PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antidepressants and the risk of hyponatremia: A Danish register based population study
AUTHORS	Leth-Møller, Katja; Hansen, Annette; Torstensson, Maia; Andersen, Stig; Ødum, Lars; Gislason, Gunnar; Torp-Pedersen, Christian; Holm, Ellen

VERSION 1 - REVIEW

REVIEWER	Won-Myong Bahk College of Medicine, The Catholic University of Korea, Seoul, Korea
REVIEW RETURNED	09-Feb-2016

GENERAL COMMENTS	The authors present an interesting data of antidepressants and risk of hyponatremia. There are some specific points raised (or omitted) in the paper that merit revision: - There are some typing errors; “venlafaxin” “duloxetin” - Inclusion/exclusion criteria are not clearly presented. - What is minimum, maximum daily dose for each drugs? Is the frequency taking more than two antidepressants? - Authors should discuss in drug-drug interactions; Co-medication should be checked potential enzyme inhibition that might be relevant for the analyzed drugs (e.g. CYP 2D6 inhibitors for paroxetine, CYP 3A4 inhibitors for sertraline). - Watch out as often no spaces are added between last word and brackets.

REVIEWER	Toine Egberts Clinical Pharmacy, University Medical Center Utrecht, The Netherlands Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, The Netherlands
REVIEW RETURNED	10-Feb-2016

GENERAL COMMENTS	This study describes an assessment of the incidence of hyponatremia for patients treated with antidepressants. The research objective is of relevance since earlies studies have consistently shown associations between (classes) of antidepressant use and the risk of hyponatremia, but none was really able to study the (differential) risk of individual antidepressants which was the primary objective of the a authors of this study. Major points:

	However, this study does not succeed in their objective particularly because: a) they define hyponatremia as <135 mmol/l. More appropriate is to define it as <130 mmol/l. The latter the authors consider as severe hyponatremia, but data are only presented as supplmentary material. The appropriate outcome would have been <130 mmol/l as primary outcome and severe hyponatremia (defined as <115/120 mmol/l) as severe hyponatremia. I guess that the authors chose <135 (instead of <130) for sample size reasons. b) the frequency of serum sodium measurement is very low implying a high risk of selection bias c) patient factors associated with preferential choice for individual antidepressants but also associated with the outcome (i.e.confounders) are insufficiently taken into account. Therefore it can not validly be concluded whether differences in risk between individual antidepressants can be attrinuted to the antidepressant or to the user (characteristics). The authors should recheck the STROBE guidelines especially with respect to the methodology section. Non-major points Abstract The setting is mentioned in the description of participants. It seems double to additionally mention the setting as a paragraph in the abstract. I would recommend to include a time frame within the abstract. Incidence per how many patient years? If the authors would like to use the abbreviation p-value, this should be explained first between (..) Background Page 4: the authors should add a reference for line 34 and 52. It may be useful to combine some paragraphs. Some paragraphs are existing of a single or double sentence. Page 5: add a reference for line 4. The aim of the research is not completely clear to me: Do the authors want to look at the antidepressant drug classes and the individual antidepressants? The conclusion in the abstract only states the findings of specific drugs, while the conclusion of the full article only presents the findings of the antidepressant drug classes. Please rephrase the aim or make it into a primary and secondary aim. For the following sentence: “A review concluded that current evidence suggests a relative higher risk of hyponatremia with SSRIs and venlafaxine and a lower risk for mirtazapine, but for several antidepressants, however, data were insufficient to determine the risk of hyponatremia.” It should be mentioned compared to what a higher risk was assessed. Methods Use the past tense for the methods section: “where we linked exposure to”. I would recommend to move the information on Laboratory data directly after the Methods section. Population: emigration is double in sentence 23, I would suggest to remove it in this line, since it is explained in the previous sentence. Line 25: The study population is rather homogeneous. Based on

