PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper underwent another round of review and revision at BMJ Open before being accepted for publication.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antidopaminergic drugs and acute pancreatitis – a population based study
AUTHORS	Robert Bodén, Tomas S Bexelius, Fredrik Mattsson Jesper Lagergren, Mats Lindblad and Rickard Ljung

VERSION 1 – REVIEW FOR THE BMJ

REVIEWER	Christoph Correll, The Zucker Hillside Hospital, Psychiatry Research

GENERAL COMMENTS	This is a Swedish register study assessing the relationship between antidopaminergic agents and pancreatitis in a large total sample, finding no significant associations after adjustment for relevant covariates. The study uses straight forward methodology and analyses. The manuscript is very well written and accessible, the limitations are well described. Further strengths include the large and complete overall data base and careful adjustment of the analyses using known risk factors for pancreatitis as relevant covariates. Overall, I believe that the topic and the "negative" finding are of potential interest and relevance. However, a number of issues reduce the enthusiasm for this manuscript in its current form, which should be addressed in a major revision: Main Issues: 1. The actual number of pancreatitis cases on current antipsychotic and of antiemetic/anxiolytic treatment is still quite small (n=108 and n=36), with even less patients being in the recent (n=14 and n=10), past (n=21 and n=13) and former (n=51 and n=19) "antipsychotic" use groups. This calls into question whether the study had sufficient power, especially when starting to adjust for this many (relevant) covariates. Thus, I strongly believe that this study can only be useful if the N is increased. The authors should add the data from years 2009 and 2010, which should double their number of cases (and controls) to eliminate the possibility of a type II error in the presented results. 2. The second main problem besides the small N of cases includes the occurrence of pancreatitis during hospitalization for which no medication treatment data seem to be available in the Swedish registry (as indicated in the discussion section). This was not clearly noted in the methods section (see #4). 3. The authors did not analyze all antidopaminergics together as a secondary analysis, providing additional power, and they did not analyze separately the risk for phenothiazines and low potency,

	which have been implicated with a higher risk for pancreatitis in one prior epidemiological data set each (see also #6). Again, to conduct these meaningful and relevant analyses, more data are needed from additional years of observation (see #1). Additional points are outlined below: General comment: 4. Please use the term dopamine blocking medications or antidopaminergics instead of “antipsychotics” if you refer to all D2 blockers that include antiemetics and anxiolytics, which are not “antipsychotics”. Abstract: 5. Accordingly, please revise “Antipsychotics were grouped into antiemetics/anxiolytics and other antipsychotics” to something like “Antidopaminergic agents were grouped into antiemetics/anxiolytics and antipsychotics”. (Also: data are plural). 6. Please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group. Methods: 7. It is unclear whether pts with pancreatitis during hospitalization for which no antipsychotic prescription data are available were treated. Were they excluded? How many such cases were there in relationship to the analyzed outpatient cases? Were the inpatient cases counted as ”unexposed”, as alluded to in the discussion?! This would be a serious problem/confound. 8. Why were no formal analyses of a dose relationship conducted/presented using DDDs? The lack of a dose response relationship is alluded to in the discussion. DDDs should be available in the prescription data base. 9. The analyses should also be conducted combining all antidopaminergic agents together and – for comparison sake with the study by Gasse et al (Pharmacotherapy 2008) also separately for low potency, medium potency and high potency FGAs, as well as SGAs. Results: 10. In the text, please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group that the analyses and results are each based on. 11. Table 1: Please specify the N per each antipsychotic and class.

The article received a second review at the BMJ but the reviewer did not give permission for their comments to be published. However, their comments, as well as the authors' response to them, were taken into account by the editor of BMJ Open.

VERSION 1 – AUTHOR RESPONSE

Comments:
This is a Swedish register study assessing the relationship between antidopaminergic agents and pancreatitis in a large total sample, finding no significant associations after adjustment for relevant covariates.

The study uses straight forward methodology and analyses. The manuscript is very well written and

accessible, the limitations are well described. Further strengths include the large and complete overall data base and careful adjustment of the analyses using known risk factors for pancreatitis as relevant covariates.

Overall, I believe that the topic and the "negative" finding are of potential interest and relevance. However, a number of issues reduce the enthusiasm for this manuscript in its current form, which should be addressed in a major revision:

Main Issues:

1. The actual number of pancreatitis cases on current antipsychotic and of antiemetic/anxiolytic treatment is still quite small (n=108 and n=36), with even less patients being in the recent (n=14 and n=10), past (n=21 and n=13) and former (n=51 and n=19) "antipsychotic" use groups. This calls into question whether the study had sufficient power, especially when starting to adjust for this many (relevant) covariates. Thus, I strongly believe that this study can only be useful if the N is increased. The authors should add the data from years 2009 and 2010, which should double their number of cases (and controls) to eliminate the possibility of a type II error in the presented results.

