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Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoepidemiological and qualitative study

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 04/36/02. The contractual start date was in May 2008. The draft report began editorial review in July 2008 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoepidemiological and qualitative study

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Objectives: To estimate the prevalence of attention deficit hyperactivity disorder (ADHD) pharmacological treatment, and its demographic and clinical details, and to estimate the proportion of patients in the target group who stopped ADHD treatment and investigate possible factors for continuation or cessation of treatment.

Design: A pharmacoepidemiological study using an automated database and a qualititative study using patient interviews. Part 1 was a pharmacoepidemiological study that provided accurate data on use and cessation of ADHD drugs. Part 2 was an in-depth interview study to investigate the reasons, processes and outcomes of treatment cessation.

Setting: Part 1: primary care using the General Practice Research Database (GPRD). Part 2: secondary and tertiary care paediatric clinics, child and adolescent mental health and adult mental health clinics in London, Nottingham, Dundee and Liverpool.

Participants: Part 1: patients were 15–21 years old during the study period (1 January 2001 and 31 December 2004), had at least one prescription for methylphenidate, dexamfetamine or atomoxetine and had at least 1 year of research-standard data available in the GPRD. Part 2: patients fulfilled Part 1 criteria, had a diagnosis of ADHD as detected by a predefined algorithm and had been treated with methylphenidate, dexamfetamine or atomoxetine for at least 1 year. Child and adolescent psychiatrists, adult psychiatrists and paediatricians involved in the treatment of young people with ADHD were also interviewed as part of the study.

Results: Part 1: prevalence of prescribing averaged across all ages increased eightfold, from 0.26 per 1000 patients in 1999 to 2.07 per 1000 patients in 2006. The increase in prevalence in the younger patients was less evident in the older patients. Prevalence in 15-year-old males receiving a study drug prescription increased from 1.32 per 1000 patients in 1999 to 8.31 per 1000 patients in 2006, whereas the prevalence in 21-year-olds rose from 0 per 1000 patients in 1999 to 0.43 per 1000 patients in 2006. Survival analysis showed that the rate of treatment cessation largely exceeded the estimated rate of persistence of ADHD. The reduction in prescribing was most noticeable between 16 and 17 years of age. Kaplan–Meier analysis showed that approximately 18% of patients restarted treatment if they had stopped treatment after the age of 15. Patients who restarted treatment were more likely to restart within the first year following treatment cessation. Part 2: the Child Health and Illness Profile (CHIP) was chosen as the quality of life questionnaire for the Part 2 study because the CHIP-CE scale has been validated in children with ADHD in the UK. Because of the age range of participants, the adolescent version (CHIP-AE) was administered to patients after interview. Of the 15, a total of nine patients finished the questionnaire. Interviews showed that although some young people felt able to cope after stopping medication, others felt the need to restart to control symptoms. Some patients had difficulty re-engaging with services and clinicians

recognised the lack of services for young adults. Patients continuing on treatment considered cessation as an option for the future, but were concerned about the process of stopping and its impact on behaviour.
Conclusions: Part 1 study demonstrated that the prevalence of prescribing by GPs to patients with ADHD dropped significantly from age 15 to 21. The fall in prescribing was greater than the reported age-related decrease in symptoms, raising the possibility that treatment is prematurely discontinued in some young adults where ADHD symptoms persist. Part 2 of the study identified that some young adults had difficulty in obtaining treatment after discharge from paediatric services. Future work should include randomised placebo-controlled trials into long-term treatment with stimulants, particularly methylphenidate.

Contents

List of abbreviations

AAQoL	Adult Attention Deficit Hyperactivity Disorder Quality of Life Scale
ADHD	attention deficit hyperactivity disorder
ADORE	Attention-deficit Hyperactivity Disorder Observational Research in Europe
AHRQ	Agency for Healthcare Research and Quality
AIM	ADHD Impact Module
APA	American Psychiatric Association
BAP	British Association for Psychopharmacology
CAMHS	child and adolescent mental health services
CD	conduct disorder
CHIP	Child Health and Illness Profile
CHIP-AE	Child Health and Illness Profile – Adolescent Edition
CHIP-CE	Child Health and Illness Profile – Child Edition
CHQ	Child Health Questionnaire
DBDs	disruptive behaviour disorders
DSM-III-R	*Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition revised
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision
EMEA	European Medicines Agency
EUNETHYDIS	European Network for Hyperkinetic Disorders
FDA	Food and Drug Administration
GCSE	General Certificate of Secondary Education
GP(s)	general practitioner(s)
GPASS	General Practice Administration System for Scotland
GPRD	General Practice Research Database
HKD	hyperkinetic disorder
HRQoL	health-related quality of life
IBSS	International Bibliography of the Social Sciences
ICD-10	*International Classification of Diseases*, 10th edition
IPA	International Pharmaceutical Abstracts
ISAC	Independent Scientific Advisory Committee
KINDL	Munich Quality of Life Questionnaire for Children
MEMO	Medicines Monitoring Unit

continued

MRC	Medical Research Council
MTA	Multimodal Treatment Study of Children with ADHD
NICE	National Institute for Health and Clinical Excellence
ODD	oppositional defiant disorders
PedsQL	Pediatric Quality of Life Inventory™
POM	prescription-only medicine
Q-LES-Q	Quality of Life Enjoyment and Satisfaction
QLQ	Quality of Life Questionnaire
QoL	quality of life
RCT	randomised controlled trial
SF-36	36-item short-form health survey
SUD(s)	substance use disorder(s)
TEDDY	Taskforce European Drug Development for the Young
WFIRS	Weiss Functional Impairment Rating Scale
WHO	World Health Organization
YQOL	Youth Quality of Life Instrument

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

There is increasing evidence to suggest that attention deficit hyperactivity disorder (ADHD) is no longer a condition of childhood alone. Studies have shown that the condition can persist into adulthood in a significant proportion of patients. What is unknown at present is the extent to which adolescents and young people continue with medication as they get older, the reasons for treatment cessation and the experience of patients undergoing this process. This report aims to review current practice in treating patients with ADHD so that more information will be available to plan for future clinical trials and service provision.

Objectives

1. To estimate the prevalence of ADHD treatments in the target population using a large general practice automated database.
2. To describe 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. To estimate the percentage of patients in the target group who stopped the ADHD pharmacological treatments and investigate possible factors affecting the continuation or cessation of pharmacological treatments.
4. To search the literature for potentially appropriate quality of life (QoL) measures for this patient population and to test feasibility with interviewees.
5. 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 QoL.
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).

Design

This project combined quantitative and qualitative approaches to investigate current practice in the UK.

Setting

The General Practice Research Database (GPRD) was used to answer objectives 1–3 (Part 1). The Part 2 study was designed to answer objectives 4–6. A literature review on QoL was undertaken in March 2007 to identify appropriate QoL questionnaires for patients with ADHD. Patients and clinicians were recruited from London, Nottingham, Dundee and Liverpool to take part in interviews.

Participants

Part 1

The GPRD is one of the world's largest computerised databases of anonymised patient data from general practice. It currently contains information on over 3.5 million patients, equivalent to approximately 5% of the UK population. As of 2 June 2006, there were 668,387 patients registered on the database aged 19 years.

Part 2

A total of 15 eligible patients (active and discharged) were recruited. An active patient was defined as a patient who is under the care of the collaborating clinics for their ADHD management. A discharged patient was defined as a patient who was no longer under the care of the collaborating clinics (includes patients who have either stopped treatment, transferred to adult psychiatric care or primary care or who have moved away). Patients were stratified into the following three groups: patients who remain on treatment and have not attempted stopping; patients who have successfully stopped treatment; patients who were unsuccessful in stopping treatment. A total of 10 clinicians were interviewed. This included community paediatricians (associated with mental health clinics), child and adolescent psychiatrists and

adult psychiatrists The clinicians were recruited from the collaborating centres.

Results

Part 1: Patient characteristics and prevalence

Prevalence of prescribing averaged across all ages (15–21 years) increased eightfold over the study period, from 0.26 per 1000 patients in 1999 to 2.07 per 1000 patients in 2006. The increase in prevalence over the study period occurring in the younger patients was less evident in the older patients. The prevalence of 15-year-old males receiving a prescription for a study drug increased from 1.32 per 1000 patients in 1999 to 8.31 per 1000 patients in 2006, whereas the prevalence of 21-year-olds rose from 0 per 1000 patients in 1999 to only 0.43 per 1000 patients in 2006. A survival analysis was conducted to investigate the cessation of treatment and showed that the rate of treatment cessation largely exceeded the estimated rate of persistence of ADHD. The reduction in prescribing was most noticeable between the ages of 16 and 17 years. Kaplan–Meier analysis was also conducted to examine the restarting of treatment. Approximately 18% of patients restarted treatment if they had stopped treatment after the age of 15. For those patients who restarted treatment, they were more likely to restart within the first year following treatment cessation.

Part 2: Quality of life literature review

Twelve QoL scales were identified; eight had been used in children and four in adults. The most frequently used scale in the UK studies was the Child Health and Illness Profile (CHIP) and, overall, it was the second most cited QoL scale used in ADHD. The CHIP-CE scale is a generic scale used to assess QoL; however, it has been validated for use in children with ADHD in the UK. On this basis, the CHIP was chosen as the QoL questionnaire to be tested (in the Part 2 study), in terms of feasibility for use in future studies. Due to the age range of the study participants, the adolescent version of the CHIP (CHIP-AE) was selected and administered to patients after the interview and in accordance with the instructions outlined in the user manual. Of the 15, a total of nine patients completed the questionnaire; the time it took to complete ranged from 12 to 25 minutes. Four participants had difficulties with reading and comprehension and so took the questionnaire home so they could have more time and support from parents; only one was returned. Two participants did not have time to complete the questionnaire during the session because of the time taken to conduct the interviews, but were given the questionnaire to take home; neither were returned. Of those participants who completed the questionnaire, all described it as easy to work through, but considered it lengthy. The majority of participants asked for clarification of questions that would be more appropriate for young people in the USA.

Interview study

The results of the qualitative study showed that although some young people felt able to cope after stopping medication, others felt the need to restart to control symptoms. Some patients had difficulty re-engaging with services and clinicians recognised the lack of services for young adults. Patients continuing on treatment considered cessation as an option for the future, although were concerned about the process of stopping and impact on behaviour. The process of cessation varied depending on the individual and whether it was planned or unplanned. From a clinical perspective the process typically involved four key stages: preparation, choosing an appropriate time to stop, commencing cessation and follow-up.

Conclusions

The Part 1 study demonstrated that the prevalence of prescribing by general practitioners to patients with ADHD drops significantly from age 15 to 21. The fall in prescribing is greater than the reported age-related decrease in symptoms, raising the possibility that treatment is prematurely discontinued in some young adults where ADHD symptoms persist. The Part 2 study also identified that some young adults had difficulty in obtaining treatments after discharge from the paediatric services. This scoping exercise shows further research is needed to improve the care of young people with ADHD.

Implications for healthcare

CADDY was commissioned as a scoping project with a focused objective to identify current practice in ADHD treatment cessation in order to support the planning of an randomised controlled trial. Hence, it can only make very limited recommendations. Nevertheless, both the pharmacoepidemiological and interview

studies raise the possibility that treatment may be prematurely stopped by or for some adolescents and young adults with ADHD. Also overall the fall in treatment prevalence may be out of step with the numbers of people who still require treatment as young adults. In addition, deficiencies in ADHD services within adult mental health have been highlighted both in the literature and by respondents in the interview study. Factors in adult services such as poor transition arrangements from child services, lack of resources, poor training of adult psychiatrists in the diagnosis and management of ADHD, competing priorities, unwillingness to prescribe unlicensed medications, and beliefs that the condition does not exist in adulthood are all likely to contribute to patients failing to be identified for initiation or continuation of treatment for ADHD, even where this is clinically indicated. Guidelines and further research are needed to help patients, families and clinicians make informed and evidence-based decisions about whether cessation is appropriate.

