Author's response to reviews

Title: The epidemiology of pharmacological treatments for attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care.

Authors:

Suzanne McCarthy (s.mccarthy@ucc.ie)
Lynda Wilton (lynda.wilton@pharmacy.ac.uk)
Macey Murray (macey.murray@pharmacy.ac.uk)
Paul Hodgkins (phodgkins@shire.com)
Philip Asherson (philip.asherson@kcl.ac.uk)
Ian CK Wong (ian.wong@dpp.pharmacy.ac.uk)

Version: 2 Date: 4 April 2011

Author's response to reviews: see over
Editorial request:
Please could we ask you to provide a statement, within the Methods section of the manuscript, clarifying whether ethical approval was required and obtained or whether permission to use the data was obtained.

Response: Ethical approval was obtained and a statement of such has been added to the manuscript.

Response to reviewer 1 comments:

No comments to address or changes made to the manuscript based on the reviewer’s report.

Response to reviewer 2 comments:

The article introduction is very broad with a quite lengthy review of ADHD presentation and treatment modalities, which might be well-known to interested readers. It is followed by a review of the available body of evidence on ADHD drug utilization, which the authors evaluate as insufficient. However, while the number of previously published utilization studies might be small, the authors might want to clarify the shortcomings of these studies and how their study would contribute additional evidence. In order to position their study properly it would be useful to highlight knowledge deficits that are specifically addressed by the study at hand.

Response: this point has been addressed in the manuscript. The limitations of the existing data in the literature and the aim of this study to bridge the knowledge gap have been highlighted.
Since the THIN may not be known to all readers it would be important to comment on the generalizability of the physician sample. The methods used to extract specialist prescription from free-text consulting notes and detail on the sensitivity of this approach would furthermore be important to allow the reader to evaluate the accuracy of the presented data.

Response: the first point has been addressed in the method section with regards to the generalisability of the GP sample. With regards to the second point, in the UK, it is recommended in the recently updated NICE guidelines that while the initial diagnosis of ADHD is made by a healthcare professional with expertise in the area, continued prescribing is undertaken by the GP in primary care. 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.

Most importantly, there appear to be several problems with the definition of the study sample and the two outcomes measures, ADHD drug use prevalence and incidence, which made it impossible for me to interpret the presented results. If all subjects were required to have an ADHD drug prescription for study inclusion how was prevalence calculated? I assume that the inclusion criteria were relaxed to include all patients with some type of ADHD diagnosis but the timing of the presence of such diagnosis is unclear to me. Or did the authors indeed require presence of at least one prescription at some point in time – an approach, which seems counterintuitive? It is furthermore unclear how truncated follow-up was handled. There is reference to a requirement for a minimum of 12 months presence in the database, but it is unclear how incomplete presence in a calendar year was handled.

The definition of prevalence does not specify whether the ADHD diagnosis had to occur in the respective study year or not. Note that annual prevalence estimates in drug utilization studies usually utilize period prevalence estimates where all patients with complete eligibility in a given year are extracted for the denominator. This would allow an appropriate time window to establish presence of ADHD diagnosis.

The incidence definition does need clarification as well – and potentially revision. To accurately measure incidence the denominator can only include patients “at risk” for the outcome, in this case initiation of an ADHD drug. Thus, the denominator should only include patients who have not received ADHD drugs in the past. The look back period that was used to define drug naïve patients needs definition as well.

Response: we will address the above points together as there is some overlap in the points made. 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. The reviewer raises the point regarding the timing of the presence of the ADHD diagnosis. As mentioned previously, NICE recommends that an initial diagnosis of ADHD/HKD is made by a healthcare professional with appropriate expertise in the area. For the majority of patients, this diagnosis will be made by a healthcare professional in secondary/tertiary care, most commonly a child/adolescent psychiatrist, a paediatrician, or for adult patients, an adult psychiatrist. Dependent on patient symptoms, patient/parent preference etc, a patient may not start taking medication for the condition immediately after a receiving a diagnosis. Some may try other modalities of treatment such as behavioural therapy prior to initiating pharmacological therapy. Therefore, the year in which a diagnosis is made may not be the same as the year in which a patient starts drug therapy. In addition, the THIN database is a medical records database and so GPs may enter a diagnosis, that was made by a specialist, only once onto the database, but continue prescribing for the condition for many years. Therefore, there may not be a diagnosis in the medical records corresponding to each prescription issued. Also, ADHD is now considered to be a trait like condition rather than an episodic one and therefore for the reasons above, we only required the patient to have one entry in the medical notes of a diagnosis of ADHD. We have clarified in the manuscript that this entry was required to occur after the ‘start date’ of the patient, to ensure that these data met the quality standards required for the study.

We have clarified the definition of incidence to include that people in the denominator are only those ‘at risk’. We have made minor amendments to the results in Table 4 as a result.

On the point of how incomplete presence in the database was handled, we took the following approach: a person was included in the denominator data for a particular year if they were registered in the database at the mid-year point. If a person transferred out of a practice before this time, they did not contribute to the denominator in that year or subsequent years. If the person transferred out of the practice after the mid-year point, then they were included in the denominator data for that year but not for subsequent years. The 12 months of research standard data required patients to have 12 months of continuous registration on the database from their ‘start date’ i.e. that they didn’t transfer out of the practice within their first year of contributing data. We have modified our manuscript to reflect this point.

As for the inferential statistics presented, the comparison of prevalence over time needs to consider lack of independence between denominator populations and adjust standard errors accordingly. See for example our utilization study in Ann Pharmacother 2008 (Winterstein et al). I would also reconsider the presentation of ratios (eg, male/female) to evaluate predictors for ADHD initiation over time.
Instead ratio of these ratios can be used to summarize differences between the denominator and the drug use population. Furthermore, any type of point estimate should be accompanied by estimates of precision (ie, confidence intervals).

Response: we have taken further statistical advice on this matter and have removed the analysis for trend data from the manuscript. In its place, we have provided estimates of precision (confidence intervals) around the estimate for the change in prescribing over time. We appreciate the constructive comments made by the reviewer and the suggestion for additional ways to present the data on ratios (e.g. male/female etc). 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. We do feel that by providing the data as is presented, it will allow the reader to analyse the data in this way if they so wish.

Since I was not sure about the underlying definitions of prevalence and incidence I deferred my assessment of results and discussion until such clarifications have been made and proper statistical techniques have been employed. However, I did note that the discussion section appears to include more quantitative information than the result section. The authors might want to consider moving some of this information earlier in the manuscript.

Response: we have ensured that data appearing in the discussion section also appears in the results section.

Discretionary revisions
It should be noted that ADHD medications are also prescribed for disorders that are closely related to ADHD such as ODD or conduct disorder. These would be more likely indications that made it in the exclusion criteria (rather than narcolepsy or epilepsy)

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.