Author's response to reviews

Title: The epidemiology of pharmacologically-treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care.

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Author's response to reviews: see over
Reviewer's report

**Title:** The epidemiology of pharmacologically-treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care.

**Version:** 3  **Date:** 18 September 2011  **Reviewer:** Almut G Winterstein

**Reviewer's report:**

Like the authors I do not look forward to another round of revisions, but continue to have concerns about this manuscript. I have focused on the major issue to narrow the scope.

Response: We agree with the reviewer’s point that if the aim of the study was to determine how many patients with an ADHD diagnosis received a prescription for a study drug, then we would include patients with a diagnosis of ADHD and determine the number of them with a prescription for a study drug. In that instance, a prescription for a study drug would not be in the inclusion criteria.

However, the aim of our study is to determine the number of patients in the THIN database (representative of UK primary care) who have both an ADHD diagnosis and a prescription for a study drug i.e. pharmacologically-treated ADHD in the general population. For this reason, patients included in the numerator of the calculations performed are patients with both an ADHD diagnosis and a prescription for a study drug. To clarify the point further in the manuscript, we have altered the title so as to read ‘The epidemiology of pharmacologically-treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care’ and have clarified this point throughout the text.

**Authors New Response:** Indeed, our study has the similar objective as a previous study (Jick et al 2004), their study estimated the incidence and prevalence of treated ADD in the UK for the years 1996–2001. It allows us to have some degree of insight of changing in the prescribing pattern pre and post 2000.

Reviewer’s new comment:

You continue to define your inclusion criteria as patients with a stimulant prescription and ADHD diagnosis. How are you going to estimate prevalence if you require everyone to have the conditions that qualify for the numerator? Please revise your inclusion criteria, which appear to be the entire THIN population between 2003-2008 with at least 12 months continuous registration, age >6 (not at time of first prescription as erroneously stated but perhaps at the beginning of each study year?), and known gender.

**Author’s New Response:**

We have modified the methods section of the paper to reflect the suggestions made by the reviewer, in particular how the source population were identified and from these, the prevalence and incidence cohorts. We hope that these revisions provide clarification on how patients were included into the study.

(Pages 6 – 9)
Response: The figures we present for the denominator includes patients registered on the database aged 6 years or over between 2003 and 2008 inclusive who were ‘at risk’ of becoming a case. This is in line with standard definitions for incidence calculations. Any patient who met the definition of a case before the study period i.e. was incident before 2003 was not ‘at risk’ of becoming a case during the study period and so was excluded from the denominator for all years in the study period.

Reviewer’s comment:
1. You define earlier that you included registry data from 2003-2008. Please revise this so that it is clear that you had 2002 data as well, which you used to establish previous drug exposure.
2. This is quite unusual. Your definition would imply that you used a 1-year look-back for 2003 and a 6-year look-back for 2008. Why did you not use a consistent look-back period of one year?
3. You use the term index date in your incidence definition in the manuscript but fail to provide a definition of index date.
4. Please clarify what the midyear THIN population at risk is. Midyear suggests that you simply provided a count of everyone in THIN at June 30. Did you not require continuous registration for the entire year? Does being at risk at June 30 mean that patients with stimulant initiation between Jan 1 and Jun 30 were excluded from the denominator?
5. How was age for the age bands defined? Age at Jan 1 of each year?

Author’s New Response:
We have made significant changes to how information on the methods is presented. We have incorporated the points made above.

1. The methods section has been updated to explain how drug exposure was identified. (Page 8)
2. As above, the explanation of how incident patients were identified is given in Page 8.
3. We accept this point, and have modified the terminology used. We identify the ‘start date’ as the date they registered with the GP practice, the date the GP practice started to use the Vision practice system or the date of the practice’s Acceptable Mortality Reporting (AMR), used as a quality indicator for the practice. (Page 7) We use this term consistently throughout.
4. The mid-year date has been clarified on Page 8 under Prevalence calculation. The 1-year continuous registration is required, however this 1-year is calculated from the ‘start date’ as described on Page 7. Yes, patients who had a prescription for a study drug prior to the mid-year date were excluded from the denominator of that year and subsequent years for incidence calculations.
5. This point has been clarified on Page 7.
Response: we thank the reviewer for clarification of the previous comment. We agree that the overlapping confidence intervals suggest that there is not sufficient statistical power to deduce significant changes for most of the presented comparisons and therefore we believe that presenting the data in such a way would be of limited benefit to the reader. We have made modifications in the write-up of the results such that statistical significant changes are not inferred when the data do not support such statements.

Response:
In the UK stimulants (methylphenidate and dexamfetamine) are (with the exception of dexamfetamine for sleep disorders) only recommended and used for the treatment of children with a diagnosis of ADHD (NICE 2008). Clearly some of these patients may also have co-occurring CD or ODD, but stimulants/atomoxetine would not be used in the UK unless a child or adult met clinical diagnostic criteria for ADHD or hyperkinetic disorder.

Reviewer’s comment:
Don’t the authors consider this comment somewhat naïve? Is there no off-label use in the UK? Since you require treatment AND ADHD diagnosis it is rather likely that the stimulant was intended for ADHD and nothing else, but if you have the time I would urge you to calculate the volume of stimulant use in absence of ADHD dx.

Author’s New Response:

One of the authors of this paper (PA) is the leading expert in the UK on adult ADHD and it is his view that “In the UK clinicians are careful to restrict the use of stimulants to the treatment of patients who are diagnosed with ADHD, apart from the use of dexamfetamine in those with recognised sleep disorders for which this is indicated and typically prescribed to adults.”

Abstract:
I would truncate reported prevalences to one decimal point.
Since you nowhere estimate the prevalence of adult ADHD, please remove this statement from your conclusions: ..”however the numbers treated are much lower than the estimated prevalence of ADHD.”

Author’s New Response:
Prevalences have been truncated to 1dp in the abstract except for older adults where figures are given to 2dp. The prevalence of adult ADHD has been added to the introduction. (Page 2)
Results:
Please update the total number of patients who met the inclusion criteria as the total number of patients who made it into your denominator, not your numerator.

Author’s New Response:
These figures have been included on Pages 10 and 11.

“Between 2003 and 2008, whilst the prevalence approximately doubled in children and adolescents and those patients over 45 years old, the largest increase was observed in adults 18-24 years (4.46 fold increase, 95% CI 3.30-6.02) and 25-45 years (4.90 fold increase, 95% CI 2.70-8.90).”

Would the authors please explain how the estimate for the increase was calculated? The confidence intervals will need to include a corrected standard error for the overlap of patients between comparison years. The denominators are not completely independent.

Author’s New Response:
We thank the reviewer for this comment. We have looked into this issue of potential overlap and estimate that the overlap in patients within the same age category contributing data to the numerator is approximately 3%. In terms of the denominator, due to the age categorization used, there would be limited potential for overlap for children, adolescents and young adults within the two years (2003 and 2008). We acknowledge that there is greater potential for this overlap in the other two age categories. Overall, we have decided to acknowledge this point in the limitations and we have removed the confidence intervals around the estimates for increases between 2003 and 2008.

“These patterns were also evident when the data were further stratified by gender (Table 2). For both genders and across all age categories (with the exception of patients aged over 45 years), the annual prevalence increased significantly from 2003-2008, with the prevalence being lower in female patients for all age categories.”

Please provide confidence intervals or p values for the comparison. Simple observation that confidence intervals overlap or don’t is NOT a statistically sound test to evaluate differences. If you are not prepared to make formal comparisons for any of the reported results, please reword your results in such a fashion that they are purely descriptive and that no formal inferences are inferred.

Author’s New Response:
The wording has been altered as suggested. New wording on Page 10 is as follows: “These patterns were also evident when the data were further stratified by gender (Table 2). For both genders and across all age categories (with the exception of patients aged over 45 years), the annual prevalence increased from 2003-2008, with the prevalence being lower in female patients for all age categories.”

Also, while you might feel that statements are more carefully worded, please consider the following:
“Although these changes were not statistically significant due to overlapping
confidence intervals, the data suggest that for these age categories, the rate of increase in prevalence was greater in females than males.”
The data suggest that you don’t have the statistical power to deduce any conclusion. Please reword this accordingly.

Author’s New Response:
These points have been taken on board and appropriate changes made on Page 11. New wording is as follows: “The data suggest that for these age categories, the rate of increase in prevalence was greater in females than males.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.