Author’s response to reviews

Title: Adverse drug reactions due to opioid analgesic use in New South Wales, Australia: a spatial-temporal analysis

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Response to Reviewer 1

Thank you for the opportunity to review manuscript PHAT-D-19-0010 entitled, Adverse drug reactions to opioid analgesic use in New South Wales, Australia: a spatial-temporal analysis. The use of a spatial temporal analysis to examine opioid adverse drug responses is innovative and has potential to inform healthcare policy and practice. The manuscript is generally well written. There are a few areas that need to be addressed prior to publication.

RE:
We appreciate the recognition and we have made revisions according to reviewer’s comments.

* Figures 1 and 2 are difficult to read online or in print

RE:
We have created and uploaded new figures, which are all in standalone format.
Page 8, lines 40 - 42, the trend appears to be increasing throughout the 10 years rather than only in comparison to the second five years compared to the first five years. Please clarify and address.

RE:

We have amended this sentence to the manuscript, which now reads (Result section, page 10) “A total of …. were hospitalised for acute care from 2004-05 to 2013-14, demonstrating an overall increasing trend over time, of which 59.3%....... (Table 1)”.

The findings on page 9, lines 17 -29 are very interesting. More discussion on the findings would be helpful.

RE:

We have added this discussion to the manuscript “… may relate to an overall increasing use of opioid analgesics in healthcare settings,1-3 lack of accredited multidisciplinary services for chronic pain in those local health districts in regional NSW during the study period,59 and therefore leading to greater use of potentially inappropriate opioid analgesics in various clinical scenarios.50-51”.

We have also added the following: (Discussion section, page 13) “… our findings further highlight an unmet healthcare need in pain management as well as potentially inappropriate use of pharmaceutical opioid analgesics in socioeconomic disadvantaged population groups with low education and income from places with sufficient healthcare resources. Increasing the coverage of ADR countermeasures in relation to appropriate use of pharmaceutical opioid analgesics…”.

Page 11, lines 5-12 the sentence needs to be written more clearly. Pages 12 and 13 need to be broken into appropriate paragraphs.

RE:

We have re-organised the original two paragraphs into three, and made a revision to the manuscript, which now reads (Discussion section, pages 13-14) “Of relevance to the significant increase in the use of prescription opioid analgesics in older people,45 second-line prescription opioids were commonly used to initiate pain management in older people,46 as well as those living with mental health problems,47 which in turn increases the risk of ADRs”. 
* Please add to the discussion content on how the method can be combined with other data and methods to address opioid ADR identification and prevention efforts.

RE:

We have made a revision to the manuscript, which now reads (Discussion section, pages 12-13) “Our study demonstrated the utility of this approach and future studies should aim to combine with other data such as number of visits to general practitioners, specialists, psychiatrists, pharmacists, and allied health professionals to address opioid-related ADR identification and prevention efforts in the decision making process, for example to encourage collaboration and coordination of healthcare services as well as allocate resources in communities of great needs”.

Response to Reviewer 2

This is an interesting study examining adverse drug reactions due to opioid analgesic use in New South Wales, Australia: a spatial-temporal analysis. The study provides new information on the space and time variation on the opioid ADR. A number of observations require a little bit explanation to improve the clarity of the manuscript.

RE:

We appreciate the recognition and we have made revisions according to reviewer’s comments.

Methodology

There will be added value to the manuscript if the type of opioid adverse events and type of opioid drugs are included in this study. Whether the accessed codes refer to general opioid adverse events or to various types of opioid adverse events?

RE:

Unfortunately, data on different types of opioid analgesics are not available. We have made a revision to the manuscript, which now reads (pages 7-8) “Data on specific opioid analgesics were not available and hereinafter ADRs refer to any use of opioid analgesics related adverse reactions”.

We have added further information on broad groups of adverse events, which now reads (Result section, page 10) “Approximately 22.5% of the study population were admitted for injurious conditions as the primary reason for admission, followed by conditions to the digestive systems (17.2%) and less well-defined bodily symptoms and signs (15.4%)”.
Unclear on the hospital separation. Does that refer to admission or discharge and when were the data recorded?

RE:

We have made a revision to the manuscript, which now reads (page 7) “Medical reasons for hospital admission were coded at the time of discharge using ….”