-We agree that adding additional years (2009 and 2010) to foremost increase the number of exposed cases among recent and past users could be valuable. Though, at present we have no possibility to do this. However, we plan to initiate an updated data application also including year 2011, but this cannot be possible until then end of 2012. Despite the possible low power for recent and past users we feel that the findings regarding present users are valid and of great interest and should thus be published as soon as possible. Regarding number of potential confounders in the model we find no extreme difference in the estimates when adding additional covariates. However, we agree that the "fully" adjusted model could be presented with only adding number of concomitant drugs, as this variable seems to be a good proxy for co-morbidity.

2. The second main problem besides the small N of cases includes the occurrence of pancreatitis during hospitalization for which no medication treatment data seem to be available in the Swedish registry (as indicated in the discussion section). This was not clearly noted in the methods section (see #4).

-This has been added to the last sentence in the paragraph "Sources of data" in the Methods section.

3. The authors did not analyze all antidopaminergics together as a secondary analysis, providing additional power, and they did not analyze separately the risk for phenothiazines and low potency, which have been implicated with a higher risk for pancreatitis in one prior epidemiological data set each (see also #6). Again, to conduct these meaningful and relevant analyses, more data are needed from additional years of observation (see #1).

-These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table.

Additional points are outlined below:

General comment:

4. Please use the term dopamine blocking medications or antidopaminergics instead of "antipsychotics" if you refer to all D2 blockers that include antiemetics and anxiolytics, which are not "antipsychotics".

-Great idea to increase clarity! This has been changed throughout the manuscript.

Abstract:

5. Accordingly, please revise "Antipsychotics were grouped into antiemetics/anxiolytics and other

antipsychotics" to something like "Antidopaminergic agents were grouped into antiemetics/anxiolytics and antipsychotics". (Also: data are plural).
-This has been changed accordingly.

6. Please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group.
-Theses numbers are given in table 1.
Methods:
7. It is unclear whether pts with pancreatitis during hospitalization for which no antipsychotic prescription data are available were treated. Were they excluded? How many such cases were there in relationship to the analyzed outpatient cases? Were the inpatient cases counted as "unexposed", as alluded to in the discussion?! This would be a serious problem/confound.
-Exposure is measured from filled prescriptions only. Hence, we have no information on drugs given during hospitalization. A potential misclassification of exposure would be that we miss patients exposed to antipsychotics administered during hospitalization (without any record of a filled prescription), i.e. we do not know what drugs they were given during hospital stay. However, this misclassification would be non-differential, i.e. unrelated to later pancreatitis or not. Thus, this misclassification would dilute the risk estimates towards null results. This could be of a concern as we report no association of antipsychotic use and acute pancreatitis. However, the apparent confounding by foremost disease related to high alcohol consumption speaks against that we miss a true increased risk of pancreatitis.

8. Why were no formal analyses of a dose relationship conducted/presented using DDDs? The lack of a dose response relationship is alluded to in the discussion. DDDs should be available in the prescription data base.
-As the only information we have is DDD, and not Prescribed Daily Doses, we prefer not to use DDD. The DDD is a rather blunt measure, especially when trying to evaluate dose from depot injections.

9. The analyses should also be conducted combining all antidopaminergic agents together and – for comparison sake with the study by Gasse et al (Pharmacotherapy 2008) also separately for low potency, medium potency and high potency FGAs, as well as SGAs.
-These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table.

Results:
10. In the texr, please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group that the analyses and results are each based on.
-This has been added as a third sentence in the results section

11. Table 1: Please specify the N per each antipsychotic and class.
-The numbers of each class of antidopiminergic drugs are already given in table 1. Giving the numbers of each antipsychotic drug is in our opinion unnecessarily detailed while the calculations are based on composite groups.

VERSION 2 – REVIEW

REVIEWER	Christoph Correll, The Zucker Hillside Hospital, Psychiatry Research
REVIEW RETURNED	26/03/2012

GENERAL COMMENTS	This is a Swedish register study assessing the relationship between antidopaminergic agents and pancreatitis in a large total sample, finding no significant associations after adjustment for relevant covariates. The study uses straight forward methodology and analyses. The manuscript is very well written and accessible, the limitations are well described. Further strengths include the large and complete overall data base and careful adjustment of the analyses using known risk factors for pancreatitis as relevant covariates. Overall, I believe that the topic and the “negative” finding are of potential interest and relevance. In their response to the reviewers’ comments for their prior BMJ submission, the authors have further improved the manuscript. However, a few issues remain inadequately addressed. Below, I am referring to the numbered comments/responses as provided in the authors’ response and after that I am adding a few final comments and requests for the authors’ consideration: Reviewer 2: 7. It is unclear whether pts with pancreatitis during hospitalization for which no antipsychotic prescription data are available were treated. Were they excluded? How many such cases were there in relationship to the analyzed outpatient cases? Were the inpatient cases counted as ”unexposed”, as alluded to in the discussion?! This would be a serious problem/confound. Response: -Exposure is measured from filled prescriptions only. Hence, we have no information on drugs given during hospitalization. A potential misclassification of exposure would be that we miss patients exposed to antipsychotics administered during hospitalization (without any record of a filled prescription), i.e. we do not know what drugs they were given during hospital stay. However, this misclassification would be non-differential, i.e. unrelated to later pancreatitis or not. Thus, this misclassification would dilute the risk estimates towards null results. This could be of a concern as we report no association of antipsychotic use and acute pancreatitis. However, the apparent confounding by foremost disease related to high alcohol consumption speaks against that we miss a true increased risk of pancreatitis. REVIEWER COMMENT: In their reply, the authors did not specify the number and proportion of cases of pancreatitis during inpatient vs outpatient epochs. Please provide these numbers in your response and add them to the manuscript. The magnitude of this ratio will help judge how much the lack of medication data is or is not a reason for predominating of disease related factors. The authors need to acknowledge in the limitations section that their lack of medication information in cases of pancreatitis that were diagnosed during inpatient hospitalization could dilute the risk estimates towards null results, which should cause readers to evaluate the results with caustion, necessitating additional and larger studies. 8. Why were no formal analyses of a dose relationship conducted/presented using DDDs? The lack of a dose response

	relationship is alluded to in the discussion. DDDs should be available in the prescription data base. Response: -As the only information we have is DDD, and not Prescribed Daily Doses, we prefer not to use DDD. The DDD is a rather blunt measure, especially when trying to evaluate dose from depot injections. REVIEWER COMMENT: Since DDD information is available, these should be analyzed and results be added to the manuscript. Despite the caveats around using DDD, analyzing them as a proxy variable is standard in the field of Scandinavian database studies, and these analyses can yield potentially valuable additional information. The authors should explore whether their null finding holds up in high dose group. The argument that DDDs are problematic in patients receiving long-acting injectable antipsychotics is unconvincing, as the number of such patients is likely small (but unknown at this point, as the authors did not want to provide information about individual antipsychotics, not even in an appendix). 9. The analyses should also be conducted combining all antidopaminergic agents together and – for comparison sake with the study by Gasse et al (Pharmacotherapy 2008) also separately for low potency, medium potency and high potency FGAs, as well as SGAs. Response: -These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table. REVIEWER COMMENT: Thank you very much for performing the additional analyses. However, I have a comment regarding the interpretation of these results: Discussion: P 16, lines 22-26: The authors have the strong belief that their null finding is valid and they are readily willing to dismiss any other findings as chance findings. However, due to their small number of cases on antidopaminergic drugs and due to the related wide confidence interval, this is clearly only one possible explanation, especially as the two findings they are willing to dismiss as “chance findings” are in line with prior results. Thus, the authors need to tone down their somewhat overconfident interpretation and be more neutral. They could say, for example, that it is possible that these are chance findings, but that they cannot be certain about this because similar results have been found previously and the confidence intervals in the present study are relatively large. However, it is reassuring that, at least, no findings in the current use group approached significance. Nevertheless studies with larger numbers of patients exposed to these individual agents are needed to confirm the present findings. Additional comments: Article Summary: 1) Key Messages: The first bullet point needs to be amended to say that there was no association WHEN ADJUSTING FOR POTENTIALLY CONFOUNDING VARIABLES, as there WAS a significant association when NOT doing so. 2) Strengths and Limitations:

	Under strengths and limitations, please expand the second bullet that deals with the limitations to: Limitations include the relatively small number of acute pancreatitis cases during antidopaminergic exposure, lack of information on medication treatment during hospitalization and lack of information about adherence to the prescribed medications. 3) Supplemental Table 1: In the header, please add the n of patients and controls to each of the subgroups of antidopaminergic agents (i.e., "any, atypical, high potency, medium potency and low potency"), and add typical after each "high potency, medium potency and low potency". Fix typo ("Timebefore") 4) Supplemental table 2: In the header, please add the n of patients and controls to each of the subgroups and fix typos ("Timebefore", "proklorperazine")

VERSION 2 – AUTHOR RESPONSE

7. It is unclear whether pts with pancreatitis during hospitalization for which no antipsychotic prescription data are available were treated. Were they excluded? How many such cases were there in relationship to the analyzed outpatient cases? Were the inpatient cases counted as ?unexposed?, as alluded to in the discussion?! This would be a serious problem/confound.

