**Author’s response to reviews**

**Title:** Gender differences in acute recreational drug toxicity: a case series from Oslo, Norway

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**Author’s response to reviews:**

Dear dr Khoshnood and reviewers

Thank you for this opportunity to revise our manuscript and thank you for your valuable comments.

Reviewer 1

Lykke Syse et al performed a retrospective study which aims at the description of patients treated for acute recreational drug toxicity, and aims at describing gender difference in clinical state and toxic agents.

General comments: Unfortunately, the paper does not follow the STROBE guidelines. I suggest that the authors revise the manuscript according the STROBE guidelines, and add a STROBE checklist to the resubmission.

- The manuscript has been revised according to the STROBE guidelines, and a STROBE checklist has been added to the resubmission.
Background

It is not clear, why the study was performed, please clarify.

- The study was performed to look for gender differences among patients treated for acute recreational drug toxicity. This has been clarified in the revised Background section.

Scientific background is presented, but should be more comprehensive. The authors might elaborate the gap of knowledge, why this study is necessary, and present the objectives more clearly.

- We have rewritten the Background section, clarifying the gap of knowledge and why we consider this study necessary. We have also stated the objectives more clearly in the revised Aims subsection.

Methods:

Design: The authors should state that this is a retrospective study.

- This has now been stated in the Study design subsection.

Participants: Here already results are presented, this should be shifted to the result section.

- The general information on the participants has been shifted to the Results section.

Eligibility criteria and exclusion criteria should be presented more clearly.

- We have elaborated on and clarified the eligibility and exclusion criteria in the revised Participants subsection.

Outcome measures: Here, objectives are presented, but not outcomes. Objectives should be described clearly in the Introduction section, not in method section. Describe outcomes in the statistic section.

- We have described our objectives more clearly in the Introduction section, and revised the Statistical analyses subsection according to the STROBE guidelines and your suggestions.
Statistics: Please clearly define predictors and outcomes here. Describe all statistical methods.

- We have revised the Statistical analyses subsection according to the STROBE guidelines and your suggestions.

Results: Present results according to STROBE guidelines

- The Results section has been revised according to the STROBE guidelines.

Discussion: Please discuss the relevance of the study for clinical practice.

- We have commented on the clinical implications in the 4th paragraph in the Gender differences subsection in Discussion.

Reviewer 2

I have read the manuscript entitled "Acute recreational drug toxicity in women: a case series from Oslo, Norway". The manuscript presents a potentially interesting topic for the readers; However, it may be better if you pay attention to the following suggestions: This is a research article. Why is the title of the article "a case series"?

- Technically, the study is a case series, albeit a large one. Cases were collected retrospectively. Individual patients may be represented with several cases. There is no follow-up data. We might have called it an observational study, but we found case series more appropriate.

Some of the data in the background can be taken to the discussion section.(US, Australian study, Spanish study, Swiss, Norwegian)

- We have moved some of the elements from the Background to the Discussion section, and deleted some.

In the discussion section, please shorten the "Strengths and limitations" too long.

- We have shortened the Strengths and limitations subsection somewhat and kept only the limitations. Accordingly, we have also renamed it.
Reviewer 3

The objective of this case series study of female recreational drug users was to report gender differences in clinical state and toxic agents. The author cites various references that female drug abusers (as defined by heroin dependence, overdoses, psychiatric disease, and substance use disorders) have higher mortality and worse morbidity than their male counterparts. Comparative gender studies associated with recreational drug use, as opposed to abuse, was not cited. Therefore, the background comments that the health of female drug users are generally poorer than males may not be substantiated when studying recreational users.

- The patients in our study encompass both heavy drug users and party drug users. We agree that our background comments only substantiate poorer health among the heavy drug users. This was why we made the proxy differentiation between heavy and party drug users by analyzing the cases with and without opioids separately. We have not found any reports on gender differences in health and background concerning party drug users. We have elaborated on this in the revised Background section.

Patients receiving methadone or are part of a drug rehabilitation program might have been used as controls.

- Unfortunately, we did not have access to data for any suitable control group.