Recommendations for research

In light of the results obtained from this study and the latest results from the Multimodal Treatment Study of Children with ADHD (MTA) and the NICE guideline, the research priorities should be:

1. investigations into whether stimulants, particularly methylphenidate, are still effective after long-term treatment, i.e. by conducting a randomised placebo-controlled trial
2. once the above study is conducted, then a further study optimising the cessation and/or continuation process is needed to guide clinicians on future practice.

Chapter 1
Introduction

Attention deficit hyperactivity disorder and hyperkinetic disorder

Symptoms and diagnosis of the disorder

Attention deficit hyperactivity disorder (ADHD) is a condition which has received much media coverage in recent times; however, it is not a 'new' condition. Over a century ago, an article in *The Lancet* by Still, an English paediatrician, described a condition where patients had '…marked inability to concentrate and sustain attention…'.[1] Currently there are two terms to describe this disorder: ADHD and hyperkinetic disorder (HKD).

Diagnosis of the condition (ADHD/HKD) is made based on the clinical history of the patient usually obtained from the patient, parents and teachers. The diagnosis for ADHD is described in the American Psychiatric Association (APA)'s *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision (DSM-IV-TR, 2000) and those for HKD in the *International Classification of Diseases*, 10th edition (ICD-10, 1992) published by the World Health Organization (WHO).

There are three symptom domains which constitute the condition of ADHD/HKD: inattention, hyperactivity and impulsivity. Examples of the 18 symptoms used in the diagnosis of the condition using the DSM-IV (ADHD) criteria include the following:

1. Inattention: difficulty in sustaining attention, failing to finish tasks, losing things, forgetfulness.
2. Hyperactivity: fidgeting, talking excessively, motor excess.
3. Impulsivity: difficulty waiting turn, interrupting and blurting out answers to questions.[1]

The differences between the diagnosis of ADHD and HKD include the number of criteria in each symptom group required for a diagnosis, the issue of pervasiveness and the existence of comorbid conditions.[2] The main difference between ADHD and HKD is that ICD-10 (HKD) sets more stringent criteria for symptom pervasiveness and requires symptoms in all three domains.

As a result, HKD can be considered a severe form of ADHD with a prevalence of 1% of school-age children compared with 3–5% for ADHD.[3] The term 'ADHD' has increasingly been adopted by the public, media and UK clinicians, although many children with 'ADHD' in clinical services would also meet criteria for HKD.

A diagnosis of ADHD accommodates subtypes of the condition if symptoms are predominantly from one of the symptom groups mentioned above. The 'combined type' requires the presence of six or more inattentive and six or more hyperactive-impulsive symptoms; the 'predominantly inattentive type' requires the presence of six or more inattentive symptoms and less than six hyperactive-impulsive symptoms and the 'predominantly hyperactive/impulsive' type requires the presence of six or more symptoms of hyperactivity/impulsivity and less than six symptoms of inattention. There are no subtypes of HKD and a diagnosis requires the presence of all three core signs: six inattentive symptoms, three hyperactive symptoms and one impulsive symptom.[1] A diagnosis of HKD is similar to a severe combined type of ADHD. Regarding the issue of pervasiveness, the ICD-10 diagnosis of HKD requires that all criteria are present both at home and at school (or another setting), whereas the DSM-IV diagnosis of ADHD requires the presence of symptoms in one setting with impairment arising from the condition present in another setting.[2]

Many children with ADHD meet the criteria for another psychiatric disorder. Comorbid conditions often occurring include oppositional defiant disorder (ODD), conduct disorder (CD), learning disorders, tic disorders and Tourette's syndrome. The DSM-IV criteria for ADHD diagnosis recognise the coexistence of other conditions with the exception of schizophrenia, autism and pervasive developmental delay. In general, the ICD-10 criteria do not allow comorbid conditions to coexist, with the exception of conduct disorder.[1]

In addition to their presence and pervasiveness, symptoms must have persisted for at least 6 months to a degree that is inconsistent with the developmental level of the child, must significantly impair academic or social functioning and must have been present before the age of 7 years.[3] For the sake of simplicity, in this report the term ADHD will be used to describe both ADHD and HKD.

Aetiology of ADHD

ADHD is a disorder that has multiple theoretical causes, although the extent to which these exert their effect either alone or together is not known.[2] The first of these is a neurobiological theory which implicates dysregulation of neurones in regions of the brain involved in executive control and attention, namely dopamine and noradrenaline.[2,4] Executive functions controlled by the frontal–subcortical circuits include response inhibition, planning, working memory and sustained attention. These are the types of functions commonly affected in ADHD.[4]

Studies using structural and functional magnetic resonance imaging have also shown the area of the brain involved in executive control to be smaller and less symmetrical in patients with ADHD compared to matched controls.[2]

Many studies have demonstrated a genetic component to ADHD.[1,4,5] Family, twin and adoption studies have estimated a heritability of ADHD of 0.80, highlighting the importance of genetics in the aetiology of the condition. Genetic influences on ADHD are likely to be the result of multiple genes of small effect size and their interaction with environmental risk factors. The best evidence for an association are the variants of the genes for the D_4 dopamine receptor (DRD_4) and D_5 dopamine receptor (DRD_5) and the dopamine transporter (DAT_1). An association between the 480-bp allele of the dopamine transporter gene and ADHD has been demonstrated by family and population-based studies.[5] There is also evidence for associations with the genes for the D1 dopamine receptor (DRD_1) and serotonin 1B receptor ($5\text{-}HT_{1B}$), and with *Taq* polymorphisms of the dopamine beta-hydroxylase gene and the synaptosomal associated protein-25 (SNAP-25), which is involved in the regulation of neurotransmitter release.[6]

A study by Rutter *et al*.[7] of children on the Isle of Wight and an inner borough of London provided compelling evidence of how psychosocial risk factors influence child psychopathology. Six risk factors were identified within the family environment, including (1) severe marital discord, (2) low social class, (3) large family size, (4) paternal criminality, (5) maternal mental disorder and (6) foster placement. It was the combination of these rather than any single factor that was implicated with impairment. A number of these psychosocial factors have also been associated with the development of ADHD. Fetal exposure to toxins resulting from maternal smoking, alcohol or drug use along with perinatal obstetric complications and prematurity has been implicated with the development of ADHD.[2] Other studies have shown a higher incidence of ADHD in patients exposed to 'chronic conflict, reduced family cohesion, and maternal psychopathology' compared with control families.[5]

The National Morbidity Survey (2000) also found a significant inverse social gradient for ADHD, whereby children in families of social class V (14%) were more likely to have a mental disorder than those in social class I families (5%).[8]

Epidemiological data on ADHD

The prevalence of the condition depends on a number of criteria, such as diagnostic criteria (whether a DSM-IV diagnosis of ADHD or an ICD-10 diagnosis of HKD is made), the diagnostic measures used (such as rating scales for parents/teachers or interviews), the number of people involved in the diagnostic process (parents only, teachers only or both), the age of the population (school-age children or adolescents/adults) and the area from which the population was sampled (inner city or rural areas).[2] A difference also exists as to the definition of prevalence used. The term 'administrative prevalence' refers to the numbers clinically diagnosed in the population while the 'true prevalence' refers to the number of people in the population with the condition (whether recognised clinically or not). There has been debate as to whether the prevalence of ADHD truly differs among different countries, particularly whether the rate in the USA is significantly higher than that reported elsewhere. Due to the variables mentioned above which can affect the prevalence of ADHD, it is difficult to compare the rates reported in various studies from different countries. A study by Faraone *et al*.[9] examined studies from US and non-US populations to determine whether ADHD was an American condition, stemming from social and cultural factors more predominant in US society. The conclusions from this study were that prevalence of ADHD was at least as high in many non-US children as in US children and that the highest prevalence of the condition was detected

using the DSM-IV criteria. There is still some thought that overdiagnosis of the condition may occur in the USA, with clinicians going beyond guidelines, particularly when treating very young children.[10] It is likely therefore that the variations between countries occur in administrative prevalence, with the highest rates seen in the USA.

The prevalence of ADHD in school-age children in England and Wales is estimated at 3–5%, whereas the prevalence of HKD in the same population is approximately 1%.[3] Patients with ADHD are also more likely to be male (ratios ranging from 2 : 1 to 9 : 1 depending on subtypes used) and school-aged.[2]

Guidelines for the treatment of ADHD in children

There are a number of different interventions used in the treatment of patients with ADHD, including psychological, behavioural, social and medical interventions. The former interventions are beyond the scope of this project; this study will focus on the pharmacological agents available for the treatment of the condition.

Currently in the UK, there are three medications licensed for the treatment of ADHD, the stimulants (methylphenidate and dexamfetamine) and atomoxetine. Further information on these medications follow. Other drugs used less commonly to treat ADHD include clonidine (Catapres®), bupropion (Zyban®), modafinil (Provigil®), impiramine, risperidone (Risperdal®) and nicotine patches. None of these agents are licensed for the treatment of ADHD, and it is outside the scope of this project to study these medications.

In 2006, NICE produced Review of Technology Appraisal 13, the focus of which was the medications used in the treatment of ADHD: methylphenidate, atomoxetine and dexamfetamine.11 The recommendations of the Technology Appriasal were encorporated into the National Institute for Health and Clinical Excellence (NICE) clinical guideline on the pharmacological and psychological interventions for ADHD in children, young people and adults. 12 The guidance recommends that when drug treatment is considered appropriate for the treatment of ADHD, methylphenidate, dexamfetamine and atomoxetine are recommended, within their licensed indications, for the management of the condition. Drug treatment should only be initiated by an appropriately qualified health-care professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. The continued prescribing and monitoring of drug therapy may be performed by general practitioners (GPs), under shared care arrangements. The decision of which product to use should be based on a number factors, including the presence of comorbid conditions, the different adverse effects of the drugs, specific issues surrounding the area of compliance or the need to administer these medications during school, the potential for drug diversion or misuse and the preferences of the child and parents.

The European Network for Hyperkinetic Disorders (EUNETHYDIS) produced the first upgrade of the European clinical guidelines for HKD in 2004.[6] These guidelines provide recommendations on the diagnosis and management of HKD and ADHD and include information on the presence of comorbid conditions, differential diagnoses, patient evaluation, and various modes of treatment. As a summary, this group recommends that before a diagnosis of ADHD or HKD is made, a full assessment of the child or adolescent should be performed. This would comprise a clinical interview with the parents and separately with the child, and information from the child's school on the child's behaviour, their developmental and social functioning, situational variations in behaviour and symptoms indicating comorbid conditions or a differential diagnosis. The child's intelligence, achievement, attention and impulsivity should also be clinically assessed. Behavioural observations should be made during the clinical examination, and this would be repeated on a number of occasions. The ADHD symptoms should be examined against the developmental level of the child, and any alternative explanations of the symptoms or any comorbid conditions should be sought. A physical examination should also be performed to exclude any underlying medical conditions that may either mimic ADHD symptoms or contraindicate drug treatment; hearing should also be checked, and any history of epilepsy should be sought. Only after these examinations have been completed should treatment be initiated. In terms of pharmacological treatment, the consensus recommendation of the group is that initial medication should be as a trial, and methylphenidate is usually the first choice. In terms of treatment evaluation, there are a number of scales such as SNAP (Swanson, Nolan and Pelham checklist) and ADHD-RS (ADHD Rating

Scale) that can be used to measure behaviour change. In addition, parents and teachers may select a number of problem behaviours before treatment initiation, and these can be re-evaluated after treatment has stabilised to detect improvement.

Regarding the recommended duration of treatment, the guidelines acknowledge that length of time patients need treatment is not fixed. For some patients, treatment will be required for many years, and practitioners are now increasingly called upon to treat ADHD in adulthood.[13] The NICE guidelines recommend that 'following an adequate treatment response, drug treatment for ADHD should be continued for as long as it remains clinically effective. This should be reviewed at least annually.' They do recognise that although 'drug holidays are not routinely recommended; however, consideration should be given to the parent or carer and child or young person with ADHD working with their healthcare professional to find the best pattern of use, which may include periods without drug treatment'.[12]

In 2004, an international consensus statement was presented by a number of international experts in child and adolescent psychiatry on clinical implications and treatment practice suggestions for ADHD and disruptive behaviour disorders (DBDs).[14] The DBDs refer to ODDs and CD. As a summary of the recommendations given, this group highlights that comorbidity among patients with ADHD and DBDs is high and should be considered the rule, not the exception.

