Reviewer’s report

Title: Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine

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Reviewer: Bodil Monwell

Reviewer’s report:

Reviewer comments on the manuscript Polydrug abuse among maintenance treatment patients is related to inadequate dose of maintenance medicine, BMC Psychiatry, BPSY-D-17-00097.

The study described is of great interest since it is based on an extremely vulnerable and marginalized group and combines outcome data with individuals' experiences of treatment which can provide important information for improving healthcare. This is also a study of great importance because the study design is easy to replicate in other OMT programs/clinics and enable to create comparable data from, for example, different regions or countries.

Overall comments:

This study has its origins as a retrospective register-based study of 60 OMT patients. The intervention is to compare the differences in outcome between - in a previous study - two identified groups, 1) a group that reported experienced inadequate dose of OMT medicine (IA) and a group experienced adequate dose of OMT medicine (A).

1) Several references used are based on populations who mainly use heroin. Are these references applicable to the Finnish context or is it possible that it could affect hypotheses and conclusions that relate to these specific references?

2) The researchers have the great privilege to have a material from sophisticated analyses and can identify different drugs used beside the OMT-medication. It would be interesting if the researchers could mention - or discuss- some hypothesis related to illness as liver and renal impairment (HIV, hepatitis etc) and that could affect the outcome comparable to the discussion concerning pregabalin/gabapentin's impact on the plasma concentration of OMT-medication. It is mentioned in the method that the researchers have access to the somatic register data. (Page 5, line 23). Is it possible that somatic illness can be a confounder for the results of the variable (Harris, Dylan G. "Management of pain in advanced disease." British medical bulletin (2014): ldu010.; Drewes, Asbjørn M., et al. "Differences between opioids: pharmacological, experimental, clinical and economical perspectives." British journal of clinical pharmacology 75.1 (2013): 60-78.)

3) There is some confusion in the manuscript concerning the term opiates vs opioids. A more stringent use of these is desirable so that the reader does not perceive any error, for example, if
the authors relates specific to "opiates" =opium alkaloids or the entire substance group according to ICD, DSM and the ATC classification. (Page 6, line 22 - even though it is opiates in the instrument used ; Page 7, line 4 and 5; Page 13, line 13; Page 17, line 10).

Specific comments:

Page 1: I would welcome the title or profession for each researcher

Page 3:

Line 9. Is it only the opioid heroin mentioned that OMT reduces abuse of?

Line 9. Mattick et al. as a reference is kind of problematic as reference, if only heroin is referred to. This is a great reference, but in the material

Mattick et al. alternating uses the term opiates vs opioids - including a lack of stringency of defined terms/populations compared in the Meta-analyze.

Line 13. Evaluating drug or poly-drug use, beside the OMT-medication the potential substances are divided in six groups; BZD, amphetamines, opioids, cannabis, NPS and N-PPM. This is operable due to the way the results in this study is presented in Table 4.

But the substance groups per definition in some ways overlap and make me as a reader confused. In particular, if we would like to replicate the study. The name N-PPM is an open definition and in the study preferred to "Broad-spectrum polydrug abuse includes besides traditional illicit drugs also non - prescribed psychotropic medicines (N-PPM) and new psychoactive substances (NPS) [1, 7]besides traditional illicit drugs” (page3, line 11). I cannot find the criteria for this group-definition in your references, can you help me?

You mention at page 8, line 13: "The N-PPM group included those substances which can be prescribed in Finland but were not prescribed for the study patients by the attending physician at the out-patient clinic for opioid-dependent patients of Helsinki University Central Hospital. The use of N-PPM was against the written patient contract given by all the study patients. We were unaware whether the medicines were prescribed by some other physicians, whether they were diverted, or whether they were illegally imported to Finland."

My conclusion is that if you state that everything, defined as medicine in Finland, determined in the tests not prescribed by the OMT physician, i.e. out-side the contract, it logical ought to be named N-PPM. This due to that it is a non-prescribed psycho-tropic substance register as a medicine. This is in accordance with your statement that you cannot confirm if it is diverted from the health-care, doctor-shopping or traded from the regular illegal drug-scene. Most of the BZD ought to be included in the N-PPM group as well as the majority of the opioids and methylphenidate if you refer to the ATC-classification.
The NPS-group according to the UN World drug report referred to (i.e. new substances at the international drug scene, most of it not classified as drugs yet due to regulations but with identified psycho-tropic effects) is a group with a sprawling content. A lot of the specific substances in this group relate to the main groups in your study. Is it possible to in the discussion relate to this? For example, in the NPS group we can find opioids that most likely be used if the OMT-dose is reported as inadequate - in the same way that BZD and gabapentinoids can boost the effect of opioids/OMT.

The World Drug Report, referred to, uses the classification ATS-amphetamine-type stimulants. Can the UN classification be relevant discussing if this kind of substances (both in the NPS-group and for example methylphenidate presented in the N-PPM group) relate to the material?

The group N-PPM and NPS is problematic because they are not groups comparable to your drug-specific groups and can be confusing if the reader perceive conclusions regarding substance-related mechanisms based on assumptions of group level in this study.

Page 4:
Line 12. Beginning with Contrary to.. is really well formulated.

Page 6:
Line 4, you refer to "substance dependences of the patients (the DSM-IV,..)".

If cocaine were detected, would it be defined as a specific group in your study according to DSM?

Page 12:
Line 15-17. Did you evaluate the causes of drugs used related to modulation of the psycho-active effects of the OMT-medication (see below, page 13, line 12)?

Page 13:
Line 9. The gabapentinoid positive samples seems to be 16, 6% which ought to be 17% in the table.

Line 12. The OMT-programs have experienced that gabapentin/pregabalin is used due to their psycho-tropic effects and there is research available concerning this. What are your assumptions concerning this?

Page 14:
Line 8. Only 2% of urine samples were opioid-positive among Group A patients. This is only one person and I presume that it is not a methadone patient (less common to use buprenorphine
beside a full agonist as methadone is prescribed?). Can it be a buprenorphine patient with inadequate dose?

Page 15:

Line 18. See previously comment concerning the populations somatic status

I think that the authors have an interesting and unique material with potential that need a minor revision.

My conclusion is that the manuscript should be reworked due to

1) Shape a more stringent way to define opioids and how some substances could belong to other groups. This can affect both the result and the conclusion.

2) Replace a number of references based on a heroin-population (specified in the method section in respectively reference) that is not comparable with the Finnish context.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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