The criteria excluded those who used drugs for suicide or self harm, and for cases involving harm to others. GHB is specifically used in some social communities as a disinhibiting medication given often to females intentionally as a 'date rape' drug. This study reports a significantly higher rate of ingestion/coingestion of GHB in female from both the outpatient and Hospital ED group. The trial also reports that it excluded those who were given it unbeknownst to them. How did the study group control for the potential for accidental but intentional inflicted ingestion? Would this have been less significant if the subjects were able to verify that they voluntarily took GHB as part of their substance usage during their visit?

- The assessment of whether an ingestion was inflicted by others was based on reports from the patients themselves or their companions, as registered in the electronic medical records by the doctor treating the patient. Thus, voluntary ingestion of GHB (and other drugs) was verified by the patients or their companions. This point has been clarified in the revised Participants subsection in Methods.
The reported findings citing a lack of clinical difference between gender is more consistent with recreational drug users, as is the study group. The background citations describe a more chronic abusers with much more health issues. To enhance this study, a differentiation must be made between patients with preexisting health issues related to chronic drug abuse and those who actually used drugs recreationally.

- Unfortunately, we did not have any background information on our patients. However, as a proxy differentiation between chronic drug abusers (heavy drug users) and recreational users (party drug users), we grouped the cases according to whether any opioids had been taken or not. Hence, we would primarily expect the gender differences stemming from the poorer health among female drug users to appear in the clinical course of the acute poisonings among the patients in the opioid groups. Still, gender differences were few. We have clarified this differentiation in the revised Statistical analyses subsection and in the revised Results. We have also elaborated on this point in the first paragraph in the Gender differences subsection in Discussion.

Confidence intervals would have yielded more precision for the mean Peak CK and Cr data,

- As these data did not follow the normal distribution, we found it more appropriate to use medians and interquartile ranges.

and would could have yielded more information to the reader if the mean SBP was reported (as opposed to 'SBP≤ 90').

- We found it more interesting to compare proportions of patients with deranged vital signs than comparing medians or means. This allowed us to explore both hypotension and hypertension as clinical problems in acute recreational drug toxicity. As can be seen in the tables below, there are statistically significant differences between males and females in most comparisons of median and mean SBP. However, these differences are hardly clinically significant.

Opioid group – comparisons done with Mann-Whitney U-test (medians) or Student’s T-test (means)

<table>
<thead>
<tr>
<th></th>
<th>Outpatient clinic</th>
<th>Hospital ED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>SBP median</td>
<td>110</td>
<td>117</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(98- 119)</td>
<td>(106- 128)</td>
</tr>
<tr>
<td></td>
<td>Outpatient clinic</td>
<td>Hospital ED</td>
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<td>----------------</td>
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</tr>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>SBP, median</td>
<td>119 (106-132)</td>
<td>126 (111-138)</td>
</tr>
<tr>
<td>(IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (95%</td>
<td>120 (117-123)</td>
<td>126 (124-128)</td>
</tr>
<tr>
<td>CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-opioid group – comparisons done with Mann-Whitney U-test (medians) or Student’s T-test (means)

Also, comparatively worse hypotension in the outpatient group of females coingesting drugs with opioids is an interesting clinical finding worth mentioning, though not reported in the conclusions.

- We have mentioned this finding in the revised Results section, and commented on it in the 4th paragraph in the Gender differences subsection in Discussion.

In summary, the outcomes of the trial reported that only about ¼ of recreational drug users presenting to a Norway health care system were female. Reports from the European Monitoring Centre (http://www.emcdda.europa.eu) support this study's findings, adding that Norway has the 10th highest lifetime prevalence for illicit drugs. In it, the ratio of females to males with illicit drug problems is comparable to this trial.

- We have added this point in the 2nd paragraph in the Gender differences subsection in Discussion.

Reviewer 4

The topic of the submitted is interesting and relevant as understanding both drug abuse and gender differences in drug toxicity is important, but the paper needs improvement and clarification in many aspects.
Introduction is not clear - even if the presented study concentrates on recreational drug toxicity, the studies mentioned in „Background" section are about dependency in abuse, not about just recreational misuse, so long term consequences and short term snapshot in the study are compared.

