Title: Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: a naturalistic comparison of cognitive performance relative to healthy controls

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Author's response to reviews: see over
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Dear Editorial Team, Dear Drs Specka and Verdejo-Garcia

Thank you very much for constructive comments on our manuscript. Especially, opioid switching effect from buprenorphine abuse to methadone treatment is potentially important, and was not explicitly stated in the previous version. The same applies to common prevalence of buprenorphine abuse in our area. In the discussion section working memory deficit is now addressed first and discussed more thoroughly. Not expand our text some other parts had to be condensed. Because this is written for pharmacological journal the discussion deals mainly with pharmacological issues. The associations between cognitive performance cerebral blood flow abnormalities, and neurochemical alterations of opioid-dependent patients are of highly important, but practically terra incognita – an interesting one.

Major compulsory revisions

Revisions asked by Dr Specka

1) Rationale for testing patients in the very early stage of their treatment

The second paragraph of the introduction section now highlights the importance of early opioid-substitution treatment (OST) and relates this to patients experiences and expectations of cognitive disturbances. There are no studies concerning prevalence of experienced cognitive disturbances during the OST. The study of (Dursteler-MacFarland et al., 2006) concerning short-acting opioid heroin-substitution treatment, however, shows that at least some of these patients experience cognitive disturbances and relate them to OST drug.

2) Pronounced cognitive deficits in early OST

This issue is now addressed in the third paragraph of the introduction section. It is stated that: “...switching from opioid of abuse to different opioid for OST purposes may cause transient cognitive side-effects.” As our participants were mainly abusing buprenorphine before their treatment there may be a cognitive opioid-switching effect in methadone patients due to different pharmacological profiles of buprenorphine and methadone. This issue is further discussed in the limitations subsection.

3a) Reasons for restricting the group sizes to 17 members each

We aimed at 25 participants in each group. However, several volunteers starting OST in out-patient settings turned out positive for non-prescribed drugs or substances of abuse. We tested few of them before we were informed about their status. However, inclusion of these patients would have obscured the interpretation of the results. We first studied also few patients with zero opioid dose waiting for methadone treatment or starting OST with buprenorphine. Then the OST procedures we changed and we had to exclude these patients.
3b) What kind of population the opioid-dependent samples are from?

Our patients came from a cohort that started their opioid-abuse mainly with heroin. However, by the millennium a major shift to buprenorphine abuse occurred in our country. This is an international trend, though to smaller extent in traditional heroin route countries. United Nations or European drug monitor centre EMCDDA reports clearly show this. This information is now given in the method section.

3c) Criteria used for deciding whether a patient received methadone or buprenorphine?

In this naturalistic study the clinics decided for drugs used for single patients. Some clinics preferred mainly buprenorphine for their patients and some methadone. There is some conventional wisdom arguing for methadone use for patients with more “severe” opioid-dependence. However, our demographic data in Table 1 does not confirm the systematic use of this selection criteria in our sample. The patients groups showed were even distributions in all studied variables. It is possible that “over-representation” of patients with recent buprenorphine abuse among bup/nal group is a planned preparation for bup/nal treatment.

4) How were exclusion criteria for current uncontrolled polysubstance abuse and acute alcohol abuse assessed?

The majority of patients in both groups were studied in inpatient ward where they started their OST: 10 meth and 13 bup/nal patients. We were allowed to receive information about recent drug screens of out-patients the day before the test. If this was negative the patients were screened again the day of testing or sometimes, for practical reasons, the next day. If all these data were negative the patients test scores were entered into analyses. There were few alcohol abusing patients as well. These patients were screened by breath analyzer. All patients and controls were interviewed about recent substance abuse and this information was kept confidential. As stated in the method section the controls were randomly screened for substance abuse.

5) How many patients had to be excluded according to exclusion criteria?

In total we excluded nine buprenorphine/naloxone patients, six methadone patients and one control. The control participant and one bup/nal participant were excluded due to epilepsy, the rest were excluded due to substance abuse.

6) Is buprenorphine the main opioid of abuse currently in Finland?

This is the case Finland: Our country is probably “on top” in this matter because of well-organized trafficking. In addition, there has been significant diversion or trafficking of buprenorphine in several other countries like France, UK, India, Spain, Singapore and some parts of USA. For reasons not fully known there is an international trend towards synthetic opioids instead of heroin.

7) Could recent switch from buprenorphine have an impact on performance of the methadone group?

This might be the case, though this issue is practically unstudied. This question is now explicitly stated in the discussion (see earlier pronounced deficits section)
8) How many participants were on (more or less) stable dose?

In the clinics involved in the study methadone treatment started usually with the dose of 20 mg and within two weeks this dose was usually “stabilized” at the level of 60-80 mgs. This means that some methadone patients had not reached their stable doses. Buprenorphine treatment started with most often with the dose of 4 mg, and within first week a “stable” level of 16 - 20 was reached. This means that there was less variance in the doses in the buprenorphine group. However, it cannot be stated that the doses were in the stabilized level in bub/nal group. There were recent changes also among them.

