PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol
AUTHORS	Peacock, Amy; Larance, Briony; Farrell, Michael; Cairns, Rose; Buckley, Nicholas; Degenhardt, Louisa

VERSION 1 – REVIEW

REVIEWER	Craig T Hartrick, MD Oakland University, USA
REVIEW RETURNED	23-Oct-2017

GENERAL COMMENTS	The limitation pointed out by the authors regarding teasing out tapentadol from other opioids in certain poisoning settings is problematic. When definitive drug identification has not been made (or recorded) perhaps other surrogate information might be useful inferentially, since tapentadol is unique in its ability to inhibit norepinephrine reuptake. Concomitant cardiovascular disturbance might suggest tapentadol poisoning over other opioids in some circumstances

REVIEWER	Kevin L. Zacharoff, MD SUNY Stony Brook School of Medicine, USA
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	I think there are some presumptions made in this manuscript that are of concern. First and foremost, the definition of "extra-medical" use in my opinion falsely encompasses both misuse and abuse, as well as diversion. The phenomenon is multi-faceted, and while it may be convenient to categorize all aberrant drug-related behaviors into a single category, it is not representative of real-world experiences. Next is the fact that opioid attractiveness encompasses much more than just "street price" of drugs. Research performed under the presumption that opioid attractiveness is solely based on market value and availability is a false premise. Further, it would be worthwhile for the authors to look at what data does exist with regard to illicit use of the medication, and what the preferred routes of administration are. I'm not confident that interviews with IV substance abusers will be worthwhile for gauging oral abuse statistics or potential. I think that there are other numerous limitations in the protocol presented regarding the limitations of data obtained regarding recreational use, as in many cases recreational users may be reluctant to share that information. I don't feel confident that the data streams will answer the proposed questions

	sufficiently.

VERSION 1 – AUTHOR RESPONSE

Dear Dr Clark,

Please find attached the revisions for the manuscript submitted for publication in BMJ Open (bmjopen-2017-020006): "Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol".

We are indebted to the peer reviewers and the editorial group for their very kind comments regarding this manuscript and for several helpful suggestions. We have used the 'track changes' function to identify any changes to, or deletions from, the text. To facilitate reviewing we will provide a tracked and untracked document in this submission (page numbers for changes are in reference to the tracked document; please let me know if you would prefer an alternative format).

Reviewers' Comments to Author:
Reviewer #1:
The limitation pointed out by the authors regarding teasing out tapentadol from other opioids in certain poisoning settings is problematic. When definitive drug identification has not been made (or recorded) perhaps other surrogate information might be useful inferentially, since tapentadol is unique in its ability to inhibit norepinephrine reuptake. Concomitant cardiovascular disturbance might suggest tapentadol poisoning over other opioids in some circumstances.

RESPONSE: We thank the reviewer for their thoughtful and thorough response. To maintain rigour we need to adhere to robust identification and confirmatory processes, and have opted to retain analysis of cases identified as involving tapentadol.

Reviewer #2:
I think there are some presumptions made in this manuscript that are of concern. First and foremost, the definition of "extra-medical" use in my opinion falsely encompasses both misuse and abuse, as well as diversion. The phenomenon is multi-faceted, and while it may be convenient to categorize all aberrant drug-related behaviors into a single category, it is not representative of real-world experiences.

RESPONSE: We agree with the reviewer that the phenomenon of extra-medical use is multi-faceted, as we have outlined in our paper of definitions related to the use of pharmaceutical opioids (Larance et al., 2011, Drug and Alcohol Review). We would note that by definition, extra-medical use comprises "any use of a medication either without a prescription (i.e. obtained from outside the formal medical system), or not as directed by a doctor, not excluding the possibility that the user may have medically driven reasons for using the drug". Based on this accepted definition we have included these outcomes as facets of extra-medical use.

We would also note that we have distinguished the various aspects of extra-medical use rather than treating it as a single category. Table 1 outlines the primary outcomes of interest, with those falling under extra-medical use comprising: diversion, injection, snorting, chewing and perceived diverted availability. This approach has been adopted in various post-marketing studies of pharmaceutical opioids (e.g., Larance et al., 2018, Lancet Psychiatry).

Next is the fact that opioid attractiveness encompasses much more than just "street price" of drugs. Research performed under the presumption that opioid attractiveness is solely based on market value and availability is a false premise.