- The patients in our study were both heavy drug users and party drug users. We agree that the studies cited in the Background section only substantiate poorer health among the heavy drug users. We have not found any reports on gender differences in health and background concerning party drug users. We have elaborated on this in the revised Background section. To look for long term consequences in our snapshot of acute intoxications, we made a proxy differentiation between heavy and party drug users, analyzing the cases with and without opioids separately. We have clarified this differentiation in the revised Statistical analyses subsection in Methods and in the revised Results section.

Some of references cited here deal with alcohol intoxications, which is a different pattern and authors state that alcohol problems are not enrolled in this submitted study (only as a secondary drug).

- We have removed the reference to the alcohol users (Adam et al, ref 20) in the Background section. However, we still cite the study twice in the Discussion section, where it seemed appropriate. Though mainly focusing on alcohol users, substance use in these patients was also studied by Adam et al.

Maybe more information on specific features of the drug scene in Norway compared to other EU or other countries could be more interesting for international audience (reference 1 and 2 can be a good source for this) - e.g. spectrum of favorite drugs, preferred application ways, incidence and prevalence of drug abusers in Norway etc.

- We have expanded on these issues in the revised Background section.

The reason why acute recreational drug toxicity is of special interest is not explained (why to study this form of drug abuse) and it is not defined anywhere in the text.

- By recreational drug use we mean all use of recreational drugs, both by chronic heavy users with problems related to addiction and more intermittent use among the party crowds. Hence, we study acute toxicity related to all potential substances of abuse (except alcohol), irrespective of the characteristics of the users. We have clarified this in the Methods section, and stated the knowledge gap and the objectives more clearly in the Background section.
The „Aims“ are not described precisely, I’d prefer more structured introduction part with citing only those papers related to the topic of tis study and more clear explanation of the aims of the study.

- We have rewritten the Background section accordingly and stated our aims more clearly.

„Methods“ section: inclusion criteria should be presented, there is only information that: …"eligible cases were identified retrospectively from the patient registration lists"…. Inclusion was based on case history, information form the patient or other people, screening tests, toxicological analysis?

- Inclusion was based on information in the case history as noted in the electronic medical records by the doctor treating the patient. We have added this information in the revised Participants subsection.

What about patients presenting with some other chief complaint and drug intoxication as a secondary symptom?

- Patients presenting with other chief complaints were included if the drug intoxication in itself warranted observation and/or treatment. This information has been added in the revised Participants subsection.

„Data collection and classification“ - why peak serum levels of kreatine kinase and kreatinin were measured only in the first year of data collection, was the reason clinical or organizational or other?

- After the first year of data collection the variable set was simplified. This was mainly due to organizational reasons to make the data collection less cumbersome.

„Result section“ is insufficient to my opinion and very few data (compared to tables) are presented.

- We have expanded the Results section.

Which drugs authors classify as „opioid group“?
- The “opioid group” refers to the patients reporting one or more opioids among the drugs taken. We constructed the opioid group and the non-opioid group for analytical purposes, to differentiate between heavy drug users and party drug users. We think this has become clearer in our revised Statistical analyses subsection (3rd paragraph) and in our revised Results section. The opioids appearing among the reported agents in our study were heroin, methadone, buprenorphine, morphine, codeine, tramadol, pethidine, ethylmorphine, opium, and oxycodone.

Moreover, opioid group and heroin intoxications are mentioned separately in the first and second paragraph.

- We have tried to clarify in the revised Results section by reporting drugs taken before we report the analyses differentiating between heavy drug users (opioid groups) and party drug users (non-opioid groups).

Based on table 1, there is a mix of various drugs including alcohol as a secondary drug, a group „more than 1 toxic agent“ and other/unknown, this classification doesn’t seem concise.

- As many patients had taken more than one drug, the numbers and percentages add up to more than the total. We have stated this in a foot note and revised the table for improved clarity.

„Discussion section" - is insufficient, too.

- We have expanded the Discussion section on several points.

What is the explanation/hypothesis for higher abuse of GHB in females?

- The absolute number of GHB intoxications was larger among males than females at both locations. However, the proportion of GHB intoxications was larger within the female group than within the male group. We have tried to make this distinction more clear in the revised Results section (2nd paragraph) and in the Summary of main findings subsection in Discussion. We have no explanation for this finding.

Intubation is mentioned in the discussion without any previous remark about this airway management technique - why, if it was in a small number of cases ?
- We have removed the mention of intubation from the summary of main findings. However, we have added some information on intubation in the Results section and discussed it along with the other therapies in the Gender differences subsection in Discussion.

