Pharmaceutical opioid poisonings in Victoria, Australia: rates and characteristics of a decade of Emergency Department presentations across nine pharmaceutical opioids

SUPPLEMENTARY MATERIALS

Contents

Table S1. The RECORD statement – checklist of items extended from the STROBE statement that should be reported in observational studies using routinely collected health data. ........................................2

Figure S1. Flowchart of cases identified at each stage of the search .........................................................6

Table S2. Estimated supply-adjusted rates with confidence intervals for each opioid in Victoria, from July 2009 - June 2019 ..............................................................................................................7

Table S3. Supply adjusted trends for ED presentations by opioid type, Victoria July 2009 - June 2019 (aim 1 sensitivity analysis). .................................................................................................8

Figure S2a. Raw ED presentation rates by opioid type, July 2009 - June 2019 ........................................9

Figure S2b. Raw opioid supply, Victorian community pharmacies July 2009 - June 2019 ..........10

Figure S3. Association between Age and probability of ED Attendance by Opioid Type (controlling for sex and year) ...........................................................................................................11

Figure S4. Association between Sex and probability of ED Attendance by Opioid Type (controlling for age and year) ...........................................................................................................12

Figure S5. Association between Patient Geographic Region and probability of ED Attendance by Opioid Type (controlling for age, sex and year). ........................................................................13

Figure S6. Association between Country of Birth and ED Attendance by Opioid Type (controlling for age, sex and year). ...........................................................................................................14

Figure S7. Association between SEIFA quintile and ED Attendance by Opioid Type (controlling for age, sex and year) ...........................................................................................................15

Figure S8. Association between Intent and probability of ED Attendance by Opioid Type (controlling for age, sex and year). ........................................................................................................16

Figure S9. Association between Admission Outcome and probability of ED Attendance by Opioid Type (controlling for age, sex and year). ..................................................................................17

Figure S10. Association between Triage Category and probability of ED Attendance by Opioid Type (controlling for age, sex and year). ..................................................................................18
Table S1. The RECORD statement – checklist of items extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

| Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|----------|--------------|------------------------------------------------|--------------|------------------------------------------------|
| **Title and abstract** | | | | |
| 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 1. | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 1.1 Page 2 - Emergency Department (ED) patient care records in the Victorian Emergency Minimum Dataset (VEMD). 1.2. Page 2 – Victoria, Australia. July 2009 to June 2019. |
| **Introduction** | | | | |
| 2 | Explain the scientific background and rationale for the investigation being reported | Pages 4-5. | | |
| **Objectives** | 3 | State specific objectives, including any prespecified hypotheses | Page 5, last paragraph of introduction. | | |
| **Methods** | | | | |
| 4 | Present key elements of study design early in the paper | Page 6, paragraph 2. | | |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 6, ‘Participants’ subheading and page 7 ‘Data sources – ED data’ subheading | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | 6.1. Figure S1 for database search criteria. 6.2. Page 7 for a referenced description of the database quality systems and manual checking procedure by an experienced data analyst. |
| 6 | (a) Cohort study - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed Case-control study - For matched studies, give matching criteria and the number of controls per case | Page 6, ‘Participants’ subheading, and page 7 ‘Data sources – ED data’ subheading | | |

Page 2 of 18
Table S1. The RECORD statement – checklist of items extended from the STROBE statement that should be reported in observational studies using routinely collected health data (continued).

| Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|----------|--------------|-----------------------------------------------|---------------|-----------------------------------------------|
| **Variables** | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Page 7 & 8 for description of primary outcome (overdose) and secondary outcomes (characteristics associated with overdose). | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. Page 7 & 8 for description of primary outcome (overdose) and secondary outcomes (characteristics associated with overdose). |
| **Data sources/measurement** | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Page 7-8 ‘ED data’ and ‘Sales data’ subheadings. |
| **Bias** | 9 | Describe any efforts to address potential sources of bias. Page 9-10. |
| **Study size** | 10 | Explain how the study size was arrived at. Page 6. |
| **Quantitative variables** | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. Page 8-9. |
| **Statistical methods** | 12 | (a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed. *Case-control study* - If applicable, explain how matching of cases and controls was addressed. *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses. Page 8-9. |
| **Data access and cleaning methods** | .. | .. | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. 12.1. Page 18 - JH and JB (VISU) ED data custodians. Page 8 sales data. 12.2. Page 7 and published protocol (ref 15). |
| **Linkage** | .. | .. | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. |