	what do the authors conclude that the population is rather homogeneous? Outcome assessment: What is the time frame for the outcome assessment? This should be specified in this section. What if the p-sodium was measured twice for confirmation? Would this count as one or two cases of hyponatremia? Page 7: Please explain why only these antidepressants are chosen. Why not include fluvoxamine for example? Line 19-20: For each drug, we stated minimum, maximum and typical daily dosage. How was the typical daily dosed defined? Based on the Defined Daily Dose of the WHO? Comorbidities: Please explain why only these medicines and comorbidities are included? More comorbidities and medicine of influence are known. I would suggest that the authors would read the following articles: Liamis G1, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008 Jul;52(1):144-53. Mannesse CK, Jansen PA, Van Marum RJ, Sival RC, Kok RM, Haffmans PM, Egberts TC. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas. 2013 Dec;76(4):357-63. Statistics Incidence rate ratios for hyponatremia associated with exposure to antidepressant therapy was analysed. It should be mentioned with what control group the authors compared the incidence rate to. How was time after first prescription used? Was the analysis done for the antidepressant groups or for the individual antidepressants? This is not clear from this section. How was adjusted for age? The methods sections should explain if it is used as a continuous or categorical variable. Results Page 9: I would recommend to remove the overall risk time, it does not provide additional information. In line 19 it seems a word is missing. Table 1: Is it correct that 12.42% of all users with nortriptyline have cancer? This percentage seems quite high. For clomipramine patients with kidney disease are represented as <3, I would recommend to present the number the same way as for the other antidepressants. The age of patients receiving no anti-depressants is much lower than patients receiving antidepressant. As age is an important confounder for hyponatremia, this can cause confounding. In which category would a person be after stopping with an antidepressant? If a patient has hyponatraemia after 10 days after the last consumption of an antidepressant, would this person be counted as user of the antidepressant of as no-antidepressant user? As a suggestion I would recommend to include a mean follow-up time in Table 1 for all categories of antidepressants / no-antidepressant. Sentence 30: During follow-up 60.28% of the study population had their p-sodium measured. Per what time frame? Figure 1: No. of blood test should be mentioned differently to clarify that it represents sodium measurements. Blood test could also mean other blood test, e.g. potassium. Please explain in the title of Figure 1 where the Incidence Risk Ratio is adjusted for. It would be of use to see how many patient years were taken into account, as no. of cases of hyponatremia are also presented in this figure. For the rest

	I think the figure is a nice representation of the results. For Figure 2 as for Figure 1 I would recommend to include mean patient years and to explain what was adjusted for. Major point: The title shows incidence rate ratios, but adjusted odds ratios are shown in the figure. Page 10. Line 11: Not the number of events cause large confidence intervals, but the uncertainty in the data. For figure 1, 2 and 3: If the scale of the figure is a bit broader, than the confidence intervals will fit in the figure. Line 44: Supplementary data is not provided, or without a Figure Title. Discussion: Line 54-56: All antidepressants should be all antidepressants in this study, since not all antidepressants are assessed. Page 11: Line 6: Reference 20 and 21 are not trials. Line 8: “within few hours” should be “within a few hours” Line 31: should be “controls” instead of “control” Section on definition of hyponatremia: What should we conclude on this information? Explain why you have added this information. Page 12: Comparison of drug classes: The comment on the article of Couplands shows a relevant point for discussion about the differences of the findings of this article to his findings. A difference in the studies is mentioned to be the age of the patients. I think it is important to notice in your own data that the comparison group (no-antidepressant users) have a lower mean age than the treatment group (antidepressant users). It is of importance to explain in your discussion how this could be of influence on the incidence risk ratios. Line 25-27: Duloxetine has been studied previously. Kruger S, Lindstaedt M. Duloxetine and hyponatremia: a report of 5 cases. J Clin Psychopharmacol. 2007 Feb;27(1):101-4. Page 13: Clinical relevance and implications should describe the clinical relevance and implications of the findings of this article. I would recommend to add here something about the differences in incidence of the antidepressants. Line 44-46: The limitations are mainly those that are inherent in an observational study. I would recommend to explain what these limitations are. Page 14: I have my doubts on if it is valid to say that the comparison between the drugs is valid, since the comparison group is younger. The incidence rate ratios may therefore be an overestimation. Furthermore, the study population does not consist of western Europe, but of a part of Denmark. Conclusion It is a bit confusing that the individual antidepressants are used and on other times the antidepressants groups. For a clearer story, it should be explained when which definition is used. For the last sentence of the conclusion: would the authors also for routine measurement of sodium for treatment with mianserin? The last sentence of the conclusions seems to be directed to elderly, although this study represents patients with a mean age between 40-50 years.