And why the other therapy (Table 2) is not discussed properly? (sedation, antidotes, length of stay etc.)

- We have elaborated on these therapies in the 3rd paragraph in the Gender differences subsection in Discussion.

There are some other potentially interesting differences in the tables but not discussed in the text.

- We have discussed most of the differences in the 3rd and 4th paragraphs in the Gender differences subsection in Discussion.

The reason for separate analysis of outpatient clinic and hospital ED is not clearly described.

- The patients treated in the hospital ED are systematically more severely sick than the patients treated at the outpatient clinic. The hospital patients have been seen by a primary care doctor or the ambulance service prior to presenting at the hospital. They have been assessed to be in need of more intensive observation or treatment than is available at the outpatient clinic. We have described this in our revised Statistical analyses subsection.

Reviewer 5

The wording of the Aims section is confusing to me.

"Female drug users generally report poorer physical and mental health than male drug users. To see whether this impacts on presentations to emergency medical services, we describe female patients treated for acute recreational drug toxicity, and compare them with male patients as to their clinical state and toxic agents taken." What do the authors mean by "to see whether this impacts on presentation..”? What is impacting what? The paragraph should be edited so that readers can understand it better.

- We have rewritten the Background section, including the Aims subsection, for improved clarity.
What is the Euro-DEN Plus data registration tool? This needs to be described a bit more as to its purpose and advantage over generic clinic forms?

- The Euro-DEN Plus data registration tool is a case definition and a variable set, and a pre-set excel spreadsheet for collecting data. We have described this in the revised Study design subsection.

Under settings, the authors claimed that "Patients cannot present at hospital emergency departments directly, but must initially be seen by a doctor in primary care or by the ambulance service". So, what happens when a patient comes or is brought directly to the hospital emergency department?

- A patient presenting directly to a Norwegian hospital ED without referral from a doctor nor brought by the ambulance service, will be told to go to the closest primary care emergency outpatient clinic (or a GP during office hours), unless obviously seriously sick. This is well known to the population.

72 cases were transferred from OAEOC to OUH. How were they analysed? Once (i.e. if a case has been analysed for OAEOC, it is excluded from OUH, and vice versa) or repeated for each of the centre. This wasn't clear from the text.

- These 72 cases were included in the analyses at both locations. We have rephrased this statement in the revised Statistical analyses subsection.

What the authors refer to as outcome measures are not really outcome measures. They are statistics and should come under that section.

- We have moved them to the Statistical analyses subsection, as suggested.

Table I and II need to be edited. Neither the columns nor the rows add up, so one can not say what the percentages in the brackets are referring to. What's the total row adding up?

- In table 1, many patients had taken more than one drug. Thus, the numbers and percentages add up to more than the total. We have stated this in a foot note and revised the table for improved clarity. In tables 2 and 3, percentages refer to total at the bottom of the columns. This information has been added to the tables.
Line 56, discussion page: "There were few gender differences apart from this" should read "There were no other gender differences apart from these"

- The sentence has been altered in the revised manuscript.

The discussion is rather shallow. The authors need to discuss further the reason for the surprising finding of small gender differences in their studies in the light of previous studies. What are the peculiarities of their study population leading to this surprising finding?

- We tried to adjust for the heterogeneity of our patients by comparing the patients reporting opioid use separately, as a proxy for heavy drug use. Still, gender differences were few. It is possible that the heavy drug users treated for overdose are a subgroup of heavy drug users, with even poorer health, and more equally so, among both males and females. We have elaborated on this in the first paragraph in the Gender differences subsection in Discussion.

Can it be due to the type of drugs used? Perhaps, the authors can control for GHB, and see whether the severity outcome will still be the same?

- It does not seem to be due to the type of drugs used. We did all the analyses in Tables 2 and 3 anew, correcting for GHB. The overall picture was still the same. We chose to keep our original analyses.

Finally, the title is a little bit misleading. The study is a comparison of toxicity among the two genders, not just a study of toxicity among women.

- We have changed the title accordingly, to “Gender differences in acute recreational drug toxicity.”

Oslo, 13 March 2019

On behalf of the authors

Yours sincerely

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