RESPONSE: We also agree with the reviewer that opioid attractiveness comprises more than the street price of drugs. Unfortunately, we are not able to assess other aspects of opioid attractiveness using the current data sources (see review of data sources in Australia in supplementary materials). We have now noted this in the limitations section as follows:

“It should be noted that this study is limited in terms of the number of available data sources relative to other post-marketing studies 28. However, this is a systems-level issue, as tapentadol is not differentiated from other pharmaceutical opioids in most healthcare and law enforcement data coding systems. There are a number of limitations to the chosen data sources. IDRS reflects a sentinel population at high risk of extra-medical use, and thus will not reflect general population extra-medical use, nor will it cover all aspects of various outcomes (e.g., street price is only one aspect of pharmaceutical opioid attractiveness for extra-medial use).

Further, it would be worthwhile for the authors to look at what data does exist with regard to illicit use of the medication, and what the preferred routes of administration are. I'm not confident that interviews with IV substance abusers will be worthwhile for gauging oral abuse statistics or potential. I think that there are other numerous limitations in the protocol presented regarding the limitations of data obtained regarding recreational use, as in many cases recreational users may be reluctant to share that information. I don't feel confident that the data streams will answer the proposed questions sufficiently.

RESPONSE: Our review of data sources available in Australia (see page 6 and supplementary materials) showed that only those data sources included in the protocol distinguish cases by opioid brand, necessary to identify outcomes related to tapentadol SRF. We agree with the reviewer that there are limitations to the degree to which these data sources can capture oral extra-medical use in the general population, and we have acknowledged this in the discussion, as well as being explicit that IDRS data reflects a sentinel sample. We would also note that FDA guidance highlights the challenges and resourcing required to collect primary data from the general population, and emphasises the importance of including data on extra-medical use from high-risk samples in post-marketing studies, and of utilising available secondary data (FDA, 2015; FDA, 2017).

Further, we would contend that there is a strong body of literature supporting the reliability and validity of self-report of drug use (e.g., Darke, 1998, Drug and Alcohol Dependence), and using self-report data from samples at high-risk of extra-medical use of pharmaceutical opioid use is common within post-marketing studies (e.g., Larance et al., 2018, Lancet Psychiatry).

Thus, we would argue that the proposed study is a valid and necessary step to understand potential patterns of extra-medical use and harms associated with tapentadol SRF in Australia.

We would thank the Editor and the reviewers for their support for this manuscript. We hope that the amendments are in line with the suggestions, and adequately address the concerns raised.

Kind regards,

Dr Amy Peacock

VERSION 2 – REVIEW

REVIEWER	Craig T Hartrick, MD Oakland University, USA
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	Your description should make it very clear that you are restricting your analysis to only cases documenting whether or not tapentadol was involved. Non-specific opioid poisonings should not be included, even for comparisons, if they may or may not have involved tapentadol.

REVIEWER	Kevin L. Zacharoff, MD SUNY Stony Brook School of Medicine United States of America
REVIEW RETURNED	30-Jan-2018

GENERAL COMMENTS	While there are significant limitations to the proposed study, it is a worthwhile effort to begin looking at this issue.

VERSION 2 – AUTHOR RESPONSE

Dear Dr Clark,

Please find attached the revisions for the manuscript submitted for publication in BMJ Open (bmjopen-2017-020006): "Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol".

We are indebted to the peer reviewers and the editorial group for their very kind comments regarding this manuscript and for several helpful suggestions. We have used the 'track changes' function to identify any changes to, or deletions from, the text. To facilitate reviewing we will provide a tracked and untracked document in this submission (page numbers for changes are in reference to the tracked document; please let me know if you would prefer an alternative format).

Reviewers' Comments to Author:

Reviewer 1:

Your description should make it very clear that you are restricting your analysis to only cases documenting whether or not tapentadol was involved. Non-specific opioid poisonings should not be included, even for comparisons, if they may or may not have involved tapentadol.

RESPONSE: We thank the reviewer for their suggestion. As noted in our previous response, to maintain rigour we need to adhere to robust identification and confirmatory processes and have opted to retain analysis of cases identified as involving tapentadol. This is clear in the manuscript where we state that "Trends over time in tapentadol exposures will also be modelled using generalised estimating equations." As specified in the protocol, we will also be modelling "rates of intentional pharmaceutical opioid exposure poisonings using IMS sales data as the denominator; specifically, rates per 100,000 OME grams and per 1,000 packs distributed per month. These analyses will be restricted to those cases explicitly identified as a pharmaceutical opioid exposure poisoning

attributable to a type of opioid (e.g., tapentadol, oxycodone) as per the criteria identified above" (page 9). We believe that these statements fulfil the suggestion made by Reviewer 1.

Reviewer: 2
While there are significant limitations to the proposed study, it is a worthwhile effort to begin looking at this issue.

RESPONSE: We thank the reviewer for their support of the manuscript.

We would thank the Editor and the reviewers for their support for this manuscript. We hope that the amendments are in line with the suggestions, and adequately address the concerns raised.

Kind regards,

Dr Amy Peacock