Reviewer's report

Title: The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study

Version: 3 Date: 26 August 2014

Reviewer: Judith Hahn

Reviewer's report:

I continue to believe that this is an important manuscript, and many of my comments have been addressed. Below I have included my original review and my assessment (below each comment) as to whether the issue has been sufficiently addressed.

Major compulsory revisions/concerns:

1. This paper is severely limited by how the exposures are considered.
   a. Other than crack, only injection is considered. Why not non-injection heroin, meth, or cocaine use? Benzodiazepines?
      This has been addressed, except for non-injected cocaine (other than crack). If this is not a prevalent activity (say <5%) it is ok to exclude, but do it explicitly.
   b. Also, for heroin, daily use might not be the relevant variable, given that tolerance would be high for daily use while lower tolerance from less frequent use would be a more likely biological cause of overdose. Please provide reasons for only including daily use or provide alternative measures.
      This has mostly been addressed. It would be helpful to know how “non-daily heroin injecting” was defined, and what was the comparison group. Also it would be helpful to know if this was associated with accidental mortality.
   c. Heavy episodic drinking, which is not necessarily reflected in the daily drinking variable, especially in combination with heroin use might also be an important factor but is not represented by the analyses.
      I do not see any additional alcohol use variables used. If no other variables are available, this should be noted in the limitations section.
   d. There is no attempt to examine poly-substance use. There is too little detail to determine whether data on concurrent use (e.g. speedball or goofball use, or drinking while doing other drugs? Marijuana will using other drugs?) were collected.
      Now I see that the other substance use variables were entered in the MV analysis, therefore I believe that this has been addressed.
   e. Frequency of injecting is mentioned in the discussion. Could this have been analyzed?
The authors note that this is frequency of injecting is not available. If this is really the case, this should be noted as an important limitation.

2. It is a bit odd that mortality due to HIV disease is included as an outcome; it seems like very different things are being thrown together and it makes the results hard to interpret. The authors should either remove these cases or make a strong case for their inclusion.

I think the authors may have misunderstood this comment. The response refers to covariates in the model, however the concern was about the outcome. I would consider removing the deaths due to HIV and re-analyzing, at least as a sensitivity analysis.

3. There is no description of loss to follow up – how much was there? Is there the possibility of differential loss to follow up might bias the results?

The authors have now included a description of the loss to follow up. They should discuss the possible impact of this differential follow up in their discussion section.

4. The conclusions are limited by the analyses conducted whose limitations are noted in the methods comments.

Hmm, that’s a pretty unclear sentence... Sorry. I think I wanted to say that all limitations raised in my prior questions should be discussed if they are not addressable, especially things like lack of frequency of injecting variables, etc.

5. Line 230 – a differential risk of mortality between cocaine injectors and crack smokers is mentioned but the data (mortality rates) are not given.

The authors have reminded me that the drug use variables are time varying, so rates are not readily calculated. O.K..

6. There is no mention of the implications of using drug use in the period before the death occurred, rather than right before the death. This is obviously not possible (at least by self-report) for those who died, but it does have important implications regardless and should be treated as a serious limitation.

This has been addressed.

7. The findings are less convincing given that the analysis restricted to accidental mortality did not yield the same or similar results.

This seems like it should be a limitation.

8. The note in the discussion that cocaine injectors inject much more frequently than heroin injectors is salient – and this should be reflected in the analyses (i.e. exploring not only drugs used by frequency of injecting).

Minor essential revisions:
1. The eligibility criteria with respect to drug use are not described. This has been addressed.

2. How do the results compare to studies of factors related to non-fatal overdoses? Almost 60% of the deaths are not classified. Do the authors suspect these are poorly classified overdoses? How many were cardiac arrests?

There is no discussion of the classification of the deaths in the limitations. This should be discussed.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests