Subject: BMJ - Decision on Manuscript ID BMJ.2015.029971

Body: 09-Dec-2015

Dear Dr. Shin

Manuscript ID BMJ.2015.029971 entitled "Cardiac safety of methylphenidate among pediatric patients with ADHD: a nationwide self-controlled case series study"

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.

dr. Wim Weber
European editor, BMJ
wweber@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: Elizabeth Loder (Chair), Julie Morris (Statistics advisor), José Merino, Rubin Minhas, Georg Röggla, Tiago Villanueva, Wim Weber.

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question.

We had the following concerns:

The 'event' or outcome you use is a very broad composite one. In addition to arrhythmia, you lump in MI, hypertension, stroke and heart failure. The mechanism of arrhythmia differs from the others. There is a comparability issue here - we were surprised to see hypertension alongside MI, stroke and heart failure.

A closer inspection of the rate ratio's for the components seems to point to arrhythmia as the only significant component.

A dose response curve would be desirable

The flowchart does not run logically.

If you can provide data on congenital heart disease that would be value adding, the ACC/AHA statements all call for this, with subgroup analysis.

Case-control studies do not quanitfy the absolute risk in the overall MF-taking pediatric population. It is probably very low; might you add a remark on this ?

It would be useful to have a few more details about the duration of the unexposed and exposed periods before and after the cardiac outcome (eg. median and range).

Table 1. Why is the median age at first outcome 2 years below that of the first exposure? We would have thought that it should be the other way round?

In the sensitivity analysis where pre-exposure risk periods are included, the rate ratios prior to medication are very high (Table 3), and even higher than that during exposure to the drug. This is of concern. What is the explanation for this? It could be suggested that initiation of the drug occurs when the risk of cardiac outcomes is very high ie. there are some changes in the subject's health? If so, then the study does not provide strong evidence of an increased risk of a cardiac event with drug use.

First, 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 Reviewers

Reviewer: 1

Recommendation:

Comments:
This is a rather interesting and well written study with an adequate design to pick up rare adverse events following the use of central stimulants as treatment for ADHD in children and adolescents. I think it would be of interest to the readers of BMJ if it was revised. I have some major concerns, but rally mostly minor concerns

Major concerns

I think they could have use for a language consultant.

The first paragraph of the introduction is a bit messy

In the second paragraph on age 3 they say that the design eliminates confounding – is this totally true?

Second paragraph page 5: The events included in each cluster of diagnosis range form something that is very mild disease and something that is very severe disease. This is a major problem with the paper: different things are clustered together

Page 12: strength and limitations: they need to work on the limitations bit: Something about the wash out period needs to be discussed in limitations. Likewise Diagnostic accuracy (high of course from previous study, but not 100% - how does this influence results. They don't know if prescribed drugs are taken: what could noncompliance doo to these findings. And what about the nocebo effect? It patients take amphetamine or methylphenidate they will notice this. Any event will more readily be viewed as a consequence of this intake. Thus increasing the chance of having any episodes after the intake of these drugs.

Minor concerns

I think it would be more appropriate if they were to call it adverse events or events than outcome

I think it would be more appropriate to call it cardiovascular adverse event rather than cardiac when they include stroke

Line 47 page 2: "particularly in children with mild disease" – what disease?

Line 50 page 3: "confounding between individuals" – correct phrasing?

Line 30 page 4: I would make a paragraph between "….Tenth Revision (ICD-10)" and "All researchers…."

The previous study they refer to in line 45 page 4 has measured diagnosis to "actual diagnosis" – what gold standard is this?

Line 38, page 8: "partitioned" – a good word?

Additional Questions:
Please enter your name: Jørgen G. Bramness

Job Title: professor

Institution: Norwegian Center for Addiction Research, University of Oslo

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 2

Recommendation:

Comments:
This is a well written paper on an interesting topic - the effects of methylphenidate on arrhtyhmia, hypertension, MI, ischaemic stroke and heart failure. The rationale is clear and well justified and the data and methods are mostly well described. The assumptions underpinning the SCCS method have been discussed and I agree with the authors on their assessment of these. I have a number of specific comments as detailed below:

Major comments:

1) In Table 3 we see the sensitivity analysis where a pre-exposure period has been added into the analysis to account for the possibility that the event affects the probability of future exposure. Here we see that this seems to be the case. There is n strongly increased risk of all outcomes in the 2 month period before exposure, of a similar or greater magnitude than seen during exposure, e.g. for MI, there is a 7-fold increased risk in the 31-60 days before methyphenidate starts. This suggests to me that the time of methyphenidate initiation seems to co-incide with a time when the risk of these events is raised, but that the medication initiation is not having any impact on this increased risk (it isn't getting any higher after starting the drug). This seems to suggest the association with methylphenidate is unlikely to be causal.

2. A secondary analysis looking at atomoxetine exposure might be helpful since it is used in similar patients but has a different mechanism of action (though I realise there is also some overlap in action). It might help better inform whether this is a non-drug specific phenomenon related to the peri-diagnostic time for ADHD?

