NCCHTA

21 August 2007

1 Project title

Cessation of Attention deficit hyperactivity Disorder Drugs in Young (CADDY). Commissioning Brief (04/36) Current practice in treating patients with attention deficit hyperactivity disorder (ADHD)

2 Changes made on the recommendation of the HTA board members' comments.

In order to strengthen the qualitative component of the research the following changes have been made to Part 2 of the study:

- The target number of patients who will be interviewed has been reduced from 45 to 15. Assuming the consent rate to be 50%, the research team will over-sample by 100% i.e. by asking 30 patients in total to participate.
- Data from the case-note review will be used to identify patients that meet the following stratification criteria:

  -Patients who remain on treatment and have not attempted stopping

  -Patients who have successfully stopped treatment

  -Patients who were unsuccessful in stopping treatment

  A random sample of 5 patients from each category will be contacted by a member of NHS staff (in person or by telephone) and invited to participate in a face to face semi-structured interview with the researcher (RA2). Parental consent will be required for those patients aged 15-18. If patients and parents (when required), give their verbal consent a recruitment pack including a patient information leaflet and consent form will be sent to patients at least two weeks before the proposed time for interview.
- The 10 in-depth interviews with community paediatricians, child and adolescent psychiatrists and adult psychiatrists at the collaborating centres will also be conducted face to face by the RA2.
- Funding that was originally allocated for RA2 to analyse the questionnaire data (2 months) can be reallocated (1 month) to the interview component of the study to allow for face to face interviews to be conducted. The additional costs for travel, accommodation and other expenses are expected to total £2,125. The total cost of the project has reduced by £6,855 to £114,681

3 Planned investigation

A) Research objectives

Aim: To review current practice in treating patients with attention deficit hyperactivity disorder (ADHD) between 15 and 21 years so that more information will be available to plan for future clinical trials and service provision.

Objectives: To review current practice by:

1) Estimating the prevalence of ADHD treatments in the target population using large general practice automated database.

2) Describing the demographic and clinical details of patients in the target population who received ADHD pharmacological treatment including duration of treatment, age of medication cessation, and dosage.

3) Estimating the percentage of patients in the target group who stopped the ADHD pharmacological treatments, and investigating possible factors affecting the continuation or cessation of pharmacological treatments.

As requested by the Commissioning Brief, the following objective was also included so that the data could be collected for the development of future clinical trials & service provision.

4) To conduct in-depth interviews with patients attending or discharged from specialist clinics to identify the reasons for cessation of ADHD pharmacological treatments (and the effects on symptoms), to explore perceptions of the process and outcome of cessation and to explore issues of quality of life.

5) To search the literature for potentially appropriate quality of life measures for this patient population and to test their reliability and face validity with the interviewees.

6) To conduct in-depth interviews with clinicians to obtain their perceptions of the process and outcome of cessation of ADHD pharmacological treatments (and the effects on symptoms).

B) Existing research

i) Brief introduction to ADHD and the cessation of treatment

ADHD is defined by three core symptoms: inattention, hyperactivity and impulsivity [1]. It is a condition known to affect 4 to 8% of school-age children, and impairs educational and social functioning, resulting in distress for the children and their families. Untreated ADHD is a risk factor for the development of other disorders later in life such as substance misuse, personality disorders and other problems affecting education and employment.

Long-term follow-up studies of young adults with childhood onset ADHD have shown that the disorder will persist into late adolescence (40% of patients) and adulthood (ranging from 5 to 64% of patients (depending on the definition of persistence used) between 21 and 25 years old) [2, 3]. However, there is little information on the treatment of older adolescents and young adults with ADHD, particularly the usefulness of medications and their prevalence of use. Recent studies have shown that short-term use of methylphenidate is effective in adults [4, 5, 6]. The discontinuation of methylphenidate for the treatment of ADHD is recommended during adolescence, although no firm guidelines for the withdrawal of treatment are given (NICE guidance, 2000). There may be several reasons for medication cessation during adolescence: perceived remission of ADHD with increasing age by patients and/or clinicians; doubtful response to treatment; potential for medication misuse; concurrent substance misuse; poor motivation [7]. Methylphenidate is not licensed for adults; therefore some GPs are reluctant to prescribe it to young adults. Furthermore, as ADHD treatment services for older adolescents and young adults are currently poorly developed, some patients wishing to continue on treatment may not be able to due to their falling into a gap between child and adult services (see Preliminary data analysis of GPRD in the next section).

ii) Unpublished Pilot data

a) Preliminary feasibility survey of paediatric psychopharmacology groups

A preliminary feasibility survey of two regional paediatric psychopharmacology groups (comprising paediatricians and child and adolescent psychiatrists) was conducted in March 2005, in which clinicians were asked if they had local institutional guidelines on the use and cessation of methylphenidate, dexamfetamine and atomoxetine in older adolescents and young adults. Only one clinician out of 18 responders had guidelines, even this clinician has suggested the local GPs refused to use the guideline. The feasibility survey showed that a national survey of clinicians would be futile. This highlights the need for the development of evidence-based guidelines on the pharmacological treatment of ADHD in older adolescents and young adults.

b) Preliminary data analysis of GPRD

A number of pharmacoepidemiological studies have described the utilisation of stimulants, particularly methylphenidate in children [8, 9, 10]. Jick *et al* found the prevalence of methylphenidate-treated ADHD was 5.3 per 1,000 UK boys aged 5 to 14 years in 1999. Pharmacotherapy for ADHD is more prevalent in the US where annual prevalence ranged from 25.4 to 38.4 per 1,000 aged <20 years in 1996 [9]. However, no study known to us has investigated the use and cessation of ADHD medications in older adolescents and young adults with ADHD in UK primary care.