REVIEWER	Stephanie K. Wright George Washington University School of Nursing, Washington, DC, US
REVIEW RETURNED	12-Feb-2016

GENERAL COMMENTS	Excellent study, providing badly needed data on the relationship between hyponatremia and the various antidepressants. Methods are clearly described and results are stated clearly and succinctly. Findings support monitoring of serum sodium after initiation of treatment, especially with SSRIs, as has been recommended by others. Although not the purpose of this study, with such a large dataset available, a study of the relationship of age to the phenomenon of antidepressant-induced hyponatremia would be extremely valuable.

REVIEWER	Richard Sterns University of Rochester School of Medicine and Dentistry
REVIEW RETURNED	16-Feb-2016

GENERAL COMMENTS	Using an unusually comprehensive data base of residents of Northern Denmark, the authors have rigorously analyzed the association between specific antidepressants and hyponatremia. They find that all antidepressants except Mianserin are associated with hyponatremia. Because not all patients had serum sodium concentrations measured after starting an antidepressant, appropriate statistical analyses were performed on the subpopulation whose sodium was measured and found that these associations remain. Results were less clear for patients whose serum sodium concentrations fell below 130 meq/L . The results confirm the conclusions of previously published smaller retrospective studies suggesting that the highest risk for hyponatremia occurs during the first 14 days of treatment. Unlike other studies they demonstrate a similar risk of tricyclics as for SSRI's. The most striking finding is that Mianserin, a drug not available in the US was not associated with hyponatremia. The authors speculate that this may be explained by the drug's effect on alpha-2 adrenergic receptors that may reduce thirst. Although this has all of the inherent weaknesses of a retrospective review of a large data base, and is limited to a Western European population, it is extremely well done and offers the best data available on hyponatremia and antidepressants. I have only a few minor suggestions -- on page 4, lines 39 to 44, the authors state that "nearly all cases of hypotonic hyponatremia, ADH secretion is increased" That's a little strong. Sugest changing to "most cases of hypotonic hyponatremia"l They state that one of the reasons is "appropriate response to decreased effective plasma volume as in dehydration". Dehydration means an electrolyte-free water deficit which is the opposite of hyponatremia. Please change "dehydration" to "hypovolemia". Finally, "renal insufficiency" is listed as a reason for decreased effective plasma volume -- it is a consequence rather than a cause and I would suggest omitting "renal insufficiency. Line 55 on page 4, they state that "the mechanism for hyponatremia caused by antidepressants probably is SIAD with or without elevated ADH" . It is not clear what is meant by this sentence-- it would be useful to summarize the results of reference 15.

REVIEWER	Yana Vinogradova University of Nottingham United Kingdom

REVIEW RETURNED	01-Mar-2016

GENERAL COMMENTS	Leth-Møller et al describe a study of the associations between antidepressant use and risk of hyponatremia. In general, it is clearly argued and should be interesting to a general reader. I have only two minor comments: Page 8 line 52. The wording here is a bit odd, especially use of the word 'furthermore'. Better would be to make clear first what subgroup the fifth analysis was based on and then explain the use of the measurements for exposed and unexposed. Page 9 line 24. Some of the figures here are wrong – 72,509 is 11.36% of the total sample and 6,746 is 8.9% of 72,259.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Won-Myong Bahk
Institution and Country: College of Medicine, The Catholic University of Korea, Seoul, Korea
Competing Interests: None declared

The authors present an interesting data of antidepressants and risk of hyponatremia.
There are some specific points raised (or omitted) in the paper that merit revision:

- There are some typing errors; "venlafaxin" "duloxetin"
AR: Thanks, we have checked and corrected

- Inclusion/exclusion criteria are not clearly presented.
AR: We have rephrased this in the section describing the study population (page 6)

- What is minimum, maximum daily dose for each drugs? Is the frequency taking more than two antidepressants?
AR: The choice of minimum, maximum and typical daily dosage was done for every tablet strength in order to have an algorithm to calculate treatment period. Example: for how long will a prescription of 100 tablets of mirtazapine with strength 15 mg last? Clinical experience suggest that when prescribing tablet strength 15 mg, the typical daily dose probably is 15 mg. We have tried to make the description of this procedure clearer.