3. I don't think the statment in the discussion about a higher incidence in the pre-exposure period being consistent with a higher prevalence of ADHD in children with heart disease is justified. For this, we would need data on people with and without CVD to make a comparison. This just shows there is an increased risk of CVD before and after the start of methyphenidate.

Minor Comments:
1) The overall PPV of diagnoses in the NHIS data is quoted as 83.4%. This is likely to vary considerably depending on the specific diagnosis - can the authors tell us more about the PPV for outcomes included in this study?

2) People with pre-existing cardiac disease in the preceding year to index date were excluded. To calrify, were people still eligible if they had a known CV event >12 months previously?

3) For the exposure assessment, the first exposed risk period is days 1-3, but people with events on day 1 were excluded, so should this be days 2-3 instead? I think it may be better to keep those with events on day 1, but to have day 1 as a separate category in the analysis.

4) As the authors note, there is possibly a timing issue for the recording of events like heart failure, hypertension and arrhythmia compared with when the events were truly incident. This leads to misclassification in a SCCS which could affect the results in either direction.

Additional Questions:
Please enter your name: Ian Douglas

Job Title: Senior Lecturer

Institution: London School of Hygiene & Tropical Medicine

Reimbursement for attending a symposium?: No

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Reviewer: 3

Recommendation:

Comments:
MANUSCRIPT: Cardiac safety of methylphenidate among pediatric patients with ADHD: a nationwide self-controlled case series study

SUMMARY: The authors used claims data from the South Korean National Health Insurance program (2007-2011) to assess the cardiovascular risk with recent new use of methylphenidate (within the past 12 months). In this self-controlled case series study, the population of interest are those diagnosed with ADHD (measured by ICD-10) experiencing their first of any cardiovascular event (defined as arrhythmias, hypertension, myocardial infarction, ischemic stroke, and heart failure). The study appears to be clinically relevant and thoughtfully conducted. In contrast to prior studies, increased risk was found for arrhythmias (all risk periods considered), hypertension (only within the first week), stroke (only within the first week), and heart failure (only after two months).

The authors used a self-controlled case series (SCCS) design to rule out between-person confounding e.g. differing risk factor distributions between groups that use the drug vs. do not use the drug. The authors state that prior literature did not use a case only design like SCCS, and they cite this difference as why their study results diverge from previous studies. But there are other aspects of the SCCS design that are relevant, which I will focus on here.

The issues surrounding SCCS designs and their target of inference can and should be addressed in the Discussion as it is very relevant for placing this study in context. The issue about residual and unmeasured time-varying confounding in this SCCS design can only be partially addressed, because symptoms and precipitating factors are usually unmeasured in claims data. Nonetheless, the study could motivate future studies with better clinical data.

MAJOR POINTS:

(1) The SCCS design changes the research question in an important way. By comparing exposure during the case period and control periods, it focuses on the question of how these risk periods differ among persons who ultimately developed the outcome. In the words of Malcom Maclure, it focuses on "why now" instead of "why me" (see Maclure Pharmacoepidemiol Drug Saf. 2007 Aug;16(8):850-3.) Thus, the study really appears to be asking whether or not methylphenidate use is a triggering event among children who eventually did experience cardiovascular events. This may not be the same question addressed in earlier cohort studies: whether children who take methylphenidate have higher risk of cardiovascular events compared to those who do not. It is important that the reader understand this difference.

(2) Another issue with comparing results from SCCS designs with those from cohort studies is that the populations differ (not just the comparison of persons vs. times). In the SCCS design everyone experiences a cardiovascular event. They may have already been at very high risk for cardiovascular events which begs the question of whether the results apply to children who are healthier. To be clear, this isn't an issue of bias but of generalizability. It's not possible to ascertain this population's cardiovascular risk from the author's Table 1 because it does not report distributions of cardiovascular risk factors. We cannot tell whether this population is high risk or even _how_ it differs from the populations that appear in earlier cohort studies. The authors attribute their unique findings to between-person confounding, but it is very plausible that both sets of studies are reasonably correct, but the populations have different distributions of effect modifiers (i.e. which by definition must be associated with risk factors for cardiovascular events...see VanderWeele TJ Epidemiology. 2009 Nov;20(6):863-71).

(3) As the authors point out, SCCS designs are subject to time-varying confounding. That is, risk factor distributions differ between exposed periods and unexposed periods of time. Although their models control for psychiatric diagnoses and co-medications, this is probably insufficient. There may be residual differences in ADHD symptom severity (along with symptoms of other disorders), medication dose, substance use, and precipitating factors.

MINOR POINT:

It was difficult for me to assess whether the SCCS design was bi-directional or unidirectional. Figure 1 did not resolve this issue for me. Perhaps a bit more detail is needed, like those in Maclure et al. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:50-61.

Additional Questions:
Please enter your name: John Jackson

Job Title: Research Fellow

Institution: Harvard T.H. Chan School of Public Health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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g. Footnotes and statements

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