sales data. Due to frequent ordering and limited capacity for controlled drug storage at the community pharmacy level, sales closely approximate supply. Use of sales data addresses limitations with publicly funded prescription data, which omits privately purchased prescriptions and over-the-counter medications and therefore is an incomplete measure of community opioid supply. Finally, as this is a naturalistic study, we cannot know if different patient populations are more likely to receive a given opioid. As such, there may be

unmeasured confounders. Randomised trials can address this limitation; however, patients who use opioids extramedically are usually excluded from trials.

Data statement

To protect privacy and confidentiality, data from the Ambo Project are provided to Turning Point under strict conditions for the storage, retention and use of the data. The current approval permits storage of the data at one site, Turning Point, with any analysis to be undertaken onsite, no data to be removed, and no dissemination of unit level data. Researchers wishing to undertake additional analyses of the data are invited to contact Turning Point as the data custodians.

Conclusion

This will be the first detailed study to compare coded ambulance ePCR as a population level indicator of prescription opioid-related harm. These data will complement ongoing studies examining extramedical use of tapentadol in sentinel populations of people who use drugs, and data from poisons information centres (37). The data in this study represent all acute presentations in community settings where extramedical use of a pharmaceutical opioid analgesic is considered related to the ambulance attendance. This unique dataset has national reach and demonstrated consistency and completeness over multiple years. It will provide one of the most complete analyses of relative harms due to extramedical use for a range of pharmaceutical opioids to date. The study will add to our knowledge, and lead to a more nuanced understanding of whether different pharmaceutical opioids are associated with different harms.

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Author statement

Suzanne Nielsen (SN) initially conceptualised the study and drafted the initial design, with input from Rose Crossin (RC), Debbie Scott (DS) and James Wilson (JW). Cathy Martin (CM) and Melissa Middleton (MM) provided input on, and drafted the statistical analysis plan. SN, RC, DS, JW, Tina Lam (TL), Karen Smith (KS) and Dan Lubman (DL) contributed the drafting of the protocol manuscript and revisions of the protocol. KS, DL and DS lead the broader Victorian Ambo Project and the National Ambo project from which the data is drawn and provided detailed technical advice relating to procedures from that study to inform the development of this study and analysis of the data.

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Table 1. Summary of data availability across jurisdictions

State / Territory	Notes on data available^
ACT	All cases coded one month per quarter from March 2015 until December 2017
NSW	All cases coded one month per quarter from March 2015 until December 2017
NT	All cases coded one month per quarter from March 2016 until December 2017
QLD	All cases coded one month per quarter from March 2015 until December 2016
TAS	All cases coded one month per quarter from March 2014, until December 2017
VIC	All cases coded from January 2012 till September 2018
WA & SA	Data not yet available

^ We will conduct a comparison on supply-adjusted rates of attendance for Victoria and other states utilising periods of time where corresponding data are available.