Traditionally, child and adolescent mental health services (CAMHS) have been available for young people up to sixteen years of age or up to school-leaving age. The National Service Framework for Children (2004) states “there is a broadly held view and concern that many young people of sixteen and seventeen years old are not receiving the services they require since they fall into the gap between child and adult services”[11]. We obtained unpublished data from the GPRD demonstrating that the number of patients receiving ADHD drug treatments rapidly declines by 45% between 16 and 17 years of age (Appendix 1). This is further supported by unpublished data from a co-applicant, demonstrating that the prevalence of methylphenidate in 2001 declined by 69% between the age-groups of 13-15 years and 16-18 years (Appendix 2). This current practice may be partly due to some patients “falling into the gap between child and adult services”. Such a large reduction in ADHD treatment for this group of adolescents has not been reported in a US pharmacoepidemiological study [12], and therefore lends support to the suggestion that service arrangements could play a large role in the current practice of treating patients with attention deficit hyperactivity disorder. All these factors urgently require investigation in order to support future research and practice.

iii) Brief introduction of prescribing ADHD treatment in the UK health care system

It is necessary to understand the prescribing of ADHD treatment in the UK health care system in order to design an appropriate study. ADHD treatment is usually initiated by child and adolescent psychiatrists or paediatricians, and GPs will continue to prescribe to most patients. However, in some cases (currently no known data to show the proportion), the child psychiatrists or paediatricians will continue to prescribe the treatments. Finally the difficult-to-treat cases will be referred to the national clinics, which are currently at the Maudsley Hospital and Great Ormond Street Hospital for Children. Finally, when the patients reach late adolescence, they are discharged from adolescent psychiatrists’ or paediatricians’ care. The age of discharge and transfer to adult care will depend on local policy, but in general there is no specific arrangement for transfer of care to adult psychiatrists because of the perception that the majority of patients will not require further treatments.

With the above information in mind, this proposal is designed to obtain information from primary care using a national GP database, secondary care and tertiary care clinics in order to provide an accurate account of current practice in treating patients with ADHD.

C) Research methods

Design: A pharmacoepidemiological study using an automated database and patient interviews. An informative overview of current practice in different settings could be obtained by carrying out the proposal in two main parts. Part 1 is an epidemiological study, using general practice data on the target population, to provide accurate data on the use and cessation of ADHD drugs in order to answer objectives 1 to 3. Part 2 is an in-depth interview study, set in secondary and tertiary care, to investigate the reasons, the process and the outcomes of treatment cessation in order to achieve objectives 4 to 6.

Setting:

1) Primary care using the General Practice Research Database (GPRD).
2) Secondary and tertiary care of paediatric clinics, child and adolescent mental health and adult mental health clinics.

Target population: NICE guidance No. 13 stated that methylphenidate should usually be discontinued during adolescence [1]. Therefore young people aged between 15 and 21 years are the appropriate choice.

Health Technology Assessed: Methylphenidate, dexamfetamine and atomoxetine will be assessed; however, only a limited number of patients are expected to be on atomoxetine. Other drugs in off-label use such as pemoline, bupropion, desipramine and clonidine will be excluded.

4 Proposed Research

Part 1 – Pharmacoepidemiological study using the GPRD

This part of the study is modelled using a previous study of antidepressants in children and adolescents conducted by the lead applicant using GPRD [13].

i) Rationale

This part of the study will give accurate data on the current practice of the use and cessation of ADHD treatment by describing the prevalence of medications in primary care, and the median ages at which patients stopped and restarted treatment in the target population.

ii) Selection of databases and data source

In the UK, there are five main databases which contain patients' longitudinal data. They are the GPRD, IMS Disease Analyzer-Mediplus (Mediplus), GPASS, MEMO and QRESEARCH. After detailed consideration, we chose the GPRD as our data source. GPASS and MEMO only contain Scottish data and are relatively small [14]; they are unlikely to have sufficient data to conduct this study. QRESEARCH is a new emerging database; however analyses remains to be undertaken to demonstrate the accuracy and completeness of the data; and so far no peer-reviewed publications are available to demonstrate its usefulness (http://www.nottingham.ac.uk/~mczqres/index.html). On the other hand, both the GPRD and Mediplus have been extensively used and their advantages and limitations are widely understood. Particularly, there have been over 400 research papers published in peer-reviewed journals using GPRD data [15]. As the GPRD is larger and a richer data source than Mediplus, the GPRD is the preferred data source.

The GPRD is one of the world's largest computerised database of anonymised patient data from general practice. It contains over 35 million patient years of data. The GPRD has been collecting patient records in the UK continuously since 1987, and it currently collects information on approximately 3 million patients, equivalent to almost 5% of the UK population [14]. Data are provided regularly by over 350 contributing general practices from all around the UK, including Scotland and Northern Ireland [15], and broadly represent the UK population [16]. The quality and completeness of the data are high, and data quality checks are conducted routinely [16, 17]. In 2002, there were records for 877,802 children (under 18) in GPRD and 1.3 million prescriptions were issued for this cohort (Personal communication – GPRD). The GPRD has been used to study the safety of MMR in children, and SSRIs and suicide [17, 18], and a recent report published by the Royal College of Paediatrics & Child Health recommends the use of GPRD for children's medicine research [19]. The high cost of accessing the GPRD has deterred academics in using it (a single study costs from £15,000, plus the cost of research time spent on extraction.) However, as the GPRD has a huge potential in children's medicines research, the EU Commissioners has agreed to fund the lead applicant to access the GPRD for five years under the EU Framework Sixth Research Programme. Therefore, the HTA is not required to fund the cost of accessing the data.

