Author's response to reviews

Title: Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study

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Author's response to reviews: see over
Dear Ms. Norton,

Thank you very much for the reviewers’ comments, which we have answered below and incorporated into the manuscript “Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study”.

The manuscript has been revised in accordance with the suggestions from the reviewers. The suggestion by reviewer Mr. T. Schalekamp to perform a sensitivity analysis on our definition of current SSRI users has had important consequences. In particular, we saw that SSRI users within 30 days of breast cancer surgery had increased risk of re-operation (from about 2.6% among never users to about 7% among these current users). Former users (women with prescriptions 31 days or more before breast cancer surgery) had a risk of re-operation equivalent to never users (2.7%). This analysis suggests that our original definition of current users (within 90 days of surgery) misclassified many former users as current users and biased the association to the null. We are grateful for the reviewer’s suggestion and believe this revision more clearly depicts the association between SSRI use and risk of reoperation.

We were concerned that this major change to the manuscript would require withdrawing the original submission and resubmitting from stage zero. However, in correspondence with associate editor Alam, we agreed to submit a revision with answers to the reviews.
The editor also asked about ethics board review of the study protocol. Studies based on registry data do not require formal ethical approval under the Danish law. However, handling of data was approved by the Danish Data-protection Agency. This information has been incorporated into the manuscript.

We appreciate the opportunity to submit this revision and look forward to your reply. Please do not hesitate to contact me if you have any further questions or requirements regarding the revised manuscript.

Yours sincerely,
Henrik Toft Sørensen
Corresponding/submitting author
Answer to Reviewer Antonio González-Pérez' report

Reviewer’s report:

This is an interesting and well conducted study aimed at exploring the clinical implications of known SSRI-induced effects on human platelet function on the risk of re-operation due to post-surgical bleeding in breast cancer patients. The increasing use of these drugs in this population makes even more relevant these results. The authors used a Danish Database that has been extensively used in pharmacoepidemiological research. The validity of the exposure ascertainment is expected to be quite good considering both the data source and the fact that anti-depressants are only available through medical prescription in Denmark. According to the authors, the registration of re-operation due to surgical bleeding in the Danish Registry is virtually complete, although a specific validation study (maybe based on a small subset of patients) would have been helpful since this particular endpoint does not seem to have been previously validated.

Agree – This was, however, not performed. Denmark has a long register tradition and the Danish National Registry of Patients, which is managed by the Danish National health board, has existed for more than 25 years and is regularly validated through focused quality projects. An extra reference has been added to the manuscript.

Overall the study is well conducted and analysed. However I do have one small but major comment to make: As in any negative study the statistical power needs to be assessed and considered when interpreting the study results. It does not seem sufficient to say that confidence intervals are narrow. Even though the size of the study cohort is extremely large (more than 14,000 breast cancer patients) they are studying a rare event and the total number of cases is less than 400. Under these circumstances the study is probably underpowered to detect modest effects. If true this should be acknowledged in the paper. Furthermore the authors should include the results of the power analysis and discuss the magnitude of effects (in terms of RR or RD) that can be safely excluded based on their results.

This study included all breast cancer patients diagnosed in Denmark between 1996 and 2007, the time period during which the prescription registries and outcome data were available for analysis. Sample size is therefore determined by this practical limitation, not by a sample size or power calculation, and the sample size cannot presently be increased. In addition, the statistically significant non-null association we now report for current users reduces the relevance of the reviewer’s concern about inadequate power. Nonetheless, to be complete, we offer the following power calculation. There were 389 reoperations performed out of a total of 14853 patients giving a risk of about 0.03. There were 51 patients who had a reoperation and who had ever used SSRI and 1592 who had no reoperation and who used SSRI (1643 SSRI users) and 12,872 who never used SSRI, giving an unexposed to exposed ratio of 7.83. The risk of reoperation in women who were not exposed to SSRI was 0.026 (338/12872). The study had 80% power to detect a relative risk of 1.48; and 90% power to detect a relative risk of 1.57. Our study therefore was sufficiently powered to detect modest associations between SSRI use and re-operation due to surgical bleeding.
Answers to reviewer T Schalekamp's report

Reviewer's report:

Gärtner et al. present an interesting study on the effect of SSRIs of bleeding risk after surgery in breast cancer patients. Since there are many controversies about the bleeding risk of SSRIs in different settings, the findings of this paper are interesting and of clinical relevance. The paper is well written, but needs some clarification on several points.

Major compulsive revisions:
1 I did not quite understand the statement in the Introduction about intraoperative and postoperative bleeding. I understand that intraoperative bleeding is very rare (could the authors add a reference for this statement?). But what do the authors mean with ‘Significant postoperative bleeding’? Does it occur frequently in patients after surgery or do the authors mean that postoperative bleeding is also a rare event, but if occurring, frequently resulting in re-operation? Please, clarify.
   Agree – the section has been rewritten. To our knowledge unfortunately no data on Intra-operative bleeding after surgery for breast cancer has been published.
   Although the results of this study indicate a low risk of re-operation, it would be interesting to know what is already known about this subject.
   Agree – Only one study to our knowledge has reported on risk of re-operation. The Incidence of risk of re-operation reported in this study has been added to the Introduction to indicate the magnitude of the risk.

2 Considering the above-mentioned point, I would suggest to add a power calculation. What was the power to find a meaningful difference in reoperation due to SSRI use in this cohort?
   See response to Reviewer 1.

3 In the Discussion the authors rightly state that misclassification of current use or former use could have been a problem. Did they consider any sensitivity analysis, varying the definition of current use of SSRIs? They defined current anti-depressant use as a receipt of a prescription of an SSRI within 90 days before hospital admission, but they could also reanalyze their results if only prescription within 60 or 30 days before admission are considered. I would suggest to add such a sensitivity analysis and, if this is not possible, to mention the absence of a sensitivity analysis in the Discussion section as a limitation.
   As suggested we performed a sensitivity analysis, which showed that a prescription within 30 days was significantly associated with an increased risk of re-operation due to post-surgical bleeding. See the adjusted conclusion and the changes in the methods, results and discussion section.

Minor essential revisions
1 Is there any reference for choosing a time-window of 14 days after surgery for re-operation?
   Based on our clinical experience, re-operation due to postoperative bleeding is in most cases performed within 24 hours. We have no references for choosing a time-window of 14 days. The window was chosen to make sure that we did not miss any re-operations due to postoperative bleeding.

2 What is exactly meant by ‘SSRI use is ever more prevalent’ in the Introduction?
   The sentence has been re-phrased.
   Could the authors indicate to what extent SSRI use has been increased during the last
decade?
    The Information has been added to the Introduction.

3 In the paragraph about potential confounders: what are oral anticoagulants next to platelet inhibitors and vitamin K antagonists?
    The best method to group these medications is a matter of debate. The exact ATC codes for the prescriptions we termed "oral anti-coagulants" can be found in the appendix. For example, B01AB05 is enoxaparin, a low-molecular weight heparin.