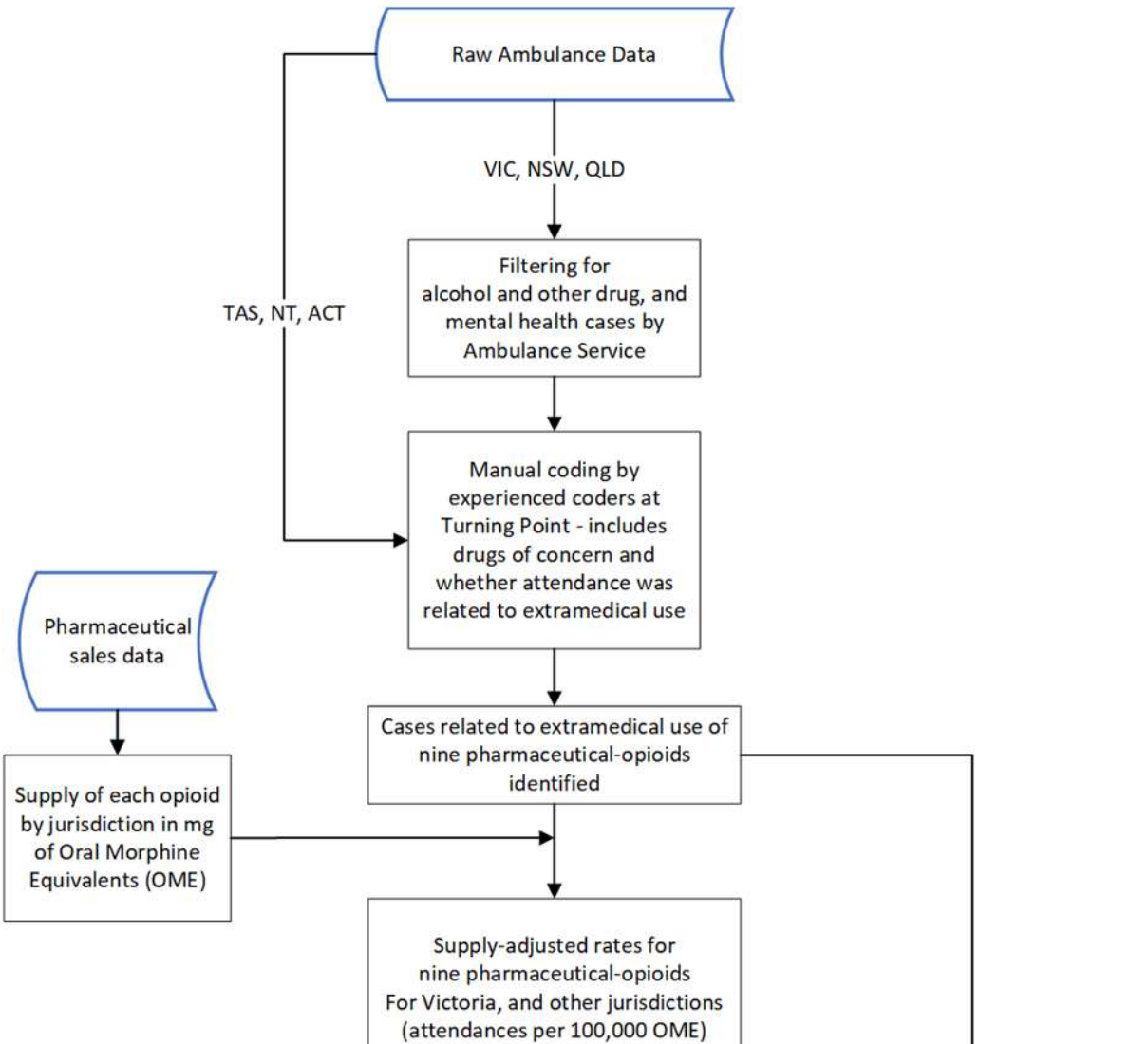
Table 2. Variables and response options to be examined in association with pharmaceutical opioid-related ambulance attendances

Variable	Response options
Presenting Glasgow Coma Scale (GCS)	3 (non-responsive), 4-12 (moderate-severe impairment), 13-15 (minor-no impairment)
Presenting respiratory rate (breaths per minute)	<6, 6-12, >12
Transport to hospital	Not transported, transported
Naloxone administered: not stated, yes	Not states, yes
Naloxone response: not effective, effective	Not effectives, effective
Sex of patient	Male, female, other/unspecified
Age of patient	12-34, 35-54, 55-65 (nearing retirement age) and 65+^
Socio-economic status based on residential postcode	Quintile 1-5 based on SEIFA-IRSD 201s, IRSD 2016 (30)
Concurrent alcohol involvement	Not stated, alcohol involved but no evidence of intoxication, alcohol intoxication∞
Concurrent heroin involvement	Not stated, present
Concurrent illicit drug use (excluding heroin)	based on the presence of at least one of the illicit drugs coded for; meth(amphetamine), cannabis, synthetic cannabinoids, emerging psychoactive substances, cocaine, MDMA, GHB, ketamine, LSD, psilocybin, inhalant, illicit drug other or unspecified)
Concurrent non-opioid extramedical pharmaceutical use	not stated, present (based on the presence of at least one of the pharmaceutical groups coded for; non-opioid analgesics, benzodiazepines, anti-depressants, anti-psychotics, anti-convulsants, opioid-dependence treatments, pharmaceutical stimulants, other medication)
Co-morbid mental health symptoms	not stated, present (based on the presence of at least one of; symptoms of anxiety, depression, psychosis, social / emotional distress, symptoms associated with disorders with clinical evidence, and mental health unspecified)
Co-morbid suicidal thoughts or behaviours	Not stated, present (based on the presence of at least one of; suicidal ideation, suicide attempt)
Co-morbid non-suicidal self-injury	Not stated, present (based on the presence of at least one of; threat of non-suicidal self-injury, non-suicidal self-is, non-suicidal self-injury)
Accidental overdose	Not stated, yes
Unknown intent overdose#	Not stated, yes
Past history of psychiatric issues	Not stated, present (based on the presence of at least one of; past history of mood disorder, psychosis, suicidal ideation, suicide attempt, alcohol and other drug misuse)

^based on previous age categories used in studies of opioid use for pain (38). We will exclude cases where age is reported to be less than 12 due to the unclear intention of use in children of this age, consistent with previous research (39, 40).
#(where information provided in the patient care records by the paramedic means that the coding team cannot determine if the overdose was accidental or if there was suicidal intent)
∞The involvement of alcohol is coded as 'alcohol involved' and 'alcohol intoxication'. Attendances where the person has consumed alcohol, but the paramedic notes do not clearly indicate alcohol intoxication are coded as 'alcohol involved' and 'alcohol intoxication is a subset of 'alcohol involved'. The default code is for 'alcohol involved' unless the paramedic notes provide clear evidence of alcohol intoxication.

Figure Captions:

Figure 1- Overview of study processes and data sources (VIC = Victoria, NSW = New South Wales, QLD = Queensland, TAS = Tasmania, ACT = Australian Capital Territory, NT = Northern Territory)



Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study

Supplementary materials

Appendix A. Description of coder training and inter-rated reliability processes

Research Assistants undertake extensive and ongoing training to ensure coding is consistent. To assist with this, coding guides are utilised that detail categories, the process of classification, provide examples of typical attendance types, and examples of uncommon attendance types. When a new Research Assistant commences, they are first trained by senior researchers, and then paired with multiple experienced Research Assistants on a rotating basis, until they and their senior coding partner are confident of coding consistency. Senior researchers review attendances coded by new Research Assistants to ensure inter- and intra-coder reliability. In addition to training upon appointment, all Research Assistants participate in monthly ongoing training. This training covers issues like complex cases or the introduction of new variables. This training is completed with workshops and "dummy case exercises".

On a day-to-day basis, if Research Assistants are not confident in coding a specific attendance, the attendance is escalated to a senior researcher for review (<1% of attendances). These review cases then feed into regular workshops, which are also used to identify common coding issues, and disseminate coding clarifications on an ongoing basis.

To maintain inter-coder validation, inter-rater review audits are completed by a senior researcher. These are used as a personal learning tool for Research Assistants, and to identify common issues that may need to be addressed across the coding team. As an example of inter-coder validation, results of the most recent coding audit are described below: A maximum of 90 previously coded attendances per Research Assistant were extracted, from the Victoria Quarter 1, 2017 dataset. The 90 attendances met 26 criteria for case-classification. Each Research Assistant then re-coded a random selection of attendances for which they were not the original coder. At that time, there were 23 individual Research Assistants, and the attendances they re-coded came from an average of 9±3 (mean±standard deviation) other Research Assistants. A total of 1,718 attendances were re-coded, which meant 221,622 AOD variables were re-coded, of which only 470 differences were identified (i.e. 0.2% of variables). Differences were systematically identified, and reviewed by a senior researcher for personalised feedback to each Research Assistant and then followed up with systemic team training.