- Authors should discuss in drug-drug interactions; Co-medication should be checked potential enzyme inhibition that might be relevant for the analyzed drugs (e.g. CYP 2D6 inhibitors for paroxetine, CYP 3A4 inhibitors for sertraline).
AR: CYP activity is very dependent on individual genetics and we therefore did not include analysis on confounding due to comedication in the present study. We acknowledge that this may be a limitation of the study and have included á commentary on this in the discussions section on limitations

Watch out as often no spaces are added between last word and brackets.
AR: Thanks, we have corrected.

Reviewer: 2
Reviewer Name: Toine Egberts
Institution and Country: Clinical Pharmacy, University Medical Center Utrecht, The Netherlands;

Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, The Netherlands
Competing Interests: None declared

This study describes an assessment of the incidence of hyponatremia for patients treated with antidepressants. The research objective is of relevance since earlies studies have consistently shown associations between (classes) of antidepressant use and the risk of hyponatremia, but none was really able to study the (differential) risk of individual antidepressants which was the primary objective of the a authors of this study.

Major points:
However, this study does not succeed in their objective particularly because:
a) they define hyponatremia as <135 mmol/l. More appropriate is to define it as <130 mmol/l. The latter the authors consider as severe hyponatremia, but data are only presented as supplmentary material. The appropriate outcome would have been <130 mmol/l as primary outcome and severe hyponatremia (defined as <115/120 mmol/l) as severe hyponatremia. I guess that the authors chose <135 (instead of <130) for sample size reasons.
AR: It is an open discussion when the level of hyponatremia should be considered mild or severe. As mentioned in the discussion section several studies have found adverse events with very mild hyponatremia. One study even found increased mortality associated with levels of p-sodium of up to 138 mmol/l

b) the frequency of serum sodium measurement is very low implying a high risk of selection bias.
AR: We agree that this is a risk. However, our aim was to compare specific antidepressants and in the analysis where we included only those cases where plasma sodium was measured, we found the same pattern of associations. But we cannot totally exclude selection bias, which we discuss in the discussion section and mention as study limitation.

c) patient factors associated with preferential choice for individual antidepressants but also associated with the outcome (i.e.confounders) are insufficiently taken into account. Therefore it can not validly be concluded whether differences in risk between individual antidepressants can be attrinuted to the antidepressant or to the user (characteristics).
AR: Selection bias is a problem inherent in the observational design and although we have tried to perform several analyses to secure that our findings are not due to selection bias it can never be fully excluded in this study design.

The authors should recheck the STROBE guidelines especially with respect to the methodology section.

Non-major points

Abstract
The setting is mentioned in the description of participants. It seems double to additionally mention the setting as a paragraph in the abstract. We have changed this in the abstract.
I would recommend to include a time frame within the abstract. Incidence per how many patient years?
AR: In the abstract we have chosen to report incidence rate ratios, since those are the adjusted results. In the result section in the main text we have reported person years included.

If the authors would like to use the abbreviation p-value, this should be explained first between (..)
AR: We have done that.

Background
Page 4: the authors should add a reference for line 34 and 52.
AR: We have inserted references.

It may be useful to combine some paragraphs. Some paragraphs are existing of a single or double sentence.
Page 5: add a reference for line 4.
AR: We have done that.

The aim of the research is not completely clear to me: Do the authors want to look at the antidepressant drug classes and the individual antidepressants? The conclusion in the abstract only states the findings of specific drugs, while the conclusion of the full article only presents the findings of the antidepressant drug classes. Please rephrase the aim or make it into a primary and secondary aim.
AR: We have rephrased the aim in the abstract section.

For the following sentence: “A review concluded that current evidence suggests a relative higher risk of hyponatremia with SSRIs and venlafaxine and a lower risk for mirtazapine, but for several antidepressants, however, data were insufficient to determine the risk of hyponatremia.” It should be mentioned compared to what a higher risk was assessed.
AR: We have done that.

Methods
Use the past tense for the methods section: “where we linked exposure to”.
AR: Corrected.

I would recommend to move the information on Laboratory data directly after the Methods section.
AR: Good suggestion, we have done that.

Population: emigration is double in sentence 23, I would suggest to remove it in this line, since it is explained in the previous sentence.
AR: Good point, we have done that.

Line 25: The study population is rather homogeneous. Based on what do the authors conclude that the population is rather homogeneous?
AR: The Danish population is very homogeneous since there are few immigrants and socioeconomic equality is high compared to many other countries. However, this statement does not belong in the methods section, and we have deleted it.

Outcome assessment: What is the time frame for the outcome assessment? This should be specified in this section.
AR: We have included the information on timeframe in the section where the population is described.

What if the p-sodium was measured twice for confirmation? Would this count as one or two cases of hyponatremia?
AR: Hyponatremia is the outcome in the Poisson analysis and can only happen once for every individual. This is described in the section on population in the sentence: “Individuals were followed until end of study, emigration, death or an event of hyponatremia, whichever occurred first”

Page 7: Please explain why only these antidepressants are chosen. Why not include fluvoxamine for example?
AR: We included the most commonly used antidepressants in Denmark, we have added a sentence

stating this.

Line 19-20: For each drug, we stated minimum, maximum and typical daily dosage. How was the typical daily dosed defined? Based on the Defined Daily Dose of the WHO?
AR: The choice of minimum, maximum and typical daily dosage was done for every tablet strength in order to have an algorithm to calculate treatment period. Example: for how long will a prescription of 100 tablets of mirtazapine with strength 15 mg last? Clinical experience suggest that when prescribing tablet strength 15 mg, the typical daily dose probably is 15 mg. We have tried to make the description of this procedure clearer.

Comorbidities: Please explain why only these medicines and comorbidities are included? More comorbidities and medicine of influence are known. I would suggest that the authors would read the following articles:
Liamis G1, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008 Jul;52(1):144-53.
Mannesse CK, Jansen PA, Van Marum RJ, Sival RC, Kok RM, Haffmans PM, Egberts TC. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas. 2013 Dec;76(4):357-63.
AR: We have chosen to adjust for these medicines and comorbidities because they are the most common drugs and comorbidities known to be associated with hyponatremia. Some drugs used in cancer treatment may also be associated with hyponatremia, but this is adjusted for through the cancer diagnosis.

Statistics
Incidence rate ratios for hyponatremia associated with exposure to antidepressant therapy was analysed. It should be mentioned with what control group the authors compared the incidence rate to. How was time after first prescription used?
AR: In the Poisson analyses the control group consists of the individuals not getting the specific drug. Time after first prescription is used to calculate person years of exposure.

Was the analysis done for the antidepressant groups or for the individual antidepressants? This is not clear from this section.
AR: We performed 5 Poisson analyses. In four of them we performed analysis for individual antidepressants. In one we analysed the clases of antideprssants. We have rephrased this explanation in the section on statistics and hope it is clearer now.

How was adjusted for age?
AR: Age was updated at the beginning of each one year timeband, and afterwards categorized into ten year intervals. These ten year intervals were adjusted for in the Poisson regression.

The methods sections should explain if it is used as a continuous or categorical variable.
AR: Age is included as a categorical variable, this is added to the statistics section.

Results
Page 9: I would recommend to remove the overall risk time, it does not provide additional information,
AR: Quite right, we have removed the risk time.

In line 19 it seems a word is missing.
AR: Thanks, corrected.

Table 1: Is it correct that 12.42% of all users with nortriptyline have cancer? This percentage seems quite high. For clomipramine patients with kidney disease are represented as <3, I would recommend

to present the number the same way as for the other antidepressants.
AR: We have checked table 1, and the cancer incidence among nortriptyline users is correct. Due to Danish rules on research use of register data, we are not permitted to state numbers lower than four.

The age of patients receiving no anti-depressants is much lower than patients receiving antidepressant. As age is an important confounder for hyponatremia, this can cause confounding.
AR: In table 1, the age of patients receiving no antidepressants is calculated at day of entrance in the study. This means that it will be lower, but it does not necessarily mean that age of the controls in the Poisson analysis is lower. We controlled for age in all the analyses. We have inserted a sentence explaining this in the legend for table 1.

In which category would a person be after stopping with an antidepressant?
AR: In a Poisson analysis the unit of analysis is not persons but time intervals in a patient history. The same person can contribute with person time as unexposed in some time periods and exposed in other time periods.

