**Author’s response to reviews**

**Title:** Systematic Review of Nephrotoxicity of Drugs of Abuse, 2005-2016

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**Author’s response to reviews:**

Dear Editor,

On behalf of myself and my coauthors, we would like to thank you and the reviewers for taking the time to review our work. Below, we are including our responses in bold letters to each comment and suggestion made by the reviewers. Every correction and modification in the manuscript has been highlighted as well.
Reviewer reports:

Massimo Torreggiani, M.D., Ph.D. (Reviewer 1): In this manuscript, Mansoor and Colleagues aim to review the literature published between 2005 and 2016 about the nephrotoxicity of the drugs of abuse.

The review is well written and deals with an unusual topic that is not often discussed but is clinically relevant in everyday practice.

In my opinion this manuscript deserves publication.

Response:

We thank Dr. Torreggiani for his review and comments.

Bernard G Jaar, M.D., M.P.H. (Reviewer 2): I read with interest the manuscript by Dr. Mansoor et al. This is a comprehensive review of drugs of abuse related nephrotoxicity. The authors reviewed the topic from the English literature using PubMed/Medline from 2005 to 2016 and provide detailed nephrotoxic effects of different illicit drugs of abuse.

Please find below specific comments.

Response:

We thank Dr. Jaar for his review and comments. We have included our responses highlighted below each comment.

Background:

- It needs to be shortened. It needs to be to the point of nephrotoxicity rather than an exhaustive review of the epidemiologic data of drugs of abuse.
Response:

The background was shortened as suggested. We believe that the epidemiology of drugs of abuse is of particular interest to this topic which would attract the attention of the readers and policy makers. Specifics of nephrotoxicity related to these drugs are included in the body of the manuscript. We did not find good quality literature that would link the epidemiology with the nephrotoxicity.

Methods:

- Under Search strategy - please identify by their initials the two qualified healthcare professionals who conducted the literature search.

Response:

Initials of the authors who did literature search were included in the methods section and are highlighted

- In the manuscript, the authors report that they searched PuMed. Did they search other databases? No one database can search all the medical literature. What about Medline, EMBASE, Cochrane Central, …?

Response:

Initial literature search encompassed Pubmed and Medline but due to high number of articles and constant duplication, It was decided amongst the authors to thoroughly search Pubmed and utilize the articles from it.

- Phrases and MESH terms used for the search could be more comprehensive and also include the following: acute tubular necrosis, acute interstitial nephritis, …
Response:

Broad MeSH terms were selected as to encompass all the articles on PUBMED as opposed to narrowing the search to terms like acute tubular necrosis (ATN) or others because not all drugs cause specific diseases. These terms were initially tested but the search was not effective thus the authors decided to use broad MeSH terms.

- Under Study Inclusion criteria - please identify by their initials the two independent reviewers who evaluated the abstracts. Are these the same reviewers who did the literature search?

Response:

Initials of the authors who reviewed abstracts and full text articles were added and included under study inclusion criteria

Results:

- Authors could consider reporting the kidney biopsy findings in the discussion section under each separate drug of abuse and be more descriptive of the kidney biopsy findings.

Response:

Kidney biopsy findings were reported and modified as suggested in the discussion section

- In the section, it would be good to summarize the findings reported in the tables, particularly tables 1 and 2.

Response:

Findings of table 1 and 2 were summarized in the result section as suggested.
Discussion:

- In the text, please make sure that references are cited in order.

Response:

References were revised and cited in order

- Some abbreviations need to be defined. For example, HR, CDC, PICU under "Opioids".

Response:

Abbreviations were defined as suggested

- The authors report a direct effect of methadone on the muscle tissue. Please provide a better description of this possible direct effect of methadone on muscles.

Response:

It is postulated that methadone may have direct effect on muscles but primarily immobilization leading to rhabdomyolysis is the cause of AKIs in methadone users. Appropriate citations were added.

- Typo under cocaine for Colombia and not Columbia.

Response:

Typo corrected

- Provide references for information on cocaine such as "cocaine seizures have increased …" and "The per gram price of cocaine surged …"
Response:

Reference provided as suggested “U.S Department of Justice, Drug Enforcement Administration. 2016 National Drug Threat Assessment Summary. 2016”