Author’s response to reviews

Title: The Effects of State Rules on Opioid Prescribing in Indiana

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Author’s response to reviews:

Dear Editor,

Thank you very much for considering our paper for publication at your respected journal. We appreciate the comments and suggestions provided by the reviewers, which have helped us improve our manuscript. Below please find point-by-point responses to the reviewers comments. Attached also is the revised manuscript for your consideration.

Sincerely,

The Authors

REVIEWER 1

1. The first sentence is overly dramatic and is drawn from a single author’s work. Please replace with a data-driven statement.

RESPONSE 1: We have changed this to reflect the latest CDC statistics. (Background section, lines 42-43, page 4)

2. “In response to this epidemic, several states…” Use of the word several suggests very few. If one is considering prescription drug monitoring programs as “regulation and policy”,
which they are, then 49 states have enacted. If referring to “emergency rules” then please clarify.

RESPONSE 2: Thank you for this comment. We have edited the statement to reflect that almost all states had PDMP’s in place, while several of them have emergency rules as well. (Background section, lines 45-47, page 4)

3. Line 38. A “1)” is missing before the word “undertreating”

RESPONSE 3: Done. (Background section, line 59, page 4)

Data

4. Line 36. Please clarify if mandatory use of INSPECT requires checking on all opioid recipients or a subset, like new patients or chronic recipients only.

RESPONSE 4: The mandatory use of INSPECT rule is applicable for all patients that have been prescribed schedule II-V drugs, for more than three consecutive months: 1) >60 opioid-containing pills per month; or 2) A morphine equivalent dose (MED) >15 mg/day. Only the following are exempt: 1) Patients with a terminal medical condition 2) Residents of an Indiana-licensed health facility 3) Patients enrolled in an Indiana-licensed hospice program 4) Patients enrolled in an inpatient or outpatient palliative care program of an Indiana-licensed hospital or hospice. Prescribers issuing tramadol at > 60 MED must also query INSPECT. Prescribers must query at initiation and at least yearly. (Methods section, lines 82-97, pages 5-6)

Statistical analysis

5. What class of models are being used to characterize the auto-regressive components? ARIMA? Please add.

RESPONSE 5: Our interrupted time series analysis relies on OLS models with lagged terms to account for the autoregressive nature of the data. OLS models, compared to ARIMA models are much more flexible while still broadly capturing the interrupted time series autoregressive context. Refer Box and Jenkins (1976) and Velicer and Harrop (1983).

6. How were the pseudo-start points along the pre-intervention continuum determined? This would give context to the description of “wide-array” of start dates in the results.

RESPONSE 6: We have added footnote 1 (page 7) that clarifies that a random number generator was used to randomly draw 100 pseudo start dates along the pre-intervention continuum. No significant discontinuity in opioid prescribing was found at any other pseudo start data. In
absence of other ‘disruptive’ changes occurring around the same time that the emergency rules kicked in, our results are suggestive of an effect of the emergency rules on opioid prescriptions.

7. Line 40. Is the list of commonly prescribed opioids given in rank order? If so, please indicate.

RESPONSE 7: The list includes opioids that are commonly used in practice and frequently referred to in opioid prescribing rules (see Medical Licensing Board of Indiana. Emergency Rule on Opioid Prescribing. Medical Licensing Board of Indiana; 2013. [cited 09 March 2016] Available from: http://www.in.gov/pla/files/Emergency_Rules_Adopted_10.24.2013.pdf.) We had no intention to rank the opioids by the frequency of their use or by any other factor.

8. Please avoid use of the term “narcotic” throughout and use “opioid” or “opiates” as appropriate.

RESPONSE 8: We have removed all instances of the term “narcotic” from the text and replaced it with the more appropriate terms of opioid or opiates.

Results

9. Patient Age. What is the age range for PDMP monitoring in Indiana? Is the 0-20 year old age range true? The decline in prescribing in this age group is surprising to me (and may be to other readers) so a thorough look at the age data quality/completeness is warranted. Is there anything specific in the emergency prescribing that focuses on this group? Did rules apply to dentists, the number one prescriber of opioids to adolescents?

RESPONSE 9: There is no age range limitations for PDMP in Indiana; every scheduled drug II-V script that is dispensed has to be reported irrespective of the recipient age. Our data consists of the full population of all dispensed schedule II scripts for our observation window, including those dispensed to recipients in the ages of 0-20 years.