Response: -Exposure is measured from filled prescriptions only. Hence, we have no information on drugs given during hospitalization. A potential misclassification of exposure would be that we miss patients exposed to antipsychotics administered during hospitalization (without any record of a filled prescription), i.e. we do not know what drugs they were given during hospital stay. However, this misclassification would be non-differential, i.e. unrelated to later pancreatitis or not. Thus, this misclassification would dilute the risk estimates towards null results. This could be of a concern as we report no association of antipsychotic use and acute pancreatitis. However, the apparent confounding by foremost disease related to high alcohol consumption speaks against that we miss a true increased risk of pancreatitis.

REVIEWER COMMENT:
In their reply, the authors did not specify the number and proportion of cases of pancreatitis during inpatient vs outpatient epochs. Please provide these numbers in your response and add them to the manuscript. The magnitude of this ratio will help judge how much the lack of medication data is or is not a reason for predominating of disease related factors.
The authors need to acknowledge in the limitations section that their lack of medication information in cases of pancreatitis that were diagnosed during inpatient hospitalization could dilute the risk estimates towards null results, which should cause readers to evaluate the results with caustion, necessitating additional and larger studies.

Author response:

We are sorry if our reply was unclear. All cases of pancreatitis were hospitalized for their pancreatitis. We cannot totally accurately distinguish between patients getting their pancreatitis while in-patients (treated for something else) and those acutely admitted from "the street". However, if a patient was in a psychiatric ward and starts to develop pancreatitis that patient would be discharged from the psychiatric ward and admitted to a surgical ward. Hence, we would capture the admittance to the surgical ward. Accordingly, some of the pancreatic cases had previously been hospitalized in somatic and/or psychiatric wards, but mostly brief hospitalizations. This is now described in the manuscript (see changes in manuscript below).

Changes in manuscript:

We have added the following paragraph on page 14 second paragraph:

Within 114 days of pancreatitis 1098 (18%) of cases were hospitalized at least once, for within 60 days before and 30 days before the corresponding hospitalized cases were, 850 (14%) and 608 (9.9%), respectively. The corresponding figures for hospitalization in a psychiatric ward was, 78 (1.3%), 43 (0.7%), and 26 (0.4%), respectively. The median length of stay for somatic hospitalizations was 4.3, and 3 days for the three time intervals respectively and for psychiatric hospitalizations 4.3, and 2 days.

And we have added the following sentence in the discussion at the bottom of page 15:

However, as other hospitalizations prior to index hospitalization for acute pancreatitis were not common and were of short duration we consider this potential misclassification negligible.

8. Why were no formal analyses of a dose relationship conducted/presented using DDDs? The lack of a dose response relationship is alluded to in the discussion. DDDs should be available in the prescription data base.
Response: -As the only information we have is DDD, and not Prescribed Daily Doses, we prefer not to use DDD. The DDD is a rather blunt measure, especially when trying to evaluate dose from depot injections.

REVIEWER COMMENT:
Since DDD information is available, these should be analyzed and results be added to the manuscript. Despite the caveats around using DDD, analyzing them as a proxy variable is standard in the field of Scandinavian database studies, and these analyses can yield potentially valuable additional information. The authors should explore whether their null finding holds up in high dose group. The argument that DDDs are problematic in patients receiving long-acting injectable antipsychotics is unconvincing, as the number of such patients is likely small (but unknown at this point, as the authors did not want to provide information about individual antipsychotics, not even in an appendix).