Appendix B. Description of variables to be examined in association with pharmaceutical opioid-related ambulance attendances

Variable	Description	Transformations/ intended aggregations and final response options used for analyses	Data source
Presenting Glasgow Coma Scale (GCS)	The Glasgow Coma Scale [1] is a 13 point (range 3-15) scale that assesses injured patients' level of consciousness. The GCS's overall reliability is adequate [2], and it is used by prehospital and hospital staff in most English speaking countries and most of Europe [3].	Response Options: 3 (non-responsive), 4-8 (severe impairment), 9-12 (moderate impairment)), 13-15 (minor-no impairment), consistent with previous research with substance-related attendances [4, 5]. This study further isolated the "non-responsive" group (GCS=3) who would not have responded at all, to any of the three components of eye, verbal and motor response to external stimuli.	GCS score is assessed and directly entered into the ePCR by trained paramedics.
Presenting respiratory rate (breaths per minute)	There are not clearly defined standard grouping for respiration rate. However, the normal adult respiration rate is generally considered 12-20 breaths per minute [6], and high doses of opioids depress ventilation [7]. The dispatch protocols from the ambulance systems involved in this study class less than 6 breaths a minute as ineffective breathing.	Grouped into three response Options: <6, 6-12, >12	Respiration rate is assessed and directly entered into the ePCR by trained paramedics.
Transport to hospital	Transport outcome relating to attendance	Response Options: Not transported, transported	Outcome of attendance directly entered into the ePCR as a binary variable by trained paramedics and validated by trained coders after reviewing free-text fields.
Naloxone administered: not stated, yes	Naloxone is an opioid antagonist that reverses the effects of opioid overdose [7].	Response Options: Not stated, yes	Binary variable in ePCR, entered by trained paramedic and validated by trained coders after free-text fields.

Naloxone response: not effective, effective		Response Options: Not effective, effective	Binary variable entered by trained paramedic and validated by coders checking free text field on clinical descriptions e.g. GCS ~3 returning to GCS ~15.
Sex of patient	Sex is coded into male, female and non-binary options, however states vary on how they to record non-binary gender. Coders validate and re-code gender as male, female, and other/unknown.	For these analyses response options are coded as: Male (0), female (1), other/unknown (9), missing (.) All patients regardless of sex included in analyses related to Aim 1 (rates) and Aim 3 (context of presentation). Those with unknown sex will be included in the analyses for Aim 2, with missing data quantified.	Four options in the ePCR entered by paramedics, missing data may be coded based on information in free-text.
Age of patient	Our categories were based on previous age categories used in studies of opioid use for pain which were <55, 55-65 and 65+ [8] to enable comparison. In Australia, most overdoses occur in adults with the peak age category in 35-44 [9] and increases observed in older age categories. For this reason we have split those aged from 12 -54 into two categories, 12-34 and 35-55, to enable comparison with national overdose trends. Smaller age groups are not possible due to low rates in younger adults leading to potential censoring of cells. We will exclude cases where age is reported to be less than 12 due to the unclear intention of use in children of this age, consistent with previous research [10, 11].	Response Options: 12-34, 35-54, 55-65 (nearing retirement age) and 65+	DOB is entered by paramedic, missing data may be coded based on information in free-text.

Socio-economic status based on residential postcode	The Socio-Economic Indexes for Areas (SEIFA) ranks geographic areas according to relative socio-economic advantage and disadvantage [12, 13]. The SEIFA is one of the most commonly used measures for socioeconomic status in Australia, and it has been updated every 10 years with Census data since 1986 [14]. Lower scores indicate more disadvantaged areas and higher scores indicate more advantaged areas.	Response Options: Quintile 1-5. At Turning Point, the postcode from the ePCR is linked to the Australian Bureau of Statistics' (ABS) database of SEIFA ranks by postcode (2016), and then these ranks were aggregated into quintiles specific to each state.	Postcode is entered by paramedic
Concurrent alcohol involvement	Concurrent alcohol use is captured because the simultaneous use of multiple depressant drugs (e.g. opioids, alcohol and heroin) increase the risk of overdose [15].	Response Options: Not stated, alcohol involved but no evidence of intoxication, alcohol intoxication. The involvement of alcohol is coded as 'alcohol involved' and 'alcohol intoxication'. Attendances where the person has consumed alcohol, but the paramedic notes do not clearly indicate alcohol intoxication are coded as 'alcohol involved', and 'alcohol intoxication' is a subset of 'alcohol involved'. The default code is for 'alcohol involved' unless the paramedic notes provide clear evidence of alcohol intoxication. For this study, these cases were recoded into exclusive categories – not stated, alcohol involved but no evidence of intoxication and alcohol intoxication.	Coders extract information about alcohol involvement from free-text fields as 'not stated' or 'alcohol involved'. There is a subcategory of 'intoxication' under 'alcohol involved'.

