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
Response to Reviewer’s report

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

Version: 2 Date: 30 April 2011
Reviewer: Almut G Winterstein

We would like to thank the reviewer for their additional comments on the manuscript. We have made a number of changes to the manuscript to further clarify the points made by the reviewer, including modification of the manuscript title. In light of the positive review received from the first reviewer along with the significant changes we have made to the manuscript to address the concerns of the second reviewer, we hope that with these revisions, the manuscript will be accepted for publication. We detail below our responses and changes which are underlined in the revised manuscript.

Reviewer’s report:
I appreciate the presented revisions and detailed response to my comments but remain concerned about the epidemiologic methods. I am sorry to say that I remain confused about the inclusion criteria. The authors state in their response to my previous review the following:

With regards to defining the study population, the aim of the study was to ‘investigate the prevalence and incidence of methylphenidate, dexamfetamine and atomoxetine prescribing to children (over 6 years), adolescents and adults with ADHD/HKD in UK primary care’ i.e. the level of drug-treated ADHD in the general primary care population. For this reason, the inclusion required both a prescription for a study drug and a diagnosis of ADHD/HKD. We have aimed to clarify the above point in the manuscript.

Incidence and prevalence are both estimates that result in a proportion or rate. As per the above cited aim this would be the rate or % of patients with ADHD who receive pharmacological treatment. However, the authors continue to require drug treatment in their inclusion criteria.

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.

As for the definition of prevalence, it appears from the results that this was calculated as annual prevalence. This is not reflected in the definition that is provided in the methods section.

Response: we have included this in the definition stated in the methodology.

Likewise, the definition of incidence remains to be flawed. It appears from the first statement that the authors required a 12-months run-in period from index date to define an incident user (not case). However, the definition of “k” in the formula requires being “at risk” in the mid-year population in a particular year. With all
due respect, I have no idea what this means and I am still not sure that prevalence and incidence estimates were calculated correctly.

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. Likewise, any patient who was a ‘prevalent case’ before the study period was not included in the denominator as they too were not ‘at risk’ of becoming incident during the study period. Any patient identified as incident during the study period was included in the denominator figure until the point at which they received their first prescription. After this point, they were no longer ‘at risk’ and so were excluded from the denominator. Any patient identified during the study period as not being incident i.e. had a first prescription within the first 365 days from index date was not included in the denominator figure as they too were not ‘at risk’ of becoming an incident case.

Would the authors please provide the denominator (ie, total number of patients meeting inclusion criteria) for table 1, and denominator values were table 2?

Response: Table 1 displays data on the number of prescriptions issued in total and the breakdown for each of the study drugs (both number of prescriptions and % of the total number of prescriptions issued) during each year of the study period. Therefore, the total number of patients meeting the inclusion criteria for this table is not applicable. We have included in Table 2 the denominator data, which is the number of patients aged 6 years or older who were registered in the mid-year population. We included data for 2003 and 2008, for males, females and the total number of patients. We have also included denominator data for Table 4.

Note to Editor: due to restricted space in Tables 2 and 4, we have only included total denominator data (i.e. all ages) for 2003 and 2008. Denominator data are available for other years if it is required.

Table 3. If the first set of values shows truly prevalence (ie, the proportion of patients in a certain stratum that received medication) there is no reason to show the ratio (female/male) for the denominator. This is because the definition of prevalence would take care of this. Or did the authors simply report the sum of patients with drug for each gender category and calculated the ratio of this? Same applies for age. Based on the overlapping confidence intervals there is no statistically significant change of any of the ratios presented in table 3 and no respective conclusions can be drawn. The same concerns to a large extend table 4. Also, based on what date was age defined for inclusion in the age bands? Considering the confusing definitions as well as the presented data I still am not sure what type of data is actually presented.

Response: Table 3 shows the ratio of male: female prevalence [i.e. (the number of male patients meeting the inclusion criteria in that year / number of males registered on the database in that year) ÷ (the number of female patients meeting the inclusion criteria in that year / number of females registered on the database in that year)]. Our rationale for including data on the ratio of males: females registered on the database was that one could argue that an explanation for the changing ratio of male: female prevalence observed could be as a result of changes in the ratio of males and females receiving the drug (i.e. the numerator) or a change in the ratio of males to females registered on the database (i.e. the denominator).

e.g. In our study cohort, for males aged 6-12 years in 2003, the prevalence calculated was 7.062 per 1000 patients mid-year population [= 939 / 132973]. The figure for females for the same age and time period was 1.162 per 1000 patients mid-year population [= 147 / 126556]. The ratio of male to female prevalence was 6.080. In 2008, for males aged 6-12 years, the prevalence calculated was 13.83 per 1000 patients mid-year population [= 1728 / 124945]. The figure for females for the same age and time period was 2.498 per 1000 patients mid-year population [= 299 / 119682]. The ratio of male to female prevalence was 5.536.

From both sets of calculations, we can see that the number of patients in the numerator increased for both males and females. Similarly we can see that the denominator figures dropped, however the proportion of males to females remained similar for both years 1.051 and 1.044. Without including these last two figures, it would not be apparent to the reader whether the drop in ratio was due to a change in the ratio of numerator male:female or denominator male:female figures as this raw data is not included in the manuscript.

Abstract
The abstract is still lacking quantitative data and estimates of precision/error or statistical significance.

Response: we have included these data in the abstract

Further concerns related to the authors response:
As this study sought to examine the prescribing of the study drugs in primary care, only the prescriptions contained on the database within the therapy files were utilised. If a prescription was issued for a study drug by a specialist, it would not be systematically recorded by GPs on the database and thus we did not seek to extract these data from freetext information. Is there any data on the distribution of ADHD drug prescriptions between GPs and specialists? This seems important. If specialists prescribe a significant amount it would be important to clarify that the database can capture only a proportion of drug utilization and that data is not representative of drug utilization in UK.

Response: The reviewer is correct in the point that is made, and we have acknowledged this limitation in the manuscript. We state that we aim to estimate the prevalence and incidence of pharmacologically-treated ADHD in UK primary care only. We do not state that the data is representative of drug utilization in the UK as it is not possible to do so using this database. The system of care and the infrastructure surrounding it in the UK does not facilitate linking of data between primary, secondary and tertiary care. There is no data known to us as to the distribution of ADHD drug prescribing between GPs and specialists. The UK national guidelines on ADHD recommend that drug treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD however continued prescribing of pharmacological treatment and monitoring of drug therapy may be performed by general practitioners. Therefore, we expect that the prescribing identified is not initiated by the GP but is the continuation of treatment initiated by a specialist. If a GP is not happy to prescribe these ADHD medications for a patient, then we would expect that we would not identify any prescriptions on the database for this patient. Therefore, in our limitations, we state that it is likely that figures reported in the paper underestimate the ‘true’ level of prescribing of these drugs in the UK, however it is not possible for us to state to what extent this may be the case.

As for the calculation of ratios and my respective suggestions the authors state:
It is a method of analysis that we will certainly consider in future studies however we feel that this was not an aim of this study to evaluate predictors for ADHD drug initiation and therefore we have not performed these calculations. I worry that the authors have misunderstood my suggestions. I was not suggesting a risk model but rather the calculation of the ratios of the ratios that are presented in table 3 and 4. In other words if the ratio between males and females is 1.4 in 2003 and 1.8 in 2008, the ration of 1.4/1.8 along with confidence intervals can provide a direct estimate if the change if these ratio along with statistical significance. Of note, the overlapping confidence intervals suggest that there is not sufficient statistical power to deduce significant changes for most of the presented comparisons. This seems ignored in the write-up of results.

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.
The authors state further:
Response: in the UK, ADHD medications are very rarely prescribed for other behavioural disorders except in a few cases for sleep disorders. In this study, the inclusion criteria required the presence of a diagnosis of ADHD/HKD but did not preclude any comorbidities such as CD or ODD. I would appreciate a reference for this statement as it conflicts quite significantly from US practice.

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.