The emergency rules, as detailed in 4 above, mandated use of INSPECT for all patients that have been prescribed schedule II-V drugs, for more than three consecutive months: 1) >60 opioid-containing pills per month; or 2) A morphine equivalent dose (MED) >15 mg/day. Only the following are exempt: 1) Patients with a terminal medical condition 2) Residents of an Indiana-licensed health facility 3) Patients enrolled in an Indiana-licensed hospice program 4) Patients enrolled in an inpatient or outpatient palliative care program of an Indiana-licensed hospital or hospice.

So even though lower dose and shorter opioid scripts would be included in our data, the emergency rules did not require prescribers to monitor them using the INSPECT. Consequently,
they wouldn’t directly be impacted by the emergency rules. However, we are unable to rule out an overall increase in monitoring of all opioid scripts and a general move away from prescribing opioid analgesics, as an unintended side effect of the emergency rules.

Once again, there were no age limitations for the implementation of the emergency prescribing rules. But, the emergency rules in most cases would not impact dentists as they are unlikely to prescribe high dose opioid painkillers for continuous durations lasting more than three consecutive months.

Finally, opioid recipients in the ages of 0-20 comprise a small proportion of the total opioid scripts dispensed both before and after the policy change, with little change in the proportion but a significant change in the total number of scripts. The number (proportion) of the scripts by age category are as follows:

<table>
<thead>
<tr>
<th>Age category (in years)</th>
<th>Before policy (1079 days)</th>
<th>After policy (325 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>15,523 (0.13)</td>
<td>7,867 (0.14)</td>
</tr>
<tr>
<td>6-10</td>
<td>25,424 (0.22)</td>
<td>12,345 (0.22)</td>
</tr>
<tr>
<td>11-15</td>
<td>43,459 (0.37)</td>
<td>20,627 (0.37)</td>
</tr>
<tr>
<td>16-20</td>
<td>196,615 (1.68)</td>
<td>91,647 (1.63)</td>
</tr>
<tr>
<td>20-40</td>
<td>2,936,072 (25.09)</td>
<td>1,298,789 (23.12)</td>
</tr>
<tr>
<td>40-60</td>
<td>5,098,638 (43.57)</td>
<td>2,405,988 (42.82)</td>
</tr>
<tr>
<td>60+</td>
<td>3,385,685 (28.93)</td>
<td>1,781,253 (31.70)</td>
</tr>
<tr>
<td>Total</td>
<td>11,701,416 (100.00)</td>
<td>5,618,516 (100.00)</td>
</tr>
</tbody>
</table>

In absence of information on the condition for which the opioid prescription is written, we are unfortunately unable to comment further on which areas of medical practice responded most strongly to the emergency rules, particularly those prescribing opioids to younger patients between 0-20 years. The significant reduction post emergency rules for recipients aged 0-20 years could be resulting from significant reductions in opioid prescriptions, for instance, for sports injuries. It could also be, that greater awareness among prescribers of greater incidence of addiction and non-medical use of opioids among adolescents, could have led prescribers to curb opioid prescribing particularly significantly for this group. But as mentioned above, our data does not allow us to investigate the mechanism underlying the significant reduction in opioid prescribing for a particular subpopulation. Future research, with data on prescriber specialties
and patient medical conditions, would provide valuable insight into potential areas of opioid non-
medical use over the past years and responses to policy change.

10. Zip code. Are you using the prescribers practice location zip code as a proxy for the income of the provider? It is not clear to me how valid this measure would be. Please clarify this calculation in the methods.

RESPONSE 10: The prescriber zip codes are imported directly from the Drug Enforcement Administration list provided by the Department of Justice each week. Unfortunately, the address they provide could be their place of employment or their residence, the majority being the latter.

11. Number of prescribers. It is not clear if the data analysis longitudinally follows a group of providers prescribing patterns before and after the policy change.

RESPONSE 11: The patient and provider fixed effects analysis (eTable 1) longitudinally follows a group of providers and patients before and after the policy change and the results can be interpreted as the change in opioid prescribing correlated with the change in policy. The aggregated interrupted time series results in Tables 1, 2, and 3 are for the aggregate group of providers or patients within the state of IN on a given day. Individuals within this group may vary each day.

12. Given the impact on high dosages, what is the explanation for declines seen in 0-20 year olds? I would expect relatively low dosages in this age group?