Information collected from general practitioners (GPs) includes:

- Demographics, including year of birth and gender of patient (information on ethnicity is not collected)
- Medical diagnoses, including comments

- All prescriptions issued by the practice
- Events leading to withdrawal of a drug or treatment
- Referrals to hospitals and specialists
- Treatment outcomes, including hospital discharge reports in cases where patients are referred to hospital for treatment
- Medical tests, including laboratory results and pathology
- Immunisations
- Miscellaneous patient care information e.g. smoking status, height, weight, laboratory results

The coverage of the study drugs in the GPRD will depend on GPs' agreement to prescribe them, particularly methylphenidate and dexamfetamine. Prescriptions for methylphenidate and dexamfetamine are handwritten, but a study has shown that over 80% of handwritten prescriptions are recorded electronically [20]. Therefore, some underestimation of treatment prevalence is expected.

The data of eligible patients will be obtained according to the specified selection criteria. The database is updated regularly, so the data will accurately portray the current practice of ADHD treatment in primary care.

iii) Sample size consideration

A preliminary feasibility study identified approximately 750 patients in the target group who were prescribed methylphenidate, dexamfetamine or atomoxetine between January 2001 and December 2004 (post NICE guidance) on the GPRD (Figure 1). Data is collected regularly by the GPRD, so by the time the project is initiated, the study period may be extended to **December** 2005, and the target group will be larger.

The objective of the study is to review the current practice of cessation of ADHD treatments; therefore sample size calculation is not relevant. The GPRD was selected not just for its size, but also because the demographic distribution of its population is broadly similar to that of the UK population, so that the results will be generalisable and representative of current practice in the UK.

iv) Selection criteria of eligible patients

It is proposed that the following two-stage criteria will be used in the selection of patients. This is subject to an analysis of the age distribution of patients prescribed at least one of the study drugs.

Stage 1 selection

Patients must:

- be aged between 15 and 21 years in the study period between 1 January **1999** and 31 December 2005 and have at least one prescription for methylphenidate, dexamfetamine or atomoxetine.
- have at least 1 year of research-standard data available in the database.

Patients must not:

- be temporarily registered to their general practices.

Stage 2 selection

Patients must:

- fulfil Stage 1 criteria
- have a diagnosis of ADHD as detected by a predefined algorithm (details given in 'Identification of ADHD diagnoses')
- have at least one year's duration of treatment with methylphenidate, dexamphetamine or atomoxetine. This will ensure only patients who have had good response to treatment will be included in the study.

Patients must not:

- be prescribed methylphenidate, dexamfetamine or atomoxetine for other reasons, such as narcolepsy, or epilepsy (to counter toxic effects of anticonvulsants).

v) Data synthesis and analysis to obtain information on current practice

a) Identification of ADHD diagnoses

Patients must have a confirmed diagnosis of ADHD associated with the first prescription of methylphenidate, dexamfetamine or atomoxetine (whichever was issued first). Diagnoses of ADHD will be identified by using a predefined algorithm, as the GPRD does not directly link prescriptions to medical diagnoses. Several methods will be included in the algorithm for the identification of ADHD diagnoses in the patient records such as:

- For each consultation, a consultation identifier code is allocated which is used to associate referrals, prescriptions and diagnoses with the consultation. This indirect linkage between prescriptions and diagnoses can be used to identify ADHD diagnoses associated with the first prescriptions of the study drugs.
- In cases where a prescription has no associated diagnosis, the medical records with the same date as prescriptions issued for the study drugs will be screened for diagnoses of ADHD.
- The medical records will be screened in the six-month period before and after the first prescription date for diagnoses of ADHD.
- Free-text fields, which will include hospital discharge reports, will be screened for ADHD diagnoses.

b) Prevalence of study drugs

Gender and age specific annual prevalence of methylphenidate, dexamfetamine and atomoxetine will be calculated. Prevalence is defined as the number of patients with one or more prescriptions per 1,000 patients in the mid-year population of the GPRD. There may be an underestimation of prevalence as some prescriptions will be hand-written, and may not be recorded electronically.

c) Duration, cessation and restart of treatments

The duration of each prescription will be calculated from the daily dosage and the quantity of medication prescribed. If a new prescription is issued before the previous one has “run out”, and the drug was the same for both prescriptions, it will be assumed that the second overlapping prescription started the day after the previous one finished. Overlapping prescriptions for different stimulants will be considered to indicate a switch from one stimulant to another. If a switch is identified, the initial prescription will be shortened to end on the day the second stimulant is prescribed.

Patients who have stopped treatment will be identified by applying a method previously used [13]. Also, patients’ data will be screened for any records of treatment cessation. A minimum gap of six months between prescriptions will indicate a stop in treatment. Cox regression and/or Kaplan-Meier analysis will be used to estimate the percentage of patients in the target group who stopped treatment and to identify possible factors affecting cessation such as age, gender, dosage of treatment. The percentage of patients restarting treatment will be examined using Cox regression and/or Kaplan-Meier analysis and possible factors affecting treatment restart will also be investigated.

Part 2 - In-depth interview study with patients from specialist ADHD clinics and clinicians who work with ADHD patients.

i) Rationale

The Commission Brief specified that “As far as possible applicants should also plan to explore the clinical and social outcomes of these patients”. Although automated databases are able to provide epidemiological data on medication use, they do not record the reasons for medication cessation, outcomes and patients' experience. Therefore Part 2 is proposed to investigate the above factors. The HTA Designated Commissioning Board Members’ Comments agree that this part of study will flesh out the understanding of the current practice.