Patients with these conditions require early identification, and careful differential diagnosis to eliminate other diagnoses and to detect other comorbidities. As recommended by EUNETHYDIS, assessment should span multiple domains and involve multiple informants.

They state that while effective treatments for ADHD and DBDs exist, their efficacy does not continue after they are stopped, and so treatment may be required in the long term. Suggested treatment options will depend on the primary diagnosis and whether one or more disorder is present.

Stimulant medication is the first-line pharmacological treatment for patients with pure ADHD. Pharmacological treatments require careful titration and monitoring in order the maximise efficacy and minimise the occurrence of side effects. Long-term follow-up is also necessary with patients with these conditions.

Pharmacological treatments

Stimulants

Methylphenidate (Ritalin®, Concerta®, Equasym® and Medikinet®) and dexamfetamine (Dexedrine®) belong to a group of drugs known as central nervous system stimulants. The mechanism by which stimulants act in reducing symptoms in ADHD is not completely clear; however, it is believed that they inhibit the reuptake of dopamine and noradrenaline into the presynaptic neurone and increase their release into extraneuronal space, thus increasing intrasynaptic concentrations.[5] Many studies have examined the efficacy of stimulants in ADHD and have shown a response rate of 70%.[14] Improvements are seen in many areas including inattentiveness, impulsiveness and self-esteem.

Methylphenidate

Methylphenidate, usually used as first-line therapy, has been used for over 50 years for the treatment of ADHD. The current license for Ritalin® (Novartis Pharmaceuticals UK), an immediate-release form of methylphenidate, was issued in the UK in August 1988. Methylphenidate is a Schedule 2 prescription-only medicine (POM). It is licensed as part of a comprehensive treatment programme for ADHD in children aged 6 years and above.[15]

Methylphenidate as the immediate-release formulation is normally started at a dose of 5 mg twice or thrice daily at breakfast, lunchtime and late afternoon (after school). Dosage and frequency can be titrated slowly over time according to symptom response to a maximum recommended daily dose of 60 mg.[15]

With a shorter duration of action of approximately 4 hours, some patients find the effects of the twice or thrice daily dose regimen diminish in the evening and require an additional dose, though a balance needs to be achieved as methylphenidate can cause insomnia. This multiple dosage regimen also brings with it other difficulties such as the administration of medication during school, causing problems with storage of a controlled drug and also stigmatises the child for having to take medication.

This led to the development of sustained-release preparations of methylphenidate: Concerta XL® (Janssen-Cilag Ltd), Equasym XL® (UCB Pharma

Ltd) and Medikinet® (Flynn Pharma Ltd). These medications are taken once daily (although Equasym may be taken twice daily) resulting in an initial release of medication similar to the immediate-release formulation followed by a gradual release over several hours.[16,17]

The long-acting stimulants are as effective as the immediate-release formulation and also have a similar side-effect profile.[4] The most common side effects experienced with methylphenidate include sleeplessness, nervousness, reduced appetite, headache, abdominal pain, tachycardia, changes in blood pressure and heart rate. Rarer effects include reduced weight gain and growth reduction occurring with prolonged use.[15] Many of these effects are transient and can also be managed by reduction in dose.

More data from follow-up studies are required to confirm the safety data in the long term, though information currently available suggests that stimulants are effective and safe in the medium to long term.[18] The recent controversy surrounding the issue of mortality in patients taking ADHD drug treatment will be discussed later in this report.

Another concern raised, particularly in the media, suggests that patients taking stimulant drugs are at increased risk of drug and alcohol abuse and dependence. A meta-analytical review of literature in the area revealed that the use of stimulant therapy was not associated with an increased risk for subsequent substance use disorders (SUDs), but in fact has a protective effect against later SUD.[19]

Dexamfetamine

Dexamfetamine (or dexamphetamine) is available in the UK as Dexedrine® (UCB Pharma Ltd). A stereoisomer of amphetamine, it was introduced by Smith, Kline and French (or GlaxoSmithKline as it is now) in the early 1950s.[20] Dexamfetamine is licensed for use in children with 'refractory hyperkinetic states'. With a longer duration action than methylphenidate, dexamfetamine can be administered as a once-daily dose. Whereas methylphenidate is only licensed for use in children aged 6 years and over, dexamfetamine can be used in children aged 3 years and above. Treatment for patients aged 3–5 years should be initiated at a dose of 2.5 mg daily whereas patients aged over 6 can be treated with an initial dose of 5–10 mg daily.[21] The common adverse effects of dexamfetamine are similar to those experienced with methylphenidate. NICE have concluded that the lack of good-quality clinical trials on the drug in recent years combined with its high potential for misuse and its limited licensed indication limit its use as first-line therapy. However, it does have a place in therapy in certain conditions.[11]

Atomoxetine

Atomoxetine, available as Strattera® (Eli Lilly and Company), is a non-stimulant drug licensed for use in children over 6 years for the treatment of ADHD and in adults over the age of 18 in whom treatment was initiated before this age. Its precise mechanism of action in the treatment of ADHD is not clear but it is thought that it works by selectively inhibiting the presynaptic noradrenaline transporter thus inhibiting noradrenaline reuptake. As it is neither a stimulant medication nor a controlled substance, it has less abuse potential and does not require the same strict prescribing and storage conditions as methylphenidate and dexamfetamine.[22]

Strattera is taken as a once-daily dose in the morning, though some patients may benefit from dividing the daily dose and taking it twice daily, in the morning and late afternoon or early evening. The dose administered depends on the weight of the patient, with patients weighing 70 kg or less starting on an initial dose of 0.5 mg/kg daily. The maintenance dose for these patients is normally approximately 1.2 mg/kg daily. For patients weighing over 70 kg, doses of 40 mg should be initiated with a recommended maintenance dose of 80 mg daily.[22]

Adverse effects associated with atomoxetine include abdominal pain, nausea and vomiting, decreased appetite with associated weight loss and somnolence. These effects are normally transient and do not usually require discontinuation of treatment. Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine.[22]

In double-blind clinical trials, suicide-related behaviours occurred at a frequency of 0.44% in atomoxetine-treated patients (6 of 1357 patients treated; one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group ($n = 851$). The age range of children experiencing these events was 7–12 years. It should be noted that the number of adolescent patients included in the clinical trials was low.[22] Other side effects include increases in heart rate and blood pressure.[22] Atomoxetine has been shown

to significantly improve the symptoms of ADHD compared with placebo. [22]

There is a lack of evidence comparing atomoxetine, methylphenidate and dexamfetamine. No studies have directly compared atomoxetine and dexamfetamine. One study by Wang *et al*.[23] compared atomoxetine and methylphenidate, the evidence from which suggested there that is little or no difference in efficacy between atomoxetine and methylphenidate in either reducing ADHD core symptoms or in general clinical improvement. However, this study did suggest that patients taking atomoxetine were at increased risk of adverse events when compared with methylphenidate. Few other trials have compared atomoxetine and methylphenidate and these do not provide any conclusive evidence due to poor trial design.[12] Atomoxetine is frequently used in patients with ADHD with comorbid tics as stimulant treatment can exacerbate tics.[22]

Safety concerns of ADHD treatment

In February 2006, the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) in the USA voted to recommend a 'black-box' warning describing the cardiovascular risks of stimulant drugs used to treat ADHD. The move followed reports of sudden deaths from stroke, heart attacks and high blood pressure in US patients taking drugs to treat the disorder, including Adderall® (mixed amphetamine salts) and Ritalin® (methylphenidate).[24]

The review, from the FDA's Adverse Event Reporting System, included 19 cases of sudden death in children under 19 (12 cases in children taking Adderall/Adderall XR® and seven cases in children taking methylphenidate) and six cases of sudden death in adults (five cases of adults taking Adderall/Adderall XR® and one case of an adult taking methylphenidate). Six of the 12 Adderall/Adderall XR® paediatric sudden death cases and four of the seven methylphenidate paediatric cases occurred in patients with structural cardiovascular abnormalities or other potential risk factors for sudden death. In the paediatric population (1–18 years), they reported a rate of sudden death of 0.36 per million amphetamine prescriptions dispensed and 0.16 per million methylphenidate prescriptions dispensed.

In the adult population (19+ years) the rate of sudden death reported was 0.53 per million amphetamine prescriptions dispensed and 0.07 per million methylphenidate prescriptions dispensed.[25] The 'black-box' warning was not implemented; however, the FDA directed manufacturers of these products to revise product labelling for doctors to reflect concerns about adverse cardiovascular events. An additional part of this revised labelling process was the creation of a Patient Medication Guide for each individual product.[26]

The FDA and the Agency for Healthcare Research and Quality (AHRQ) are collaborating in the largest study ever to examine the potential for increased risk of heart attack, stroke and other cardiovascular problems associated with medications used to treat ADHD.[27] This study was still ongoing when this report was being prepared in 2009.

ADHD in adolescents and adults

Though once perceived as a condition of childhood only, increasing evidence has highlighted the existence of ADHD in adolescents and adults. Prevalence of the condition in adults is estimated at approximately 1%.[28] Interestingly the difference in prevalence between males and females seen in childhood is less pronounced in older patients. This is most likely to be attributed to the fact that girls with ADHD tend to be less hyperactive and less severely conduct disordered than boys and so are less likely to be clinically referred.[29] These patients may then present to medical services when they are older, enabling the condition to be diagnosed. Compared with younger patients, adults with ADHD are more likely to exhibit inattentive symptoms, as hyperactive symptoms tend to diminish throughout the course of the condition.[29] However, they still suffer from symptoms such as the inability to sustain attention over a long period of time, disorganisation, forgetfulness and poor time management skills to name but a few.

As with younger patients, ADHD also impairs many functional aspects of adult daily life. In the area of education, these patients are likely to academically underachieve, having completed fewer years in school, achieved poorer marks in exams and had more frequent disciplinary actions against them.[29,30] These patients also face problems in the workplace, with poor performance, frequent job changes, lower rates of professional employment and lower socioeconomic status.[29,31] The condition also affects social and personal aspects of life. Adolescents and adults with ADHD are more likely to have a poor motoring history with a higher

rate of speeding offences, suspension of licenses and involvement in crashes than controls despite having the same knowledge of driving.[29,31]Adults with ADHD are at an increased risk of SUD (alcohol and drugs) and are more likely to become involved in crime and consequently the criminal justice system.[30] Finally, interpersonal relationships are also affected, with patients having difficulties maintaining relationships with family, friends and work colleagues. Rates of separation and divorce have been reported to be higher in adults with ADHD.[29,31]

There are two groups of adolescents and adults with ADHD: those who have had a diagnosis of ADHD in childhood with symptoms persisting into later life and those who are presenting for the first time with ADHD-associated impairment in adolescence and adulthood.

There are a number of reasons why patients may present for diagnosis in later life. As previously mentioned, those with primarily inattentive symptoms, especially girls, are less likely to be referred for diagnosis. Secondly, some children with a higher IQ may be able to compensate for deficits in attention, thus not impacting on schoolwork in primary school. However, these patients may then struggle to compensate in secondary school when academic demands increase.[32] Other patients diagnosed in adulthood are parents of children with ADHD, who recognise the symptoms of the condition in themselves after their children have been diagnosed and treated. Studies have also shown that this cohort is at increased risk of the condition compared with parents of non-ADHD children.[29]

As previously mentioned, ADHD is no longer considered to be a condition which all children outgrow. A number of follow-up studies have examined the persistence of ADHD in adolescents and young adults. Weiss *et al*.[33] conducted 5-, 10- and 15-year follow-up studies of 104 children with ADHD. These patients were aged between 6 and 12 years at the beginning of the study; 88% of patients were followed up at 5 years, 73% at 10 years and 49–61% seen at 15 years. A control group were also recruited to the study. The authors reported that up to two-thirds of ADHD patients still experienced at least one disabling symptom of the childhood syndrome at adult follow-up, and about half of the patients had not outgrown all aspects of the condition. Patients at a mean age of 19 had completed less schooling, on average 2–3 years less, and had achieved lower grades. They also had significantly lower occupational positions, and were rated as significantly worse than controls on work satisfactoriness and completion of tasks. Low self-esteem and poor social interaction associated with the condition in childhood also persisted into adulthood. Compared with controls, patients with ADHD had fewer friends and scored less on tests of social skills. Patients were also rated by observers as being more restless during interviews compared with controls. In addition, patients had a higher rate of impulsiveness and were more likely to be involved in motor accidents than those without the condition.