RESPONSE 12: The significant reduction in high dosage scripts in the post policy period is not inconsistent with reduction in opioid prescriptions to 0-20 year olds in the same period. In the pre-policy period, the proportion of high dosage scripts was lower in young patients relative to older patient cohorts. But in absolute numbers, Fortuna et al (2010) report high prescribing rates including high dosage scripts for adolescents and young adults as well in their cross-sectional study (2005-2007). Furthermore, these rates nearly doubled since 1994. Post-policy the relatively small proportion of high dosage scripts in 0-20 year olds further reduced to almost zero.

Discussion

13. Line 51. Conclusions are drawn to broadly on “provider behavior” and “patient care”. Please describe as “provider prescribing behavior”.

RESPONSE 13: We have changed all instances of “provider behavior” and “patient care” to more appropriate “provider prescribing behavior”. (Discussion Section, Line 238, page 12)
14. It seems inconsistent to note in the second paragraph that effects were found across all variables examined but then describe differential effects in the third paragraph.

RESPONSE 14: We have edited the text to provide further clarification. The rules were associated with a decline across different groups, the decline was not the same, however, when we compare between these groups. For example, there was decline for both males and for females, but the decline was more prominent for males.

15. Please present the results for Medicare and Medicaid. The only insurance type mentioned in the results is Workers Comp yet Medicare/Medicaid are chosen for discussion.

RESPONSE 15: We have presented the results for all the payer subgroups, including those for Medicare and Medicaid, to subsection ‘2) Patients and providers analysis’. Both changes in levels and trends have been presented as well. (Table 1)

16. Please indicate that the current thinking on fentanyl abuse is that it is largely driven by synthetic fentanyl illegally manufactured. See recent reference (below) for argument that fentanyl prescriptions themselves have not increased at nearly the same pace as fentanyl deaths.

RESPONSE 16: We have added your comment and the provided citation to the manuscript. (Discussion section, lines 290-292, page 15). Thank you.

17. Please confirm that the study period did not include major rescheduling (e.g. hydrocodone) or scheduling (e.g. tramadol) or other changes in Indiana.

RESPONSE 17: Hydrocodone became schedule II effective October 6, 2014. Since prescriptions of both schedule II and III drugs required the same PDMP query under the emergency rules, rescheduling of hydrocodone from category II to III would not change the implications of the PDMP. Tramadol became schedule IV effective August 18, 2014. Prior to this rescheduling Tramadol scripts were not subject to the emergency rules whereas post the rescheduling they were. Consequently, our results that exclude all Tramadol scripts are a lower bound of the association between the emergency rules and the decline in Schedule II-V drug prescribing. Inclusion of Tramadol would only further strengthen our results, unless prescriptions of Tramadol increased rather than declined post it’s rescheduling, which is highly unlikely. As a final robustness check, we re-estimated our interrupted time series estimates using the data up-to August 17, 2014. Our results, are robust in both sign as well as magnitude.
18. What about out-state possible effects? Were there any major changes in border states? Couldn't the sample be restricted to in-state residents and in-state prescribers to avoid this problem?

RESPONSE 18: Our sample only includes in-state residents and in-state prescribers. Also, our main results consider the aggregate volume of MED of opioids dispensed in the state of Indiana only. So our data is unlikely to capture out of state effects.

19. Please consolidate table 1 and 2 into single table so that all variables can be seen together.

RESPONSE 19: Done. New table 1 combines original tables 1 and 2.

20. Please describe “impact of policy” as “level”, “abrupt” or “immediate”, or “instantaneous”.

RESPONSE 20: Done throughout the manuscript.

21. The trend coefficients are not that informative given all the zeros. Can they be transformed for tabular presentation?

RESPONSE 21: Transformation is done.

22. On the 0-20 years old, the results seem to indicate an immediate decline of 27 people 0-20 year olds being prescribed any opioid [is this the correct interpretation of the coefficient? This interpretation, for all variables, should be presented in the results] and a downward trend prior to the policy but then an upward trend after the policy.

RESPONSE 22: We have added the interpretation of the ITSA regression coefficients, with an example, at the beginning of subsection 2 (titled “Patients and providers analysis”) of the Results
section. A coefficient of -27.26 for the ages 0-20 years implies that post policy period saw a decline in daily levels of opioids dispensed of 27.26 million MEDs for this age group.

