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.

**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.

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?

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.

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.”

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.

“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.

“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.

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.

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.