Gittelman *et al*.[34] and Mannuzza *et al*.[35] conducted a 9- and 16-year follow-up of 103 patients aged between 6 and 12 years. All patients were clinically diagnosed with hyperkinetic reaction of childhood (a term used to describe the condition before the introduction of ADHD). A control group was also recruited to the study for the 9-year follow-up. At the 9-year follow-up, with a mean age of 18 years, 98% of patients were assessed. At the 16-year evaluation, 88% of patients were interviewed. Patients and controls were interviewed by blinded clinicians. The persistence of ADHD into adulthood was found to be much lower than that reported by Weiss *et al*., with 11% of patients exhibiting symptoms in later years. Mannuzza *et al*.[36] also conducted a prospective follow-up of clinically diagnosed ADHD boys. At the mean age of 24 years, of the 85 patients interviewed (82% of the original cohort), only 4% had the full ADHD syndrome.

Barkley *et al*.[37] conducted an 8-year follow-up of 123 hyperactive patients and 66 controls, and observed persistence of the condition in 80% of patients with ADHD. Rates of antisocial acts were considerably higher among hyperactives than normals, as were cigarette and marijuana use and negative academic outcomes.

These studies, along with others, have demonstrated the persistence of ADHD into adolescence and adulthood and the impact the condition can have on the lives of these patients. However, the rate of persistence into later years is not clear.

Studies conducted in this area have reported various rates of persistence, possibly because of the methods used and the definition of persistence or remission used. Keck *et al*.[38] distinguished among syndromatic, symptomatic and functional recovery when studying the 12-month outcome of patients with manic or mixed episodes. Based on these classifications, Biederman *et al*.[39] examined these

three patterns of remission in relation to the 14 DSM-III-R symptoms of ADHD. They defined syndromatic remission as '…failing to meet the full diagnostic criteria for ADHD (i.e., having fewer than eight of the 14 possible symptoms, or 57%)…' or the maintenance of full diagnostic status; symptomatic remission was defined as having '…fewer than the number of symptoms required for a subthreshold diagnosis (i.e., fewer than five symptoms, or 36% of symptoms).' or the maintenance of partial diagnostic status with impairment; and functional remission was defined as having '…fewer than 36% of the symptoms of ADHD and no impairment (score on the Global Assessment of Functioning Scale higher than 60).'. They used these criteria to define the prevalence of ADHD in a cohort of 140 ADHD patients and 120 controls who were assessed at baseline, 1 year and 4 years. A total of 128 patients were followed up at the 4-year interval and were included in the analysis.

In addition to the data available at baseline, 1 and 4 years, information was gathered retrospectively on symptoms that the patients had experienced at the onset of the condition and symptoms occurring 2 years after beginning the study were noted retrospectively at the 4-year follow-up. Symptom decline was measured as a function of age. The results from this study proved that the definition of remission used greatly affected the rate of symptom decline. In the older patients aged 18–20 years, the rate of syndromatic remission was 60%, while the rate of functional remission was only 10% (*Figure 1*). This would suggest that a significant number of patients continue to exhibit ADHD symptoms and suffer the impairment associated with these symptoms.

Another important finding from this study showed that although the definition of remission used affected the prevalence for the three core symptoms, inattention was more persistent than hyperactivity or impulsiveness within each definition. This supports the theory that the symptoms of hyperactivity and impulsiveness decline at an earlier age and at a higher rate than those of inattention. Knowledge of the symptomatic persistence is very important as it gives both clinicians and patients a better idea of the prognosis of the condition. Use of syndromatic persistence only may provide an overly optimistic view of the long-term outcome. A meta-analysis of follow-up studies in patients with ADHD by Faraone *et al*.[40] found that persistence was low when the syndromatic definition was used to define persistence, with a figure of about 15% at age 25. However, use of the symptomatic definition of remission resulted in a persistence rate of 40–60%. The study also calculated that the probability of persistence of ADHD symptoms associated with a 1-year change in age was 83% for patients meeting full criteria and 96% for patients with residual symptoms of ADHD.

Theoretical consequence of long-term stimulant treatment in children

The persistence of ADHD symptoms into adulthood could be due to the persistence of ADHD itself; however, alternative explanations cannot be excluded. From a pharmacological perspective, it is theoretically possible that children who have been started on stimulants need to stay on the treatment when they become adults due to remodelling of their central neuropharmacology

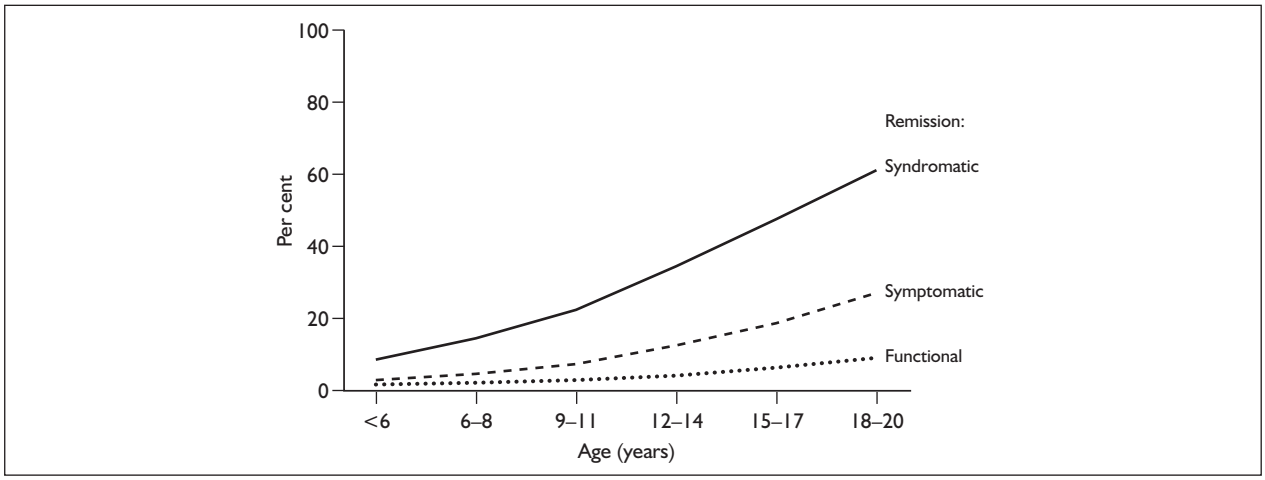

FIGURE 1 *Syndromatic, symptomatic and functional remission of adolescents and young adults with ADHD.*[39]

(down-regulation of receptors) as a result of chronic exposure to monoamine active drugs.[41] This theoretically could explain the persistence of ADHD into adulthood in some patients who started treatment during childhood, but would not explain ADHD cases presenting in adult clinics for the first time, with a clear childhood-onset disorder. Further research is needed to support or refute the drug remodelling hypothesis.

Guidelines for the treatment of ADHD in adolescents and adults

As mentioned previously, NICE published clinical guidelines for the treatment of ADHD in young people and adults in 2008.[12] In 2006, the British Association for Psychopharmacology (BAP) produced guidelines for the management of adolescents with ADHD in transition to adult services and for the management of ADHD in adults.[42] Again, a summary of the recommendations and guidance have been made. ADHD is currently understood to be a lifelong condition and a diagnosis of adult ADHD needs to include childhood impairment. As there is an absence of specific markers common to the entire group of ADHD patients, assessment and treatment are guided by patients' symptoms, behaviours and impairments. As mentioned previously in guidelines on the treatment on ADHD in children, comorbidity is common in adult ADHD patients and so clinical assessment of ADHD needs to include a careful evaluation for other disorders. The assessment of patients should include information on past and present symptoms, the presence of impairment in different settings, the influence of changing demands through life and the exclusion of other disorders that may better explain the presenting symptoms. Diagnosis is made using the same DSM-IV or ICD-10 criteria used in children and neither have special definitions or assessments for ADHD for adults. As previously mentioned, a diagnosis of ADHD requires a history of symptoms beginning in childhood which were inconsistent with the developmental level. These developmentally inappropriate symptoms need to be pervasive and present before the age of 7. Social, academic or functional impairment may not be present at an early age, but arise later in life as the adolescent or adult fails to compensate as environmental demands increase. In adults who are in transition from childhood to adulthood, the recall of symptoms may not be as problematic as adults presenting for the first time in adulthood, as this would require the retrospective analysis of behaviour as a child, either by the patient or the patient and parent. The BAP also include in the guidelines a 22-item extended adult symptom checklist, which includes items such as lack of attention to detail or carelessness, failure to follow instructions, poor organisational skills, ready distractibility, and stress intolerance. Various rating scales have also been developed to help in the diagnosis of ADHD in adults, including the 61-item Wender Utah Rating Scale, the Adult Self Report Scale, the 40-item Brown Adult Attention Deficit Disorder Scale and the Barkley Self, Other and Past ADHD symptom checklists. While these scales are not sufficient to diagnose ADHD in adults, they may be used in addition to a formal clinical evaluation. They may also be useful to evaluate changes in symptoms. The diagnosis should be clear before treatment is initiated in these patients. In terms of pharmacological intervention, drug treatment is usually done on an off-label basis, as these medications are mainly unlicensed for the treatment of ADHD in adults.

However, controlled clinical trials have shown significant short-term improvement in ADHD symptoms with the stimulants (methylphenidate and dexamfetamine) and atomoxetine compared with placebo, with similar effect sizes as those seen children. Longer-term trials of methylphenidate, though less in numbers, have also demonstrated ongoing effectiveness and tolerability in adults.[12]

There is a lack of evidence comparing these three medications, and so the choice of treatment may depend on factors such as the potential for abuse, the side-effect profile of the drug, the presence of comorbidities, and patient choice. As with the younger patients, older patients require regular follow-up to monitor the effectiveness of the medications on the ADHD symptoms and global and specific functioning, to determine any issues with adherence, and to assess the presence of adverse effects such as psychiatric side effects and cardiovascular effects, an issue which can be especially pertinent to older patients.[12]

Background of the CADDY project

While there is evidence of persistence of ADHD from childhood into adulthood, there are limited data from the literature on treatment of ADHD in adolescents and young adults. This gives rise to uncertainty about the continuing benefit of drug treatment in older adolescents and adults, costs associated with treating and not treating, and the best advice to give to patients and their families.

Only a large randomised trial that compares the effects and costs of a programme of continuation of medication against one of discontinuation in young people will answer the above questions. Such a study is also recommended by the NICE guideline group on ADHD treatment.[12] However, before undertaking such a large and complex study, more data are required on the current prescribing patterns of medication to adolescent patients and on the reasons why people do or do not stop treatment as they grow older. These data are essential for the development of a randomised trial as without such data, a trial of this nature would be unlikely to be successful. Consequently, in 2006 the HTA commissioned a scoping study in order to obtain the information necessary to inform future research. A multidisciplinary research team was convened to conduct the scoping study and named Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY).

Aim and objectives of the CADDY project

The aim of the project is to review current practice in treating patients with ADHD between 15 and 21 years old so that more information will be available to plan future clinical trials and service provision. Current practice will be reviewed 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
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
4. conducting 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), exploring perceptions of the process and outcome of cessation, and exploring issues of QoL
5. searching the literature for potentially appropriate quality-of-life measures for this patient population and testing the feasibility of use with adolescents and young adults with ADHD
6. conducting 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).

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 1–3. Part 2 is an in-depth interview study to investigate the reasons, the process and the outcomes of treatment cessation in order to achieve objectives 4–6.