Page 3 of 18
Table S1. The RECORD statement – checklist of items extended from the STROBE statement that should be reported in observational studies using routinely collected health data (continued).

| Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|----------|--------------|-----------------------------------------------|--------------|-----------------------------------------------|
| **Results** | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) | Figure S1 of a flowchart of cases identified | RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | Page 6 ‘Participants’, Page 7-8 ‘ED data’, and Figure S1 of a flowchart of cases identified. |
| Descriptive data | 14 | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) Cohort study - summarise follow-up time (e.g., average and total amount) | (a) Table 2 – ‘Patient and presentation characteristics’ (b) Page 9-10 ‘Missing data’ subheading | | |
| Outcome data | 15 | Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures | Table 2 – ‘Patient and presentation characteristics’ | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | (a) Raw (unadjusted) ED presentation and opioid supply data Figure S2a and Figure S2b (b) Page 8 and Table 2 | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | Table S3. Reports aim 1’s sensitivity analysis. | | |

Page 4 of 18
Table S1. The RECORD statement – checklist of items extended from the STROBE statement that should be reported in observational studies using routinely collected health data (continued).

| Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|----------|--------------|-----------------------------------------------|--------------|-----------------------------------------------|
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 14, paragraph 1 of Discussion | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 16-17, ‘Limitations’ subheading | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | Page 16-17, ‘Limitations’ subheading |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 17, ‘Conclusions’ subheading | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 6-7 - state’s opioid harms similar to national patterns, and the country is 8\(^{th}\) in the world for licit consumption. ED cost is covered in Australia. | |
| **Other Information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 3. | |
| Accessibility of protocol, raw data, and programming code | . | Protocol is published (reference 15), and describes data access. | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | Protocol is published (reference 15), and describes data access. |

Benchimol EI, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elin E, Langan SM; RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS medicine. 2015;12(10):e1001885.
Figure S1. Flowchart of cases identified at each stage of the search

All ED presentations for injury in the 10-year study period  
\( n=3039282 \)

All ED records associated with a Pharmaceutical Opioid (PO)  
identified using free-text search and ICD-10-AM codes\(^1\)  
\( n=30474 \)

Manual case reading & hand coding

Included records

Excluded records

Specific PO able to be identified in  
PO poisoning using the narrative text field  
\( n=5520 \)

Specific PO identified in PO poisoning  
through ICD-codes only  
(i.e. Methadone T40.3 cases)  
\( n=178 \)

Excluded records where  
PO mentioned, but not in the context of a PO poisoning  
\( n=24776 \)

ED records for PO overdose used for analysis  
\( n=5698 \)  
(5698 records related to 5403 attendances, as some attendances involved multiple opioids)

\(^1\) Summary of the search criteria:

| Type of search          | Description                                                                                                                                                                                                 |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FREE-TEXT SEARCH        | Specific names for the pharmaceutical opioids \[All pharmaceutical opioid drug name including variations that include generic and brand names for the opioids of interest along with common misspellings (e.g. “Tramadol/ tramal/ zydol”, “Morphine/ MS contin/ MS mono/ kapanol/ anamorph/ sevredol”, “Oxycodone/ oxycodeine/ oxy/ oxycontin/ endone/ targin/ oxnorm/ proladone”)\]  |
|                         | AND Classification of Poisoning/overdose \[The ICD-10-AM diagnosis code ‘T40’ appeared in any of the 3 diagnosis fields, T40=‘Poisoning by narcotics and psychodysleptics (hallucinogens) [excludes intoxication/inebriation] (range T40.0-T40.9) OR The text field indicated poisoning - narcan, naloxone, overdose, od, o/d, over dose, drug abuse, poisoning, poison, toxicity, selfharm, harm self, suicide, intentional, deliberate OR Cause of injury was coded as ‘poisoning’ (note that the VEMD does not use ICD10-AM cause codes, instead the hospitals have a drop-down list of causes)\]  |
| ICD-10-AM code          | For methadone only, the code ‘T40.3’ – Methadone, appears anywhere within the three VEMD diagnosis codes (where drug name does not appear in the text field).  |
Table S2. Estimated supply-adjusted rates\(^1\) with confidence intervals for each opioid in Victoria, from July 2009 - June 2019