Author response:

We agree that DDD's may shed some further light on this issue, even though being a blunt measure and even though the questionable correlation between DDD's and actual equivalent potency among the antidopaminergic drugs. Thus, we have now calculated cumulative dose (total amount of DDD) divided into quintiles since start of the Drug Register 1 July 2005.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
sex	0.994	0.944	1.046
AlderIndexd	0.998	0.996	1.000
KalenderAr	1.008	0.976	1.040
dddgrp q0+ vs none	1.991	1.582	2.507
dddgrp q25 vs none	1.910	1.584	2.303
dddgrp q50 vs none	1.402	1.190	1.651
dddgrp q75 vs none	1.718	1.438	2.051
dddgrp q90 vs none	0.928	0.715	1.206

The cumulative dose gradient is in part inverse, the higher the cumulative dose, the lower the risk of pancreatitis.

Changes in text

We have included a paragraph (page 14, first para) briefly describing the results of the cumulative dose analysis:

Analyzing cumulative dose of antidopaminergic drugs since start of the Drug Register in 1st July, 2005 and risk of acute pancreatitis yielded the highest OR for the lowest quartiles of total amount of Daily Defined Dose (DDD) (OR 2.0, 95% CI 1.58-2.51) and the lowest OR for the 10% with the highest amount of DDD (OR=0.93, 95% CI 0.72-1.21) in the crude model. Adjustment for alcohol related diseases attenuated the association for all categories of cumulative dose (data not shown).

And in the discussion we have added the following phrase in the amendment discussed below on p.16 :

However, it is reassuring that…*and that there was an inverse relationship between cumulative DDD and risk of pancreatitis.*

9. The analyses should also be conducted combining all antidopaminergic agents together and ? for comparison sake with the study by Gasse et al (Pharmacotherapy 2008) also separately for low potency, medium potency and high potency FGAs, as well as SGAs.

Response: -These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table.

REVIEWER COMMENT:
Thank you very much for performing the additional analyses. However, I have a comment regarding the interpretation of these results:
Discussion: P 16, lines 22-26: The authors have the strong belief that their null finding is valid and they are readily willing to dismiss any other findings as chance findings. However, due to their small number of cases on antidopaminergic drugs and due to the related wide confidence interval, this is clearly only one possible explanation, especially as the two findings they are willing to dismiss as ?chance findings? are in line with prior results. Thus, the authors need to tone down their somewhat overconfident interpretation and be more neutral. They could say, for example, that it is possible that

these are chance findings, but that they cannot be certain about this because similar results have been found previously and the confidence intervals in the present study are relatively large. However, it is reassuring that, at least, no findings in the current use group approached significance. Nevertheless studies with larger numbers of patients exposed to these individual agents are needed to confirm the present findings.

Author response

We agree that the possibility that our null-finding could be a chance product cannot be dismissed and the following statement has been amended to the discussion below the section mentioned by the reviewer:

Changes in text

However, an actual effect cannot be entirely ruled out as similar results have been found previously and the confidence intervals in the present study are relatively large. However, it is reassuring that, at least, no findings in the current use group approached significance and that there was an inverse relationship between cumulative DDD and risk of pancreatitis. Nevertheless studies with larger numbers of patients exposed to these individual agents are needed to confirm our findings.

Additional comments:
Article Summary:
1) Key Messages:
The first bullet point needs to be amended to say that there was no association WHEN ADJUSTING FOR POTENTIALLY CONFOUNDING VARIABLES, as there WAS a significant association when NOT doing so.

Author response

Done

2) Strengths and Limitations:
Under strengths and limitations, please expand the second bullet that deals with the limitations to: Limitations include the relatively small number of acute pancreatitis cases during antidopaminergic exposure, lack of information on medication treatment during hospitalization and lack of information about adherence to the prescribed medications.

Author response

Done

3) Supplemental Table 1: In the header, please add the n of patients and controls to each of the subgroups of antidopaminergic agents (i.e., ?any, atypical, high potency, medium potency and low potency?), and add typical after each ?high potency, medium potency and low potency?. Fix typo (?Timebefore?)

Author response

Typos fixed. N exposed in patients and controls in each subgroup was not possible to add to the table without crowding of data. Thus, we added this information in a 2nd supplemental table.

4) Supplemental table 2: In the header, please add the n of patients and controls to each of the subgroups and fix typos (?Timebefore?, ?proklorperazine?)

Author response

We assume that the reviewer refers to table 2 and not supplemental table 2. Typos fixed. N of exposed patients and controls are already given in table 1.

VERSION 3 - REVIEW

REVIEWER	Christoph Correll, The Zucker Hillside Hospital, Psychiatry Research
REVIEW RETURNED	04/04/2012

GENERAL COMMENTS	Although only a response letter to the reviewers' comments made in response to the original BMJ submission was added by the authors, their tracked changes reflected the response to the additional comments regarding the first submission to BMJ Open. I have no further comments.