16-Nov-2015

Dear Dr. Coupland

Manuscript ID BMJ.2015.027737 entitled "Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using a primary care database"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Anita Jain
Editor The BMJ
ajain@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (Chair), Richard Riley (statistician), Georg Roeggla, Rubin Minhas, Tiago Villanueva, Jessamine Bagene, Anita Jain

Decision: Put points

Detailed comments from the meeting: The committee was interested in the research topic. However, we felt that there are several aspects that need to be further clarified for us to appraise the paper and ensure robustness of the findings. We also include below a report by the statistical editor.

Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
This article is very clear, detailed, and discussing very important subjects. The sample size is sufficient to answer to sub-questions that are discussed. The lenght of follow-up is reasonnable.

I have some concerns about the method and the answer to one question.

-the method : the question that emerges immediately is "if some subjects are carrying known risks of CV events, GP will prescribe them the most secure drug, that will appear as the most associated with events, because of these prescription biases". The answer provided could be bettered : only adjusting on some covariables will not provide the good correction about precription biases : it would be probably better to use propensity scores for prescription of each drug, in association with risk factors for CHD, stroke and sudden death.

-the question : atrial fibrillation is rarely a cause of sudden death, and is due tu ectopic pace makers. Torsades de pointes (TdP) are very frequently inducing sudden death and are linked to an excessive QT length : so I am not sure wether the observation of new atrial fibrillation (which is very interesting per se) could predict TdP and sudden death. Regarding this outcome, the propensity score associated with prescription of each drug could include other factors linked to QT length : basal QT, hypokaliemia and hypokaliemiant drugs, history of familial sudden deaths.
If this is impossible, conclusion should be changed regarding the reproaches done to Citalopram which are not ruled out by this study as written.

However, if those remarks could be taken into account by modifying analyses or conclusion as proposed, the study appears of great interest.

Additional Questions:

Please enter your name: Péquignot

Job Title: MD,MPH

Institution: INSERM U970 Paris

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

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If you have any competing interests (please see BMJ policy) please declare them here: I received Fees for my participation in research concerning Alzheimer disease.

Reviewer: 2

Recommendation:

Comments:
This paper presents a cohort study about the relationship of the use of antidepressants (AD) with aryhtmia, myocardial infarction, and stroke/TIA among 238 963 patients with a first depression. The study fine-tunes earlier publications on this topic, focussing on young adults only (20-64), individual drugs, and dose and duration of use. The study is based on a very large database and it is written well. Yet, the paper suffers from a lack of focus, the subsequent great number of results, and a number of methodological limitations. I explain in more detail below.

Major limitations
In the introduction the authors present a number of interesting research questions. Instead of choosing one and working it out well, the authors set out to test all. For instance, the authors might have hypothesized why there is a significant association between SSRIs and stroke in elderly but not in younger adults (Shin 2014). Is it not weird that SSRIs are generally known to induce bleeding disorders, but apparently increase the risk of hemorrhagic AND ischemic stroke? Was history of stroke accounted for in all included studies? Were the age groups similar in case-control and cohort studies? Likewise, the authors refer to a number of observational studies reporting discrepant findings about the association between AD and arrhythmias, but again they do not give a potential interesting and testable explanation for these discrepancies. The authors do not explain either why they might want to test the association between AD and myocardial infarction. As a result it remains unclear what the clinical and scientific relevance of this study is.

The general design and analytic approach are customary for this type of pharmaco-epidemiological studies. However, the authors used the same confounding factors for all three outcomes, even though it is unlikely that they are the same. Moreover, their definition of a confounding factor (i.e. affects the risk of the exposure OR outcome) is not in line with that in the literature (i.e affects exposure AND outcome) (Hernan 2002). Consequently, they list a long list of potential confounders. Over-adjusting might lead to bias just like under-adjustment.

The exclusion of patients with a history of arrhythmia, myocardial infarction, and stroke/TIA seems an omission because the results of the study are not generalizable to these patients. Yet, physicians will be extra keen on information about cardiovascular risk of AD in these patients (much less in young patients without such a history).

