Author's response to reviews

Title: A 20-year prospective study on mortality and causes of death among hospitalized opioid addicts in Oslo

Authors:

Mari A Bjornaas (mabjornaas@gmail.com)
Anette S Bekken (asbekken@yahoo.no)
Aasa Ojlert (vaniljsemla@hotmail.com)
Tor Haldorsen (tor.haldorsen@kreftrегистret.no)
Dag Jacobsen (daja@uus.no)
Morten Rostrup (moro@uus.no)
Oivind Ekeberg (oivind.ekeberg@uus.no)

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Author's response to reviews: see over
Dear Sir,

Revised manuscript by Mari Asphjell Bjørnaas, Anette Skei Bekken, Aasa Ojlert, Dag Jacobsen, Tor Haldorsen and Oivind Ekeberg: A 20-year prospective study on mortality and causes of death among hospitalized opioid addicts in Oslo (MS: 1244858977146148).

Thank you for your letter of August 4th, 2007, with comments from the three reviewers. We would like to thank the reviewers for pointing out important aspects of the methods section that needed clarification, and raising important questions to the discussion of the findings of the study.

Enclosed, please find our revised manuscript. Our responses to the comments from the reviewers are outlined below. Changes in the manuscript are outlined in italics.

We have tried to address all the issues raised by the reviewers, and hope that our manuscript is now acceptable for a new consideration for publication in BMC Psychiatry.

Yours sincerely,

Mari Asphjell Bjørnaas, MD
Department of Behavioral Sciences in Medicine
University of Oslo, P.O.Box 1111 Bindern
NO-0317 Oslo
Norway

Oivind Ekeberg, MD, PhD, Prof.
Department of Acute Medicine
Ullevaal University Hospital
NO-0407 Oslo
Norway

Correspondence:
Mari Asphjell Bjørnaas
Department of Behavioral Sciences in Medicine,
University of Oslo
P.O.Box 1111 Bindern
NO-0317 Oslo
Norway
E-mail: mabjornaas@gmail.com
Comments to reviewers’ responses

Reviewer 1 (Nordentoft)

Minor essential revisions:

**Abstract:** We have included the cause-specific SMRs as suggested.

**Background:** We have removed the details regarding differences in mortality rates in other studies to the discussion section (page 10), as suggested, and we have therefore modified the first paragraph of the background section.

**Results:** We have removed table 6, see also comments from reviewer 3.

**Discussion:** We thank the reviewer for pointing out that our results regarding gender difference corresponds to the results in the study by Hwang et al. We have included this reference at page 11 in the discussion.

Reviewer 2 (Oyefeso)

**General**
We have tried to correct the typographical errors. We had a native English speaking colleague to revise the manuscript, but will be happy to do so again if the editor insists.

**Major compulsory revisions:**

1. **Diagnostic criteria:**

The inclusion in the cohort was based on the classification of opioid dependence/addiction, which may differ from drugs used at the actual poisoning episode. Here, the classification was based upon patient interviews and records. The basic criteria were information of daily or regular use of the respective compound, including withdrawal symptoms if the compounds were not administered [1]. There was no clear distinction between abuse and dependence. Toxicological tests were not used, because of the possible bias of including prescribed medications or incidental misuse not reflecting abuse/dependence of the compound. We have included more about the inclusion criteria at page 5. Due to the short duration of stay for uncomplicated acute poisonings, the opportunity for a more accurate psychiatric screening was limited. There was no clear distinction made between opioid dependence and abuse. As for polydrug abuse, the most prominent compound was chosen. The categories were ethanol abuse, opioid abuse, abuse of other sedatives, and other substance abuse. The evaluation was based on all available information, including patient history, clinical signs and symptoms, information from companions, previous case records or information from the patient’s GP. ICD-8 was the basis for the classification, but was not used systematically.

All patients voluntarily admitted for detoxification had a history of long-standing and serious opioid addiction.

To differentiate between acute overdose on opioids and acute overdose due to polydrug consumption, a clinical evaluation of the most toxic compound was done by the physician...
treating the patient [1]. However, the inclusion in the cohort was based on the classification of opioid addiction/dependence, as mentioned above, which might differ from substances used at the actual poisoning episode.

2. We agree with the reviewer that there is a clear distinction between treatment for acute drug overdose and opioid detoxification. Those who were once admitted for self-poisoning and at another time for detoxification were classified as voluntarily detoxifications in the further mortality analyses, as a marker of their willingness to undergo further treatment and rehabilitation. We are however fully aware of the differences between the treatments. The sentence mentioned by the reviewer was unclear, and we have changed it in order to clarify this point.

3. Description of the detoxification regime offered in Ullevaal University Hospital: The treatment facilities for opioid addicts in 1980 in Oslo were rather poor. Therefore, the Department of Acute Medicine at Ullevaal University Hospital (previously Medical Department 7) from 1980 on accepted the responsibility to treat up to three opioid addicts simultaneously that were in need of detoxification, either before further treatment in drug addict units, or due to general poor health, see page 5. Ullevaal University Hospital served the whole city regarding this function. The patients were admitted voluntarily. Before admittance they were interviewed, to agree on the rules of the ward, and they were informed that no opioids or benzodiazepines would be prescribed. Their health contact person was usually present. Patients could admit themselves or be admitted by their GPs. In 1980, no substitute medication such as methadone was used in Norway. The treatment was symptomatic. The treatment was in many cases completed in other facilities, and we therefore do not know enough about the completion of the treatment. Since 1980, the routines for detoxification have changed dramatically, and we have therefore not included more details about the detoxification programme in the manuscript as this would be space consuming. We would however include this if the editor insists.

Minor Essential Revisions:

1. The subheadings are changed as suggested.

2. The sentence has been corrected.

3. We agree that it is also possible that patients treated for self-poisonings also later sought detoxification during the period of study. We have, however, only information about the admissions for voluntary detoxification during 1980-81. To evaluate the influence of repeated treatment on mortality, we used subgroups in our analyses. However, the groups were then too small to reveal any statistically significant differences, Pearson’s Chi square p=0.24. There might still be a difference between these subgroups (type II error), and this may be further investigated in larger studies. We have now included this point in the discussion, page 14.

Subgroups among the patients:
<table>
<thead>
<tr>
<th>Status of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total alive</td>
</tr>
<tr>
<td>Total dead</td>
</tr>
<tr>
<td>Total emigrated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status of Patients</th>
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</thead>
<tbody>
<tr>
<td>Total alive</td>
</tr>
<tr>
<td>Total dead</td>
</tr>
<tr>
<td>Total emigrated</td>
</tr>
</tbody>
</table>

| Total alive       | 110      | 70 | 185 |
| Total dead        | 11       | 0 | 17 |
| Total emigrated   | 5        | 0 | 5 |

4. We agree with the reviewer that the use of the term “violent deaths” has not been specific enough in this paper. We have now used the term “other violent deaths” consistently. This group included violent deaths except suicides and accidents, since these were outlined in separate categories. This classification was in consistence with the categories used by Statistics Norway, and enabled us to compare our study population with the general population. We have clarified the use of these terms at page 6. A table outlining the categories used are listed below.

Classification according to the ICD system:

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>001-989</td>
<td>001-E989</td>
<td>A00-Y89</td>
</tr>
<tr>
<td>All diseases</td>
<td>001-796</td>
<td>001-799</td>
<td>A00-R99</td>
</tr>
<tr>
<td>Cancer</td>
<td>140-209</td>
<td>140-208</td>
<td>C00-C97</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>390-441.1</td>
<td>390-459</td>
<td>I00-I99</td>
</tr>
<tr>
<td></td>
<td>444.3-458</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>782.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidents</td>
<td>E800-E929</td>
<td>E800-E929</td>
<td>V01-X59</td>
</tr>
<tr>
<td></td>
<td>E940-E942</td>
<td></td>
<td>Y85-Y86</td>
</tr>
<tr>
<td>Suicides</td>
<td>E950-E959</td>
<td>E950-E959</td>
<td>X60-X84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y87.0</td>
</tr>
<tr>
<td>Other violent deaths</td>
<td>E930-939</td>
<td>E930-958</td>
<td>Y88-89</td>
</tr>
<tr>
<td></td>
<td>E960-989</td>
<td>E960-989</td>
<td></td>
</tr>
</tbody>
</table>

