Author's response to reviews

Title: Persistence of pharmacological treatment into adulthood, in UK primary care, for ADHD patients who started treatment in childhood or adolescence

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 (wongick@hku.hk)

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Author's response to reviews: see over
We thank both the reviewers for their constructive comments on this manuscript. We have addressed the comments from Reviewer 2 below.

Principally the topic of adherence to pharmacologic treatment in ADHD, especially during adolescence is of high interest and so far this manuscript could be an important contribution to this issue. Unfortunately the paper contains a number of serious deficits in substance and methods that restricts its meaningfulness.

Response: With regards to the point made here by the reviewer, we feel that it is important to note that this paper does not seek to examine the topic of adherence (i.e. the extent to which patients take medications as prescribed by their health care providers) in relation to pharmacological treatment in ADHD. This paper seeks to describe persistence with treatment as indicated by continuation of prescribing by the GP that is captured in the THIN database. Similar to many database studies, the analyses are limited by the availability of data collected for the purpose of patient care. Hence, some of the analyses recommended by Reviewer 2 are not feasible.

The Background section
- contains statements being not empirically demonstrated, e.g. “there are two populations of adults with ADHD; those who are recognized for the first time to have ADHD-associated impairment in adulthood,….”. Actually the diagnostic criteria of ADHD still require a symptom onset during childhood before or 7 years and even the awaited DSM V only considers a symptom onset of 12 years.

Response: We agree with the reviewer’s point here; diagnostic criteria does require symptom onset during childhood. Whilst many patients receive a diagnosis of ADHD in childhood, some of whom continue to receive treatment for the condition in adulthood, it is well recognised that for a variety of reasons, some patients only receive the diagnosis of ADHD in adulthood. The European Consensus on the diagnosis and treatment of adult ADHD (Kooij, 2010) highlight this point when they refer to the changes implemented in DSM-V that recognise “the age-dependent changes in the course of the disorder, since the lower threshold in adults is still clinically significant where there is clear evidence of impairment from the symptoms of ADHD; and better reflects the characteristics and natural course of the disorder”. We therefore changed the wording to say that some adults are ‘recognised and diagnosed by a health professional as having ADHD-associated impairment for the first time in adulthood’ to account for the fact that the onset of the symptoms and impairments occurred in childhood.

Almost only considers data originating from the U.K. Comparable international study results are essential to cite. As for treatment guidelines not only NICE should be cited but also European and American treatment recommendations. Long-term follow-up studies as the MTA Study at 8 years give us important informations being essential for the subject of this paper.
Response: We have now also made reference to European and North American guidelines on treatment of ADHD in adulthood along with details of the MTA study in the introduction.

The Method section lacks of specificity in the data extraction

a. No differentiation between patients with or without F 90.0 or F 90.1 diagnosis is given but for the interpretation of the results this information is essential.

a. Differentiation is not provided as stated; in the THIN database the diagnoses for patients are coded using ‘Read codes’ which are entered by the primary care physician and not by the secondary/tertiary care physician who made the initial ADHD/HKD diagnosis. The Read codes for ADHD/HKD were used only to identify patients with a diagnosis of ADHD/HKD coded on the database and not to differentiate between these patients. To this point, we have stated in the limitations that ‘detailed information on the ADHD diagnoses is not systematically coded in the database and therefore it was not possible to determine the severity of ADHD…’

b. Neither informations are given about comorbidities of the study sample nor any socio demographic descriptions though these conditions essentially affect the course and prognosis of the disorder and consequently contribute to the indication of an ongoing pharmacologic treatment.

b. Comorbidities have not been included and thus we acknowledge this as a limitation in the discussion ‘this research did not examine the presence of comorbid mental health conditions and the influence that these may have on the persistence of treatment’. We have done some further analysis of the data according to gender and have stratified results accordingly. These are presented in the updated manuscript. A study by Lara et al, (Biol Psychiatry. 2009 January 1; 65(1): 46–54) which examined childhood predictors of adult ADHD through the use of data from the World Health Organization World Mental Health Surveys reported that persistence was strongly related to childhood ADHD symptom profile, symptom severity, comorbid major depressive disorder, high comorbidity, paternal (but not maternal) anxiety mood disorder and parental antisocial personality disorder. We have stated in the limitations that these have not been examined in the current study; however we do agree that these are important considerations which should be investigated in future studies and have included this point in the discussion.

c. No differentiation is given concerning used medication. Due to different efficacy of stimulant and non-stimulant medication in ADHD differences concerning treatment adherence can be expected between the two treatment groups.

c. As stated above, adherence to therapy was not measured; persistence with ADHD pharmacological treatment was the focus of the analyses. The point raised by the
reviewer is valid as data from the US and Canada (Christensen et al Current Medical Research & Opinion Vol. 26, No. 4, 2010, 977–989; Lachaine et al Postgraduate Medicine, Volume 124, Issue 3, May 2012, 1941-9260) have demonstrated differences in persistence between patients prescribed stimulants and non-stimulants. However, previous work conducted by us in the area of pharmacological management of ADHD in the UK (BMC Pediatr. 2012 Jun 19;12(1):78) highlighted that the majority of prescribing in ADHD is stimulant medication (~90%), with increases in atomoxetine prescribing being observed in recent years. Currently, the atomoxetine-treated cohort is too small with insufficient follow-up to conduct meaningful analysis. We do agree that it is important to examine persistence of prescribing of stimulant vs non-stimulant drugs, and that this should be done in future work when a cohort of patients prescribed atomoxetine which sufficient follow-up time can be identified. We have stated this in the discussion.

d. One more important deficit of the study is the fact that no informations are given if the patient group underwent any regular diagnostic work-up during the development from childhood to adolescence. The reader must rely on informations about the medical status assuming that this fact correlates with the diagnostic stability of ADHD.

d. This point is valid however it must be borne in mind that the data source used for this study is from general practice (primary care). The issue of patients receiving diagnostic work-up from an appropriately experienced practitioner is important; however it is not possible to examine this using the current data source and thus was not the focus of the study. Again, this is an important area for future work and is acknowledged as such in the manuscript.

e. For the reviewer it is not clear why patients with multiple treatment episodes were excluded from the analysis as this practice describes the natural treatment course in ADHD.

e. We acknowledge that the many patients may take some treatment holidays such as at weekends or during holidays etc. and so we allowed for this in our definition of treatment cessation. We believe that the 6-month window was sufficient to allow for drug holidays and to differentiate between these and treatment cessation. As stated in the manuscript, patients with multiple treatment episodes were excluded from the current analyses as they were not considered persistent, which was the focus of the study.