PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing rates and characteristics of emergency department presentations related to pharmaceutical opioid poisoning in Australia: a study protocol for a retrospective observational study
AUTHORS	Nielsen, Suzanne; Lam, Tina; Hayman, Jane; Berecki-Gisolf, Janneke; Sanfilippo, Paul; Lubman, D

VERSION 1 – REVIEW

REVIEWER	Omid Mehrpour Birjand University of medical sciences,Iran
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	This is an interesting study that aims to evaluate pharmaceutical opioid poisonings treated within EDs to inform clinical treatment and prevention strategies. Some comments: 1. Please provide more information about the data collection/data registry system in this study. 2. The authors will study Buprenorphine, Codeine Fentanyl, Methadone, Morphine, Oxycodone, Oxycodone-naloxone, Tapentadol, Tramadol, Multiple opioids. Why they excluded other opioids? 3. How do the authors rely on the data registry system and how they excluded garbage data? 4. What is the definition of opioid poisoning in this study? 5. How will the authors differentiate between poisoning and exposure? 6. Why do the authors include patients above 12 years old? Why they opted 12 years old as a cut-off? 7. Please provide the aim of the study in the abstract clearer.

REVIEWER	SUNG RYUL SHIM Department of Preventive Medicine, KOREA university College of Medicine, Seoul, Korea
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	Reviewers' comments: Title : bmjopen-2020-038979, Comparing rates and characteristics of emergency department presentations related to pharmaceutical opioid poisoning in Australia: a study protocol for a retrospective observational study. Thank you for the opportunity to review your manuscript.

	The concept of current study seems interesting In fact, due to the type of protocol, there is not too much information to review, so I would like to recommend some comments. Please check below. Major comments 1. How to adjust when crude data is biased. A. Basically, this is observation data, which means you have some possibility to obtain the skewed data. For example, nine-selected opioids will be affected by other covariates such as age, sex, region, etc. The authors want to calculate with nine opioids as important independent variable. But if nine opioids were already biased by other covariates, how to adjust it. It is very common problem in observational study because of non-randomization. B. If your data are usually collected over time and over the same individuals, panel data analysis is very useful to identify the time-trend effects. 2. VEMD specifically describe data source, especially VEMD. is it a commercial company or a national health agency? IQVIA also. 3. The logic of selection nine opioids.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Omid Mehrpour
Institution and Country: Birjand University of medical sciences,Iran Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below This is an interesting study that aims to evaluate pharmaceutical opioid poisonings treated within EDs to inform clinical treatment and prevention strategies. Some comments:

1. Please provide more information about the data collection/data registry system in this study.

RESPONSE: We have added further description about the VEMD to the study design section which now reads:

“The study design is a retrospective observational study that uses administrative emergency department data in the VEMD, the Victorian Emergency Minimum Dataset. Australia has a universal health care scheme which covers the cost of public hospital services (1). It is mandatory for all public ED presentations in the state of Victoria to be entered into the VEMD by ED staff, and the database itself is managed by the state government’s Department of Health and Human Services (2).”

2. The authors will study Buprenorphine, Codeine Fentanyl, Methadone, Morphine, Oxycodone, Oxycodone-naloxone, Tapentadol, Tramadol, Multiple opioids. Why they excluded other opioids?

RESPONSE: We have now revised the explanation of the “opioids of Interest” section to read:

“The opioid categories we will analyse are: (i) Buprenorphine, (ii) Codeine (iii) Fentanyl, (iv) Methadone, (v) Morphine, (vi) Oxycodone, (vii) Oxycodone-naloxone, (viii) Tapentadol, (ix) Tramadol, (x) Multiple opioids.

The first nine categories represent the opioids most commonly used for analgesia in outpatient settings in Australia. Our previous work demonstrated that less common drugs such as pethidine and dextropropoxyphene are captured in too few numbers to report on, given the requirement to suppress cell sizes of less than five (3). We will not examine opioids that are rarely used (e.g. dextropropoxyphene), not available in Australia (such as hydrocodone), and those used only in inpatient settings (such as alfentanil and sufentanil).”