If a patient has hyponatraemia after 10 days after the last consumption of an antidepressant, would this person be counted as user of the antidepressant of as no-antidepressant user?
AR: This person would contribute person time as exposed as long as he is being treated with an antidepressant and as unexposed in the period when he is not treated with an antidepressant. As soon as a person has an episode of hyponatremia, he has reached an endpoint and cannot contribute with person time thereafter.

As a suggestion I would recommend to include a mean follow-up time in Table 1 for all categories of antidepressants / no-antidepressant.
AR: We have added total number of person years to table 1.

Sentence 30: During follow-up 60.28% of the study population had their p-sodium measured. Per what time frame?
AR: During follow up; from January 1st 1998 to 31th 2012.

Figure 1: No. of blood test should be mentioned differently to clarify that it represents sodium measurements. Blood test could also mean other blood test, e.g. potassium. Please explain in the title of Figure 1 where the Incidence Risk Ratio is adjusted for.
AR: In figure 1 no. of blood tests have been changed to no. of blood tests measuring p-sodium. We have changed the figures, thus they now state what is adjusted for.

It would be of use to see how many patient years were taken into account, as no. of cases of hyponatremia are also presented in this figure.
AR: We have added total number of person years to table 1.

For the rest I think the figure is a nice representation of the results. For Figure 2 as for Figure 1 I would recommend to include mean patient years and to explain what was adjusted for. Major point: The title shows incidence rate ratios, but adjusted odds ratios are shown in the figure.
AR: Absolutely true, we have made a mistake in the title, which is now corrected.

Page 10. Line 11: Not the number of events cause large confidence intervals, but the uncertainty in the data.
AR: We have rephrased this line.

For figure 1, 2 and 3: If the scale of the figure is a bit broader, than the confidence intervals will fit in the figure. Line 44: Supplementary data is not provided, or without a Figure Title.

AR: We have changed the scale of figure 1, 2 and 3, plus added figure title to supplementary data (Appendix A and B).

Discussion:
Line 54-56: All antidepressants should be all antidepressants in this study, since not all antidepressants are assessed.
AR: We have rephrased the sentence.

Page 11: Line 6: Reference 20 and 21 are not trials.
AR: Ref 20 (Movig et al) is a case control study. Ref 21 (Spigset et al) is a register based cohort study. We have rephrased and replaced the term “trials” with “studies”

Line 8: “within few hours” should be “within a few hours”
AR: We have corrected.

Line 31: should be “controls” instead of “control”
AR: Corrected.

Section on definition of hyponatremia: What should we conclude on this information? Explain why you have added this information.
AR: We have added this to address the discussion on what level of hyponatremia one should consider important. We have revised the text in order to make the purpose of this section clear.

Page 12: Comparison of drug classes: The comment on the article of Couplands shows a relevant point for discussion about the differences of the findings of this article to his findings. A difference in the studies is mentioned to be the age of the patients. I think it is important to notice in your own data that the comparison group (no-antidepressant users) have a lower mean age than the treatment group (antidepressant users). It is of importance to explain in your discussion how this could be of influence on the incidence risk ratios.
AR: See explanation above. We have added information concerning this in the legend of table 1.

Line 25-27: Duloxetine has been studied previously. Kruger S, Lindstaedt M. Duloxetine and hyponatremia: a report of 5 cases. J Clin Psychopharmacol. 2007 Feb;27(1):101-4.
AR: Thanks, we have inserted Kruger as a reference.

Page 13: Clinical relevance and implications should describe the clinical relevance and implications of the findings of this article. I would recommend to add here something about the differences in incidence of the antidepressants.
AR: Thanks, we have done that.

Line 44-46: The limitations are mainly those that are inherent in an observational study. I would recommend to explain what these limitations are.
AR: We have elaborated on that.

Page 14: I have my doubts on if it is valid to say that the comparison between the drugs is valid, since the comparison group is younger. The incidence rate ratios may therefore be an overestimation. Furthermore, the study population does not consist of western Europe, but of a part of Denmark.
AR: We have changed “Western European” into “Caucasian”

Conclusion
It is a bit confusing that the individual antidepressants are used and on other times the antidepressants groups. For a clearer story, it should be explained when which definition is used. For

the last sentence of the conclusion: would the authors also for routine measurement of sodium for treatment with mianserin?
AR: Yes, we find it reasonable as a routine to control p-sodium when patients start treatment with antidepressants even in mianserin. We found no associations with mianserin in our study, but we would like to see that confirmed in other studies.