Unclear on how the author differentiate between acute care and chronic care. Why were the multiple episodes excluded from the study? The counting can be multiple and should not be an issue to the study. Patients with multiple episodes may provide important information on why the ADR keep occurring. The author could stratify how many patients with one episode and how many with >1 episodes

RE:

The use of unique identifier ascertains persons with one or multiple episodes of care. The NSW Admitted Patient Data Collection does not have a unique identifier, and therefore we were not able to stratify the analysis. To reflect true incidence, we selected cases with urgent admissions to reduce multiple counting of the same incident. Multiple episodes for different incidents were considered.

We have made a revision to the manuscript, which now reads (page 8) “Because the APDC consisted of de-identified episodes of hospital care, we only considered cases admitted for acute care based on their admission status being urgent to reduce the impact of multiple counting of the same ADR event”.

In the method, need to also include the number of postcode areas included and not only mentioned in the results.

RE:

We have made a revision to the manuscript, which now reads (Statistical Analysis section, page 9) “Kulldroff’s scan statistics was used to … adverse reactions across a total of 570 post-code areas, which ….”

Lack of explanation on type of socio-economic status. It might be different from other countries. What does it mean by the most disadvantaged vs. least disadvantaged?

RE:
The inclusion of pharmacy as one of the healthcare facilities needs further explanation. Does this refer to only obtaining opioid medication from pharmacy? What about other healthcare facilities such as health clinics or general practitioners. Are they involved in prescribing the opioids that consequently lead to opioid ADR?

RE:

We considered convenience to pharmacies as a composite measure of dispensable medications (see reference 25), which measures geographic remoteness as well as professional isolation (e.g., travelling distance to the five closest pharmacies for patients to obtain prescribed medications). We agree that use of other health services might be associated with opioid analgesics related ADRs.

We have made a revision to the manuscript, which now reads (pages 12-13) “Our study demonstrated the utility of this approach and future studies should aim to combine with other data such as number of visits to general practitioners, specialists, psychiatrists, pharmacists, and allied health professionals to address opioid-related ADR identification and prevention efforts in the decision making process, for example to encourage collaboration and coordination of healthcare services as well as allocate resources in communities of great needs”.

Results

A little bit explanation on the total ADR for how many patients. Or this is already refer to the number of patients as one episode for one patient.

RE:

We have made a revision to the manuscript, which now reads (page 10) “A total of 26,776 opioid-related ADR incident cases (reflecting the real incidence in the NSW residential population)”.

Unclear on the majority of clinical conditions were cancer and diabetes. But then the commonly seen in the identified cluster were brain disorder and mental disorder. Explanation is required to improve clarity
RE:

We have made a revision to the manuscript, which now reads (page 12) “Cancers and diabetes accounted for the majority of the selected clinical conditions in the study population. Brain degenerative disorders and mental disorders were over-represented in those from the identified clusters in comparison to those from the rest of NSW during the 10-year study period”.

Discussion

The potential shift of opioid adverse events was lack of supported. Other studies mentioned on potential link between health service utilisation and opioid ADR. What was the health service utilization referring to? Was that referring to only pharmacy as included in the current study?

RE:

We have made a revision to the manuscript, which now reads (pages 12-13) “Our study demonstrated the utility of this approach and future studies should aim to combine with other data such as number of visits to general practitioners, specialists, psychiatrists, pharmacists, and allied health professionals to address opioid-related ADR identification and prevention efforts in the decision making process, for example to encourage collaboration and coordination of healthcare services as well as allocate resources in communities of great needs”.

On the unmet healthcare needs in socioeconomic disadvantaged……from places with sufficient healthcare resources. How this conclusion was made?

RE:

We observed more patients from urban areas or places with more convenient access to pharmacies, for example 90% of the study population had more convenient access to pharmacies (Table 1). We also observed cases with disadvantaged socioeconomic status were more commonly seen in the clusters as opposed to the remainder areas (for example, 27% versus 19% of those with the most disadvantaged status) during the second 5-year period (Table 3).

We have made a revision to the manuscript, which now reads (page 13) “…our findings further highlight an unmet healthcare needs in pain management as well as potentially inappropriate use of pharmaceutical opioid analgesics in socioeconomic disadvantaged population groups with low education and income from places with sufficient healthcare resources.
For cancer, the evidence on the opioid effectiveness is established but the author stated that limited evidence for both cancer and non-cancer. Unclear on the study that the author is referring to line 36, page 12

RE:

We have made a revision to the manuscript, which now reads (page 15) “Given opioid analgesics should be used with great care for either cancer or non-cancer pain,55,61 regular update of guidelines for….”