3. How do the authors rely on the data registry system and how they excluded garbage data?
RESPONSE: The VEMD data has standard procedures for accuracy, validity, completeness and coherence and we have summarised these processes as:

• Data submitted by health services is subject to a validation process, checking for valid values and compliance with VEMD business rules. Where anomalies are detected health services are required to correct the data.

• The VEMD is subject to audits. The audit program is managed by Health Data Integrity Unit in the Victorian Agency for Health Information (VAHI).

• The VEMD validation process provides reports for the health service to check the total number of records submitted, the number of rejections, and make appropriate corrections and re-submissions until they have a clean (zero rejection) submission by the ‘clean’ date.

• The Department distributes a monthly compliance report to monitor completeness of submissions to the VEMD. The department monitors completeness through regular analyses of the VEMD, sending out compliance emails to health services when a reporting deadline is missed. Quarterly reconciliation reports are sent to health services for review.
In addition to these standard procedures around data quality, every case identified for this study will be checked by a data analyst who is experienced with the VEMD system to confirm that is relevant to the search criteria. That is, the search criteria will be used to identify cases which are likely relevant to opioid overdose, but this will be confirmed manually by a person.

We have added a brief outline of this process:
“The VEMD manual (2) documents the standardised procedures used to ensure the accuracy, validity, completeness and coherence of captured and reported data across datasets and over time. These procedures include that data submitted by the health services is checked for valid values and compliance with VEMD business rules, and a requirement for corrections and resubmissions until the service has a ‘clean’ (zero rejection) submission. The Department of Health and Human Services circulates a monthly compliance report to monitor the completeness of submissions to the VEMD, runs regular analyses, and sends out compliance emails when reporting deadlines are missed. The VEMD is also subject to audits by the Health Data Integrity Unit in the Victorian Agency for Health Information.

In addition to data quality systems with the VEMD database, an experienced data analyst will manually check all extracted cases to ensure there are no inconsistencies between coded cases and the narrative (i.e. excluding cases where only non-opioid drugs are stated in the narrative) to confirm the ED presentation relates to a pharmaceutical opioid overdose or poisoning.”

4. What is the definition of opioid poisoning in this study?

RESPONSE: “Opioid poisoning” is largely synonymous with “opioid overdose”. The World Health Organisation states that “In the field of toxicology, the term poisoning is used more broadly to denote a state resulting from the administration of excessive amounts of any pharmacological agent, psychoactive or not”.

We have expanded the Introduction section on page 4 to read:

“There is a need for further research to extend these findings with other datasets, and particularly to focus on the outcome of opioid poisoning. Opioid poisoning is also referred to as 'opioid overdose’, and is an acute condition resulting from the absorption of excessive amounts of opioids into the body (4).”

5. How will the authors differentiate between poisoning and exposure?

RESPONSE: Our search terms will include terms such as “poisoning”, “overdose”, “toxicity” and ICD-10 T40 codes relating to “poisoning by narcotics and psychodysleptics”. Furthermore, as described in the response to comment 2, an experienced analyst will read through every case to confirm that it relates to an overdose, rather than merely reflecting incidental exposure to opioids in a case that relates to another condition.

6. Why do the authors include patients above 12 years old? Why they opted 12 years old as a cut-off?

RESPONSE: On page 9 of the methods, we note that “Cases will be restricted to those aged 12 years and over to omit cases of accidental poisoning by children (5, 6).”

The two papers we cite are previous examinations of drug overdoses using hospital data, which also exclude children under 12 years of age. Gunnel (2004) for example, stated that “to avoid including accidental overdoses among children we excluded all episodes among individuals aged <12 years.”

We differentiate between the initial ingestion of the opioid, and the later overdose. Both ingestion and overdose could be accidental or intentional.