The last sentence of the conclusions seems to be directed to elderly, although this study represents patients with a mean age between 40-50 years.
AR: We have removed the sentence about the elderly.

Reviewer: 3
Reviewer Name: Stephanie K. Wright
Institution and Country: George Washington University School of Nursing, Washington, DC, US
Competing Interests: None declared.

Excellent study, providing badly needed data on the relationship between hyponatremia and the various antidepressants. Methods are clearly described and results are stated clearly and succinctly. Findings support monitoring of serum sodium after initiation of treatment, especially with SSRIs, as has been recommended by others. Although not the purpose of this study, with such a large dataset available, a study of the relationship of age to the phenomenon of antidepressant-induced hyponatremia would be extremely valuable.

Reviewer: 4
Reviewer Name: Richard Sterns
Institution and Country: University of Rochester School of Medicine and Dentistry
Competing Interests: None declared

Using an unusually comprehensive data base of residents of Northern Denmark, the authors have rigorously analyzed the association between specific antidepressants and hyponatremia. They find that all antidepressants except Mianserin are associated with hyponatremia. Because not all patients had serum sodium concentrations measured after starting an antidepressant, appropriate statistical analyses were performed on the subpopulation whose sodium was measured and found that these associations remain. Results were less clear for patients whose serum sodium concentrations fell below 130 meq/L .
The results confirm the conclusions of previously published smaller retrospective studies suggesting that the highest risk for hyponatremia occurs during the first 14 days of treatment. Unlike other studies they demonstrate a similar risk of tricyclics as for SSRI's. The most striking finding is that Mianserin, a drug not available in the US was not associated with hyponatremia. The authors speculate that this may be explained by the drug's effect on alpha-2 adrenergic receptors that may reduce thirst.

Although this has all of the inherent weaknesses of a retrospective review of a large data base, and is limited to a Western European population, it is extremely well done and offers the best data available on hyponatremia and antidepressants.

I have only a few minor suggestions -- on page 4, lines 39 to 44, the authors state that "nearly all cases of hypotonic hyponatremia, ADH secretion is increased" That's a little strong. Sugest changing to "most cases of hypotonic hyponatremia"l They state that one of the reasons is "appropriate response to decreased effective plasma volume as in dehydration". Dehydration means an electrolyte-free water deficit which is the opposite of hyponatremia. Please change "dehydration" to "hypovolemia". Finally, "renal insufficiency" is listed as a reason for decreased effective plasma

volume -- it is a consequence rather than a cause and I would suggest omitting "renal insufficiency.
Line 55 on page 4, they state that "the mechanism for hyponatremia caused by antidepressants probably is SIAD with or without elevated ADH" . It is not clear what is meant by this sentence-- it would be useful to summarize the results of reference 15.
AR: The meaning of this sentence was to state that the physiological mechanism of antidepressant related hyponatremia is antidiuresis either due to elevated ADH or due to increased renal response to ADH. As suggested by the reviewer we have summarized the findings in ref 17 (Mannesse et al 2013).

Reviewer: 5
Reviewer Name: Yana Vinogradova
Institution and Country: University of Nottingham, United Kingdom
Competing Interests: None declared

Leth-Møller et al describe a study of the associations between antidepressant use and risk of hyponatremia. In general, it is clearly argued and should be interesting to a general reader.
I have only two minor comments:
Page 8 line 52. The wording here is a bit odd, especially use of the word ‘furthermore’. Better would be to make clear first what subgroup the fifth analysis was based on and then explain the use of the measurements for exposed and unexposed.
AR: We have rephrased the sentence.

Page 9 line 24. Some of the figures here are wrong – 72,509 is 11.36% of the total sample and 6,746 is 8.9% of 72,259.
AR: Thanks, we have corrected.

VERSION 2 – REVIEW

REVIEWER	Won-Myong Bahk The Catholic University of Korea
REVIEW RETURNED	05-Apr-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Richard H Sterns University of Rochester School of Medicine and Dentistry, USA
REVIEW RETURNED	04-Apr-2016

GENERAL COMMENTS	The authors have addressed my concerns