The authors thoroughly discuss residual confounding and information bias. What is not mentioned is that many strokes and myocardial infarction (esp. in women) go unnoticed. Could silent stroke and MI prior to depression have confounded the results? Could stroke and MI have been missed during follow-up and decreased the power of the study? In addition, selection bias needs to be discussed. It is possible that the study outcomes have been missed in patients that died even though death certificates were used.

Minor limitations/ questions
The standard comparison group is not described. What is it when non-users were excluded?
Why were the monoamine oxidase inhibitors not included in the group 'other AD'?
Were the proportional hazard assumptions confirmed?
Could selective preference explain the fluoxetine findings as well? Is it not prescribed to the very fit/ young specifically?
I do not understand the suggestion to test the cardio-preventive effect of fluoxetine in a trial. A large population at risk of cardiovascular disease and with depression would need to be included. Fluoxetine is generally avoided in elderly patients due to its long half time.
The abstract and text seem too long, and the number of tables and figures seems too large for a BMJ article (not

taking supplementary content into account).
There are some textual mistakes.

References
Shin D, Oh YH, Eom CS, Park SM. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. J Neurol. 2014 Apr;261(4):686-95.
Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 2002 Jan 15;155(2):176-84.

Additional Questions:
Please enter your name: HJ Luijendijk

Job Title: Senior researcher

Institution: University Medical Center Groningen

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 3

Recommendation:

Comments:
This paper considers the cardiovascular risks of antidepressant medication in adults. It presents the findings of a cohort study of almost a quarter of a million UK adults aged 20-64 with a first diagnosis of depression, and examines the risks of MI, CVA and arrhythmia in relation to different classes of and individual antidepressants. Data are drawn from the well-respected QResearch database of primary care electronic records, with supplementary information on cause of death from the Office of National Statistics. The authors provide a clear and cogent description of their methodology, including inclusion/exclusion criteria, confounders and statistical methods of analysis. The key elements of analysis include comparison of risks of adverse cardiovascular events when taking vs. when not taking antidepressants. Findings are presented clearly. There is a thorough and well-balanced discussion of study strengths and limitations - the latter including possibilities of selection bias for lofepramine, and relatively small numbers on high dose citalopram - and of the implications of the findings for clinical practice.

This is a strong and well-presented paper, which provides convincing evidence that in adults aged 20-64 there are low risks of adverse cardiovascular events associated with antidepressant medication in general, and with SSRIs in particular. The specific evidence in relation to higher dose citalopram is potentially significant in policy terms, and is likely to be of interest to US and European drug monitoring agencies in view of existing advice regarding risk of prolonging QT intervals: the authors are suitably cautious on the implications of their findings. The suggestive evidence that SSRIs, especially fluoxetine, may reduce the risk of adverse cardiovascular events in adults is intriguing, and worthy of further investigation.

Additional Questions:
Please enter your name: Christopher Dowrick

Job Title: Professor of Primary Medical Care

Institution: University of Liverpool

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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If you have any competing interests (please see BMJ policy) please declare them here: 25 November 2014:participation in a symposium organised by the Economist magazine, sponsored by Lundbeck, on 'The Global Crisis of Depression'

Reviewer: 4

Recommendation:

Comments:
This is a well-written and well reported article, as expected from the set of authors involved. The authors have clearly worked hard to address an important topic using the primary care database available. It is good to see that a protocol was published for this cohort study. I have reviewed this from a statistical perspective, and although standards are generally good as expected, I have some comments for improvement and areas for clarification to be addressed in any subsequent revision:

1) When reading the article, my initial impression was that there are a lot of analyses here, for example across different 3 outcomes, different classes, individual drugs,, and different follow-up times. For the latter it says in the methods that 'As sensitivity analyses we repeated the analyses firstly restricted to the first year of follow-up, then including the entire follow-up period' and also time since starting treatment is investigated as categories, e.g. first 28 days.

But in the protocol, though 5 years and 28 days are mentioned, I cannot see mention about the 1-year analyses. Can the authors clarify please why they focused on 1-year in the end, if not mentioned in the protocol (perhaps I am missing something)?