23. Does that mean a one-time adjustment was made by providers but now the prescribing in this age group is on the rise? Were the emergency rules lifted? If so, this would seem to be a stronger argument for causal inference given that prescribing increased after the emergency provisions.

RESPONSE 23: Yes. However, our data does not allow us to comment on whether as an immediate response to the emergency rules the prescribers ‘over’ constrained the prescriptions of opioids to for this age group and the small, but statistically significant, upward trend is compensating for the initial abrupt decline. The emergency rules are still in place and over the next few years, as more data from subsequent years becomes available, we will be able to analyze the cumulative effect.

24. Etable1. Please present the trend coefficients.

RESPONSE 24: The ‘Impact of policy on trend’ in the second row of table eTable 1 is the trend coefficient from the fixed effects regression. So, for the recipient fixed effects regression the interpretation of the coefficient of -0.045 is that the implementation of the policy (change in policy dummy from 0 to 1) is associated with a significant reduction, by the amount of 0.045, of the trend coefficient.


REVIEWER 2
25. The submitted paper is a time series pre/post comparison of drug prescription data and census data in the state of Indiana.

While the authors have presented very important work - both from a clinical and policy perspective - especially given the increase in fatal opioid overdose across the USA and including in Indiana, the paper should not be accepted in its current form.

The authors use inappropriate language throughout - while changes pre and post the Implementation of the Drug Monitoring Program have been shown (though not clearly described), causation should not be inferred to this association - throughout the article the authors start with the assumption that a change has occurred, and state what the new policy has caused.

What they have observed, are different rates of prescribing, across different groups/doses/drugs, over time and claiming all these changes are from the change in policy/implementation of the monitoring program. They do not, in the introduction or discussion, adequately explain that no other events could impact on prescribing rates (they briefly mention in the discussion only) - this makes the article unpublishable in its current form.

RESPONSE 25: We fully agree with your concern that given this is a before-after study purely causal interpretation of the results is inaccurate. Throughout the manuscript we have further emphasized the association nature of our results and acknowledged that despite careful controls for trends and discontinuous shifts in trends, our results are at best only plausibly causal. We do however believe that despite this limitation our study makes an important contribution to the existing literature. To the best of our knowledge, this is the first study that considers how the opioid prescribing practice changed in response to the Indiana emergency rules. Several dimensions of opioid prescribing practice were considered – by patient subpopulations (by gender, age, insurance type, aggregate socioeconomics), drug types (strength, days of supply, short versus long acting) and short and long term changes in prescribing behavior. In so doing, our results shed light on whether implementation of the policy by prescribers was correlated to patient demographics closely linked to opioid non-medical use.

Other suggestions to strengthen their findings:

26.

* An analysis of data from another jurisdiction where a monitoring program was not implemented at the same time would strengthen the association. - neighbouring states are only briefly mentioned - without any supporting data provided or a reference provided
RESPONSE 26: At this time, we unfortunately do not have access to data from PDMP’s from neighboring states to evaluate ourselves and present as supporting data. We have applied for the same and hope to have the data in the future to further re-evaluate and reiterate our findings from this study. In the meantime, per your advice, we have added appropriate references to support our claim.

27.

* Use of the (modified) Bradford Hill criteria to assess an association in a study that does not have an experimental design.

RESPONSE 27: As mentioned above in Response 25, our study is a before after study estimating the correlation between the implementation of the Indiana opioid emergency prescribing rules and the changes in opioid prescribing. Since the study relies exclusively on temporal changes in levels and trends associated to an exogenous policy change our results can only be interpreted as plausibly causal. The Bradford Hill criteria provide further support to our plausibly causal interpretation of the results. The individual criteria are as follows:

a. Strength (effect size): The coefficients from our ITSA regressions for the association between the policy and the change in levels as well as the trend of opioid prescribing are highly statistically significant at the 1% level of significance. In particular, the coefficient sizes for the instantaneous shifts in opioid prescription levels (measured in millions of MED) in the post policy period are particular large and therefore more likely to be a result of the emergency rules.

b. Consistency (reproducibility): our results are consistent with other studies considering the causal impact of emergency rules in other states (for instance, Buchmueller and Carey (2016)).

c. Specificity: Our data is limited to scripts written and dispensed in the state of Indiana only, and therefore subject to the emergency laws whose effectiveness we are attempting to study. During our observation window there were no other major rescheduling or scheduling of opioid based drugs nor were there other state specific or federal policies that may have influenced our results.

