Peer Review Report

Review Report on Nationwide Population-Based Study about patterns of prescription opioid use and misuse among young adults in Spain
Original Article, Int J Public Health

Reviewer: Henrike Häbel

EVALUATION

Q 1   Please summarize the main findings of the study.

The authors give an overview on opioid misuse in the US, Canada and Europe and compare findings from previous studies to their study on opioid use and misuse among young adults in Spain. They observe that 4.89% of the young adults reported to have used prescription opioid of which 13.4% admitted having misused these drugs. They conclude that the percentage is higher in women (which should be phrased more carefully, see detailed review report). They identify Codine and Tramadol as the most frequently consumed prescription opioids. Most importantly, they identify risk factors for opioid use and misuse and create statistical evidence that can be helpful for policymakers.

Q 2   Please highlight the limitations and strengths.

The authors identified the main strength and weaknesses of their study well. The main strength is that the conducted study is one of the first of his kind and made it possible to identify specific drugs that are commonly misused. A clear limitation is the nature of the data given that it is self-declared. Hence, the conclusions highly depend on the truthfulness of the answers. Another limitation is the lack of information on why opioids were prescribed, meaning information on diagnosed comorbidities.

Q 3   Please provide your detailed review report to the authors. The editors prefer to receive your review structured in major and minor comments. Please consider in your review the methods (statistical methods valid and correctly applied (e.g. sample size, choice of test), is the study replicable based on the method description?), results, data interpretation and references. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.

Please see attached file. Copy below:

Review report for: Manuscript ID: 1604755
Title: Nationwide Population-Based Study about patterns of prescription opioid use and misuse among young adults

Dear authors,
This was a very interesting article to read and an important topic to study. You provide a thorough overview on opioid misuse in the US, Canada and Europe and compare findings from previous studies to their study on two primary outcomes, namely opioid use and misuse among young adults in Spain. You observe that 4.89% of the young adults reported to have used prescription opioid of which 13.4% admitted having misused these drugs. You conclude that the percentage is higher in women (which should be phrased more carefully, see comments 7 and 8). You identified Codine and Tramadol as the most frequently consumed prescription opioids. Most importantly, you identify risk factors for opioid use and misuse and create statistical evidence that can be helpful for policymakers.
You identified the main strength and weaknesses of your study well. The main strength is that the conducted study is one of the first of his kind and made it possible to identify specific drugs that are commonly misused.

A clear limitation is the nature of the data given that it is self-declared. Another limitation is the lack of information on why opioids were prescribed, meaning information on diagnosed comorbidities.

I feel that there is room for improvement especially regarding the statistical analysis. I have some major comments regarding the statistical interpretation of your results. Furthermore, the article will gain in readability – in my opinion – if you make some changes to the text as suggested under major comments.

Major general comments:

1. Prevalence of misuse depends on prevalence of use/prescription. Please discuss this dependency and the differences between use and misuse in more detail either in the Introduction or in the Discussion. In this context, you can also discuss why opioids are prescribed. Could the reasons for prescription be a reason for higher numbers in females?

2. Model selection: Usually when choosing variables to include in a multivariable model based on preceding univariate analyses, the confidence level is set to be 0.2 (instead of 0.05). Disregarding any of the respective p-values obtained in the univariate analyses, I found it confusing that perceived health risk and availability of opioids were included in the model for use, but not for misuse of opioids. It would have been interesting to see their adjusted OR for misuse as well. I also recommend including sex in the model for misuse; especially since you state that you found a gender difference on page 7, line 153 and Figure 1.

3. It is more correct to write about odds rather than probabilities. Especially on page 11, line 247.

Major specific comments:

4. Methods, Measures: Starting with page 5, line 109, please state how the independent variables were included in the model, e.g. sex (male, female) was included as a categorical variable.

5. Methods, Data analysis: Page 6, line 126 and other places: Change multivariate to multivariable. Explanation: In a multivariate analysis one has multiple outcome/dependent variables, you have multiple independent variables.