2) In relation to this point, most analyses over the 5 year period are not significant, but there are more significant results by 1 year. This suggests that the hazard ratio is not proportional over time, but this is not evaluated formally (statistically) and raises the question about the HRs from years 1 to 2, and 2 to 3 etc. Therefore I find the focus on 1-year an incomplete picture, and wonder whether the authors could comment in the results about whether the proportional hazards assumption was appropriate (the methods say it was examined, but we don't see the details). I would find it strange that the HRs at 1-year are significant but not at 5-years, if the proportional hazards assumption is actually ok.

Many 1-year results are the main message in the abstract and conclusions, yet they are only given in the supplementary material in the actual paper. I think they should be brought into the main article tables, and this may link to a more detailed investigation of the proportional hazards assumption (if the HR is constant over time, or what the HR is within each year interval upto 5 years).

Of fundamental interest: if the SRIs are associated with benefit for the first year but overall the 5 years there is no difference, does this mean that the SRIs are associated with harm in the latter years?

3) Further, the authors look at 3 outcomes in the paper 'arrhythmia, myocardial infarction and stroke or transient ischaemic attack'. Yet, in the protocol there were far more than 3 outcomes listed (see below), and none were mentioned as primary outcomes. Can the authors clarify why they looked at these three outcomes in this paper as a priority over other outcomes listed below:

•all-cause mortality
•suicide (including open verdicts)
•attempted suicide/self-harm
•sudden death
•overdose/poisoning with an antidepressant
•myocardial infarction
•stroke/transient ischaemic attack (TIA)
•cardiac arrhythmia
•epilepsy/seizures
•upper gastrointestinal bleeding
•falls
•fractures
•adverse drug reactions (including bullous eruption)
•motor vehicle crash.

4) The authors adjust for confounding using Cox regression, and it is good to see that many confounders are indeed adjusted for. That being said, I would also have liked to see whether conclusions are robust to the use of propensity score matching methods. Or can they justify in the Discussion why this wasn't considered beneficial over traditional regression adjustment? Perhaps, due to the time-varying nature of the use of antidepressants, this was problematic

5) Can the authors clarify in the paper the use of the time-varying antidepressants covariate and its interpretation for an individual who stopped. If an individual stops antidepressants, then do they then (for subsequent follow-up periods) move to the non-treatment group? If so, then how does this handle the potential for events to be due to the earlier use of antidepressants? Could it be that the lack of any differences between groups is because some of those who were on anti-depressants or moving into the non-treatment group, and therefore any genuine difference is being attenuated?

6) "Even for doses of citalopram ≥ 40 mg/day there was no significantly increased risk (adjusted hazard ratio=1.11, 95% CI 0.72 to 1.71)." – though this statement is correct, the confidence interval is 0.72 to 1.71 and is therefore wide: is there low power? Indeed, there are not many events in many analyses. This is worthy of discussion please in the strengths and limitations section.

7) I am also concerned about missing data: the authors say 'We included all eligible patients in the database in our analyses to maximise power' – but there are no details about how missing data were handled. I notice that under a table it says '5.0% of prescriptions had missing information on dosage.', so there is some missing data – but how was it handled? It is also not mentioned in the protocol.

8) The authors used 'robust standard errors to allow for clustering of patients within practices' – such methods are done when the model used is mis-specified (or the correct model is difficult to actually fit), and therefore the 'robust' standard errors used to inflate uncertainty accordingly. However, here I do not understand why the clustering within practices was not accounted for by using, for example, using a stratified Cox model or adding a frailty term (with a random effect on the baseline hazard to allow for separate one for each practice). Though this is a minor point, I would like the article to clarify if alternative approaches to accounting for clustering affected the conclusions.

9) In places, the authors infer a difference between individual drugs, which is often not justified. This is most apparent in the 'absolute risks' section, where they say 'Absolute risks of arrhythmia and myocardial infarction were highest for lofepramine' – this is not justified, as the CIs for the risks and NNH are very wide and overlap with the other drugs. This therefore needs to be re-written. Please check elsewhere for this issue too.