This part of the study will allow patients and clinicians to express their views on current practice. Furthermore, according to the Commissioning Brief, it is the HTA's intention to commission a trial in the future. It is clear to this research team that it is essential to collect qualitative information on the process of cessation and outcomes to support the development of a good trial protocol in the future. Particularly, we foresee the methodology is likely to be a randomised withdrawal study, similar to a previous study in antiepileptic drug withdrawal [21]. A randomised withdrawal study is likely to be complicated and patients' and clinicians' involvement are likely to be a key factor for the success of the future study. Therefore the understanding of the experience and feeling of patients and clinicians we would gain from this part of the study is essential. It is cost effective for the HTA to fund this part of the study in order to better support future trials.

ii) Methods

a) Patients selection and data collection

Collaborators at London, Nottingham, Dundee and Liverpool* will identify all active patients (**aged 15-21 years from the 1st January 2001**, after the year NICE guidance was issued) in the clinics receiving treatment for ADHD or who have received ADHD treatment in the past which has now stopped. An active patient is defined as a patient who is under the care of the collaborating clinics for their ADHD management. Collaborators at each centre will also identify all discharged patients. A discharged patient is defined as a patient who is no longer under the care of the collaborating clinics for ADHD management including patient transfer to adult psychiatric care, primary care or moved away. **Discharged patients must be aged 15-21 after the 1st January 2001 at the time of discharge**. Collaborators will ascertain whether these patients are still on treatment by contacting their GPs or patients directly. The collaborating centres have expressed interest in running the future RCT and we expect all future collaborators will have similar characteristics, so we can also obtain information about the potential recruitment rate. **Patients who received treatment as an inpatient will be excluded from the study.**

A structured data capture form will be designed to enable a systematic case-note review of all patients at the collaborating clinics (estimated to be **120** patients in total in order to identify appropriate patients for interview. The lead applicant has experience in case-note review of over 1,000 patients [22]. From the case-note data the CADDY team will stratify patients according to the following three categories:

- patients who remain on treatment and have not attempted stopping.
- patients who have successfully stopped treatment
- patients who were unsuccessful in stopping treatment

Stratified random sampling will be used in this study in order to identify a wide range of experience. We aim to recruit 15 patients in total; 5 who remain on treatment, 5 who have successfully stopped treatment and a further 5 who were unsuccessful in stopping treatment. Purposive sampling will be used if sufficient numbers of patients in each of the three categories cannot be obtained through random sampling. Each patient will be invited via letter to participate in a face to face semi-structured interview with the researcher (RA2). Parental consent will be required for patients aged between 15 and 17. The letter will be sent to both patients and parents (when required) and will include a patient information leaflet and consent form. If patients do not reply after two weeks, a reminder will be sent. If patients do not respond to the second reminder, the non-response will be regarded as a refusal to participate.

The data from this case note review is also crucial for allowing us to obtain information on the potential recruitment rate in the centres likely to take part in future trials. We will be able to estimate the proportion of patients that would fit criteria for eligibility assessment in a future trial. Also, we will be able to estimate the proportion both overall and within each stratum that consent and the differences between those who consent and those who do not. This will help establish how representative the sample of interviewees is of the target population for a future trial.

***We previously specified that Derby would be a separate site, however, now Derby and Nottingham will act as one site.**

b) Clinician selection

Furthermore, we will also conduct 10 face to face in-depth interviews with community paediatricians (associated with mental health clinics), child and adolescent psychiatrists and adult psychiatrists of our collaborating centres to explore the issues related to cessation of ADHD treatment in the target population. A recruitment pack including an information leaflet and consent form will be sent to these clinicians at least two weeks before interview to allow them sufficient time to consider whether to take part or not. If these clinicians do not reply after two weeks, a reminder will be sent.

iii) Sample size consideration

Assuming the consent rate to be 50%, the research team will over-sample by 100% of both patients and clinicians i.e. by asking ~10 patients in each patient group (~30 patients in total) and 20 child and adult psychiatrists to participate. These figures were selected because it is a reasonable number to recruit within the time and resource constraints. An alternative approach would be to continue recruiting patients and clinicians until theoretical saturation was reached [23] but this is beyond the scope of the present study.

iv) Data Collection

The patient interviews will explore patients' experience and feelings about taking medication, and the process and outcomes of cessation (in both clinical and social terms) so that lessons could be learnt in managing cessation appropriately (using communication, information and family support etc). A face to face semi-structured interview will be conducted which should last **approximately 55 minutes**. **To give more context to the information obtained from the interview study, two different scales will be administered. The first of these involves the administration of the Du Paul scale which will be used to assess patients' level of symptomology. This scale is completed by patients' parents. Therefore, for participants aged 17 and under, it will be sent with the initial recruitment pack and parents will be requested to post it back before the interview. For participants aged 18 and over, consent will be obtained from them at the interview for us to post the Du Paul scale to their parents or relevant carer. We appreciate that for some patients it may not be appropriate to contact parents/carers as the patient has long since moved away from the parental home and therefore we will only send the questionnaire to the parents of patients who are still living at home with their parents. The second scale, used to assess patient' attitudes towards treatment will be administered during the interview. This information is important to obtain because research conducted in this area suggests that attitudes are important to explore in the context of patients' medication-taking behaviour.** The interview schedule will be developed by a co-applicant, a health psychologist, in conjunction with clinicians and patient representatives according to steps recommended by Bowling [23]. The interviews will explore patients' unique experiences with the medication and topics that will be covered include:

- Adherence to medication
- Beliefs about medication
- Medication-related problems
- Quality of life issues
- The process of medication cessation:
    - Reasons for cessation
    - Decision-making about cessation
    - Communication issues with health care professionals at the time of cessation
    - Family support available at the time of cessation

A number of issues related to quality of life measurement will be addressed within this part of the

study. The choice of a rating scale to assess quality of life in future trials with this patient population is not clear and so **we propose to undertake a full literature search of the scales available**. We will review the scales that are located and select two or three that appear to be most appropriate for our target population and purposes. We will ask our interviewees to complete these. This will provide information on the parameters (e.g. means and standard deviations) required to estimate sample size based on quality of life in future trials. It will also provide information on the proportion of missing data to be expected from each scale. We will ask our interviewees to comment on the face validity of the scales and to nominate a scale they feel is most appropriate. This will enable use to select the most appropriate scale and to estimate the sample size required with better accuracy.

A separate interview schedule will be developed to elicit clinicians' perspectives of the process of patients' stopping medication for ADHD. SC will be supervising the research assistant in this part of the study; she will provide training in interview skills and techniques to ensure the validity and reliability of using this method.

v) Analysis

The interviews will be tape-recorded and transcribed verbatim. The transcripts will be analysed using a grounded theory approach, which is an inductive methodology that allows theory to be developed from the systematic gathering and analysis of data [26]. The initial transcripts will be read and coded by the research assistant and SC in order to develop an initial coding structure. Thereafter, all transcripts will be coded and meetings will be held between the research assistant and SC regularly to discuss emerging themes from the data. Data quality will be assessed using several methods recommended in the literature, which include checking the meaning of outliers or extreme cases and checking out rival explanations during data analysis [27]. This information from the patient and clinician interviews will be useful for planning future services and research.

The data from the quality of life measures will be subjected to analysis by **Laura Potts** in order to identify the most appropriate quality of life measure to use in the future withdrawal trial.

5 Ethical arrangement and considerations

Part 1 study

The GPRD is owned by the Health Secretary of the UK Government. The anonymity of GPs and patients is assured. All patient data received by the GPRD Division is in anonymised form and patient identifiers are encrypted. The GPRD complies with current UK regulation.

All research protocols for GPRD studies will have to obtain approval from the GPRD Scientific and Ethical Advisory Group (SEAG). The SEAG will consider the scientific and ethical soundness of research projects for which data from the GPRD are requested. Our proposal will obtain SEAG approval to safeguard the scientific and ethical standards of the project. Furthermore, the chief investigator has conducted a similar study in antidepressant use of children and adolescents [13]; the research team do not foresee any scientific or ethical problems.

Part 2 study

This part of the study will require Multicentre Ethics Committee approval (MREC). We will adhere to the guidelines from the ethics committee regarding research with children and adolescents, to ensure that no ethical problems arise. We will also follow the British Medical Association's consent tool kit on informing children and obtaining consent for research. Care will be taken to ensure that patients understand that taking part in the study is entirely confidential and that they can withdraw at any time without their care being affected. We do not anticipate the interview causing distress to participants. However, if this occurs then we would terminate the interview and, if necessary, refer them to an appropriate clinician to discuss it further. Please see below for more detailed discussion of potential ethical issues in this part of the study:

- Family tension: If evidence of family tension emerges during the interview and the participant is upset by discussing this then the researcher will ask whether they would like to stop the interview. The patient will be offered the opportunity to speak to medical staff involved in their care, or the PALS staff in the hospital. If there is reasonable cause to suspect potential child protection issues as a result of this family tension then the researcher would follow the

steps outlined in section f below.

- Child protection issues: In the event of disclosure of child protection issues we are prepared to deal with it professionally and legally. Following the advice of the Medical Research Council [28], if the researcher has reasonable cause to suspect that a child is suffering or likely to suffer harm then she has a clear responsibility to urgently contact those responsible for the child's clinical care. The child would then be referred to social services. The decision to disclose this information would, if possible, be discussed with the child before any action was taken.

- Gaining consent from parents &/or children is an important ethical issue. We will ensure that we adhere to guidelines from the BMA on how to obtain consent from children and young people in research [29]. We will follow recommendations that for patients under 18 years of age, we need to recruit via their parents or carer. For these participants we will send an invitation letter addressed to their parents (see attached) but also include an invitation letter for their parents to pass on to them (see attached). Consent will be deemed to have been given only if BOTH parent and child/young person provides consent. We will be vigilant for signs of any conflict that may arise due to recruiting participants via a "gate-keeper" (their parents). The interview will not proceed unless we have written informed consent from both.

- Potentially upsetting subject matter. The researcher has a sound understanding of ADHD and common difficulties associated with the condition (e.g. family conflict, difficulty holding attention for periods of time). Care will be taken to ensure that participants understand that their participation is entirely voluntary and confidential and that they are free to withdraw at any time they like. The interviews will be terminated if there is any indication that the participant is distressed or expresses a wish to terminate the interview. Clinicians will be available if the patient wishes to speak with them. In the event that there are no clinicians at the specific moment, then the Patient Advisory Liaison Service (PALS) will be called upon to assist the patient if required.

- Potential for participants with ADHD to have impaired educational and social functioning. The researcher will take this potential into consideration. As recommended by other researchers who have interviewed children and young people will learning difficulties [30], the following steps will be taken:

    - The researcher will explain clearly and make sure that the participants understand the purpose of the research, what their participation will entail and what the results will be used for. She will ensure that participants fully comprehend that they do not have to take part in the study and that even if they do take part; they are free to withdraw at any time, with no explanation required and at no cost to their ongoing medical care.