Based on previous research, we use the age of 12 as is accepted that individuals aged at least 12 and over would understand that pharmaceutical opioids are a medicine, rather than another item, such as confectionary. That is, they intentionally used the opioid as a medicine, or drug.

We separately consider the intentionality of the overdose as a part of our analyses. For example, in some cases it is documented that the overdose was a part of a self-harm attempt, and in others the overdose may have been a result of unintentional over ingestion (see Table 2; “Context of presentation (intent of use, indicator of misuse)”.

We have revised this section in the manuscript to read:

“Consistent with previous overdose research, cases will be restricted to those aged 12 years and over to omit cases of accidental poisoning by children (5, 6). This age limit means that it is likely most individuals who used the pharmaceutical opioid were aware it was a drug.”

7. Please provide the aim of the study in the abstract clearer.

RESPONSE: The third sentence of the abstract now reads:

“We aim to compare commonly used pharmaceutical opioids in terms of (1) rates of harm, and (2) demographic and clinical characteristics associated with that harm.”

Reviewer: 2
Reviewer Name: SUNG RYUL SHIM
Institution and Country: Department of Preventive Medicine, KOREA university College of Medicine, Seoul, Korea Please state any competing interests or state ‘None declared’: NONE

Please leave your comments for the authors below Reviewers’ comments:

Title : bmjopen-2020-038979, Comparing rates and characteristics of emergency department presentations related to pharmaceutical opioid poisoning in Australia: a study protocol for a retrospective observational study.

Thank you for the opportunity to review your manuscript.
The concept of current study seems interesting In fact, due to the type of protocol, there is not too much information to review, so I would like to recommend some comments.
Please check below.

Major comments

1. How to adjust when crude data is biased.

A. Basically, this is observation data, which means you have some possibility to obtain the skewed data. For example, nine-selected opioids will be affected by other covariates such as age, sex, region, etc. The authors want to calculate with nine opioids as important independent variable. But if nine opioids were already biased by other covariates, how to adjust it. It is very common problem in observational study because of non-randomization.

RESPONSE: We have revised this section to include further information on the adjustments we include in the multinomial logistic regressions:
“We will use multinomial logistic regression to analyse opioid-poisoning characteristics. Characteristics include the patient demographics of age, sex, region, country of birth and socio-economic status; and the presentation characteristics of whether the overdose was intentional, admission outcome, and clinical severity (Table 2). Separate regressions will be run with each attendance characteristic serving as the primary independent variable. Opioid type will be the outcome variable in all regressions with morphine, a mid-potency opioid commonly used as a standard reference for calculating opioid doses (7), as the reference category. Results will be expressed as the estimated odds of each opioid (relative to morphine) being involved in the ED presentation for a particular attendance characteristic. In addition, year will be included as an independent variable in all regressions to assess whether characteristics changed over time – the potential of time as an effect modifier in the relationship between the attendance characteristic and opioid type will be evaluated by testing the statistical interaction between the two independent variables in the regression model. When considering the triage category, the model will be also be adjusted for by age and sex, in addition to other characteristics identified in univariate analyses to be associated with severity of overdose. VEMD categories will be aggregated where necessary to ensure that all analyses report cell sizes of at least five.”
We also acknowledge in the limitations section of the discussion that there may be unmeasured confounders that may determine the likelihood of an individual being prescribed a specific opioid that

we cannot account for using a naturalistic study design. While acknowledging that this is a common limitation, we still believe there is valuable information to learn from this study.

B. If your data are usually collected over time and over the same individuals, panel data analysis is very useful to identify the time-trend effects.