In summary, this is an important piece of work, and I hope my comments help to improve the article further, especially in regard to the outcome investigated, the time-points considered and the use of time-varying covariate.

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 5

Recommendation:

Comments:
This is a very well written and organized paper by Coupland et al. that examined the association between different antidepressant prescriptions and 3 cardiovascular outomes within a large UK primary care database. The principal finding is that there there is no overall significant association between different antidepressant classes and the onset of MI, stroke or TIA, or arrhythmia.

There are a number of strengths:
1. Clinically relevant question. The regulatory warnings had a clear effect on comfort level in prescribing antidepressants in general and at particular dosages, therefore the findings have clinical application.
2. Very large dataset
3. The authors have tried to address the main limitations to the data (e.g. validity of primary outcomes.
4. Excellent analytic plan.

Main issues:
1. The precision of the key aims. The mechanism by which antidepressants may raise the risk of arrhythmias is very different than the mechanism that may impact rates of stroke, TIAs and MIs. Furthermore, the time frame for the effect is vastly different. The impact on arrhythmia being much shorter than the others. Lumping them together without adequate consideration of these issues is problematic.
2. The paper focuses on differences between antidepressants, yet the primary analyses use comparisons with periods of no antidepressant treatment. This complicates the interpretation of results, since there are many additional factors that influence prescribing of any antidepressant and which could impact the primary outcomes. The authors are encouraged to clarify why they did not select on antidepressant or class as the reference, and then compare others to this reference. This would have decreased the potential bias.
3. The results are important and meaningful, but are ultimately more confirmatory than new.

Minor issues:
4. It is unclear why the authors selected to only focus on patients with depression. Couldn't the results have included all antidepressant prescriptions? A sensitivity analysis could then examine whether there are unique results for the depression group. The explanation on page 12 that "....depression itself is an established risk factor for cardiovascular outcomes..." is unconvincing, since this same statement could be made for bipolar disorder or schizophrenia.
5. Related to this, it is unclear why the authors selected cohort from patients with a first recorded diagnosis of depression.
6. A rationale for the duration of follow-up should be provided.
7. A rationale for the age restriction of 25-64 should be provided.
8. Page 6: the wording regarding ages 20-64 is unclear. Is this current age or age at time of first diagnosis of depression?

Additional Questions:
Please enter your name: Ayal Schaffer

Job Title: Head, Mood and Anxiety Disorders Program

Institution: Sunnybrook Health Sciences Center, University of Toronto

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

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Reviewer: 6

Recommendation:

Comments:
This study describes a cohort study from family practices across the United Kingdom which tracks over 230,000 patients aged 20 to 64 who were diagnosed with depression and exposed to antidepressants, in terms of their risk for subsequent myocardial infarction, stroke or transient ischaemic attack or arrhythmia based on antidepressant exposure, over five years.

This study represents a very large database and is an important contribution to the literature; there are, however, some limitations.

1. Is the ratio of MI to CVA/TIA expected? Generally, the prevalence of coronary heart disease is higher rather than lower than cerebrovascular disease. Does this ratio match with the general population? If not, comment is warranted about how the exclusion criteria may have impacted this ratio and what importance that may have.
2. The abstract lists 25-64yo age range, looks like it should be 20-64yo.
3. Reasons for excluding angina or other non-MI diagnoses reflecting atherosclerotic heart disease should be provided. There are many more patients with atherosclerotic heart disease (e.g. angina, require bypass/stent) that don't have a frank MI.
4. The justification for the study is weak. Although the study is of value, the principal reason stated for this study is

that previous studies haven't explored a younger age group. However, the literature review include studies that refer to subjects with a range of ages but the issue of age and how it might impact on these particular findings is not discussed.
5. Recruitment ended in 2011 and follow-up ended in 2012. Therefore, there is the possibility that a not insignificant proportion of subjects could not have reached five years of follow-up. As new medications became available over time, how might this have affected the chance of finding the outcome (or no outcome) with newer antidepressants?
6. The analysis explored 4 categories of antidepressants and a subsequent analysis chose to look at the 11 most frequently prescribed antidepressant drugs. The justification for selecting 11 (As opposed to 10 or 12 or 13) most prescribed antidepressants is not provided.
7. There is no explanation as to why "year of diagnosis" is considered a risk factor.
8. Severity of initial diagnosis was determined using codes previously published and "some additional classification by a member of the study team". It is possible that severity of initial diagnosis could be an important predictor. The process of this "additional classification" is not described and deserves more clarity.
9. No justification is provided for the eligibility criteria that the diagnosis of depression must have occurred at least 12 months after registration.
10. Previous depression is an exclusion criteria at entrance. The reason for this exclusion is not provided. The presence of a previous stroke, myocardial infarction or arrhythmia is not an exclusion criteria at baseline. This might create a bias in that people with a previous event such as myocardial infarction may be preferentially prescribe one kind of antidepressant when they eventually become depressed. There is an exclusion of people with one of these outcomes at baseline but it is described in multiple different ways in different sections of the manuscript. This makes it hard to interpret. At one point the manuscript states, "patients were excluded from the analysis of each outcome if they had the outcome recorded a baseline". In another place it is suggested that one confounding variable was "comorbidities at baseline (coronary heart disease,stroke/transient ischaemic attack (except when stroke/transient ischaemic attack was the outcome)". and then on page 9 the manuscript states "these patients were excluded from analysis of each respective outcome." Regardless of the way it is expressed (and interpretation of each definition is subtly different), there needs to be clear justification as to why a prior outcome will be included for some people but not others.
11. In general, there are many exclusion and inclusion criteria are not justified. For example, why are subjects excluded if they received prescriptions for antidepressant more than 36 months before the first recorded diagnosis of depression (i.e. how was 36 months chosen)? What is the justification for the categorization for the number of days taking antidepressant and the number of days after stopping treatment - why are these ranges of days chosen? Why are the classifications or categorization of the intensity of drug dose used?
12. There is no description of how eligible subjects would be handled if they left the practice, before 5 years; in other words, how is this outcome coded?
13. There needs to be more description of how confounding variables were coded (as individual dichotomous variables or as composite variables)
14. "Deprivation" was derived from patient's postcodes, "in fifths". Does this mean "quintiles"? Why quintiles, and how reliable is this scale?
15. Ethnicity was categorized using "white/not recorded". Is there evidence that this is an appropriate classification? What proportion of the "not recorded" are actually white? Or perhaps, those that don't record ethnicity should not be included in the analysis of ethnicity, or included as their own group.
16. On page 7, lines 51 to 54 there appears to be a missing parenthesis and maybe missing a short description as to why this list is included and whether these variables will be considered yes/no or some composite.
17. The main analysis is based on the first five years of follow-up. It is not clear why the cut-off was made of five years when indeed the median follow-up was 5.2 years.
18. Rather than exclude the monoamine oxidase inhibitors and the 1700+ subjects that were treated with these compounds, could they not be amalgamated into the "other antidepressants" class.
19. On page 10 the manuscript states that there was an increased risk for lower doses of lofepramine but the hazard ratio and confidence interval are not reported.
20. The manuscript states on page 12 line 29 that all eligible patients were included. The more important question is whether all patients exposed antidepressants were included. Clearly they were not, for various reasons, some justified, some not. The most problematic limitation of the study maybe not the inclusiveness of the eligible sample but the exclusion criteria that were applied and may limit the generalizability of the findings.
21. The manuscript seems to suggest that including only patients with a diagnosis of depression makes it easier to separate the effects of antidepressant treatments from those of depression. But, in fact, if patients had also been included that did not have a diagnosis of major depression but received the same medications, (for example anxiety disorders), then it may have been possible to distinguish the effects of antidepressants from diagnosis. Furthermore, exploring other medications that people with depression may be prescribed, for example, anxiolytics, may also have helped to disentangle diagnosis and medication risks.

Overall the findings are intriguing and this manuscript would be a excellent addition to world literature. Nonetheless, important clarifications are important and need to be addressed to approve this manuscript for publication.

Additional Questions:
Please enter your name: Anthony Levitt

Job Title: x

Institution: x

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iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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