6. Methods, Data analysis: Page 6, line 131: Please briefly explain how the sampling weights were obtained and why they are important to a reader with no statistical background. Is there a more detailed reference (possibly in English) on the EDADES Survey other than the PDF presentation provided by Ministerio de Sanidad, Consumo y Bienestar Social, 2017?

7. Results, page 6, line 136: given the p-value of 0.175 for a gender difference in prevalence of opioids use, it can be misleading to write that the values were higher in females. It would be more correct to write that there was a tendency for higher values among the female population.

8. Results, page 6, line 144: In line with 7, you should not write that there was a greater prevalence among women and phrase it more carefully given that the CI for the OR contains 1.

9. Results, Page 7, line 168 – 170: This is wrongly written. Correction suggestion:

"The second multivariatevariable logistic regression model created for the misuse of prescription opioids (Table 4) shows behavior age as a protective factor for behaviorof the age variable, with young adults aged between 25 and 34 years presenting lower odds for misuse than 18 to 24 year oldsprobability."

10. Discussion, Page 8, line 179-182: To what study are you referring here and where is the evidence that the opioids use is significantly lower in Spain? If you are not referring to a statistical analysis here, it would be better to write prominently instead of significantly.

11. Conclusions, page 14, line 322: I would also mention the predictors you found for the misuse of opioids here.

12. Tables: I am missing a Table 1 with baseline characteristics of your sample population.

13. Tables: Table 1: I do not see the need for testing the difference between male and females as it was never mentioned as an objective of this study. Instead, I was expecting and am, hence, missing a table similar to Table 2 for prevalence of prescription opioids use.

Minor comments:

14. I would add "in Spain" to the title: Nationwide Population-Based Study about patterns of prescription opioid use and misuse among young adults in Spain.

15. In the introduction, it would be helpful if all text related to the US was next to each other, meaning moving line 35 – 43 on page 2 to after line 22 on page 1.

16. Page 6, line 129: Please add what version of STATA was used.

17. There are two typos. Please correct

a. Page 1, line 7: total populations -> the total population

b. Page 7, line 156: Oxycodone y Buprenorphine -> Oxycodone and Buprenorphine

18. Page 2, line 31: Please change 10,000 DDDs (Defined Daily Dose) to 10,000 Defined Daily Doses (DDDs).

19. Page 7, line 156: Oxycodone and Buprenorphine, please add percentages here as well.

20. Page 11, line 269: Please write cannabis instead of marijuana to be consistent, unless you intended to be specific here.

21. Page 12, line 273: Please use the same drug names as before.

22. Page 14, line 329–332: The last sentence is a hard to read. Consider splitting it into two.

23. Table 1: There are some formatting issues with Cannabis use and Cocaine use.

PLEASE COMMENT

Q 4   **Is the title appropriate, concise, attractive?**

Yes, however, I miss information on the country where the study was conducted. My suggestion would be to add "in Spain": Nationwide Population–Based Study about patterns of prescription opioid use and misuse among young adults in Spain.

Q 5   **Are the keywords appropriate?**

Yes.

Q 6   **Is the English language of sufficient quality?**

Yes, besides two typos (see detailed review report, minor comments).

Q 7   **Is the quality of the figures and tables satisfactory?**

No.

Q 8   **Does the reference list cover the relevant literature adequately and in an unbiased manner?)**

The authors seem to have conducted a thorough literature research. However, I am missing more professional and English references on the EDADES Survey methodology specifics other than the PDF presentation provided by Ministerio de Sanidad, Consumo y Bienestar Social, 2017.

QUALITY ASSESSMENT

Q 9   **Originality** — ■■■■□

Q 10   **Rigor** — ■■□□□

Q 11   **Significance to the field** — ■■■■□

Q 12   **Interest to a general audience** — ■■■■□

Q 13   **Quality of the writing** — ■■■□□

Q 14   **Overall scientific quality of the study** — ■■■□□

REVISION LEVEL

Q 15 **Please make a recommendation based on your comments:**

Major revisions.