Chapter 2

Part I study

Pharmacoepidemiological study using the General Practice Research Database

Introduction

The purpose of drug utilisation studies is to quantify the present state, developmental trends and time course of drug usage in the population in question. These data are then used to estimate drug use in the population by age, sex and other characteristics, and to identify areas of possible under- or over-utilisation. Prior to the development of automated databases, the identification and follow-up of large cohorts of patients made the examination of prescribing trends of even a single drug an extremely expensive and logistically difficult process. Now, the use of automated databases allows researchers to conduct studies with large sample sizes, and complete and accurate follow-up data. However, before any research is commenced, it is important to decide which resource is best suited to the needs of the study. This will depend on factors such as the size of the database, how representative it is of the population, and cost. In the UK, there are five main databases which contain patients' longitudinal data. They are the General Practice Research Database (GPRD), IMS Disease Analyzer-Mediplus (Mediplus), General Practice Administration System for Scotland (GPASS), Medicines Monitoring Unit (MEMO) and QRESEARCH. GPASS and MEMO only contain Scottish data and are relatively small,[43] and thus are unlikely to have sufficient data to conduct this study. QRESEARCH is a new emerging database;[44] however, analyses remain 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. On the other hand, both the GPRD and Mediplus have been extensively used and their advantages and limitations are widely understood.[43] In particular, there have been over 400 research papers published in peer-reviewed journals using GPRD data.[45] After detailed consideration, the GPRD was chosen as the preferred source for this study for a number of reasons: firstly, because the NHS provides universal coverage, no element of the population is excluded; secondly, the geographical distribution of practices in the GPRD is representative of the UK population; and finally, comparisons of age and sex distributions of the GPRD with the National Population Census have shown these to be similar.[45] This part of the CADDY study used the GPRD to give accurate data on the current practice of the use and cessation of ADHD treatment by describing the prevalence of methylphenidate, dexamfetamine and atomoxetine in primary care, and the median ages at which patients stopped and restarted treatment in the target population.

Methodology

General Practice Research Database

The GPRD is one of the world's largest computerised databases of anonymised patient data from general practice. It contains over 42 million patient-years of data. The GPRD has been collecting patient records in the UK continuously since 1987, and it currently contains information on over 3.5 million patients, equivalent to approximately 5% of the UK population.[45] Data are provided regularly by over 430 contributing general practices from all around the UK, including Scotland and Northern Ireland.[45] As of 2 June 2006, there were 668,387 patients registered on the database aged 19 years or less.[45] The database has previously been used to investigate paediatric psychotropic medication prescribing in the UK,[46–48] including an investigation of the prevalence and incidence of drug treatment of ADHD in younger boys in 1999.[49] Participating GPs enter patient data on VISION software which is anonymised at the practice by download software. The information collected from GPs includes demographics, including year of birth and gender of patient (information on ethnicity is not collected); medical diagnoses; all prescriptions issued by the practice; referrals to hospitals and specialists; and medical tests, including laboratory results and pathology and miscellaneous patient care information, e.g. smoking status, height, weight.

Quality checks are done in the Operational Data Store and then the validated data are entered into a data warehouse. This data warehouse is where customers can access the data to run Business Objects queries and extract data for analysis. Data quality markers are determined on an individual patient and practice level and validation studies show that quality and completeness of the data is high.[50,51]

Selection criteria of eligible patients

To be eligible for inclusion into the study, patients had to satisfy the following criteria:

- Be aged between 15 and 21 years in the study period between 1 January 1999 and 31 December 2006.
- Have at least 1 year of research-standard data available in the database.
- Have a diagnosis of ADHD as detected by a predefined algorithm (details given in Identification of ADHD diagnoses).
- Have at least 1 year of treatment with methylphenidate, dexamfetamine or atomoxetine. This will ensure only patients who have had good response to treatment will be included in the study.

Exclusion criteria included the following:

- Temporary registration with a general practice. It is normal practice to exclude patients with a temporary registration as these patients tend to represent those who visit a particular GP once, for example while on holidays. Although young people between the ages of 15 and 21 years tend to move quite a lot during this time (e.g. attending university), we believe that to receive regular medication for the treatment of ADHD, they would be permanently registered with a GP.
- A prescription for methylphenidate, dexamfetamine or atomoxetine for other reasons, such as narcolepsy, or epilepsy (to counter toxic effects of anticonvulsants).
- Drugs that are occasionally used on an off-label basis for the treatment of patients with ADHD. These include nicotine patches, bupropion, modafinil, antidepressants and antipsychotics. As the GPRD does not directly link individual prescriptions with their indication, it would not be possible to determine whether these drugs are being used to treat the symptoms of ADHD or to treat a comorbid disorder. For this reason, these drugs were not included in this study.

Data synthesis and analysis to obtain information on current practice

Identification of eligible patients

Initially, the Product Dictionary tool in the GPRD was used to identify all codes of methylphenidate, dexamfetamine and atomoxetine. The Product Dictionary contains a GPRD product code together with details such as product name, drug substance and *British National Formulary* category. The GPRD product codes for methylphenidate, dexamfetamine and atomoxetine are included in Appendix 1. The codes were then copied to Business Objects Query, a data management tool that enables the generation of queries and outputting of data. In this case, a query was constructed to determine the number of prescriptions issued for methylphenidate, dexamfetamine and atomoxetine during the study period. The outputted data was then saved and transferred to the statistical package (STATA/SE 9.1) where further analysis was performed.

Identification of ADHD diagnoses

For inclusion into the study, patients required both a prescription for a study drug along with a diagnosis of ADHD. See Appendix 2 for a list of clinical codes for ADHD. As GPRD does not directly link prescriptions to medical diagnoses, an algorithm was devised to identify the condition.

- 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 was used to identify ADHD diagnoses.
- In cases where a prescription has no associated diagnosis, the medical records of the patient were screened for diagnoses of ADHD.

Prevalence of study drugs

Gender- and age-specific annual prevalence of methylphenidate, dexamfetamine and atomoxetine were calculated. Prevalence is defined as the number of patients with one or more prescriptions per 1000 patients in the GPRD population. There may be an underestimation of prevalence as some prescriptions will be hand-written, and may not be recorded electronically. Trends in annual prevalence from 1999 to 2006 were examined using the chi-squared test for trend. Data were analysed

using STATA/SE, version 9.1, for Windows (Stata Corp LP, USA).

Duration, cessation and restart of treatments

The duration of each prescription was calculated from the daily dosage and the quantity of medication prescribed. *Figure 2* illustrates diagrammatically an example of how treatment duration was calculated. If a new prescription was issued before the previous one had 'run out', and the drug was the same for both prescriptions, it was assumed that the second overlapping prescription started the day after the previous one finished. Overlapping prescriptions for different stimulants were considered to indicate a switch from one stimulant to another. In this case, the initial prescription was shortened to end on the day the second stimulant was prescribed. An example of this is given in Figure 2: part (i) shows the prescriptions for drugs A and B as they were issued to the patient; and, part (ii) shows how the prescriptions are truncated and concatenated to determine the overall total duration of treatment.

Patients' data were screened for any records of treatment cessation. A minimum gap of 6 months between prescriptions was deemed to indicate a stop in treatment. The date that the last prescription ended was used as the stop date of the treatment episode. Duration of treatment was calculated and the percentage of patients in the target group who stopped treatment and possible factors affecting cessation such as age, gender, other medications and comorbidities were examined. The percentage of patients restarting treatment and possible factors affecting treatment restart were also investigated.

We hypothesised that the rate of decline in prescriptions for ADHD should mirror the expected rate of decline in diagnostic prevalence, obtained from the meta-analysis of follow-up studies by Faraone *et al*.[40] The probability of persistence of symptoms associated with a 1-year increase in age was calculated to be 83% for patients meeting full criteria (syndromatic persistence) and 96% for patients with residual symptoms (symptomatic persistence) of ADHD. Using the conservative figure of 83% for each 1-year change in age (i.e. patients who retain the full DSM diagnosis), we should expect to see an equivalent reduction in prescribing rates of around 17% each year.

Ethics

Ethics approval was granted for the project by the Independent Scientific Advisory Committee (ISAC) for MHRA (Medicines and Healthcare products Regulatory Agency) database research, which is responsible for the review of protocols for research using GPRD data (Appendix 3).

Results

Patients and prescriptions

Between 1999 and 2006, there were 983 patients in the GPRD who met the inclusion criteria. These 983 patients (896 males; 91%) received a total of 18,371 prescriptions during the study period.

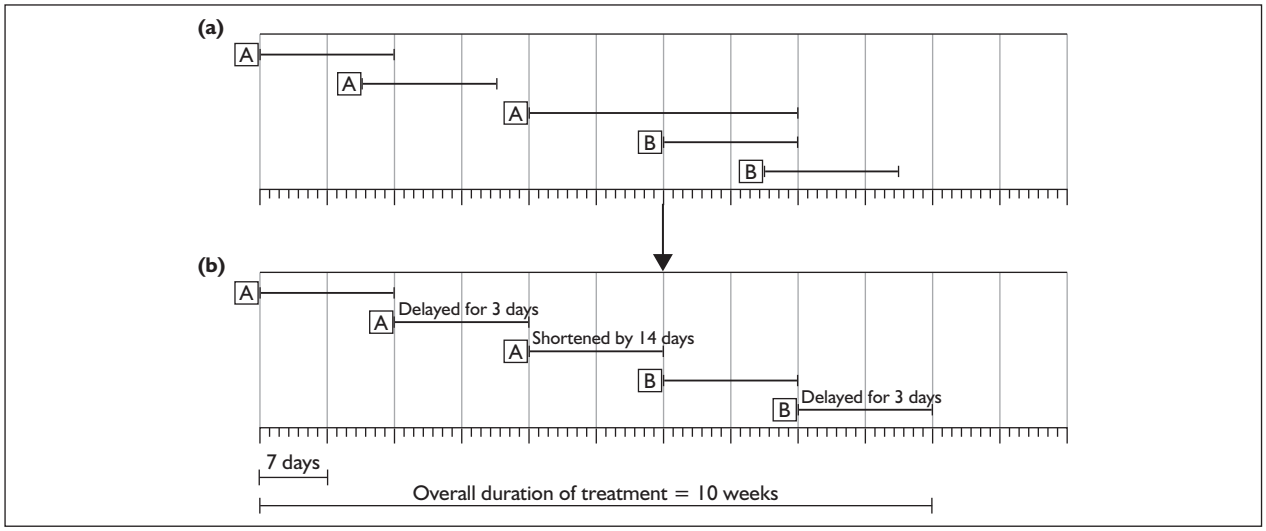

FIGURE 2 *Schematic diagram illustrating how the prescriptions in (i) are truncated and concatenated between drug A and drug B to calculate prescription and overall treatment duration (ii).*

TABLE I *Characteristics of the study population by year*

Year	Total prescriptions	Methylphenidate IR[a] (per cent of total)	Methylphenidate MR[b] (per cent of total)	Dexamfetamine (per cent of total)	Atomoxetine[c] (per cent of total)	Total patients	Ratio of male/ female patients
1999	345	329 (95.4)	–	16 (4.6)	–	55	53/2
2000	597	540 (90.5)	–	57 (9.5)	–	101	95/6
2001	756	691 (91.4)	–	65 (8.6)	–	129	118/11
2002	1194	964 (80.7)	162 (13.6)	68 (5.7)	–	197	182/15
2003	2180	977 (44.8)	1123 (51.5)	80 (3.7)	–	284	254/30
2004	3211	1022 (31.8)	2038 (63.5)	123 (3.8)	28 (0.9)	386	347/39
2005	4571	1075 (23.5)	3031 (66.3)	173 (3.8)	292 (6.4)	505	454/51
2006	5517	1116 (20.2)	3932 (71.3)	88 (1.6)	381 (6.9)	577	519/58

a Immediate-release preparations.
b Modified-release preparations first authorised in 2002.
c First authorisation in 2004.

Table 1 illustrates that both the number of prescriptions issued and the number of patients receiving prescriptions for methylphenidate, dexamfetamine and atomoxetine have risen over the study period. Prior to 2002, immediate-release methylphenidate and dexamfetamine were the only medications available for selection by clinicians, with methylphenidate accounting for approximately 95% of total usage. From 2002 onwards, with the introduction of extended-release preparations, modified-release methylphenidate and the non-stimulant atomoxetine (in 2004), there has been a shift in prescribing, particularly to the use of modified-release methylphenidate.

The geographical distribution of patients is presented in *Figures 3 and 4*. Figure 3 shows the number of patients in each region as a percentage of the total study cohort. Figure 4 displays the percentage of people in the GPRD (aged 15–21 with at least 1 year of the data on the database) who received a prescription for ADHD drug treatment, again presented by region.

Prevalence of prescribing

The overall prevalence of prescribing (males and females aged 15–21) increased 7.96-fold over the study period, from 0.26 per 1000 patients in 1999 to 2.07 per 1000 patients in 2006. *Figure 5* demonstrates the increase in prevalence stratified by gender. The prevalence increased 7.41-fold and 21.5-fold over the 8 years studied for males and females respectively.

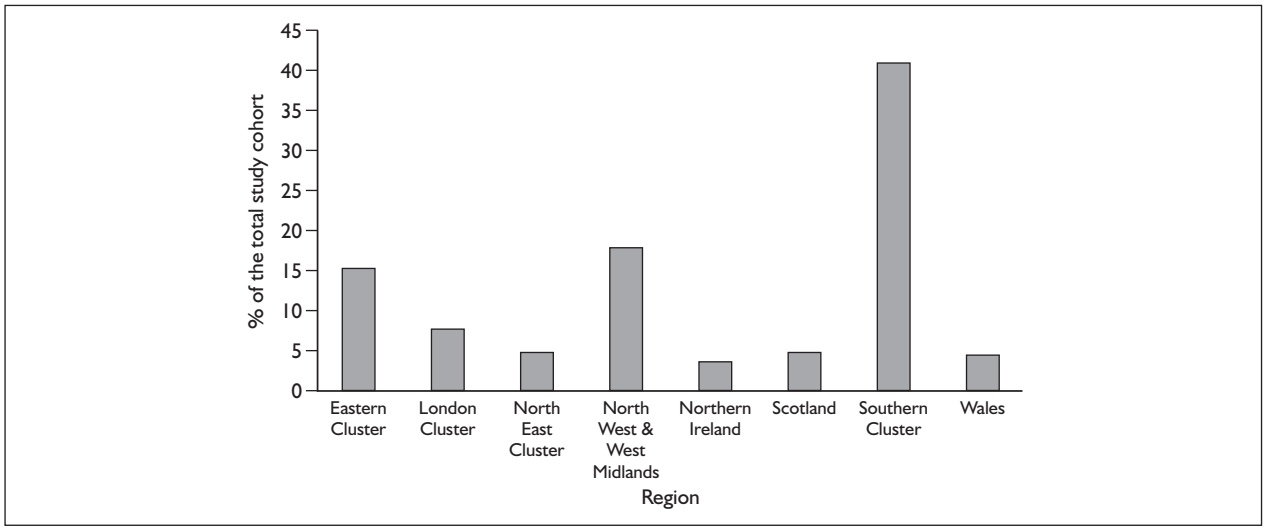

FIGURE 3 *Geographical distribution of patients as a percentage of the total study cohort (n = 983).*

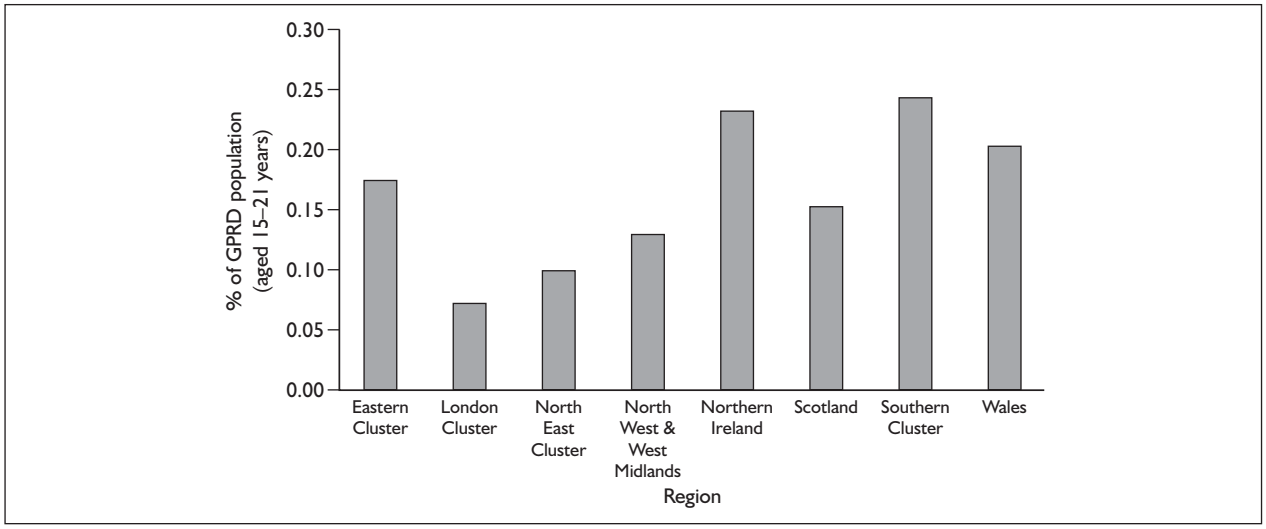

FIGURE 4 *Patients receiving ADHD drug treatment as a percentage of the total number of people (aged 15–21 years) in the region registered on the GPRD.*

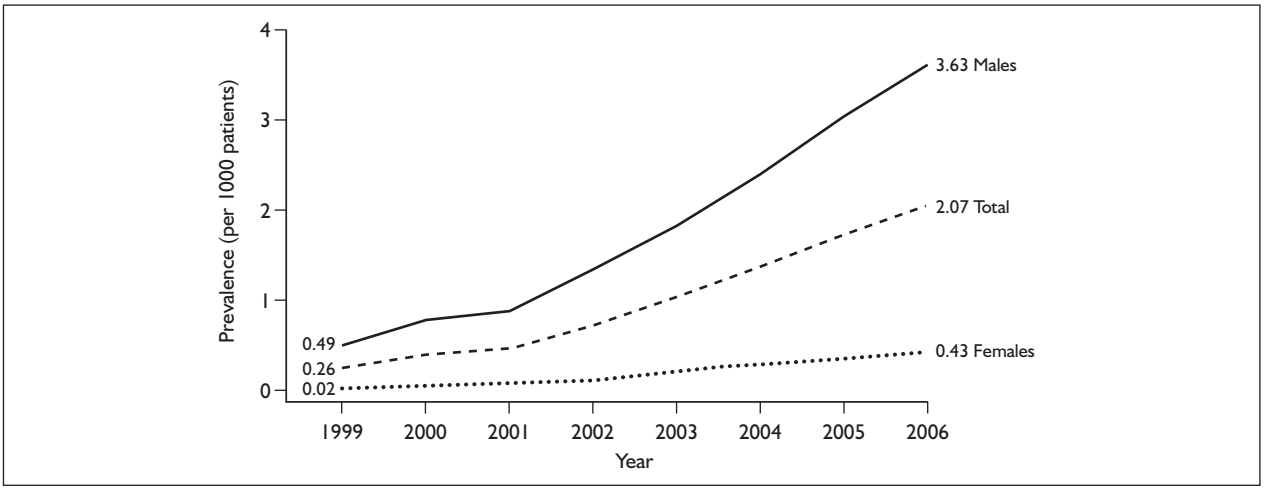

FIGURE 5 *Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine to patients aged 15–21 years from 1999 to 2006.*

Figure 6 illustrates the prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine to males, stratified by age, from 1999 to 2006. This shows a significant increase in prevalence across all ages ($p < 0.01$); however, it is noticeable that the biggest increase is in the younger patients, with the rate of increase by year becoming less evident in older patients. Values for the individual data points are given in Appendix 4.

Duration and cessation of treatment

Firstly, a cross-sectional analysis was carried out to illustrate the change in prescription rates for males aged 15–21 between 1999 and 2006. This is shown in *Figure 7*. Along with the data displayed in Figure 6, Figure 7 supports a main effect of age on stimulant prescribing. The overall increase in prescription prevalence is not consistent across all ages. The figure indicates an age-by-year interaction ($p < 0.01$) with a marked increase in prevalence for young children and adolescents, but almost no increase in the prescription prevalence for older adolescents and young adults. In the most recent year surveyed in this study (2006), the data show that the prescription prevalence for 21-year-old males was 95% lower than that for 15-year-old males (8.31 per 1000 patients compared with 0.43 per 1000 patients). The chi-squared test for trend showed a significant linear trend ($p < 0.001$), demonstrating a strong effect of age on decreasing treatment prevalence.

To determine treatment duration and to more directly address the issue of discontinuation, survival analysis was conducted. As previously described in the methodology, the duration of treatment was determined by 'mapping' prescriptions. The total treatment duration was

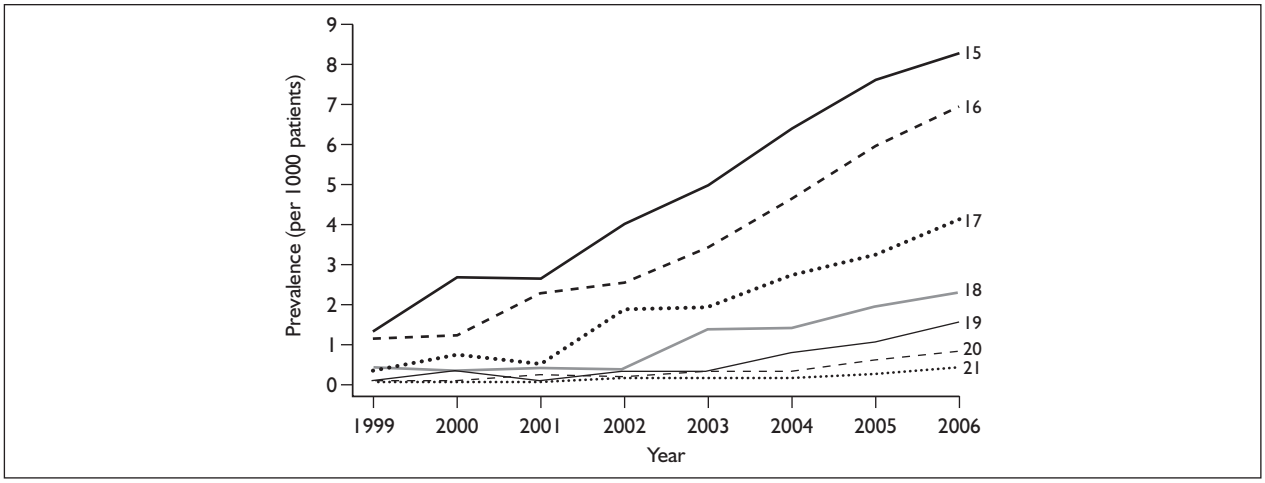

FIGURE 6 *Increasing prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine by year in males aged 15–21 years.*

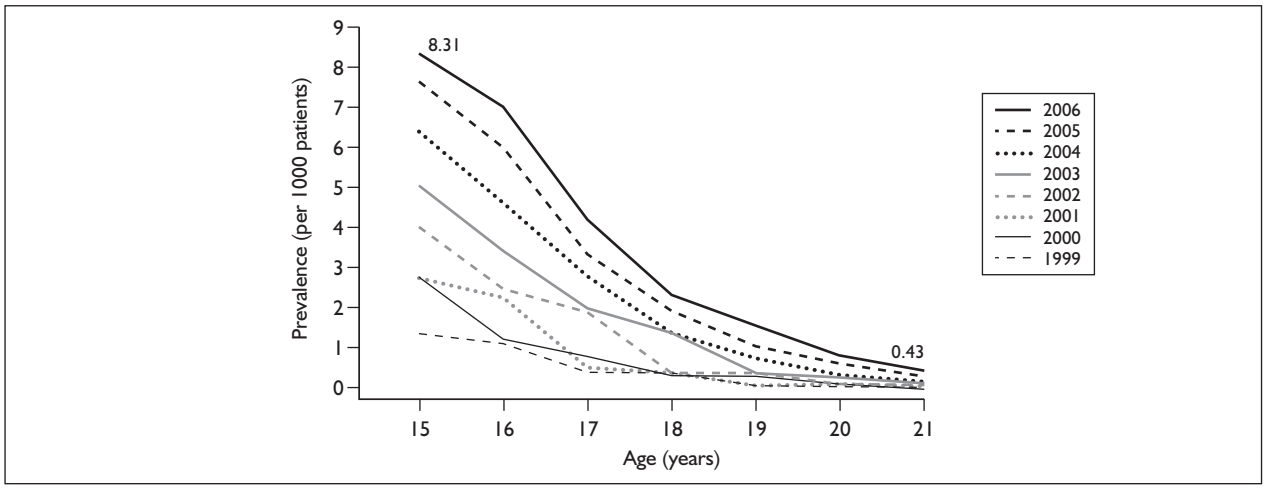

FIGURE 7 *Decreasing prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males from age 15 to 21 years from 1999 to 2006.*

determined from the date of the first prescription to the end date of the last prescription. A gap of 6 months or more was classified as a cessation in treatment. Using this definition of cessation, the number of treatment episodes per patient was calculated and is presented in *Table 2*.

To test the definition of cessation used, the time period between prescriptions was extended to 9 months. The number of treatment episodes per patient was recalculated using the definition of 9 months between prescriptions. The results of this, presented in *Table 3*, show that the number of treatment episodes varies little (7.4% change in number of patients with one episode). Based on these results and the clinical decision of the team, the initial definition of 6 months was used for all further analysis.

The startpoint for survival analysis depended on the following:

- A patient who started a treatment episode before the age of 15 entered the survival analysis on the date when he or she turned 15 (e.g. a patient with a birth date of 1 May 1988 starting treatment in 1998 at age 10 would enter the survival analysis on 1 May 2003).
- For a patient who started a treatment episode at the age of 15, the date of the first prescription (provided it was between 1999 and 2006) was the date that the patient would enter the survival analysis.
- As the main point of the study was to see what happened to patients' treatment when they turned 15 years, patients who started treatment at age 16 or older were not included in the survival analysis.

The survival analysis was conducted on 845 patients who entered the analysis aged 15 between 1999 and 2006. *Figure 8* shows the proportion of patients who stopped treatment for each year after turning 15 years.

The plot of the Kaplan–Meier estimate of the survival function shows that when patients are 16 years of age (i.e. 1 year after entering the study), 83% of patients still remain on treatment. At age 17, only 54% remain on treatment, and this falls to 36% at age 18, 24% at age 19, 22% at age 20 and 17% at age 21.

TABLE 2 *Number of treatment episodes per patient when a period of 6 months denoted treatment cessation*

Number of treatment episodes	Number of patients
1	846
2	115
3	21
4	1
Total	983

TABLE 3 *Number of treatment episodes per patient when a definition of cessation of 9 months between prescriptions has been employed*

Number of treatment episodes	Number of patients
1	909
2	67
3	7
4	0
Total	983

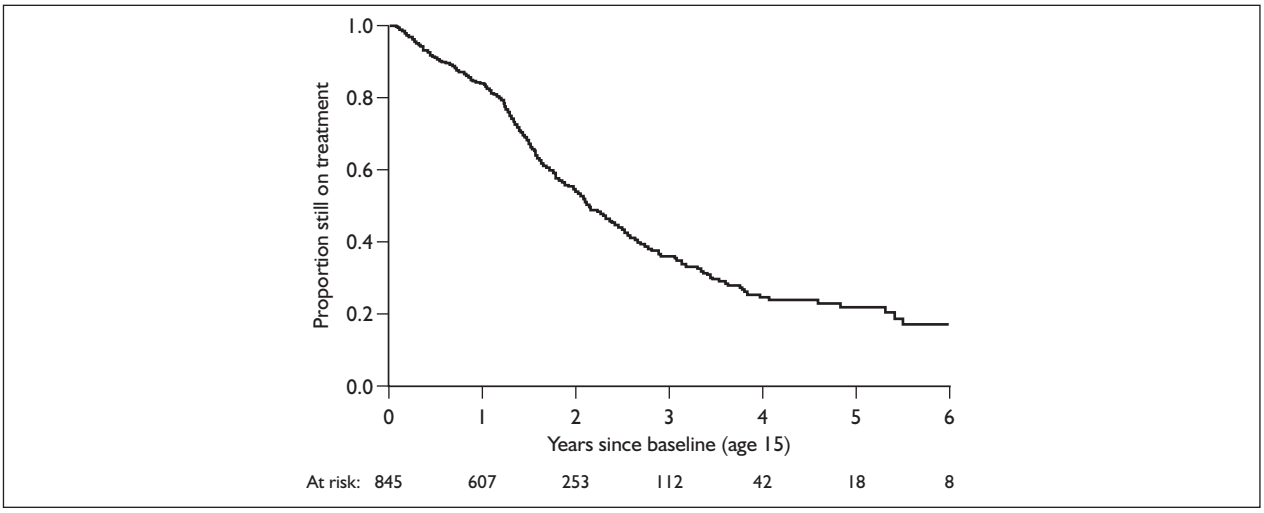

FIGURE 8 *Kaplan–Meier plot of duration of treatment after patients turn 15 years of age (n = 845).*

There is wide variation in prevalence and persistence reported in the literature; however, many experts in the field believe that these discrepancies may not be true differences, but in fact differences in methodologies and definitions of persistence used (e.g. syndromatic versus symptomatic persistence). Many of the follow-up studies on ADHD persistence have defined persistence differently, thus leading to varying rates of persistence. The use of one study alone as a comparator may lead to biased results, whereas the use of a number of studies would lead to very different, conflicting findings. To overcome this, it would be necessary to pool the information contained in these studies to determine the overall rate of persistence using defined criteria. This work has been conducted by Faraone *et al*.[40] in their peer-reviewed and published meta-analysis of the age-related decline of ADHD using follow-up studies from the literature. According to the meta-analysis findings, the probability of an individual with ADHD meeting the full criteria for the condition 1 year later is 83%. Our results correlate with these findings between the ages of 15 and 16; however, between the ages of 16 and 17, the proportion of patients who stopped treatment was twice that which would be expected (34% decrease compared with expected 17% drop). As patients become older, the rate of treatment discontinuation continues to exceed the expected rate of ADHD persistence. At age 21 years, while one would expect approximately 32% of patients to continue to require treatment for ADHD, our data show that only 17% are still receiving prescriptions to treat the condition. The number of patients at risk at each time point has been included. It should be noted that due to different periods of follow-up for patients, a large proportion of patients in the study were censored. For example, a patient who entered the study aged 15 in 2004 was only followed up for 2 years until the end of the study period. Taking this into account, it can be seen that between 3 and 4 years, the number of patients at risk has decreased significantly and so the information from the graph after this point may not be stable. The influence of informative censoring therefore cannot be excluded in this study; however, the number of patients from age 15 to age 18 (year 3) is considerable, and demonstrates the significant decrease in prescribing over time.

Cox regression was then performed to identify possible factors affecting cessation. Because of the small number of observations late on in the survival model, the analysis time has been reduced to 3 years to improve the model's fit and to allow for comparisons between the years of entry (as later years have a shorter follow-up). The following factors were examined as predictors of treatment cessation:

- number of treatment episodes prior to the current episode
- the first drug prescribed to a patient (i.e. methylphenidate, dexamfetamine, atomoxetine)
- whether a patient had a diagnosis for another mental health disorder
- whether a patient had a prescription(s) for other psychotropic medications
- whether a patient had had a referral to a specialist (e.g. child and adolescent psychiatrist)
- for patients who started their present treatment episode prior to the age of 15, the duration of treatment between the start of the episode and entering the study

- the year the patient entered the study
- gender.

In the Cox regression analysis we used a stepwise selection procedure by using log likelihood ratios to select which covariates should be included in the model. Martingale's residuals were not applied because covariates were binary rather than continuous, Schoenfield's residuals were used to assess the proportional hazards function, and Cox–Snell residuals were applied to assess the model's overall fit.

Of all the variables, only the last two (year of study entry and gender) were significant. Due to the smaller number of patients entering the study in the earlier years (see Figure 6), the year of study entry was grouped into two categories (< 2004 and ≥ 2004); 39.4% of patients included started before 2004 and 60.6% after and including 2004. A Cox model was fitted by including gender as time-varying covariate (varying at 0.5 years) as gender was found to be non-proportional.

The model in *Table 4* suggests that, for gender, there is no difference in the hazards before 6 months; however, after this time, the hazard of a female stopping treatment is 63% less than a male. However, it is worth noting that the number of females in the model was significantly less than males (74 versus 771).

The model also suggests that the patients aged 15 between 2004 and 2006 at inclusion are 40% less likely to stop treatment compared with patients age 15 between 1999 and 2003.

The Cox–Snell residuals illustrated in *Figure 9* indicate that that the model fits reasonably well with the data.

Restarting treatment

We then wanted to look at those patients who had stopped treatment, and to see what proportion of these restarted treatment, and possible factors affecting restarting. Treatment cessation was defined as having a gap of 6 months or more between prescriptions. Therefore, by definition, all patients who had stopped treatment had at least 6 months off treatment. This can be seen in *Figure 10*. From the original cohort of 845 patients, 407 stopped treatment. Of these 407 patients, 56 restarted treatment. Of the 56 patients who restarted treatment, 40 had one further treatment episode, 15 had two further treatment episodes and one had three further treatment episodes before 31 December 2006. The mean duration of these episodes was 9 months, with a range from 8 days to 3.8 years. Analyses have been performed from the time of treatment cessation to when patients restarted treatment for the first time.

After the 6-month period (defined as treatment cessation), the proportion of patients restarting treatment is very low. The highest rate of treatment restart occurred within the first year following treatment cessation. At 1 year, 11% of patients had restarted treatment. At 2 years, 15% of patients had restarted treatment. At 4 and 6 years, only 18% of patients had restarted treatment. Due to the low number of events (patients restarting treatment), it is unlikely that the sample size in this cohort would provide enough power for a formal analysis using a Cox regression model.

Also, as before, the follow-up period of patients differed according to when they entered the study. Since the majority of patients (60.6%) entered the study in the later years (2004–6), these patients would not have sufficient follow-up to accurately assess restarting of treatment and factors affecting this. Due to these reasons, we believed that a descriptive analysis was most appropriate for the data presented.

Discussion

Main findings

To our knowledge, this is the first study to examine prescribing trends of methylphenidate, dexamfetamine and atomoxetine in adolescents and young adults in primary care in the UK.

