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)	A Descriptive Report of Pharmaceutical and Non-pharmaceutical Arrests, Use, and Overdoses in Maine
AUTHORS	Simpson, Kevin; Moran, Matt; Foster, Michelle; Shah, Dipam; Chung, Daniel; Nichols, Stephanie; McCall, Kenneth; Piper, Brian

VERSION 1 - REVIEW

REVIEWER	Jolanta Zawilska Department of Pharmacodynamics, Medical University of Łódź, Poland
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	This is an interesting and important study analyzing variations in drug charges by demographics and examining recent trends in arrests, prescriptions of controlled substances and overdoses in Maine, U.S.. Comments. To increase the world-wide recognition of the work short information about groups of substances that are controlled under U.S. schedules I to V should be provided. Were any differences related to ethnics of arrestees observed?

REVIEWER	Jeanine Buchanich University of Pittsburgh, USA
REVIEW RETURNED	28-Nov-2018

GENERAL COMMENTS	The authors had access to robust data regarding drug-related arrests, prescription usage, and overdose deaths. However, the methods are poorly described and the writing is not succinct, making it very difficult to gauge the importance of the findings. There are many places throughout the manuscript where context is missing (not using "arrests" or "deaths). Examples include in the abstract pg 3, line 48, and page 4 line 8, but can be found throughout. The main concern is the with the methods. It would be impossible to replicate this study based on the description. There is no explanation of how statistical testing was done. There is also no

	mention of the deaths in the data analysis section. There is no no p value provided to understand what was considered statistically significant. Also, why were death data provided by the Atty General, and not the ME? Is that typical of the ME medicolegal system? It is unclear what the ratios in Table 1 mean or especially how statistical sig was determined. Table 2 does not make sense, especially in regard to statistical significance. They seem to be row percents? How was statistical significance determined (and what does it mean)? Table 3 should be rates instead of grams. The table would be much easier to read with right justification of the numbers and no decimal places. Was statistical significance measured for these data? Fig 1 would be much more useful if consideration was given to the counts of drugs involved, rather than just the percent per category. Figs 2A and B need explanation of how statistical significance was determined. Figs 3B and C: add numbers rather than just percents The intro needs restructured, especially the top of page 5. That paragraph is extremely difficult to follow. The discussion also needs to be restructured. It is repetitive and hard to follow in places. Watch use of language, especially terms like "overrepresented" What does that mean? Statistically significantly different? Add discussion of Creppage et al (2018) to top of page 13 regarding fentanyl analogues. Does page 17, line 45 mean that the DAP has been discontinued? Not clear from wording.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

3) To increase the world-wide recognition of the work, short information about groups of substances that are controlled under U.S. schedules I to V should be provided.

Brief definitions were included as suggested: “Drugs were categorized as Schedule I (high potential for abuse, no accepted medical use) to V (lowest potential for abuse, accepted medical use),”

4) Were any differences related to ethnics of arrestees observed?

This is an important topic. Unfortunately, the Diversion Alert Program does not receive information from law-enforcement about race/ethnicity. The limitations paragraph notes: “The DAP did not obtain information about arrestee ethnicity which unfortunately precluded examination of this variable.”

Reviewer: 2

5) The authors had access to robust data regarding drug-related arrests, prescription usage, and overdose deaths. However, the methods are poorly described and the writing is not succinct, making it very difficult to gauge the importance of the findings.

A) There are many places throughout the manuscript where context is missing (not using "arrests" or "deaths). Examples include in the abstract pg 3, line 48, and page 4 line 8, but can be found throughout.

The term overdoses was replaced with “deaths” in page 3 line 48 and “deaths involving opioids” on page 4 line 8 as suggested.

B) The main concern is with the methods. It would be impossible to replicate this study based on the description. There is no explanation of how statistical testing was done.

The data-analysis section is now much more clear regarding the data-analysis. The figures (2, 3) and tables (1 & 2) also contain information about the statistical test and the corresponding comparison group.

C) There is also no mention of the deaths in the data analysis section.

The statistics section notes: “A 2 (year) x 2 (illicit positive versus negative) chi-square tested whether the observed frequencies of drug fatalities differed relative to 2007.”

D) There is no p value provided to understand what was considered statistically significant.

As suggested, this information is now included in the statistics section: “with $p < .05$ considered statistically significant.”

E) Also, why were death data provided by the Atty General, and not the ME? Is that typical of the ME medicolegal system?

The Attorney General’s Office in Maine oversees 13 Divisions including the Office of the Chief Medical Examiner. This is described in more detail at:

https://www.maine.gov/ag/about/office_organization.html

6) It is unclear what the ratios in Table 1 mean or especially how statistical sig was determined.

The caption has been expanded to “* chi-square $p < .05$ versus [a]non-stimulants or [b]non-miscellaneous pharmaceuticals.” to clarify that 2x2 chi-squares (two-tailed) were completed. An additional analysis “The sex ratio differed between stimulants and opioids ($\chi^2(1) = 3.75$, $p < .053$).” is reported in the results.

7) Table 2 does not make sense, especially in regard to statistical significance. They seem to be row percents? How was statistical significance determined (and what does it mean)?

The key has been expanded to “*2 x 2 chi-square $p < .05$ or **$p < .001$ versus other ages or drug classes.”

8A) Table 3 should be rates instead of grams. The table would be much easier to read with right justification of the numbers and no decimal places.

