Author's response to reviews

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

Authors:

Pertti Heikman (pertti.heikman@helsinki.fi)
Leea Muhonen (leea.muhonen@hus.fi)
Ilkka Ojanperä (ilkka.ojanpera@helsinki.fi)

Version: 1 Date: 25 May 2017

Author’s response to reviews:

25-May -2017

Ph.D. Morten Hesse, Editor
BMC Psychiatry

Dear Editor Hesse,

Thank you for your letter (27- April - 2015) with important comments from the reviewers.

Please find enclosed our revised manuscript entitled ‘Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine’ (BPSY-D-17-00097) which we now re-submit to BMC Psychiatry. We have taken into account all the comments of the reviewers and revised the paper accordingly. We found the comments from the reviewers useful, and they certainly improved the manuscript. The amended manuscript text has been indicated by highlighting that text in bold font and the text which should be omitted is indicated by striking through. The answers to the reviewers are presented below point - by - point.

Reviewer 1: The study described is of great interest since it is based on an extremely vulnerable and marginalized group and combines outcome data with individuals’ experience of treatment which that 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).
Reviewer 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?

Our response: In Finland, the main abused opioid is buprenorphine (page 3, first paragraph). To our knowledge, there are no studies which have compared the effects of OMT between the heroin and buprenorphine dependent patients. On the other hand, most of the OMT studies do not specify the opioids abused. We cannot be sure how the studies which clearly report heroin dependence prior to the OMT are applicable to the Finnish context. Therefore, we have omitted the references No. 4, 5, and 6 which involved many heroin-dependent patients, but instead included a study involving buprenorphine-dependent patients (Piralishvili et al. 2015) which is more applicable to the Finnish context.

Reviewer 1: The researches 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 researches could mention-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 researches have access to the somatic register data. (Page 5, line 23). Is it possible that the somatic illness can be a confounder for results of the variable (Harris, Dylan G. 'Management of pain in advanced disease.' British medical bulletin (2014):1du010.;Drewes, Asbjörn., et al.'Differences between opioids:pharmacological, experimental, clinical and economic perspectives.' British journal of clinical pharmacology 75.1 (2013):60-78.)

Our response: We have included data concerning the somatic illnesses (Clinical assessments, page 7, last paragraph; Evaluation of polydrug abuse, page 10, second paragraph; Result, page 12, second paragraph; Discussion, page 15, third paragraph). Triumeq (combination of dolutegravir/abacavir/lamivudine) which was prescribed for the HIV patient may affect the methadone blood concentration, but we don’t have the methadone concentration for this patient. We also searched the data from the electronic register available to all the clinics of the Helsinki University Central Hospital concerning the prescriptions of the N-PPM group medicines. None of the N-PPM group medicines were prescribed medicines. In addition, we reanalyzed the medical files of the outpatient clinic for opioid-dependent patients regarding self-reports on abused substances. The patients had abused the N-PPM group medicines as follows (abuse vs positive urine sample): pregabalin in 5 vs 10 cases, gabapentin 1 vs 2 cases, and bupropione 1 vs 2 cases. This data has now been added to the manuscript (Methods, Evaluation of polydrug abuse, second paragraph, page 10). We also calculated the methadone blood concentrations in the gabapentinoid-positive (0.15 mg/L) and gabapentinoid-negative (0.21 mg/L) urine samples (p = 0.004). Despite the statistically significant difference, the difference might not be clinically significant because the concentrations in the both groups are within the normal limits.

Reviewer 1: 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).

Our response: We have corrected the expression concerning opiates vs opioids.

Specific comments of the reviewer 1:

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

Our response: The titles and professions of the authors are: Pertti Heikman, MD, PhD, Clinical lecturer, Leena Hillelu Muhonen, MD, PhD, Substance Abuse Psychiatry, Head of Department, and Ilkka Ojanperä, PhD, Professor of Forensic Toxicology. According to the Instructions for Authors, we have not placed them to the Title page.

Page 3: Line 9. Is it only the opioid heroin mentioned that OMT reduces abuse of?

Our response: We have changed heroin to illicit opioids.

Reviewer 1: 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.

