PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	CLINICAL AND ECONOMIC CHARACTERISTICS OF EMERGENCY DEPARTMENT VISITS DUE TO ACETAMINOPHEN TOXICITY IN THE UNITED STATES
AUTHORS	Altyar, Ahmed; Kordi, Lama; Skrepnek, Grant

VERSION 1 - REVIEW

REVIEWER	Budnitz, Daniel CDC
REVIEW RETURNED	23-Feb-2015

GENERAL COMMENTS	This manuscript seeks to investigate an important question – to assess trends in ED visits due to acetaminophen toxicity. Large amounts of data are presented in tables, but issues that should be addressed include: 1. There is no indication of the variability or statistical stability of the national estimates presented in text, tables, or figures. Cases in the data source (NEDS) are weighted and estimates made using the weights should be accompanied by indications of confidence intervals, standard errors, or at least notation that estimates meet stability thresholds based on a minimum number of cases and coefficients of variation do not exceed 0.30. For example, cells indicated by <0.1% may be unstable and should be noted. Ideally CIs would be provided, but addressing the stability thresholds should be done in some way. 2. While the results of multivariable modeling techniques do report CIs, it is not clear if these methods accounted for the fact that these data are weighted data from a complex sample. If the cases were treated as count data for multivariable modeling that should be noted and any limitations from this approach discussed. 3. The discussion section nicely highlights previous research on ED visits and hospitalizations from acetaminophen, but if there could be additional attention to highlighting key implications of the data in the current study, it would assist the reader in utilizing the large amount of data presented in the tables. This reviewer is not a statistician but has some familiarity with using data from national probability samples, so these comments represent general statistical principles when using such data, but a statistician who specializes in these analyses may have additional insights.

REVIEWER	Kelkar, Mugdha University of North Carolina
REVIEW RETURNED	13-May-2015

GENERAL COMMENTS	Summary – This is a very interesting article investigating the APAP toxicity related ED visits and associated clinical and economic burden in the US. The authors used a crosssectional design and report substantial public health impact of APAP toxicity. While very interesting the manuscript seems very wordy overall. Following are the specific comments that should be addressed. Introduction – • Sequence of updates issued for the APAP products listed in the introduction section makes the section very wordy. Consider organizing them in the form of a flowchart/chronological timeline to make it easier to read. • The rationale of the study has not been clearly described. Why did the authors decide to do this study? Are there relevant gaps in the existing literature that need to be addressed? Methods: Please state the rationale for starifying the age categories – example, are doses warranting toxicity different for these strata? Results – • Given that the manuscript reports multiple measures, it would be helpful to report the ratio measures graphically with a reference line at 1.0 so its easier to grasp which factors are most important predictors of the outcome. • The text seems to focus on statistical significance (p values) which would be expected to be high given the large sample sizes. Please report confidence intervals in the text as well. • The manuscript uses the word incidence when it really represents incidence proportions (cases/population). Please use the latter term to distinguish from incidence rate (cases per person-year). Please fix throughout the manuscript and the abstract. Discussion – • Consider making this setion a bit more succint. The length makes readability somewhat confusing. • Please discuss the validity of codes used to define APAP toxicity related ED visits

VERSION 1 – AUTHOR RESPONSE

1. There is no indication of the variability or statistical stability of the national estimates presented in text, tables, or figures. Cases in the data source (NEDS) are weighted and estimates made using the weights should be accompanied by indications of confidence intervals, standard errors, or at least notation that estimates meet stability thresholds based on a minimum number of cases and coefficients of variation do not exceed 0.30. For example, cells indicated by <0.1% may be unstable and should be noted. Ideally CIs would be provided, but addressing the stability thresholds should be done in some way.

Author response: We appreciate this comment. Our approach to weighting the complex study sample was based explicitly upon the AHRQ-recommended Taylor series method, articulated in https://www.hcup-us.ahrq.gov/nedsoverview.jsp, for example, controlling appropriately the case level and stratum levels. Furthermore, the multivariable analysis explicitly omitted variables with particular low sample sizes, as “Notably, if any given Elixhauser comorbidity was observed in <0.01% of cases within any age category, it was omitted to allow for appropriate statistical inference.” It would certainly be possible to include the diagnostic elements a, as these were calculated and evaluated, we would submit that this may be overly burdensome to the already extensive tables that are present.

