Reviewer's report

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

Version: 4 Date: 31 January 2012

Reviewer: Almut G Winterstein

Reviewer's report:

I appreciate the clarifications in the methods section. I believe I understand most definitions now. The three major remaining issues are as follows:

1. The requirement of ADHD diagnosis anytime during the study period results in varying time periods to ascertain this information. For example a patient who enters the database in 2007 has only one year of follow-up while patient who enters the database in 2003 has a number of years. This may or may not have a strong influence on the numerators of both incidence and prevalence. Would the authors please address this?

2. The previous inappropriate statistical comparisons have been removed but not replaced. Thus, the study presents now purely descriptive data, which given the overall sample size, may be acceptable for overall estimates of prevalence or incidence, but not for comparison across years or strata. I defer to the editor whether absence of formal inferential comparisons is acceptable for the journal or not.

3. There seems to be some issue in calculating incidence estimates as outlined below.

Comments about specific sections in the text follow:

I was somewhat puzzled by the use of the term incident such as here:

From manuscript: These patients were not considered incident and hence were excluded from both the numerator and the denominator for incidence calculations.

Incident as an adjective is usually attached to the first occurrence of something, such as an incident diagnosis or incident prescription. The patients at risk of being started on an ADHD drug would not be “incident” but rather at risk. I suggest rewording of this sentence and all following with use of this term in similar context, for example:

Patient on ADHD drugs during the one-year run-in period were not included in the risk pool.

From manuscript: Patients who were incident before the study period were excluded from the denominator during the study period. Once a patient became
incident during the study period, they were excluded from the denominator of subsequent years.

Suggestion for rewording: Patients on ADHD medication before the study period were excluded from the denominator. Likewise, patients started on ADHD medications were excluded from the incidence denominator of subsequent years.

Reviewer’s previous comment: 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?

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

Reviewer’s new comment: My question in 4 pertained to the definition of incidence. If I understand you correctly you required that a patient was captured in your database the full year preceding the particular study year and had no prescription. Did you require the same patient to be fully captured in the database during the study year (ie, presence in the database for a full 2 years)? Also, if you removed patients with an incident prescription from the denominator you have varying look back periods. For example, for the incidence calculation in 2003, you only look back one year to establish your denominator. For incidence calculation in 2008 you look back one year AND your remove all patients who were in your incidence numerator in previous years (including look back of 6 years). This may not influence reported rates significantly, but it should be fixed.

Reviewer’s previous comment: 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.

Reviewer’s new comment: Simply omitting the fact that most comparisons are not statistically significant does not really improve the validity of the write-up. Most comparisons in the result section are still presented as if they were statistically significant. Omission of the reference to statistical tests or removal of confidence intervals does not improve the situation. Overall, I still think that both the result and discussions section deserve more careful wording and inferences do require formal statistical tests.
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)

Reviewer’s new comment: I would feel much more comfortable if the authors had calculated the proportion of treated patients with a diagnosis of ADHD in their own database. Comparison to prevalence estimates from a different source are troublesome and in my opinion do not warrant a respective conclusion. I maintain my recommendation to remove this from the conclusion unless new data in support of this statement are added.

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.”

I am puzzled how this rewording above reflects any change from the previous statement.

Please consider rewording or removal of the statement below. If I read this correctly you say that prevalence was low because the numerator was low.

“It is observed from Table 2 that the prevalence of prescribing to males and females over 45 years is very low as a result of the low number of treated ADHD patients in this age category.”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests