Author's response to reviews

Title: Comorbidities in ADHD children treated with methylphenidate: a database study

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Author's response to reviews: see over
Dear reviewers,

We thank you for your comments on our study and welcome the opportunity to reply to the points you raised. Please find our point-by-point reply below.

**Comorbidities in ADHD children treated with methylphenidate: a database study**


**Response to reviewers' comments**

[Please note that authors’ responses are listed below in boldface following each comment. All modifications in the manuscript except purely linguistic changes are tracked.]

**Reviewer:** Matthias Halldorsson

**Major Compulsory Revisions:** None

**Minor Essential Revisions:** None

**Discretionary Revisions:**

1. It would be appropriate to state already at beginning of the paper why this is an important subject, especially the co-morbidity of methylphenidate users.

   **Thank you for this comment. We added “The investigation of the prevalence of co-morbid conditions in ADHD children who receive MPH provides an estimation of the magnitude of possibly affected children by the EMA safety evaluation.” in the introduction (page 5).**

2. Discussion, paragraph 1: "Treatment incidence overall was 4.75 per 1000 children and adolescents in 2006 and was 3.3-fold higher in male than in female children. No directly comparable estimates for treatment incidence have been reported in the literature”. May I here refer to a study that we did in Iceland: Zoëga H, Baldursson G, Hrafnselsson B, Almarsdóttir AB, Valdimarsdóttir U, Halldórsson M. Psychotropic drug use among Icelandic children: a nationwide population based study J Child Adolesc Psychopharmacol. 2009 Dec; 19(6):757-64. It reports both incident and prevalence figures according to age and sex.

   **Thank you for your suggestion regarding the literature. We added this study in the discussion of treatment incidence. We did not include it in the discussion of treatment prevalence, since for reasons of better comparability we only included German prevalence estimates in this part of the discussion. Since we could not make out German incidence estimates in the literature we used treatment incidence estimates from other countries.**

3. Background, paragraph 1: As stated by the authors MPH is mainly used for the treatment of ADHD and the only other indication it is licensed for in Europe is the very
rare condition narcolepsy. But why do they not omit those few individuals from the study? They have the diagnoses in the database.

You are right - those few individuals could have been omitted from the study. From the included children who were newly started on MPH only 0.04% (N=7) had a diagnosis of narcolepsy. However, at the time the cohort was set up, we focused on MPH treatment as inclusion criteria. The only exclusion criteria were missing information on sex, year of birth and on region of residence. Since it is unlikely that further exclusion of those very few individuals would have had relevant impact on the results we decided not to rerun all analyses.

4. Background, paragraph 1. It would have been interesting to get an idea of ADHD treated with other stimulants (amphetamines) or with other drugs such as atomoxetine in Germany as well as non-drug treatment of ADHD, even though, as stated by the authors, some under-coding of diagnosis in routine data in this data base may occur.

This is indeed an interesting question. Amphetamines are only infrequently used in Germany, since they have only been available on the German market as finished products since December 2011. Before that they were only available as magistral preparations which limited their use.

Regarding treatment patterns of MPH and atomoxetine we have conducted a further study which will soon be published in the Journal of Child and Adolescent Psychopharmacology: Drug Treatment Patterns of Attention Deficit / Hyperactivity Disorder in Children and Adolescents in Germany: Results from a Large Population-Based Cohort Study. Authors: Garbe,E., Mikolajczyk,R., Banaschewski,T., Petermann,U., Petermann,F., Kraut,A.A., Langner,I.

This study also showed that within a time span of a maximum of 4 years of follow-up almost 50% of children newly diagnosed with ADHD did not receive ADHD drug treatment, however, the specific types of non-drug treatment are not well captured in the database.

5. Statistical analysis, paragraph 1, line 6: Logistic regression adjusting for age as a categorical variable was used to calculate p-values for differences in the presence of comorbid diagnoses between users and the control group. Which age groups were used as categorical variables when correcting for age?

Thank you for this remark. We included one-year age groups in the analysis when correcting for age. We now added this information in the method section.

6. Discussion: Cardiovascular and other co-morbidity (P. 14): Here it would be appropriate to refer to the most recent studies done in response to a request by EMA and FDA after the discussion on stimulants and cardiac events: Winterstein et al. BMJ 2012 & Cooper et al. NEJM 2011.

Thank you for your suggestion regarding the literature. We now refer to those two studies in the discussion on page 15.
Reviewer: Guilherme Polanczyk

Discretionary Revisions

1) Given how the Results are presented, I understand the evaluation of prevalence/incidence of MPH use is also a primary aim of the study. I suggest the ms is re-written based on this.

Thank you for your remark. We have now revised the manuscript accordingly.

Major Compulsory Revisions

1) I'm curious to understand why is it not possible to disentangle ADHD diagnosis and prescription of MPH. If ADHD diagnosis is not coded validly, I would also assume that all other diagnosis (at least psychiatric diagnosis) would also not be coded validly.

The focus of this study was on comorbid conditions contraindicated for MPH use to estimate the impact of the recent EMA safety evaluation of MPH and thus used an MPH user cohort design. This does not mean that it is not possible to disentangle ADHD diagnosis and MPH use in the database. We did this in another study which investigated onset of treatment and treatment patterns in children with an incident ADHD diagnosis. This study will soon be published in the Journal of Child and Adolescent Psychopharmacology: Drug Treatment Patterns of Attention Deficit / Hyperactivity Disorder in Children and Adolescents in Germany: Results from a Large Population-Based Cohort Study. Authors: Garbe,E., Mikolajczyk,R., Banaschewski,T., Petermann,U., Petermann,F., Kraut,A.A., Langner,I.