Our response: The study by Mattick et al. (ref 2), in addition to alternating use of the terms opiates and opioids, has mainly included studies on heroin-dependent patients. Citation to this reference has now been reformulated (Page 3, first paragraph).

Reviewer 1: Line 13. Evaluating drug or poly-drug use, beside the OMT-medication the potential substances are divided in six groups; BZD, amphetamine, 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 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’ (page 3, line 11). I cannot find the criteria for this group-definition in your references, can you help me?

Our response: We agree with the reviewer that the references (1, 7) do present the widespread polydrug abuse but do not make a clear grouping of the widespread substance abuse. DSM-IV can be used as a grouping reference (see Evaluation of polydrug abuse, page 9, second paragraph). DSM-IV groups the substances into 12 classes (plus polydrug abuse) which are: alcohol, amphetamine or similarly acting sympathomimetics, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (PCP) or similarly acting arylecyclohexyl-amines, sedatives, hypnotics, and anxiolytics, polysubstance abuse, and abuse of other substances. This study now follows the DSM-IV, and consequently the NPS and N-PPM groups belong to the group of other abused substances. According to DSM-IV, methyphenidate
belongs to the amphetamine group instead of the N-PPM group of the previous manuscript and we have changed the data accordingly (Table 4). This change does not otherwise affect the results of this study because the patient with the methylphenidate-positive urine sample had also amphetamine, BZD, cannabis, gabapentin and pregabalin positive urine samples and the polydrug abuse rating was four in the first version and also in this revised version of the manuscript.

Reviewer 1: 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. The reviewers’ conclusion is that if we 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 registered as a medicine. This is 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.

Our response: In addition to our previous clarification regarding the N-PPM group, it is important to notice that all the BZD, amphetamine, cannabis and opioid group substances are controlled drugs under the narcotics legislation in Finland but the N-PPM group substances are not. The N-PPM medicines were not prescribed from physicians of the Helsinki University Hospital Clinics. The positive urine samples of prescribed medicines by the attending physician at the out-patient clinic for opioid-dependent patients of Helsinki University Central Hospital, i.e. 14 quetiapine samples and 2 oxazepam samples, were excluded from the study. The text has been changed accordingly (Page 10, second paragraph). We do not refer to the ATC-classification.

Reviewer 1: 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 opioid/OMT.

Our response: The definition of the NPS has now been added to the manuscript (Evaluation of polydrug abuse, page 9-10). Although it is a group of substances with a sprawling content, it is to our opinion well defined according to the UN. This also makes possible to follow the drug scene and its changes like e.g. we have reported on MDPV in this manuscript (Discussion, page 16, second paragraph). In addition, we have added to the Discussion the following sentence: The substance groups per definition in some way may overlap and may share similar features (Discussion, page 18, second paragraph).
Reviewer 1: 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?

Our response: We agree with the reviewer 1 that the World Drug Report is not a good reference for grouping purposes of abused substances, and consequently this study now uses the DSM-IV.

Reviewer 1: The group N-PPM and NPS is problematic because they are not groups comparable to your drug-specific group and can be confusing if the reader perceive conclusions regarding substance-related mechanisms based on assumptions of group level in this study.

Our response: We agree with the reviewer that grouping of substances can be made by different means and it is not easy. In the same way, DSM-IV reports that the following classes share similar features; alcohol shares features with the sedatives, hypnotics, and anxiolytics; and cocaine shares features with amphetamines or similarly acting sympathomimetics. Furthermore, the DSM-IV class of amphetamine includes all substances with a substituted-phenethylamine structure, such as amphetamine, dextroamphetamine, and methamphetamine, but also includes those substances that are structurally different but have amphetamine-like action, such as methylphenidate and other agents used as appetite suppressants (‘diet pills’). Our consideration has been added (The substance groups per definition in some way may overlap and may share similar features (Discussion, page 18, second paragraph).

Reviewer 1: Page 4: Line 12. Beginning with Contrary to—is really well formulated.

Our response: The sentence has been changed a little due to the changes in the narrative of the whole paragraph suggested by the reviewer 2 (Page 4, third paragraph).

Reviewer 1: 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?