| Opioid          | Buprenorphine | Codeine | Fentanyl | Methadone | Morphine |
|-----------------|---------------|---------|----------|-----------|----------|
|                 | n             | 90      | 2008     | 71        | 580      | 201      |
|                 | Rate          | LCL     | UCL      | Rate      | LCL      | UCL      | Rate          | LCL     | UCL     | Rate          | LCL     | UCL     | Rate          | LCL     | UCL     |
| 2009/10         | 0.086         | 0.074   | 0.097    | 0.006     | 0.004    | 0.008    | 0.010         | 0.006   | 0.013   |
| 2010/11         | 0.008         | 0.003   | 0.013    | 0.075     | 0.064    | 0.085    | 0.007         | 0.005   | 0.008   | 0.013         | 0.009   | 0.017   |
| 2011/12         | 0.008         | 0.003   | 0.012    | 0.071     | 0.061    | 0.081    | 0.007         | 0.005   | 0.009   | 0.008         | 0.005   | 0.012   |
| 2012/13         | 0.008         | 0.003   | 0.011    | 0.073     | 0.063    | 0.083    | 0.004         | 0.003   | 0.006   | 0.012         | 0.007   | 0.017   |
| 2013/14         | 0.008         | 0.003   | 0.010    | 0.081     | 0.070    | 0.091    | 0.005         | 0.002   | 0.007   | 0.011         | 0.006   | 0.016   |
| 2014/15         | 0.007         | 0.003   | 0.010    | 0.076     | 0.066    | 0.086    | 0.008         | 0.006   | 0.010   | 0.012         | 0.007   | 0.017   |
| 2015/16         | 0.007         | 0.004   | 0.011    | 0.091     | 0.080    | 0.102    | 0.006         | 0.003   | 0.009   | 0.009         | 0.007   | 0.011   |
| 2016/17         | 0.006         | 0.002   | 0.009    | 0.077     | 0.067    | 0.088    | 0.007         | 0.005   | 0.009   | 0.008         | 0.004   | 0.013   |
| 2017/18         | 0.006         | 0.002   | 0.009    | 0.067     | 0.057    | 0.078    | 0.007         | 0.005   | 0.008   | 0.010         | 0.005   | 0.015   |
| 2018/19         | 0.007         | 0.003   | 0.010    | 0.061     | 0.050    | 0.073    | 0.007         | 0.005   | 0.008   |               |         |         |

| Opioid         | Oxycodone | Oxycodone-Naloxone | Tapentadol | Tramadol |
|----------------|-----------|---------------------|------------|----------|
|                 | n         | 1437                | 146        | 36       | 542      |
|                 | Rate      | LCL                 | UCL        | Rate     | LCL     | UCL     | Rate          | LCL     | UCL     | Rate          | LCL     | UCL     |
| 2009/10         | 0.017     | 0.014               | 0.021      | N/A      | N/A     | N/A     | N/A           | N/A     | N/A     | 0.022         | 0.016   | 0.027   |
| 2010/11         | 0.019     | 0.016               | 0.023      | N/A      | N/A     | N/A     | N/A           | N/A     | N/A     | 0.012         | 0.008   | 0.015   |
| 2011/12         | 0.022     | 0.018               | 0.025      | N/A      | N/A     | N/A     | N/A           | N/A     | N/A     | 0.016         | 0.012   | 0.020   |
| 2012/13         | 0.028     | 0.024               | 0.032      | N/A      | N/A     | N/A     | N/A           | N/A     | N/A     | 0.015         | 0.011   | 0.019   |
| 2013/14         | 0.032     | 0.027               | 0.037      | 0.010    | 0.005   | 0.015   | 0.013         | 0.009   | 0.016   |               |         |         |
| 2014/15         | 0.033     | 0.028               | 0.038      | 0.008    | 0.004   | 0.012   | 0.011         | 0.007   | 0.014   |               |         |         |
| 2015/16         | 0.037     | 0.031               | 0.042      | 0.009    | 0.005   | 0.012   | 0.016         | 0.012   | 0.020   |               |         |         |
| 2016/17         | 0.035     | 0.029               | 0.040      | 0.009    | 0.006   | 0.012   | 0.015         | 0.011   | 0.019   |               |         |         |
| 2017/18         | 0.037     | 0.031               | 0.043      | 0.008    | 0.005   | 0.011   | 0.005         | 0.002   | 0.008   | 0.019         | 0.015   | 0.024   |
| 2018/19         | 0.044     | 0.037               | 0.051      | 0.006    | 0.003   | 0.009   | 0.005         | 0.003   | 0.008   | 0.015         | 0.011   | 0.019   |

\(^1\)Mean monthly supply-adjusted rate (per 100 000 mg oral morphine equivalents).

\(^2\)Sample size for the 2009-2019 study period

Empty cells appear where rates were not calculated as ED presentations were <10 per year for that opioid.