    - The researcher will be alert to unexpected responses from participants and be flexible in how she facilitates the discussion.

    - The researcher will ensure that participants feel relaxed. One way of doing this will be to ensure that after participants have consented to having the interview tape-recorded she will make the recording implement as unobtrusive as possible.

6 Data protection and retention

Data will be stored to comply with the current Data Protection Act and the length of retention will comply with current Research Governance recommendations from the Institute of Child Health (based on advice from the MRC); the data will be kept for 15 years.

7 Expertise

The members of the research team have been selected according to their expertise and contributions. The research proposal has been developed with the input of the whole team as well as Andrea Bilbow

from ADDISS (The National Attention Deficit Disorder Information and Support Service).

This project is investigating the current practice of ADHD treatment in adolescents and young adults, so it requires a multidisciplinary team with expertise in child, adolescent and adult psychiatry, pharmacoepidemiology, health psychology and clinical pharmacology.

Professor Wong is funded by the Department of Health (DH) via a Public Health Career Scientist Award to investigate the use of psychotropic drugs in children and adolescents; his research expertise is paediatric pharmacy and pharmacoepidemiology. He is the chief investigator of the project and responsible for overall running of the project. He is Good Clinical Practice trained (GCP) and will ensure the project complies with Research Governance recommendations.

Professor Eric Taylor is a consultant in child and adolescent psychiatry; he is an expert in ADHD and runs the national child and adolescent ADHD clinic at the Maudsley Hospital. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study, and data interpretation of both Part 1 and 2 studies. Furthermore, he is also a member of the Mental Health Research Network (MHRN), so he will be able to liaise with the MHRN in information dissemination and also obtain support from the MHRN in the development of future trials in the cessation of ADHD treatment.

Professor Philip Asherson is a consultant in adult psychiatry. He is an expert in ADHD in adults, and run the national adult ADHD clinic at the Maudsley Hospital. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study and data interpretation of both Part 1 and 2 studies.

Professor Imti Choonara is one of the only three paediatric clinical pharmacologists in the UK. He will provide his expertise in clinical pharmacology to interpret the results.

Professor Hollis is head of the division of psychiatry at Nottingham University and an expert in ADHD. He will contribute to patients/clinicians recruitment in Derby and Nottingham for the Part 2 study. He will also contribute to data interpretation of both Part 1 and 2 studies.

Mr Tony Nunn is the Chief Pharmacist of the Alder Hey Hospital. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study in Liverpool and the surrounding area. He is also the Chair of the National Service Framework (NSF) for Children Medicines Module and the Associate Director of the newly formed Medicines for Children Research Network (MfCRN). He will be able to liaise with the NSF and MfCRN in information dissemination and also obtain support from the MfCRN in the development of future trials in the cessation of ADHD treatment.

Dr Corinne de Vries is a Reader in Pharmacoepidemiology and has vast experience in conducting drug utilisation studies; her main contribution will be the methodological development and data management. Dr Tim Williams is an epidemiologist at the GPRD Division of the MHRA (it should be noted that the GPRD Division is not involved in regulatory activities); his expertise is programming and data management. He will contribute to the data extraction and processing in the Part 1 study. Dr Williams will also work as the liaison person with the GPRD Division. Permission has been obtained from the MHRA (an executive agency of the DH) to be a co-applicant. Together, Dr Wong, Dr de Vries and Dr Williams will supervise Mrs Macey Murray in data extraction, processing, analysis and interpretation.

Dr Sarah Clifford is a health psychologist with considerable experience in conducting interviews with patients; she will supervise the second research assistant (RA2) in the development of interview schedules and qualitative data analysis of the Part 2 study.

Dr Dave Coghill is a consultant in child and adolescent psychiatry. He is an expert in ADHD, and runs a specialist ADHD service in Dundee. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study. He will also contribute to data interpretation of both Part 1 and 2 studies.

Dr Kapil Sayal is a consultant in child and adolescent psychiatry, and has expertise in ADHD service development and health-services research. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study in Nottingham. He will also contribute to data interpretation of both Part 1 and 2 studies.

Dr Ruwan De Soysa is a Consultant Community Paediatrician working in Alder Hey Children's Hospital, Liverpool. He runs an ADHD diagnostic clinic jointly with the local Child and Adolescent Mental Health (CAMH) team. He will contribute to patients/clinicians recruitment and data collection in the Part 2 study together with Tony Nunn (Director of Pharmacy). He will also contribute to data interpretation of both Part 1 and 2 studies.

Ms Laura Potts is a statistician within the Clinical Trials Unit at the Institute of Psychiatry, King's College London. She will advise on planning for an RCT of cessation of ADHD medication that we will develop using the results of this pilot study, which includes advising of appropriate sample size for the pilot study and future RCT, and identifying and testing measures that will be required for the endpoints of the future study. The Clinical Trials Unit will provide epidemiological statistical expertise for the Part 1 study.

Finally, Mrs Macey Murray will be employed as research fellow to conduct the Part 1 study. She has conducted a similar study under the supervision of Dr Wong and Dr de Vries [13] and is highly competent in the use of the GPRD and data analysis.

