PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian general practice: a national longitudinal study using MedicineInsight, 2012-2018
AUTHORS	Black-Tiong, Sean; Gonzalez-Chica, David; Stocks, Nigel

VERSION 1 – REVIEW

REVIEWER	Gary Franklin University of Washington United States
REVIEW RETURNED	27-Oct-2020

GENERAL COMMENTS	This is a fine paper using a unique database representative of Australia's General Practitioner population. The findings are disturbing and need to be further investigated and explained by authorities. The cumulative increase in numbers of MSK patients on chronic opioids between 2012 and 2017, from 5.5% to 9.1%, is actually pretty horrifying. The vast majority of these long term opioid patients are either dependent or possibly addicted, and this will be a huge ongoing health care burden for Australia. This aspect of what's to come should be discussed in more detail. 2. There is mention of the potential adverse effect of pharmaceutical marketing, and of potential beneficial effect of education aimed at reducing opioid prescribing. The worsening results, contrary to what has occurred in the US, implies ongoing marketing and drug company related impacts. Mundipharma, the international subsidiary of Purdue pharma, the maker of oxycontin, has apparently been responsible for conducting pain management master classes for over 5000 Australian docs. If this education is anything like the type of falsehood-laden opioid education in the US earlier in the 21st century, this may be contributing disproportionately to the problem. (*https://www.apnews.com/cfc86f47e03843849a89ab3fce44c73c) 3. It's too bad neuopathy is excluded, or perhaps a second paper will be published on that. Many of these patients in the US have received tramadol and tapentadol 4. Do you have any idea of the amount of co-prescribing of sedative hypnotics like benzos and z drugs-this is a huge increased risk for overdose, and the Australian overdoses have climbed considerably in recent years.(According to the Australian Institute of Health and Welfare, there were 439 deaths in 2006 and 1,119 deaths in 2016, a more than doubling of the mortality rate from opioids. 5. Is there any way to tell what proportion of patients on chronic opioids have actually stopped taking opioids? This would be critical to interpret your duration data.

REVIEWER	Dr. Anita Barros Amorim

	The University of Sydney, Australia.
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This study aimed to describe trends and patterns in long-term opioid prescriptions among adults with musculoskeletal conditions. This is a well-written manuscript addressing a very relevant topic. Specific comments are listed below and will hopefully enhance the quality of this study and increase the likelihood of acceptance. Introduction 1. The first paragraph would be strengthened by adding numbers - how much (health care costs). 2. The introduction is well-written, however, is quite long. Paragraphs one and two could be combined into one paragraph. Same for paragraphs three and four as both talk about the management of chronic pain. 3. It would be helpful to include some figures in paragraph five (e.g. percentage of the rise in opioid use). 4. It seems like there is a word missing in Line 14: “Data from MedicineInsight has been* previously used…” Methods 5. How were patients involved in the design, conduct, reporting or dissemination of the results? Considering how important it is to involve consumers in research, I would welcome further details regarding this partnership with the public. Results 6. It would be interesting to see a descriptive table with information regarding the size and type of practices included from each state, as well as the participants sociodemographic and clinical conditions data. 7. It would also be helpful to differentiate the type of practice (e.g. private pain clinic, hospital, emergency department) where the opioids are dispensed and if there were any differences among them. 8. It would also be noteworthy to differentiate who is prescribing the opioids (i.e., junior doctor, specialist, GP) and which type of opioid (i.e., oxycodone, codeine, tramadol) I wonder if the number of years of experience influence this relationship. 9. Also, which MSK conditions (i.e., low back pain, fibromyalgia, knee OA) had the highest vs lowest rate of prescription? Discussion 10. The discussion is well-written, and the limitations addressed some of the concerns raised in the questions above. However, if not possible, to include the information solicited in comments 8 and 9 (above), please address this in the limitations. Conclusion 11. The conclusion should also highlight that those findings reflect prescription patterns rather than opioid use. This should also be stated earlier in the manuscript, such as in the methods section.

VERSION 1 – AUTHOR RESPONSE

Reviewer reports:

Reviewer: 1
Dr. Gary Franklin, University of Washington

This is a fine paper using a unique database representative of Australia's General Practitioner population. The findings are disturbing and need to be further investigated and explained by authorities. The cumulative increase in numbers of MSK patients on chronic opioids between 2012 and 2017, from 5.5% to 9.1%, is actually pretty horrifying. The vast majority of these long term opioid patients are either dependent or possibly addicted, and this will be a huge ongoing health care burden for Australia. This aspect of what's to come should be discussed in more detail..

R: We are grateful for the reviewer's valuable contribution and positive perspective on our paper. The suggestion has been accepted. See Page 11, lines 24-28.

There is mention of the potential adverse effect of pharmaceutical marketing, and of potential beneficial effect of education aimed at reducing opioid prescribing. The worsening results, contrary to what has occurred in the US, implies ongoing marketing and drug company related impacts. Mundipharma, the international subsidiary of Purdue pharma, the maker of oxycontin, has apparently been responsible for conducting pain management master classes for over 5000 Australian docs. If this education is anything like the type of falsehood-laden opioid education in the US earlier in the 21st century, this may be contributing disproportionately to the problem. (*https://www.apnews.com/cfc86f47e03843849a89ab3fce44c73c).