9) Differences between groups with respect to variance in the TAP reaction times

The reduced variance in the TAP reaction times in the bup/nal group surprised as too. We have no obvious interpretation for this observation. However, buprenorphine patients have surprised in earlier studies as well, like in (Pirastu et al., 2006), in which they outperformed both methadone treated patients and controls in decision-making task. As anticipated by Dr Specka there were no outliers among bup/nal patients like in other groups.

Effects sizes in attention tasks

We are now more precise in relating specific findings to attention. In the method section we refer to key articles concerning the tasks used and their relationship to attention components conceptualized by Posner et al. (2006) and Sturm et al. (1999). In the discussion section we now point out the variance of effects sizes in attention tests found in methadone maintenance patients as reviewed by Specka et al. (2000).

Revisions asked by Dr Specka

Major compulsory revisions

1) The correlations between education and verbal IQ and the different performance measures

As expected, there is mild to moderate positive correlation (.34) in total sample between years of education and verbal IQ. In patients this correlation is, however smaller than in controls (.19 vs. .41). Thus, the association between VIQ and education is different in patients and controls. Inspection of total sample correlations VIQ and all cognitive performances can be expected to yield few statistically significant correlations – if corrections for multiple testing are not used. In fact there was one positive correlation between VIQ and cognitive performance: .35 in delayed recall of the Logical Memory test. After controlling for multiple comparisons this correlation was no longer statistically significant. Between education and cognitive variables there were more positive correlations: .51 in the first trial of the MPD (verbal learning task), .40 in the PASAT, .34 in the immediate recall of the LM, and -33 in the go/nogo time. After controlling for multiple correlations the first correlation was still statistically significant. These correlations were smaller when combined patients were analyzed and reduced to nearly zero or negative among controls. Anyhow, it is possible that differences in education could still explain cognitive performance within patient
groups after controlling for other demographic and substance abuse variables. However, to do such an analysis well we would need more patients in order to run regression or multilevel analysis.

2) Is buprenorphine abuse common pattern of use in the populations studied?

Yes, that is so. Please, see answer 6 given to Dr Speck’s question. The slowly rising trend of buprenorphine abuse started already in the 80’s. International induction of Buprenorphine/Naloxone may eventually reduce the abuse of buprenorphine.

3) Differences between methadone and buprenorphine dose?

Methadone is full agonist for mu opioid receptor while buprenorphine is “only” partial agonist for the same receptor. However, only buprenorphine nearly completely actually blocks opioid receptors for heroin effects at high doses as shown by (Greenwald et al., 2003). The pharmacological basis of methadone efficacy in mu opioid receptor is different, but still poorly known. Clinically it is known that buprenorphine dose of 12 – 16 mg is close to dose 60 – 80 of methadone (Law et al., 2004). Against this background it looks likely that our methadone patients may have had clinically less efficient OST drug than bup/nal patients. However, these approximations are valid only patients with recent heroin abuse. Because our patients had mainly abused buprenorphine, we think comparison of doses would be too speculative.

4) Stage of substitution treatment and non-stable dose of methadone

As a continuation for previous question it can be said that the induction period of methadone treatment usually takes longer time to reach stable dose than buprenorphine treatment. Against this background, it is possible that methadone patients were in disadvantageous position in this respect. This possibility is now addressed as we state: …” Thus, the possible opioid switching effect in methadone treated patients during early OST cannot be ruled out. In order to investigate this issue we are currently working on a follow-up study with same patients. “

5) Rationale for modification of Memory for Persons Data

This task combines verbal person data with a photograph of this fictitious person. The task was modified by making it shorter and, if necessary, giving the participant extra trial to reach learning criterion. Modifications were done in order to study short- and long-term memory consolidation. (At the end of the session, and again after 6 months of the OST the photographs were shown again and the participants was asked to recall items from that person). Practically all participants show excellent effort in this task, even when they encounter difficulties in learning. Many of them recall this data also later on. Thus, it seems the task has good face validity. This task is developed by Dr Kalska, who is senior neuropsychology member in our group. Unfortunately there is no published data about validity and reliability of that task. Unpublished data shows reasonable reliability for the test.

6) Detailed summary of main novel contributions

The first paragraph of the discussion is now more detailed.
Minor revisions

7) Could differential impact of methadone and buprenorphine on tonic and phasic alertness be related to different neurochemical profiles of the two drugs?

This might be the case. However, as stated in our discussion, benzodiazepine comedication may affect differently between these drugs. We will address this question later on with larger sample of long-term treated patients. We will analyze those results with more sophisticated statistical tools.

8) How to interpret sign > on Table 3.

At first glance this is tricky, because in reaction times > means longer reaction times and inferior performance instead of superior. However, in note we defined > to mean superior than, and used the sign consequently. To make the table 3 easier for the reader we changed the signs in reactions times, and added to the column header words “showing better performance first”.

With best regards

Pekka Rapeli & research group

References