RESPONSE: We agree that being able to compare data on the same individuals over time would be useful, but we do not have access to such data. Our unit of analysis are episodes of attendance, not individuals. We will not be using individual identifiers that link the same patient with multiple attendances, but will be using ED attendances as the unit of analysis to examine attendance attributed to individual pharmaceutical opioids. These opioids are usually coded into a broader categories per ICD-10 coding, preventing the study of harms with individual opioids, so this provides a unique opportunity to examine trends with attendances related to specific opioids over time.
2. VEMD
specifically describe data source, especially VEMD. is it a commercial company or a national health agency? IQVIA also.

RESPONSE: Thank you for the opportunity to provide a more detailed explanation of the data sources. The VEMD data is collected as part of a state-wide public health system data collection, We have added further description about the VEMD:

“Australia has a universal health care scheme which covers the cost of public hospital services (1). It is mandatory for all public ED presentations in the state of Victoria to be entered into the Victorian Emergency Minimum Dataset (VEMD) by ED staff (2). The database is managed by the state government’s Department of Health and Human Services (2).
…
The VEMD manual (2) documents the standardised procedures used to ensure the accuracy, validity, completeness and coherence of captured and reported data across datasets and over time. These procedures include that data submitted by the health services is checked for valid values and compliance with VEMD business rules, and a requirement for corrections and resubmissions until the service has a ‘clean’ (zero rejection) submission. The Department of Health and Human Services circulates a monthly compliance report to monitor the completeness of submissions to the VEMD, runs regular analyses, and sends out compliance emails when reporting deadlines are missed. The VEMD is also subject to audits by the Health Data Integrity Unit in the Victorian Agency for Health Information.”

The IQVIA section now reads:
“This sales data (unit sales by strength of product for each of the opioids involved) will be accessed via a third party access agreement with the multinational health information and clinical research company IQVIA (iqvia.com).”

3. The logic of selection nine opioids.
RESPONSE: We have now revised the “opioids of Interest” section to read:

“The opioid categories we will analyse are: (i) Buprenorphine, (ii) Codeine (iii) Fentanyl, (iv) Methadone, (v) Morphine, (vi) Oxycodone, (vii) Oxycodone-naloxone, (viii) Tapentadol, (ix) Tramadol, (x) Multiple opioids.

The first nine categories represent the opioids most commonly used for analgesia in outpatient settings in Australia. Our previous work demonstrated that less common drugs such as pethidine and dextropropoxyphene are captured in too few numbers to report on, given the requirement to suppress cell sizes of less than five (3). We will not examine opioids that are rarely used (e.g.

dextropropoxyphene), not available in Australia (such as hydrocodone), and those used only in inpatient settings (such as alfentanil and sufentanil)."

To confirm, all commonly used opioids are included.

References cited in the response to reviewers

1. Australian Institute for Health and Welfare. Australia's health 2018 Canberra: Australian Institute for Health and Welfare; 2018.
2. Department of Health and Human Services. Victorian Emergency Minimum Dataset (VEMD): State Government of Victoria, Australia; 2019 [cited 2019 18 Feb]. Available from: https://www2.health.vic.gov.au/hospitals-and-health-services/data-reporting/health-data-standards-systems/data-collections/vemd.
3. Nielsen S, Crossin R, Middleton M, Lam T, Wilson J, Scott D, et al. Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Victoria, Australia from 2013-2018. Addiction. 2020.
4. World Health Organization. Community management of opioid overdose. Geneva, Switzerland: WHO Document Production Services; 2014.
5. Rhodes AE, Bethell J, Spence J, Links PS, Streiner DL, Jaakkimainen RL. Age-sex differences in medicinal self-poisonings: a population-based study of deliberate intent and medical severity. Social psychiatry and psychiatric epidemiology. 2008;43(8):642-52.
6. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? Emergency medicine journal : EMJ. 2004;21(1):35-8.
7. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiology and drug safety. 2016;25(6):733-7.

VERSION 2 – REVIEW

REVIEWER	Omid Mehrpour Birjand University of Medical Sciences
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	it is a nice job. I recommend publication

REVIEWER	SHIM, SUNGRYUL Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	The authors well developed the manuscript.