R: Suggestion accepted. Some additional text has been incorporated into the discussion section to provide more arguments about the marketing strategies (Page 13 lines 4-8).

It's too bad neuopathy is excluded, or perhaps a second paper will be published on that. Many of these patients in the US have received tramadol and tapentadol
R: Yes, we agree with the reviewer. However, as detailed in the background and methods, we decided to focus on musculoskeletal conditions to provide a clear message related to current guidelines in Australia.

Do you have any idea of the amount of co-prescribing of sedative hypnotics like benzos and z drugs-this is a huge increased risk for overdose, and the Australian overdoses have climbed considerably in recent years.(According to the Australian Institute of Health and Welfare, there were 439 deaths in 2006 and 1,119 deaths in 2016, a more than doubling of the mortality rate from opioids.
R: Suggestion accepted. The information has been provided and discussed together with the increasing number of opioid-induced deaths (Page 13, Lines 21-31).

Is there any way to tell what proportion of patients on chronic opioids have actually stopped taking opioids? This would be critical to interpret your duration data.
R: Suggestion accepted. This request required to include an additional figure (Figure 3), as the study involves a different cohort in each year. Additional text was included in the result (page 11, lines 4-9) and discussion sections (page 12, lines 16-20)

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Reviewer: 2
Dr. Anita Amorim , University of Sydney MEMC

Comments to the Author:
Thank you for the opportunity to review this manuscript. This study aimed to describe trends and patterns in long-term opioid prescriptions among adults with musculoskeletal conditions. This is a well-written manuscript addressing a very relevant topic. Specific comments are listed below and will hopefully enhance the quality of this study and increase the likelihood of acceptance.
R: We appreciate the reviewer's perspective on our paper.

Introduction

1. The first paragraph would be strengthened by adding numbers - how much (health care costs).
R: Suggestion accepted. See page 4, lines 6-7

2. The introduction is well-written, however, is quite long. Paragraphs one and two could be combined into one paragraph. Same for paragraphs three and four as both talk about the management of chronic pain.
R: Suggestion accepted.

3. It would be helpful to include some figures in paragraph five (e.g. percentage of the rise in opioid use).
R: Suggestion accepted. See page 4, lines 27-30

4. It seems like there is a word missing in Line 14: "Data from MedicineInsight has been* previously used…"
R: Thanks.

Methods

5. How were patients involved in the design, conduct, reporting or dissemination of the results? Considering how important it is to involve consumers in research, I would welcome further details regarding this partnership with the public.
R: We apologise for the misunderstanding. Patients were not directly involved in the process, only through the assessment of the MedicineInsight Data Governance Committee of the proposal, and insights of the two GPs involved in the study. We have made it clear in the statement that they were not directly involved.

Results

6. It would be interesting to see a descriptive table with information regarding the size and type of practices included from each state, as well as the participants sociodemographic and clinical conditions data.
R: Suggestion accepted. See page 9 (lines 16-23) and supplementary table 1. We presented the information as a supplementary table due to journal restrictions about the number of tables/figures.

7. It would also be helpful to differentiate the type of practice (e.g. private pain clinic, hospital, emergency department) where the opioids are dispensed and if there were any differences among them.
R: Suggestion not accepted. Unfortunately, that information is not available. We have included that as a limitation.

8. It would also be noteworthy to differentiate who is prescribing the opioids (i.e., junior doctor, specialist, GP) and which type of opioid (i.e., oxycodone, codeine, tramadol) I wonder if the number of years of experience influence this relationship.
R: Suggestion not accepted. Unfortunately, that information is not available. We have included that as a limitation.

9. Also, which MSK conditions (i.e., low back pain, fibromyalgia, knee OA) had the highest vs lowest rate of prescription?
R: Suggestion accepted. See page 10 (lines 5-8) and supplementary figure 1. We presented the information as a supplementary figure due to journal restrictions about the number of tables/figures.

Discussion

10. The discussion is well-written, and the limitations addressed some of the concerns raised in the questions above. However, if not possible, to include the information solicited in comments 8 and 9 (above), please address this in the limitations.
R: Suggestion accepted. See page 14 (lines 4-6)

Conclusion

11. The conclusion should also highlight that those findings reflect prescription patterns rather than opioid use. This should also be stated earlier in the manuscript, such as in the methods section..

R: Suggestion accepted. The paper states from the beginning that the study focuses on prescription patterns rather than opioid use. This is also mentioned as a limitation in the corresponding section (Page 13, lines 23-25)

VERSION 2 – REVIEW

REVIEWER	Gary Franklin University of Washington United States
REVIEW RETURNED	02-Feb-2021

GENERAL COMMENTS	The authors have been appropriately responsive to the original critiques

REVIEWER	Anita Barros Amorim The University of Sydney, Australia.
REVIEW RETURNED	05-Mar-2021

GENERAL COMMENTS	Thank you for the opportunity to review the updated version of this manuscript. The authors have addressed my suggestions, and I have no further comments to add.