We are quite willing to modify but are unclear what “rate” is referring to. Table 3 has been converted to right-justified with no decimal points as suggested.

8B) Was statistical significance measured for these data?

No. These data represent the weight of each drug in the state. Frankly, we struggled with which statistic would best fit this information. One possibility would be to complete a paired t-test within each drug class. For opioids, the weights did not significantly change from 2007 to 2012 ($t(10) = 1.82$, $p = .10$), from 2012 to 2017 ($t(11) = 2.09$, $p = .061$), or from 2007 to 2017 ($t(10) = 1.87$, $p = .091$). Note that the slightly different degrees of freedom are due to tapentadol not being on the US market until 2009. At least for 2012 to 2017, the general pattern is that most agents for pain are decreasing while buprenorphine is increasing.

9) Fig 1 would be much more useful if consideration was given to the counts of drugs involved, rather than just the percent per category.

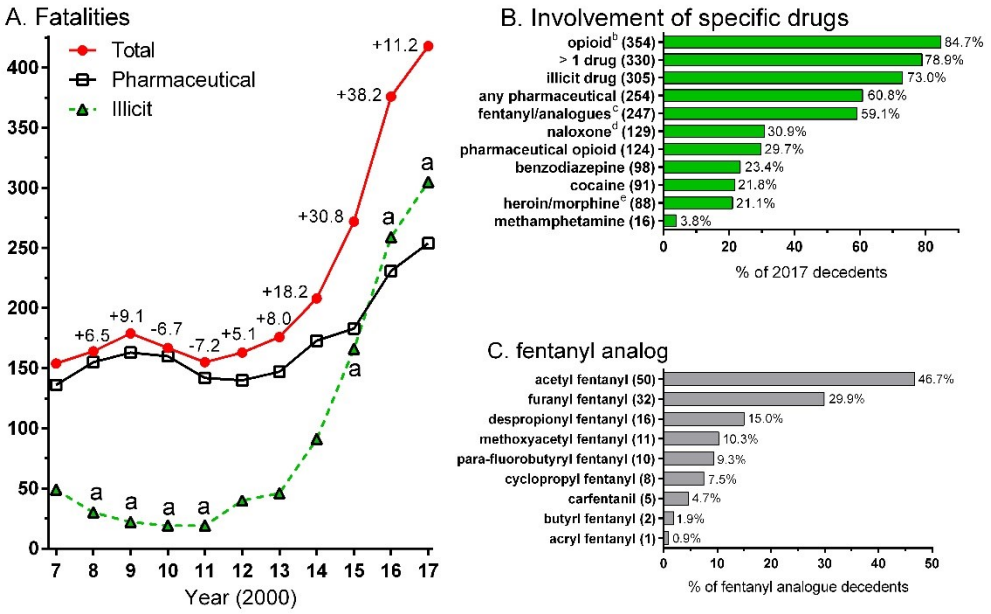
The total count per category is listed in parentheses, e.g. Opioids (N = 719). The interested reader could multiply this N by the percent (e.g. 48.82%) to obtain the N per drug (351).

10) Figs 2A and B need explanation of how statistical significance was determined.

Figure 2A is significant versus other ages. Figure 2B is versus all other Schedules.

11) Figs 3B and C: add numbers rather than just percents.

Numbers added to these panels as suggested.



12) The intro needs restructured, especially the top of page 5. That paragraph is extremely difficult to follow.

This has been broken into two paragraphs and other adjustments made.

13) The discussion also needs to be restructured. It is repetitive and hard to follow in places.

Several sentences were adjusted and non-essential content trimmed. Some sex differences content was deleted: “Differences in the numbers of prescriptions written between the sexes are most pronounced for benzodiazepines with women receiving more than men.[4] Additionally, more women go to the ER for antidepressant and benzodiazepine overdoses and adverse effects than

men.[38] There were a disproportionately high number of women DAP entries for Schedule IV agents, 88.5% of which were benzodiazepines in 2015.[2] Interestingly, this trend did not continue in 2017, and the proportion of women who were charged for benzodiazepines were comparable to those of men. … "Whether women, in general, use these prescriptions within the limits of the law, tend to be overlooked by law enforcement, or whether there are biopsychosocial factors at play that account for this discrepancy is a priority for further research."

14) Watch use of language, especially terms like "overrepresented" What does that mean? Statistically significantly different?

The term over/underrepresented have been removed from the manuscript as suggested. These referred to significant 2x2 chi-square analyses.

15) Add discussion of Creppage et al (2018) to top of page 13 regarding fentanyl analogues.

The discussion now includes "Laboratory testing showed a substantial drop from 2010 to 2016 in stamp bags from Allegheny county Pennsylvania containing only heroin.[29]

New citation:

Creppage, K. E., Yohannan, J., Williams, K., Buchanich, J.M., Songer, T. J., Wisniewski, S. R., Fabio, A. The rapid escalation of fentanyl in illicit drug evidence in Allegheny County, Pennsylvania, 2010-2016. Public Health Rep 133, 142-146 (2018).

16) Does page 17, line 45 mean that the DAP has been discontinued? Not clear from wording.

That is corrected. The wording was adjusted to be more clear: "and is no longer in operation."

VERSION 2 – REVIEW

REVIEWER	Jeanine Buchanich University of Pittsburgh, USA
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	All comments have been addressed.