Discretionary Revisions:
We have used the term mortality rates just to simplify the use of terms, but will be happy to change to “crude mortality rates” if the editor insists. We have reported on the median age-at-death at page 8, as suggested, and thank the reviewer for pointing out the usefulness of these data.
Reviewer 3 (Juel)

Minor essential revisions:

Drug dependence vs. other diseases: This is a very good point, and we agree with the reviewer. We wanted to divide the category “other diseases” into more specific groups, but Statistics Norway does not have specific reference categories for drug dependence or drug-related deaths as part of the general mortality data. The classification of drug-related deaths is problematic in the ICD-system, and is applied differently in different countries. The European Monitoring Centre for Drugs and Drug Addiction has developed the term “drug-related deaths” and is currently developing and coordinating the criteria, but this term is also used somewhat different between countries. Using this term would have meant using a supplement to the ICD system which is not completed nor used for general mortality data. We therefore chose to use the same categories as Statistics Norway, which enabled us to compare our study population with the general population using the same and well-known criteria. There is little doubt that more opioid addicts die of drug dependence than those who are not addicts, i.e. the general population, but another interesting question may be: do they die earlier than expected because of this? We have tried to address this last question in the present study. We have included more about the problems of classification at page 13.

SMR: We have now used the term “standardized mortality ratios” consistent, as suggested.

Study population vs general population: The study population is from Oslo and the mortality rates are from Norway, and this may affect the SMRs. This is a good point, and we thank the reviewer for pointing it out. The expected duration of life in Oslo is lower than the average duration of life in Norway. However, the difference is less than one year. Oslo does not have the highest mortality rate in Norway (which is found in Finnmark county), nor the lowest. However, heavy drug addicts are probably coming from all over the country to Oslo because of the availability of drugs and the anonymity the city offers. This will support the finding that mortality rates in Oslo are somewhat increased compared to the rest of the country. Our SMRs may therefore be considered somewhat high, but the difference between Oslo and the average expected duration of life is probably so small that it does not affect the major findings of the study. We have included these considerations in the discussion section, page 12.

Inconsistence in the reference to tables: All tables are now mentioned in the text.
Methods: the same classification is used for the study population as for the general population, and we have added this at page 6.

Four patients had no specific cause of death, and we have corrected the figures in the Methods section.

Ethics: The sentence was very unclear, as pointed out by the reviewer. We have changed the sentence, and hopefully clarified this point.

Shortening of the results section: The results section has been shortened, deleting some phrases duplicating results from the tables. However, some of the figures will be found in both the tables and the result section, in order to allow the result section and tables to be read independently.

Deleted sentences:
- Page 8: In the last five year period, the SMR was 13.4 (95% CI, 7.6-23.7).
- Page 8: For self-poisonings, the SMR was 28.8 (95% CI, 16.3-50.7) in the first 5-year period versus 12.1 (95% CI, 5.4-24.0) in the last period. For voluntary detoxifications, the decrease in SMR was from 38.0 (9 % CI 20.5-70.7) in the first period to 15.1 (95% CI, 6.8-33.7) in the last period.
- Page 9: The SMR for other violent deaths was 28.6 (95% CI, 7.1-114.4).

Page 8, line 14: The sentence is corrected as suggested.

Page 9, line 13: The sentence is corrected as suggested.

Main and additional causes of death: We would prefer to use the words “main” and “additional” cause of death, as these are used in a previous study of the total cohort of self-poisonings, see reference 22. We would however change to “underlying” and “contributory” if the editor insists.

Page 10, line 19: This is a very good point. However, age differences were not investigated because of the homogeneity of the material. The majority of the patients were between 20-29 years (n=133, 72%), which made the sub-classification of patients into age groups less meaningful. A misprint in the discussion section regarding age differences has been corrected.

Page 11: The SMR decreased by time period, and we agree with the reviewer that this could partly be caused by the increased level of mortality in the general population by time period. Therefore, the SMR will over time become close to one since all patients die if the follow-up period is long enough. We have added this perspective, page 11.

General vs. background population: We have made the use of the term “general population” consistent, as suggested.

Page 12, line 6: The sentence is corrected as suggested.

Table 3: we have written deaths instead of n, and dropped n=93 etc.

Table 4: the sum of the rows now equals the total.

Table 5: B20.1 is now corrected.
Table 6: Table 6 has been removed, see also reviewer 1.

Reference List