Our response: Cocaine is a separate group of abused substances according to the DSM-IV (see page 9, second paragraph).

Reviewer 1: 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)?

Our response: We did not evaluate the causes of the co-abuse of BZD and amphetamines. They were speculative, and both the sentence and the reference are omitted (Page 14, second paragraph).

Reviewer 1: 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 been 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?
Our response: The percentage of the positive gabapentinoid urine samples has been corrected (page 15, third paragraph). The gabapentinoids are used also due to their psychotropic effects (added to Discussion, page 15, third paragraph).

Reviewer 1: 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?

Our response: All the buprenorphine-positive urine samples were given by the methadone patients (added to Results, page 13, first paragraph). Abuse of buprenorphine is a clear safety risk due to the withdrawal symptoms (added to Discussion, page 16, third paragraph).

Reviewer 1: Page 15: See previously comment concerning the populations somatic status.

Our response: We have added the data concerning the somatic illnesses (Clinical assessments, first paragraph, page 8; Evaluation of polydrug abuse, page 10, second paragraph; Result, page 12, second paragraph; Discussion, page 15, third paragraph).

Reviewer 1 think that the authors have an interesting and unique material with potential that need a minor revision. The reviewers 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 may not be comparable with the Finnish context.

Our response: We have defined opioids in the stringent way. We have clarified the grouping of abused substances and how some substances can belong to other groups. We have replaced the references based on the heroin-population which may not be comparable with the Finnish context as indicated above.

Reviewer 2.

General comments: This is an interesting paper examining polydrug abuse among OMT patients by using improved laboratory diagnostics. The main findings are that polydrug abuse was common among the examined group of OMT patients in Finland. This particularly applied to the group of patients who were treated with inadequate doses of OMT medication.

However, there are some concerns. All the medications detected by the LC-TOFMS method are state as abuse. However, no information is collected on the whether the medication was prescribed and how it was used. How do the authors know that (a considerable proportion) if the detected medication was not prescribed and used by the patient as part of a treatment.

Our response: The N-PPM group is now better defined (see page 8, second paragraph; page 9, second paragraph; page 10, second paragraph).
Reviewer 2: Also, one of the main objectives is to assess whether polydrug abuse is related to the adequacy of the (adequate or inadequate) of the OMT medication as experienced by the patients. However, how this division is made is not clear. It is stated in the Method section that the rating for the dose adequacy can be too low, adequate, too high, or unsure, according to the patients’ opinion. But it does not seem to be stated how this rating leads to the division: adequate or inadequate. Furthermore, if both a dose adequacy of too low and too high are defined as one group (inadequate), how is this definition clinically relevant? Patients who are treated with either too low or too high doses of OMT medication represent two entirely different set of challenges who require entirely different treatment regimens.

Our response: We have clarified the dose adequacy rating (Methods, page 6). The patients did not make the dose adequate rating but they assessed whether her or his dose of the OMT medicine does not ‘hold’ enough or does ‘hold’ enough or whether the dose is too high or if the patient cannot be sure concerning the dose of the medicine. Based on those subjective ratings, the author PH registered the dose adequacy ratings respectively, i.e. the does not ‘hold’ enough = inadequate dose, the dose ‘holds’ enough = adequate dose, the dose is too high or the patient is unsure of the dose adequacy.

Background

1. Page 4, para 2, would stand out more clear and fluent if the narrative was more general than the present discussion between specific findings of listed papers. I recommend changing the narrative in this para.

Our response: The narrative is now more general (see page 4, third paragraph).

Methods

2. All of the medication that were detected by the laboratory methods were specified as abused. However, the study does not include information on whether the medication detected by the laboratory methods was prescribed or non-prescribed. Instead, all the detected medications were specified as abused. Could the difference in detection of BZDs between group IA and group I might be explained by other causes than abuse such as (inappropriate) prescription of BZDs by MDs.

Our response: The N-PPM group is now better defined (Evaluation of polydrug abuse, pages 9-10). We have also added data concerning the abuse liability of olanzapine and venlafaxine to the Discussion (page 19, first paragraph).