First Victorian sales of tapentadol occurred in February 2013, and of oxycodone-naloxone in August 2010 (so rates not calculated for these periods and N/A appears in these cells).
Table S3. Supply adjusted trends for ED presentations by opioid type, Victoria July 2009 - June 2019 (aim 1 sensitivity analysis).

| Opioid1 | Frequency | Supply-adjusted Rate2 (per 100 000mg OME per year, over entire Jul 2009- Jun 2019 study period) | Time trend3 (per 100 000 OME, per 6-month increase) |
|---------|-----------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------|
|         | n (%)     | Rate 95% CI                                                                                  | Incidence Rate Ratio 95% CI P-value                  |
| Codeine | 2154 (39.9%) | 0.082 0.079 - 0.087                                                                          | 0.99 0.98 - 1.01 0.32                                |
| Oxycodone | 1632 (30.2%) | 0.033 0.031 - 0.034                                                                          | 1.05 1.04 - 1.06 <0.0001                             |
| Tramadol | 644 (11.9%) | 0.018 0.017 - 0.019                                                                          | 1.00 0.98 - 1.01 0.62                                |
| Oxycodone-Naloxone | 205 (3.8%) | 0.011 0.010 - 0.013                                                                          | 0.98 0.94 - 1.01 0.25                                |
| Morphine | 229 (4.2%) | 0.011 0.010 - 0.013                                                                          | 0.98 0.96 - 1.01 0.24                                |
| Methadone | 613 (11.4%) | 0.007 0.007 - 0.008                                                                          | 1.01 0.99 - 1.03 0.32                                |
| Buprenorphine | 100 (1.9%) | 0.006 0.005 - 0.007                                                                          | 1.00 0.97 - 0.04 0.84                                |
| Tapentadol (2009-2019) | 41 (0.8%) | 0.005 0.003 - 0.006                                                                          | 1.09 0.99 - 1.19 0.07                                |
| Tapentadol (2014-2019)4 | 41 (1.3%) | 0.005 0.003 - 0.006                                                                          | 1.09 0.98 - 1.20 0.11                                |
| Fentanyl | 80 (1.5%) | 0.003 0.003 - 0.004                                                                          | 1.04 0.99 - 1.09 0.12                                |

1 Opioid categories are not mutually exclusive, therefore column percentages add up to more than 100%. Each of the categories include cases where it was the only opioid involved, as well as cases where it was one of multiple opioids involved.
2 Supply-adjusted rate of ED presentations is per 100 000mg OME per year, over the entire July 2009 - June 2019 study period.
3 Time trend Incident Rate Ratio is calculated on 6 month intervals using Poisson regression per 100 000mg OME.
4 Due to low sales volume and no attendances related to tapentadol prior 2014, overall trends are also presented for Jan 2014-Jun 2019.
Figure S2a Raw ED presentation rates by opioid type, July 2009 - June 2019

Figure S2a note. Lines start when drug was available on the market. Tapentadol was approved by the Australian Department of Health's Therapeutic Goods Administration (TGA) in November 2010, and first sales in Victoria occurred in February 2013. Oxycodone-naloxone was TGA approved in March 2010 and first sales in Victoria occurred in August 2010.
Figure S2b note. Lines start when drug was available on the market. Tapentadol was approved by the Australian Department of Health's Therapeutic Goods Administration (TGA) in November 2010, and first sales in Victoria occurred in February 2013. Oxycodone-naloxone was TGA approved in March 2010 and first sales in Victoria occurred in August 2010.
Figure S3. Association between Age and probability of ED Attendance by Opioid Type (controlling for sex and year)
Figure S4. Association between Sex and probability of ED Attendance by Opioid Type (controlling for age and year).
Figure S5. Association between Patient Geographic Region and probability of ED Attendance by Opioid Type (controlling for age, sex and year).
Figure S6. Association between Country of Birth and probability of ED Attendance by Opioid Type (controlling for age, sex and year)
Figure S7. Association between SEIFA quintile and ED Attendance by Opioid Type (controlling for age, sex and year).

Note: SEIFA deciles were grouped so there were two deciles per quintile.
Figure S8. Association between Intent and probability of ED Attendance by Opioid Type (controlling for age, sex and year).
Figure S9. Association between Admission Outcome and probability of ED Attendance by Opioid Type (controlling for age, sex and year).
Figure S10. Association between Triage Category and probability of ED Attendance by Opioid Type (controlling for age, sex and year).