Reviewer's report

Title: Opioid substitution therapy trials exclude the common addiction patient: a systematic review and analysis of eligibility criteria

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Reviewer: Richard P Mattick

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Referee comments: Manuscript details “Opioid substitution therapy trials exclude the common addiction patient: a systematic review and analysis of eligibility criteria”

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Summary of paper: This is an interesting review of the eligibility criteria used in RCTs of treatments for opioid dependence, assessing those criteria and applying them to a specific and single clinical sample to determine the extent to which they would exclude patients. The authors then go on to comment on the impacts of exclusion on the external validity/ecological validity/generalisability of the RCT results to the population of opioid dependent patients. The review also then checks guidelines for treatment from three jurisdictions and asserts that guidelines do not consider the limitations identified in the review when making recommendations. The question posed is new and well-defined, and the novelty fits with CONSORT criteria concerns that we document and understand the relation between the sample studied and the population of patients that were considered for a trial.

Pluses are that a protocol is registered. PRISMA guidelines were used (please add search strategy as supplementary material). The paper is reasonably clearly written and organised.

To use my four criteria:

It is new.

It may not be true, but … see below.

It is comprehensible (but more fully explain the kappa stat for the lay reader).

And it is potentially interesting.

My concerns relate to the representativeness of the GENOA participants, and the likelihood that they are quite different from the opioid users at large, and the failure to address the likely use of exclusion criteria, plus a failure to include sensitivity analyses changing the rates to see the impacts. I elaborate below.
Problems: Better articulation of the representativeness of the GENOA sample is warranted – it is in fact an in treatment sample, that is likely to have higher levels of comorbidity than those earlier in their drug use careers, or those opioid dependent users that do not seek treatment as they have not developed the range of problems that often coerce or force individuals into treatment, or those who drop out of treatment. I was not satisfied or at all convinced that the assurance that the clinical characteristics of GENOA patients were “consistent with those reported in previous population based studies” (plural in original page 8 second line) is enough to allow for the sole use of this comparison group. This issue has marked implications for the paper overall.

I note that the GENOA sample is described in a paper entitled "Genetic influence on methadone treatment outcomes in patients undergoing methadone maintenance treatment for opioid addiction: a pilot study" by Samaan (ref 45), which states that “The study included a cohort of individuals on MMT, recruited sequentially from OATC clinics. … [and that] patients with opioid dependency receiving MMT were enrolled, consisting of men and women, age #18 years who are able to provide written informed consent. The exclusion criteria were English language barriers and refusal to provide urine samples”. There are a number of potential problems with this sample.

How is the OATC representative of the rest of Canada, and of the world opioid users?

How many of the GENOA sample cohort did participate in the study – i.e. declined to participate? How many dropouts occurred in the OATC sample before the GENOA recruitment? What were the characteristics of these dropouts? Were they healthier, younger, and earlier in their career?

What is the effect of ignoring BMT patients in the GENOA sample – they were three but they were excluded, and clearly the sample is a MMT sample not a sample of all opioid dependent patients. What is the effect of ignoring those entering heroin MT (HMT) or entering antagonist therapy?

The GENOA participants had a very low rate of offending, and this seems unrepresentative of opioid users internationally.

While the authors assure the reader of representativeness of the GENOA sample by reference to “studies" (plural in text), in fact the sole reference to Baumeister (2014 – ref 47) is not of a population of opioid users, but in fact is a “study [which] included 613 methadone patients between April 1, 2003 and March 31, 2004” completed by “methadone prescribers who were invited until 2004 to provide anonymized patient and treatment data to the register every 12 months by means of a 2-page questionnaire. Methadone prescribers were instructed to carry out the interviews within one month and send them back to the health authorities". Thus, there are several issues.

First the population sample that GENOA patients are compared with is a treatment sample, not a population sample of opioid users.

Second the Basel sample is a single sample, and there is no evidence that this sample is similar to those elsewhere in Switzerland, Europe, or other developed
or undeveloped regions (the patients were in MMT and not necessarily the same as those in buprenorphine or antagonist treatment, or those not in treatment). Surprisingly, no data are mentioned by the authors of the inclusion/exclusion criteria used in the Basel study.

Third, that Basel sample is from 2004, and may not be representative across time in that city.

Fourth, dropout of more functional patients may have occurred in that Basel sample, and there is no assurance that the “population” is at all similar to those who are out of treatment and opioid dependent.

The exclusion criteria used in trials to date are likely being misused here. The cut-offs for clinical trials may be quite different than those used in GENOA.

Psychiatric comorbidity can vary from obvious psychotic disorders to any anxiety or depressive disorder. Depending on the thoroughness of the trial investigators and indeed the thoroughness of the clinicians using the GENOA MINI administration, differing rates of psychiatric problems will be identified and this will compromise the authors aim.

Similarly physical problems can be assessed in quite varying ways, and the assumption that the trials are all assessing similarly, and that the GENOA assessment is the standard used in the trials are both likely to be untrue.

Patients in RCTs may be using psychotropic medications, but not admit to such use at screening, whereas the OATC patients will be better described as they have presumably been in treatment for some period. What is the implication of this for the conclusions?

Minor issues:

- Explain kappa stat better for the lay/non-statistical/unfamiliar reader.
- Remove most of para 1 page 4 – we know all of that and it does not add.
- Discuss the eligibility criteria in more detail – especially focusing on the criteria that vary across studies – e.g. how psychiatric morbidity is assessed and which disorders are excluded, and how physical problems are assessed and what is actually excluded.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.

However, I am a Cochrane reviewer on RCTs of MMT and BMT.
I have received untied educational grants from ReckittBenckiser for post market surveillance of burprnorphine reporting findings in peer reviewed journals.