8 Environment for research

The Centre for Paediatric Pharmacy Research at the University of London is the only Centre in the UK dedicated to children's medicines research. It has established a reputation in paediatric pharmacoepidemiology research and has been recognised as a Centre of Excellence by the EU Commissioners, receiving funding to develop paediatric medication research in the EU with other EU partners. The Maudsley Hospital and the Institute of Psychiatry in London are the international leading research and treatment centres in psychiatry; they have a well-established research programme in ADHD led by Professor Taylor. Other academic and clinical units in Alder Hey Hospital, University of Nottingham, University of Dundee and University of Surrey are also well-established in psychiatry, child health, ADHD and pharmacoepidemiology research. Furthermore the Coordinating Centres of Mental Health Research Network and Medicines for Children Research Network are located at the Maudsley and Alder Hey hospitals. Combining the expertise and resources of the above centres will ensure the success of the CADDY project.

9 Consumers

We have invited Ms Andrea Bilbow to be an advisor of our project. The aims of Ms Bilbow's active involvement is to advise on (1) significance and feasibility of the research protocol from a consumer's point of view. (2) interpretation of the results from a consumer's point of view.

Ms Bilbow is a patient and parent representative from ADDISS. She has been involved in protocol development, and has reviewed the CADDY project. She suggested that it was essential to include adult psychiatry clinics in the Part 2 study. The research team has accepted her advice and invited Professor Asherson to take part in this study.

Ms Bilbow will continue to work with the team as an advisor. She will attend all team meetings to give advice. However at the month 13 meeting, the team will present the findings to her and she will advise us of her interpretation as a consumer, and the team will consider her comments in the writing of the report. We expect her involvement will be no more than four days in total.

10 Project Timetable

See Appendix 3.

11 Justification of support

Our experience in conducting GPRD studies suggests 10 months will be required to complete the Part 1 study. We propose to employ Mrs Murray as the first research assistant (RA1) because of her experience in using the GPRD, which will substantially reduce the duration of the Part 1 study, and will be cost effective. Her current grade at the School of Pharmacy is Grade 1A point 12.

The RA2 will conduct the interview study, and as it involves adolescents, it will be inappropriate to

employ a researcher without previous experience in qualitative research; therefore we propose to employ a researcher at Grade 1A point 10. Travel, accommodation and other expenses are expected to cost £2,125

As the study involves clinics in different parts of the country, it will be more cost effective to employ sessional researchers. They will

1) liaise with clinicians at individual clinics to review case-notes to identify appropriate patients (estimated to be 150 patients)

2) liaise with RA2 to stratify patients sample

3) obtain consent from 15 patients, and make appointments for interviews

4) obtain consent from 10 clinicians at the collaborating centres, and make appointments for interviews

5) in order to streamline the financial arrangement, the team proposes to reimburse each clinic with £30 per casenote review and £100 per patient for consent, so that total cost will be £6,000.

Cost for reimbursement of time commitment and travel for Ms Andrea Bilbow: £100 per meeting, totalling £500.

We expect the first and the last team meeting will be face-to-face meetings, the other three meetings will be conducted by telephone conferencing. A face-to-face meeting is expected to cost £1,000 for travelling expenses and refreshments. Each telephone conference is expected to cost £100.

The Executive Team consisting of Dr Wong, Dr Clifford, Professor Taylor, Professor Asherson, Ms Walwyn and the two research assistants (RA1 & 2) will meet monthly during the project (see Section 12). The cost of the meetings will be no more than £50 per meeting as all members of this team will be based in London.

The Institute of Psychiatry, King's College London has both RCT and epidemiological statistical expertise so we will enlist their support for statistical analysis and advice. Ms Laura Potts is a statistician in the Clinical Trials Unit at The Institute of Psychiatry, King's College London. She will contribute statistical advice at the Executive Team and Team meetings (£500 x 10 days for 20 half day meetings) and for 5 days ad-hoc advice (£500).

For the Part 2 study, the team plan to purchase a digital recorder for the interviews, which will cost approximately £200. Also, a recommended software package for handling qualitative datasets will be purchased (NVIVO £270).

The findings of the project will be disseminated to professionals and lay persons through publication in peer-reviewed journals, conferences and patient support services such as ADDISS. An extra £1,500 has been included to cover the cost of one co-applicant to present the project findings at a conference such as the Annual Meeting of the Royal College of Paediatrics and Child Health.

Added-value

As the EU Commissioner has already funded the chief investigator for the access of the GPRD, this has reduced the cost of the project by at least £15,000. Furthermore, under the DH Public Health Career Scientist Award, a new computer system has been installed at the Centre for Paediatric Pharmacy Research to conduct research in psychotropic drug use in children; therefore the cost of the project is further reduced by £2,000. These two aspects have represented at least £17,000 saving which is sufficient to cover the interview study proposed in Part 2.

12 Planned supervision of the work

Dr Wong will be the chief investigator of the project, and will be responsible for the overall running of the project. The RA1 conducting the Part 1 study will be line managed by Dr Wong. Dr Clifford will

line-manage the RA2 involved in the Part 2 study. An Executive Team comprising Dr Wong, Dr Clifford, Professor Taylor, Professor Asherson, Ms Walwyn and the two research assistants (RA1 & 2) will meet monthly to review and plan the progress of the project. This structure of supervision works well and has been adopted by Dr Wong on a previous project funded by the National Patients Safety Research Programme called COSMIC (Co-operative of Safety of Medicines in Children).