Concurrent heroin involvement	Response Options: Not stated, present	Analysed as binary coded variable.	Coders extract information about heroin involvement from free-text fields and code.
Concurrent illicit drug use (excluding heroin)	Response Options: Not stated, present (based on the presence of at least one of the illicit drugs coded for; meth(amphetamine), cannabis, synthetic cannabinoids, emerging psychoactive substances, cocaine, MDMA, GHB, ketamine, LSD, psilocybin, inhalant, illicit drug other or unspecified)	Not stated/ present if any one of the illicit substances listed are reported as being used in the ePCR	Coders extract information about illicit drug involvement from free-text fields and code.
Concurrent non-opioid extramedical pharmaceutical use	Response Options: Not stated, extramedical use present (based on the presence of at least one of the pharmaceutical groups coded for; non-opioid analgesics, benzodiazepines, anti-depressants, anti-psychotics, anti-convulsants, opioid-dependence treatments, pharmaceutical stimulants, other medication)	Not stated/ present if any one of the pharmaceutical drugs listed are reported in the ePCR	Coders extract information about extramedical use of pharmaceutical drugs from free-text fields and code.
Co-morbid mental health symptoms	Response Options: Not stated, present (based on the presence of at least one of; symptoms of anxiety, depression, psychosis, social / emotional distress, symptoms associated with disorders with clinical evidence, and mental health unspecified). Symptomology is reported rather than diagnoses, as paramedics do not diagnose mental illness.	Recorded as binary option of not stated/ present if any one co-morbid symptoms listed are reported in the ePCR	Coders extract information from free-text fields and code.
Co-morbid suicidal thoughts or behaviours	Response Options: Not stated, present (based on the presence of at least one of; suicidal ideation, suicide, suicide attempt)	Recorded as binary option of not stated/ present if any one co-morbid suicidal thoughts or behaviours listed are reported in the ePCR	Coders extract information from free-text fields and code.
Co-morbid non-suicidal self-injury	Response Options: Not stated, present (based on the presence of at least one of;	Recorded as binary variable of not stated or present based on either threat of non-suicidal	Coders extract information from free-text fields and code.

	threat of non-suicidal self-injury, non-suicidal self-injury)	self-injury or non-suicidal self-injury documented in the ePCR	
Unintentional alcohol and other drug overdose	Where information provided in the patient care records by the paramedic suggests that the person did not intend to die (though they may have intended to take the substance). Overdose (also referred to as *AOD poisoning*) determined using GCS < 9 or 10x dose (for pharmaceuticals), however must also be evidence available to suggest poisoning was unintentional to be coded as yes.	Recorded as binary variable of not stated, yes	Coders extract information from free-text fields and code.
Undetermined intent overdose	Where information provided in the patient care records by the paramedic means that the coding team cannot determine if the overdose was unintentional (also referred to as *'accidental'*) or if there was suicidal intent.	Response Options: Not stated, yes	Coders extract information from free-text fields and code.
Past history of psychiatric issues	Response Options: Not stated, present (based on the presence of at least one of; past history of mood disorder (including anxiety, depression, PTSD, Bipolar and OCD), psychosis, suicidal ideation, suicide attempt, alcohol and other drug misuse).	Response Options: Not stated, present	Coders extract information from free-text fields and code.

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