2) Prevalence/incidence of MPH use is based on "at least one MPH prescription filled in the year". This is an overestimation of MPH treatment, which means continuous use. It is necessary to make this distinction very clear in the ms. Would be relevant to conduct secondary analysis restricted to individuals on adequate treatment for ADHD.

This is a valid remark. Unfortunately, there is not a single standard of what is considered an adequate treatment for ADHD, but clinical guidelines state that treatment needs to be tailored to the individual patient’s needs (European clinical guidelines for hyperkinetic disorder Taylor 2004). The other German studies (Schubert 2010, JahnSEN 2007, Schmidt-Troschke 2004) used the same approach, i.e. at least one MPH prescription in the given year, for their assessment of treatment prevalence. We used this definition owing to a lack of a definition of adequate treatment duration and to be better comparable to the other German studies.

3) Is it possible to understand the temporal ordering between comorbid diagnosis and MPH prescription? It would be very relevant to understand whether comorbid diagnosis where made before of after MPH prescription. Also, because MPH use is defined as at least one MPH prescription, is it possible that those with comorbidities where more likely to be on MPH for a reduced period of time.
Comorbidity was assessed in the quarter of the incident diagnosis and the three preceding quarters, i.e. comorbidity was assessed before or at the initial MPH prescription (Methods, Assessment of Comorbidity, 2nd sentence, page 7). We did not look at the duration of treatment in children with ADHD and comorbidities in this study because the focus was on safety concerns of MPH use. So far, studies investigated the short term risks of MPH treatment (Winterstein BMJ 2012) and no conclusion about the cardiovascular safety can be drawn for long term treatment with stimulants.

4) Would be extremely relevant to have an ADHD group treated with non-stimulants as a second comparison group, or even a group with a similar condition that also would prompt clinicians’ attention to investigate comorbid conditions. It is very likely that those with ADHD, to whom stimulants might be prescribed, would receive additional medical attention and consequently, would have more diagnosis (some of them with unknown clinical meaning). This is a major potential bias in this study and might be true not only in regard to hyperthyroidism, but also in regard to all other conditions.

This is a valid concern, since MPH initiators in our study are not necessarily children newly diagnosed with ADHD. In children not newly diagnosed with ADHD, medical attention due to ADHD may have prompted diagnosis also of other medical and psychological conditions.

We addressed this concern of the reviewer by running the same analysis of previous comorbid conditions in incident ADHD patients (i.e. in patients with a first diagnosis of ADHD) in another ADHD cohort in our database. We analysed comorbidity in

1) all newly diagnosed ADHD patients (19394 male and 6165 female patients in 2005 to 2006) = comparison 1
2) in all newly diagnosed ADHD patients who started treatment with MPH within 365 days of their ADHD diagnosis in 2005 to 2006 (8045 male and 2372 female patients) = comparison 2

These figures are comparable and only slightly lower than those presented in our study:

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>%</th>
<th>Study submitted</th>
<th>% Comparison Group 1</th>
<th>% Comparison Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental and behavioural disorders (F10-F99)</td>
<td>82.47</td>
<td>79.29</td>
<td>80.25</td>
<td></td>
</tr>
<tr>
<td>Preexisting cardiovascular disorders</td>
<td>2.01</td>
<td>1.78</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Preexisting cerebrovascular disorders</td>
<td>0.17</td>
<td>0.18</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0.38</td>
<td>0.30</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1.14</td>
<td>0.48</td>
<td>0.50</td>
<td></td>
</tr>
</tbody>
</table>

Differences in the prevalence of co-morbid conditions between the group of children with MPH use in our study and the two new comparison groups are small for most comorbidities. There is a slightly higher prevalence of mental and behavioural disorders and a substantially higher prevalence of hyperthyroidism in MPH users.
compared to the other two groups. A few sentences have been added to the discussion, which describe the additional analyses and state that concerns regarding diagnostic bias have been invalidated as far as possible.

Minor Essential Revisions

1) On page 16, authors state that "Our study focussed on description of pre-existing comorbidities among children receiving MPH to investigate the impact of new contraindications implemented by the EMA." However, on page 17, authors state that "...at the time the analysis was conducted, only data for the years 2004 to 2006 were available. For that reason, we were not able to ascertain the impact of the contraindications introduced by the EMA in the beginning of 2009 on prescribing behaviour." I suggest authors explicitly state since the beginning of the ms that this study analyze data that precedes the EMA.

We revised our manuscript according to your suggestion.

2) Page 11 - "MPH is known to be used more commonly in the US than in Germany [2] which corresponds to the markedly higher prevalence of ADHD in the US." There is no evidence that indicate that ADHD prevalence is higher in the US or even vary according to country.

You are right, we revised the manuscript accordingly.

3) I suggest authors revise Table 1, Figures and text to not present the same data.

It is not clear to us what is meant here. Table 1 gives treatment prevalence and incidence of MPH per year and sex and is described in the beginning of the result section (page 8). The figures 1 and 2 display treatment prevalence and incidence of MPH by age and sex for the years 2005 and 2006 combined. The figures are described in the result section at page 9. The numbers given in the text represent the data in the two figures.