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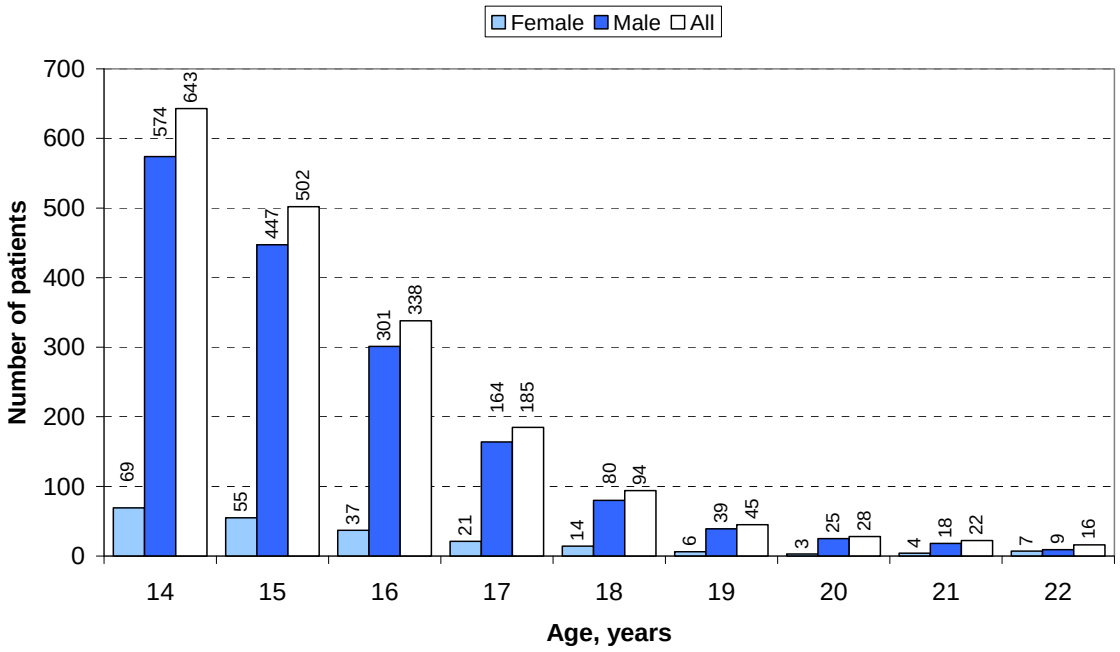
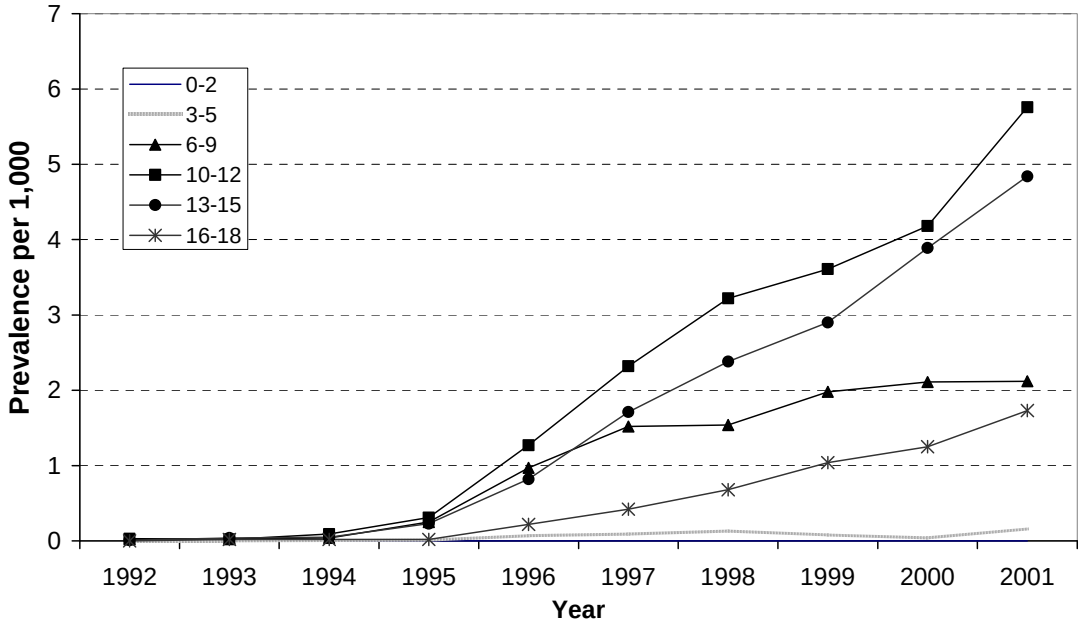
Appendix 1. Distribution of patients on the General Practice Research Database (GPRD) prescribed methylphenidate, dexamfetamine and atomoxetine between 2001 and 2004 (unpublished GPRD data)*.



*Patients may be counted twice in this data set by virtue of having different ages over the study period.

Appendix 2. Annual prevalence of methylphenidate (unpublished GPRD data from Yingfen Hsia and Corinne de Vries, University of Surrey).



Appendix 3. Timetable and milestones

	-3	0	1	2	3	4	5	6	7	8	9	10	11	12	13-16
GPRD SEAG application	←	→													
Staff recruitment	←	→													
GPRD data extraction			←	RA1	→										
Data cleansing						←	RA1	→							
Data analysis									←			RA1	→		
MREC application			←	CADDY team	→										
Case-note review & recruitment of patients for interview study						CADDY team + SRs	←	→							
Interview study and data analysis								←			RA2	+SRs	→		
Report writing														RA2 +	CADDY team →
Executive team meetings (EM)	EM			EM	EM	EM		EM	EM	EM		EM	EM	EM	EM x 3
Team meetings (TM)			TM				TM				TM				Final TM

SEAG = Scientific and Ethical Advisory Group; RA1 = Research Assistant 1; RA2 = Research Assistant 2; SRs = Sessional Researchers.