2. While the results of multivariable modeling techniques do report CIs, it is not clear if these methods accounted for the fact that these data are weighted data from a complex sample. If the cases were treated as count data for multivariable modeling that should be noted and any limitations from this approach discussed.
Author response: The entirety of the analysis did use Taylor Series weighting as recommended by AHRQ.
3. The discussion section nicely highlights previous research on ED visits and hospitalizations from acetaminophen, but if there could be additional attention to highlighting key implications of the data in the current study, it would assist the reader in utilizing the large amount of data presented in the tables.

Author response: We utilized large-scale, nationally-representative discharge records to provide an approach to gaining a broad understanding of APAP toxicity among emergency departments in the US. Data presented should increase the number of patients advised to present to hospital following accidental and supra-therapeutic ingestions and lead to unnecessary blood tests, ED stays and patient or parent burden because there is a real risk of increasing the incidence of adverse drug events to NAC and a potential for increased morbidity and mortality from APAP toxicity. Not only are there clinical and economic consequences, but also there are psychological repercussions for prolonged hospital stay.

Changes to OTC products are already underway, and will make packaging more understandable to consumers. Many patients are unaware that the over the counter (OTC) medications and prescription products they use contain acetaminophen, especially those that contain combinations of agent. The new FDA recommendations will likely result in changes to recommended dosing to attempt to add a margin of safety between over the counter medications recommended dosing and maximum safe dosing. While these modifications take an effect, we are reminded of how crucial and important it is that providers interview and educate patients regarding the use of OTC products and account for the amounts of acetaminophen consumed. This becomes ever more important when issuing prescription medications that also contain acetaminophen.

If the FDA adopts the new recommendations for OTC products, the new warnings and changes to availability will likely generate questions from patients. All practitioners can prepare for these modifications by adapting the new recommendations for OTC acetaminophen use to dosage forms and strengths available, for example adjusting recommendations for parents administering liquid

pediatric formulations if a single standard concentration is adopted.

Furthermore, this current study was able to consider the independent associations between these outcomes and a number of important comorbid conditions while adjusting for several possible confounders in the ER department setting. The findings add to the understanding of comorbidities and APAP toxicity by identifying co-existing diseases that pose a greater disease burden specifically in hospitalized patients.

Reviewer Number 2

Introduction – Sequence of updates issued for the APAP products listed in the introduction section makes the section very wordy. Consider organizing them in the form of a flowchart or chronological timeline to make it easier to read.
Author Response: We have added Figure 1.

The rationale of the study has not been clearly described. Why did the authors decide to do this study? Are there relevant gaps in the existing literature that need to be addressed?

Author Response: The study was conducted for the following reasons:
• To address a gap in the scientific literature;
• APAP safety has been looked at more closely recently due to the increased number of toxicity cases;
• There have been no articles describing total hospital charges for APAP toxicity;
• The need for continuous trend for a common medication such as APAP; and
• Provide assessments of clinical and economic outcomes.

Methods: Please state the rationale for stratifying the age categories – example, are doses warranting toxicity different for these strata?

Author response: Dosing for APAP is technically conducted on a per-weight basis, though our approach to age stratification was based upon prior research categorizing cases as pediatric, adolescent, adult, and older adult.

Results – Given that the manuscript reports multiple measures, it would be helpful to report the ratio measures graphically with a reference line at 1.0 so its easier to grasp which factors are most important predictors of the outcome.

Author response: We agree that providing forest plots would be useful, though the comprehensiveness and complexity of the overall analysis presents marked challenges and an inherent subjectiveness involving variable selection may be perceived as lacking transparency.

The text seems to focus on statistical significance (p values), which would be expected to be high given the large sample sizes. Please report confidence intervals in the text as well.

Author response: Our approach was to statistically control for false errors via the Simes p-value modification, thus presenting a more conservative method. All coefficients were also standardized via relative risk measures (e.g., incidence ratios), which are a uniform effect measure. While we could certainly present confidence intervals, our decision to omit them was merely to allow for enhanced readability of the already complex and comprehensive tables.

The manuscript uses the word incidence when it really represents incidence proportions

(cases/population). Please use the latter term to distinguish from incidence rate (cases per person-year). Please fix throughout the manuscript and the abstract.

Author response: We are appreciative of this comment and have made changes in the manuscript.

Discussion – Consider making this section a bit more succinct, the length makes readability somewhat confusing.

Author response: We appreciate this comment and reviewed the Discussion Section for clarity and conciseness.

Please discuss the validity of codes used to define APAP toxicity related ED visits

Author response: The validity of these codes is articulated, in part, in Reference 15.

VERSION 2 – REVIEW

REVIEWER	Kelkar, Mugdha University of North Carolina
REVIEW RETURNED	30-Jul-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.