3. The study included OMT-patients from a tertiary addiction clinic for OMT-patients with psychiatric/somatic co-morbidities in the capital of Finland (para 3, p5). Further, the patients all had all failed withdrawal for opioids prior admission at the clinic. Hence, the study population includes a subgroup of OMT-patients that have psychiatric/somatic comorbidities and are more hard-to-treat. Could the results have been influenced by this more than just a higher proportion
being treated with methadone (as mentioned in Limitations)? And do you have any considerations by comparing your results with the results of other studies including unselected OMT-patients?

Our response: We agree with the reviewer that the sample of patients of this study is a selected sample of comorbid opioid dependent patients. This fact has to be disclosed when the results of this study are generalized (see Discussion, page 19, second paragraph, ‘the target population’; page 19, second paragraph, ‘the psychiatric comorbidities’). On the other hand, the results of this study are comparable with the other Finnish study which included unselected OMT patients (see reference 16).

4. Regarding ethical considerations, it is not mentioned, whether and where the study has been approved.

Our response: Ethical considerations have already been indicated in the Ethics approval and consent to participate section and in the revised manuscript also in the Methods (Procedure, page 7).

Results

5. One of the main results was that craving of opioids and withdrawal were found to be associated with inadequate doses of OMT medication (para 3, p 2). However, craving of opioids and withdrawal might also be regarded as measures or indicators of inadequate doses of OMT medication. Therefore, could this association be considered a validation of your system for rating adequate doses rather than an actual result?

Our response: This point is important and it is added to the manuscript (Abstract, Background, page 2; Clinical assessments, page 7; Discussion, page 14, first paragraph; Conclusions, page 21).

6. In Table 4, the proportions in percentage seem to be missing in several places, eg. by methamphetamine, norbuprenorphine and fentanyl.

Our response: The data has been corrected in Table 4.

Discussion

7. Regarding the last sentence in page 13, para 1, it is strange that cocaine was not detected in any of the groups (para 1 p 13). But as you state this might be explained by more infrequent use of cocaine in Finland compared to many other countries.

Our response: The LC-TOFMS method of this study was capable of detecting the cocaine metabolite benzoylecgonine with reporting limit of 100 ng/mL (added to Laboratory analyses,
This fact for its part suggest that the cause of cocaine-negative urine samples is the infrequent use of cocaine in Finland (added to Discussion, page 15, second paragraph).

8. Gabapentin is a quite commonly prescribed medication in the treatment of cannabis dependence. Could the finding of this medication in group IA might reflect a medical treatment of the higher proportion of cannabis users in this group rather than gabapentin abuse?

Our response: No drug has yet been approved for the treatment of cannabis dependence because of the lack of scientific evidence (Walther L et al. Evidence-based Treatment Options in Cannabis Dependency. 2016; DOI:10.3238/arztebl.2016.0653). On the other hand, pharmacotherapy trials have been conducted as adjunctive interventions to psychosocial treatment. N-acetylcysteine and gabapentin are two of the most promising medications, although no pharmacological treatment has emerged as clearly efficacious. (Sherman BJ and McRae-Clark AL. Treatment of Cannabis Use Disorder: Current Science and Future Outlook. 2016; DOI: 10.1002/phar.1747.) The Group IA had only two positive gabapentin urine samples as compared to none in the Group A. Those two gabapentin positive-urine sample might reflect self-medication of cannabis dependence but licit medical treatment is unlikely (see Methods, page 8, first paragraph).

9. Consistency in use of key terms should be applied. The terms ‘abuse’ and ‘misuse’ (para 3, p 14. etc.) are used interchangeably.

Our response: This has been corrected (page 14, second paragraph).

10. In para 1 p 16, it is stated that: ‘In addition, the 5 number of patients was relatively small, giving rise to possible statistical type I and II errors’. How does a small number of patients give rise to a type I error?

Our response: The small sample size increases the risk of spurious findings. Although the laboratory method in this study is reliable, there might be a type 1 error in comparison between small groups of measures. Of course, the possibility of type 2 error is more likely in this study.

Regarding the Abstract, we have replaced the groups of abused substances from the Methods to the Results.

Following this revision, we hope that our manuscript is now acceptable for publication in the BMC Psychiatry.

Yours sincerely,

Pertti Heikman
Corresponding author