d. Temporality: The instantaneous shift in levels and trends in opioid prescribing closely matches the going into effect of the Indiana emergency rules. As mentioned above in response to comment 6 that no similar results could be generated with other pseudo start dates, reiterating the relevance of the timing of the emergency rules with regards our results.

e. Biological gradient: Greater incidence of opioid addiction and non-medical use is related to higher MED and longer durations of opioid use. Consequently, high MED scripts and longer duration scripts are more likely to be impacted by the Indiana emergency rules, which is exactly what our results find (refer last two panels of Table 1).
f. Plausibility: The policy was aimed to reduce non-medical prescription opioid use, by ensuring that prescribers accessed the PDMP to identify patients at risk, thereby limiting their over-access to prescription opioids. It seems highly plausible that on accessing the PDMP if a prescriber learns of potential over-use of opioids they may refrain from further over-prescribing opioids to the patient.

g. Coherence and Experiment: Since this study aims to evaluate the impact of a state policy, laboratory evidence is neither available nor applicable in this context.

h. Analogy: Other work, considering different but related outcomes and states, have found similar results relating to PDMPs. For instance, Rutkow et al. (2015) also find a decline in total opioid volume, mean MED per transaction, days of supply and number of scripts written post coming into effect of the Florida PDMP. While the population demographics and consequently pain management practices in Florida may be very different from those in Indiana, it is reassuring that our results are in line with other literature linking PDMPs with declines in opioid prescribing, further suggesting a plausible causal relationship.

28.
Terminology needs to be reconsidered throughout - for example page 7, lines 4-9
"Thus, the difference in daily prescribing between the pre- and post-intervention period can be interpreted as a result of the rule change"

The fact that an interrupted time series analysis has been performed cannot, on its own, be used to infer causation.

RESPONSE 28: Thank you for pointing this out. We have changed this to the “Thus, the difference in daily prescribing between the pre- and post-intervention period can be interpreted as plausibly associated to the rule change.”, which captures more accurately what we intend to say. (Methods section, line 109, page 7)

29. Page 8 line 55
"the policy had a statistically significant negative impact on average MME per day per patient and the total MME dispensed in the state" - again causation should not be inferred. (Results section, line 136, page 8)
RESPONSE 29: Again changed to the more accurate “…the policy is found to be statistically significantly associated with a negative instantaneous shift in MED per day and the total MED (in millions) dispensed in the state (Figures 1 and 2).”

30. Page 9 lines 4-6

"This robustness check assures us that we are truly capturing the impact of the policy and not just an interruption in the time trend" - a statistical analysis technique cannot, on its own, remove all confounders and prove causation.

RESPONSE 30: Changed to “This robustness check suggests that we may be capturing a plausible impact of the policy and not just an interruption in the time trend.” (Results section, line 139, page 8)

31. Regarding terminology

Suggest the term abuse is substituted for 'non-medical' use as abuse is no longer a DSM(5) term and can be open to misinterpretation. Also suggest the authors consider


RESPONSE 31: Throughout the manuscript we have replaced the word ‘abuse’ with the more appropriate “non-medical use”.

32. Page 9, lines 33-35

"This sensitivity analysis shows that our interrupted time series results are qualitatively robust" - the authors probably mean quantitatively - but again, this approach cannot remove all bias (known and unknown) - in fact throughout the authors use of the term qualitative is confusing - they do not present qualitative data

RESPONSE 32: Following the jargon from Economics we used the adjective ‘qualitative’ to refer to the sign of a coefficient and ‘quantitative’ to refer to its magnitude. We realize that this usage is not in line with other fields of research and is therefore misleading. We have removed the word ‘qualitative’ from the manuscript and instead referred to the sign of a coefficient directly.
33. Table 1 is not explained in the text - while it is described as a regression, the columns header should describe what is in them. In fact all tables do not adequately describe what is being reported in each column.

RESPONSE 33: We have changed table headers and added more description of how to read the tables, with examples to facilitate easier reading. Please let us know if we can make any further improvements in this regard.

34. Page 11, Lines 33-35

"a drug that experienced a significant negative post policy shock" - technically - a drug cannot receive a 'shock' - a drug is an object - the authors may be describing a pattern of prescribing behavior

RESPONSE 34: We agree. We have modified this to “a drug that experienced a significant decline in prescription rates in the post policy period” (Results section, line 230, page 12)

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- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

References


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