PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Codeine Dispensing for Privately Insured Children After FDA Drug Safety Communications.
AUTHORS	Oliveira J. e Silva, Lucas Anderson, Jana Bellolio, Fernanda Campbell, Ronna Jeffery, Molly

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Andrea L. Schaffer Institution and Country: University of New South Wales Sydney Competing interests: none
REVIEW RETURNED	28-Oct-2021

GENERAL COMMENTS	This manuscript describes a descriptive study of codeine prescribing in children over time, compared with non-codeine opioids and cough/cold medicines, with an interest in the impact of FDA communications. I have a few suggestions/comments, mostly about the methods and interpretation of results. 1. First, as a research letter there is probably a shorter word limit, but a bit more background information would be useful. For instance, why do children suffer increased morbidity/mortality? What are the recommended alternatives to codeine in children, e.g. other opioids or non-opioid analgesics? 2. The authors have looked at all codeine products, non-codeine opioids, and cough/cold medicines. Can codeine-containing medicines for pain be separated from codeine-containing cough/cold medicines? This would be a more useful comparison with non-codeine-containing cough/cold medicines. 3. Can the authors clarify how the denominator (person-years of coverage) was calculated? The authors state that the study population was children who received prescriptions for codeine, opioids or cough/cold products. But were person-years calculated for *all* insured children, or only those who received one of these prescriptions? I assume the former, as this makes most sense, but it's not explicit. 4. Much of the Results section focusses on changes over the entire study period (2010 to 2019). Given the interest in the FDA warnings, I suggest describing how prescribing seemed to change around the time of these warnings. 5. While a descriptive analysis is probably appropriate here, it does limit how much you can infer about the impact of the FDA changes, especially given that prescribing was declining prior to the first DSC (for both codeine and non-codeine products). The authors have also focused on % change for comparisons, but while the % change for codeine may be larger than for other opioids, for some outcomes the absolute change is greater for non-codeine opioids (e.g. in 12-17 year olds). While there advantages/disadvantages for both

	absolute/relative measures, the authors should be clear when discussing their findings that it is the *relative* decline that is greatest. 6. The changes in 2017 and 2018 are not mentioned in the Introduction/Methods. Also, Table 1 is not mentioned in the text. 7. The figure needs a title/legend.

REVIEWER	Reviewer name: Dr. Antonio Clavenna Institution and Country: IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Laboratory for Mother and Child Health, Department of Public Health Competing interests: none
REVIEW RETURNED	12-Nov-202

GENERAL COMMENTS	In my opinion, the research letter addresses a relevant topic, the impact of regulatory interventions on the trend of codeine prescription. The decrease in the prevalence of prescription is reassuring, even if in 2019 this drug was still prescribed to children. Have you any idea or hypothesis on why codeine is still used?

VERSION 1 – AUTHOR RESPONSE

Re: Revision of Manuscript: bmjpo-2021-001321 - "Codeine Dispensing for Privately Insured Children After FDA Drug Safety Communications"

Dear Dr. Brodlie and Dr. Choonara,
Thank you for the opportunity to review, revise and improve our manuscript. We have done our best to incorporate the insightful recommendations of reviewers. Please see below the answers (in blue).

Editor in Chief Comments:
"Title amend to "Codeine Dispensing for Privately Insured Children in the USA - a retrospective database review"
It is a retrospective study of a database, not an observational study. Please amend the abstract and text.
Be cautious in your interpretation - the decline is constant,ie not just due to FDA restrictions"
Answer: Thank you. We have changed the title, the nomenclature, and our interpretation, as suggested.

Reviewer #1 Comments:
"This manuscript describes a descriptive study of codeine prescribing in children over time, compared with non-codeine opioids and cough/cold medicines, with an interest in the impact of FDA communications. I have a few suggestions/comments, mostly about the methods and interpretation of results.

1. First, as a research letter there is probably a shorter word limit, but a bit more background information would be useful. For instance, why do children suffer increased morbidity/mortality? What are the recommended alternatives to codeine in children, e.g. other opioids or non-opioid analgesics?
Answer: Thank you. We have added slightly more details in the Background, although the word limit by the journal does not allow us to add much more information.

2. The authors have looked at all codeine products, non-codeine opioids, and cough/cold medicines. Can codeine-containing medicines for pain be separated from codeine-containing cough/cold medicines? This would be a more useful comparison with non-codeine-containing cough/cold medicines.
Answer: Thank you. We added the Figures separated for codeine pain vs cough in the Appendix. If we add this separation into the main Figure, it becomes too busy and for this reason we kept it in the Appendix. The findings are essentially the same.

3. Can the authors clarify how the denominator (person-years of coverage) was calculated? The authors state that the study population was children who received prescriptions for codeine, opioids or cough/cold products. But were person-years calculated for *all* insured children, or only those who received one of these prescriptions? I assume the former, as this makes most sense, but it's not explicit.
Answer: Thank you. The denominator were calculated for all insured children.

4. Much of the Results section focusses on changes over the entire study period (2010 to 2019). Given the interest in the FDA warnings, I suggest describing how prescribing seemed to change around the time of these warnings.
Answer: Thank you. Given the word limit, we did not add more details about changes around all warnings, but rather we focused on the most restrictive one (2017-2018). We attempted to highlight that in the Results as following:
"For both age groups, the largest single-year decline in codeine dispensing was 2017 to 2018: for children <12, codeine dispensing declined 61.2% (from 586 to 228); for children 12 to 17, codeine dispensing declined 38.1% (from 2,094 in 2017 to 1,295 in 2018)."

In the Discussion, we highlighted that this probably has to do with the FDA contraindication in early 2018.
"Codeine dispensing in children has declined substantially between 2010 and 2019, including the most severe restriction in early 2018 during which the FDA made codeine contraindicated."

5. While a descriptive analysis is probably appropriate here, it does limit how much you can infer about the impact of the FDA changes, especially given that prescribing was declining prior to the first DSC (for both codeine and non-codeine products). The authors have also focused on % change for comparisons, but while the % change for codeine may be larger than for other opioids, for some outcomes the absolute change is greater for non-codeine opioids (e.g. in 12-17 year olds). While there advantages/disadvantages for both absolute/relative measures, the authors should be clear when discussing their findings that it is the *relative* decline that is greatest.
Answer: Thank you. We changed the wording to clarify these points in the Discussion.

6. The changes in 2017 and 2018 are not mentioned in the Introduction/Methods. Also, Table 1 is not mentioned in the text.
Answer: Table 1 is mentioned in the Introduction as following: "Starting in 2013, the US Food and Drug Administration (FDA) released increasingly restrictive warnings ultimately recommending against the use of codeine-containing products in patients under age 18.4 (Table 1)."
The changes in 2017 and 2018 were highlighted in the Results because this was the period when FDA made codeine contraindicated, and it was the largest single-year decline.

7. The figure needs a title/legend.
Answer: Thank you. We believe the document with the title/legend of the Figure was not attached for revisions. We fixed this.

Reviewer #2 Comments
"In my opinion, the research letter addresses a relevant topic, the impact of regulatory interventions on the trend of codeine prescription. The decrease in the prevalence of prescription is reassuring, even if in 2019 this drug was still prescribed to children.
Have you any idea or hypothesis on why codeine is still used?"
Answer: Thank you. We are uncertain about why codeine is still used but it is partly explained by residual prescribing in the context of providers unaware of its contraindications and/or resistance to stop using it. Cultural prescribing may take years to wear off despite warnings from regulatory bodies.

We hope you find these revisions satisfactory.

Sincerely,
Molly M Jeffery, PhD
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