TABLE 4 *The final Cox model using the Breslow methods for ties*

Variable	Hazard ratio	95% Confidence interval	*p*-value
Year ≥ 2004	0.60	(0.49 to 0.74)	< 0.001
Females < 6 months follow-up	1.50	(0.75 to 3.01)	0.254
Females ≥ 6 months follow-up	0.37	(0.16 to 0.86)	0.021

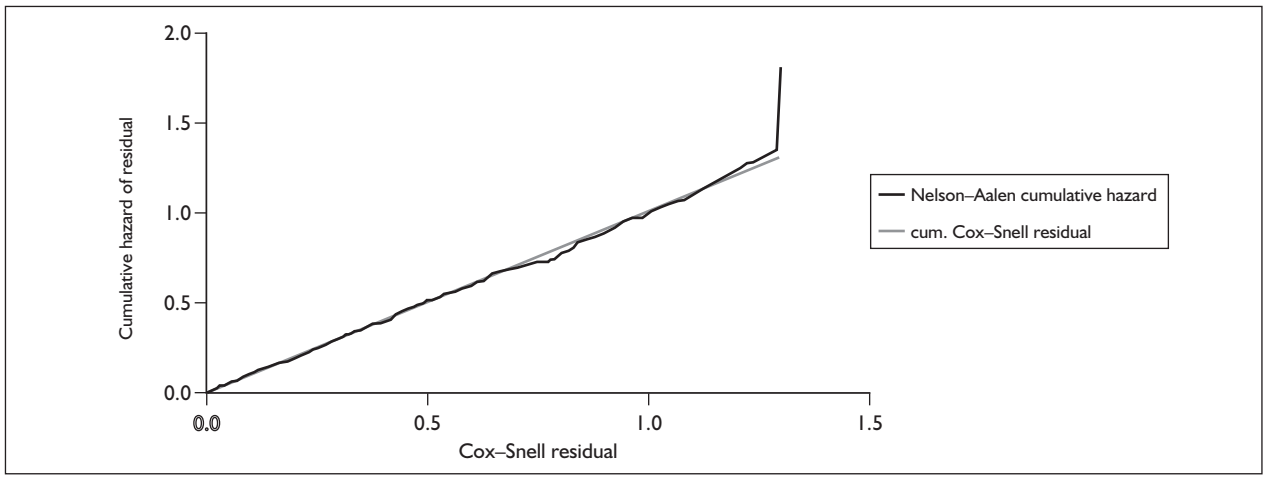

FIGURE 9 *Cumulative hazard of Cox–Snell residuals.*

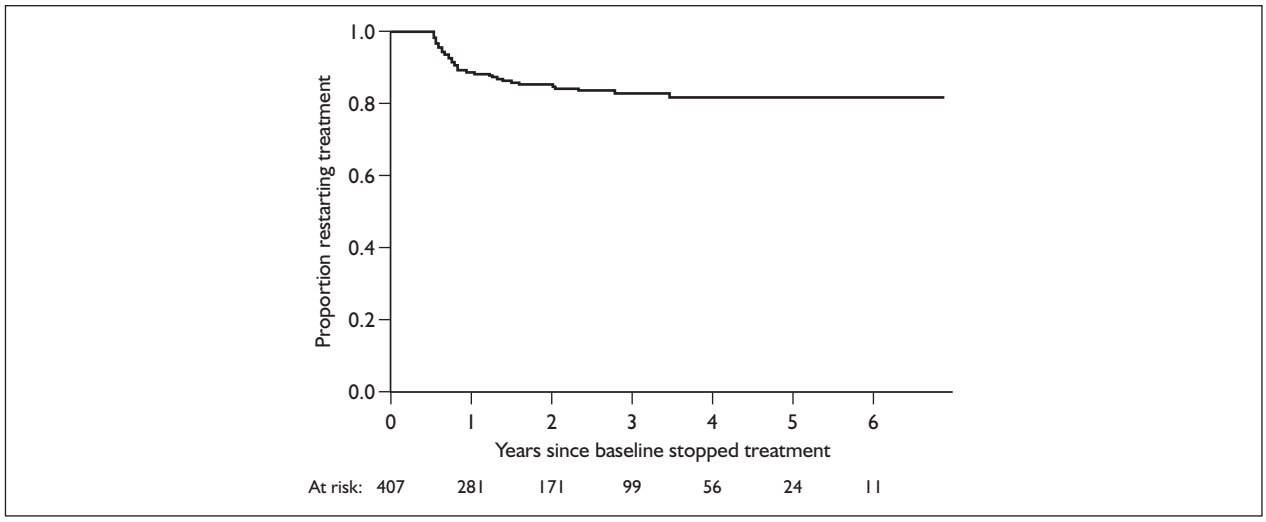

FIGURE 10 *Kaplan–Meier curve showing proportion of patients restarting treatment.*

There are four key findings.

1. There was a marked rise over time in the prescribing of stimulants and atomoxetine in adolescents and young adults. Overall, prevalence increased 7.96-fold over the 8 years studied. By gender, prevalence rose 7.41-fold in males and 21.5-fold in females during the study period.
2. The cross-sectional analysis showed an interaction between age and year, with a greater increase in prescribing over the study period in younger patients. In 2006, the prevalence of prescribing to males aged 21 was 95% less than the prevalence in males aged 15.
3. The survival analysis demonstrated that the rate of treatment discontinuation largely exceeded the estimated rate of persistence of the condition. This drop in prescribing was most noticeable between the ages of 16 and 17 years. The factors affecting treatment cessation included the gender of the patient and the year in which the patient entered the study, with the rate of discontinuation greater during the earlier years of the study.
4. A small proportion of patients restarted treatment if they had stopped treatment after the age of 15. Those patients who restarted treatment were more likely to restart within the first year following treatment cessation.

Early discontinuation of medication?

The overall trend of increased prescribing over the study period may be attributed to increased recognition and treatment of ADHD by child and adolescent mental health and paediatric services, in addition to the increased marketing and availability of drugs to treat ADHD (e.g. long-

acting methylphenidate and the non-stimulant atomoxetine). Furthermore, it was found that from 2001 onwards there is a notable increase, perhaps owing to increased awareness of ADHD as a result of the NICE health technology assessment issued in late 2000.[3] In contrast, the data indicate that there is no parallel increase in the rates of prescribing to older adolescents and young adults. Furthermore, since prescription rates show such a rapid tail-off in young adults, it is likely that in most cases prescriptions for individual patients with ADHD are tailed off and stopped during late adolescence and early adult years.

An important question is whether the low level of prescribing for young adults is appropriate and matches the clinical course of the disorder. The pattern of treatment discontinuation seen in the cohort study would be appropriate were ADHD a time-limited condition confined to childhood and adolescence or, alternatively, were drug treatment not effective in adults.

The main evidence against this view comes from longitudinal follow-up studies of ADHD that show high levels of persistence of the core ADHD syndrome and associated impairments. A recent meta-analysis[40] found that 15% of children with ADHD continued to fulfil the full criteria for ADHD as adults by age 25 years. This is significant because the individuals with persistent ADHD fulfilled the same diagnostic criteria that are applied to children, which represents a significant level of impairment compared with age- and gender-matched controls.

Furthermore, the meta-analytic data found a high level of impairment in individuals who no longer met full criteria for ADHD, but who were in partial remission, with a lower symptom count. That impairments exist in the group of people with ADHD that persists into adulthood is well documented in the follow-up studies as well as from reports of epidemiological surveys.[52,53] Findings from meta-analyses also suggest that the stimulant drug methylphenidate is equally effective in reducing ADHD symptoms in adults as it is in children.[54]

Also, both the stimulant and non-stimulant medications have been demonstrated to be efficacious and effective at reducing the symptoms and impairments associated with ADHD in adults, with effect sizes of around 0.9 for the stimulants[54] and 0.6 for the non-stimulant atomoxetine.[55] While it is clear that adults with ADHD show response rates to pharmacological treatments for ADHD that are comparable to those seen in children,[12,42,54,56] there is a lack of trial data providing direct evidence for medium- to long-term benefits of treatment; however, this is also true for childhood ADHD. Based on a thorough review of the literature and expert opinion, the BAP concluded that 'It is becoming increasingly evident that this common and impairing condition is costly and treatable, providing a significant opportunity to relieve the burden of suffering from patient and their family… '.[42] Furthermore, one of the main recommendations is the appropriateness of treating ADHD in adults in the same way as treating ADHD in children. This is the same conclusion reached by the recent NICE guideline development group.[12] As the evidence on the persistence of ADHD grows, it is possible that this is reflected in the prescribing patterns of clinicians, who are more likely to continue patients on treatment as they get older. The Cox model showed that patients aged 15 between 2004 and 2006 were 40% more likely to remain on treatment compared with patients of the same age between 1999 and 2003.

Another factor that was significant to stopping treatment was gender. The overall ratio of males to females in the total cohort was 10.4 : 1. However, the difference in gender varied greatly, when stratified by age. In 2006, the prevalence of prescribing to patients aged 15 was 8.31 per 1000 patients and 0.68 per 1000 patients for males and females respectively, giving a gender ratio of 12.2 : 1. These figures contrast with a 4 : 1 gender ratio for ADHD in population samples.[57] Few studies in the literature have examined the issue of gender-based differences among children with ADHD.

A meta-analysis of the available literature in this area by Gaub and Carlson[58] revealed that non-referred females with ADHD showed less impairment on inattention, internalising behaviour, peer aggression and peer disliking, compared to boys with ADHD. Among clinic-referred girls with ADHD, similar levels of impairment on these variables were seen, with the exception of inattention, for which females tended to have a greater severity compared with males. Girls with ADHD tend to show lower levels of hyperactivity, fewer conduct disorder diagnoses, lower rates of externalising behaviour, but tend to have greater intellectual impairment. Therefore, it is likely that girls with ADHD, who tend to exhibit fewer disruptive symptoms, are less likely to be identified by teachers and parents and referred for treatment. The discrepancy in the male to female ratio in

our study compared with that seen in the general population raises the possibility that those females who do receive treatment for ADHD are more likely to be severely affected and to remain on treatment for longer.

This hypothesis, which has also been suggested by others,[58] is supported by the data in this study which showed a treatment prevalence ratio of 1.95 : 1 for males to females for patients aged 21 in 2006 (prevalence 0.43 per 1000 patients for males, and 0.22 per 1000 patients for females). The Cox analysis also showed that after a period of 6 months (where there was no difference in the hazard), females were 63% less likely than males to stop treatment. Another possible explanation for greater continuity of treatment in female adolescents is that they may have superior treatment adherence than male adolescents.

Several factors appear to contribute to the lower level of prescribing with increasing age. First, the steepest decrease in prescribing occurred between the ages of 16 and 17 (see Figure 7). This was seen clearly in the survival analysis, which demonstrated that twice as many patients stopped treatment between the ages of 16 and 17 as would be expected, based on the expected persistence rate of the condition. At this age, adolescents normally finish their General Certificate of Secondary Education (GCSE) and may leave school. This might be critical, since the school system is known to play a key role in the identification and referral of young people with ADHD;[57] after leaving school, young people may perceive less need for sustained attention and focus and control over hyperactive–impulsive behaviour.

Furthermore, there may be less expectation from key adults (teachers and parents) that treatment is still necessary. Another factor is that young people themselves have greater autonomy in making decisions about their health care, and problems with self-evaluation and adherence to treatment regimens are recognised problems in this age group across many medical conditions. For example, the increase in self-autonomy during adolescence is often accompanied by poor drug adherence, as is typically seen in conditions such as diabetes.[59]

Second, the low level of prescribing is accompanied by the poor provision of diagnostic and treatment services for older adolescents and young adults. Typically, in the UK, both paediatric and child and adolescent mental health services (CAMHS) have been available for young people up to the age of 16 or school-leaving age.[60] In 2004, the National Service Framework for Children Young People and Matarnity Services recommended that CAMHS should be available up to age 18.[60] Although implementation is patchy, this service change may have contributed, in part, to lower discontinuation rates in the latter years of the study. ADHD services within adult mental health are currently very poorly developed,[61] and clear arrangements for transition are often lacking.[62] This can result in patients failing to be picked up by adult services for initiation or continuation of treatment for ADHD, even where this is clinically indicated. The further recommendation that prescriptions of stimulants and atomoxetine should only be provided under the supervision of a clinician with expertise in ADHD is problematic within adult mental health services where specialist services are currently very limited.

Currently, neither methylphenidate nor dexamfetamine are licensed for the treatment of ADHD in patients over 18 years and atomoxetine is only licensed for individuals over the age of 18 years who started their treatment before that age. Furthermore, the previous recommendation by NICE in their guidelines in 2000[3] was that treatment should be stopped during adolescence, although this has been removed from the current guidelines under review, which in contrast highlight the need for continued treatment subject to annual review of effectiveness.

One could argue that, in the UK, the relatively low level of prescribing to older patients is due to the inappropriate over-prescribing in the younger age group; therefore, clinicians decide to stop treatment when patients are older. However, based on our findings and existing data,[49] this argument cannot be substantiated. In our cohort in 1999, the prevalence of prescribing in males aged 15 was 1.3 per 1000 patients, which is far lower than the expected prevalence of children with ADHD or HKD in the UK, estimated to be 5% and 1% respectively.[3]

A recent national survey also concluded that concerns about over-prescribing of stimulant medications in the UK were unfounded.[63] This found that all children (aged 5–16) receiving stimulant treatment had evidence of pervasive hyperactivity (overactivity, impulsiveness and inattention).

Despite this, a large proportion of children (~57%) with HKD, which represents a severe form of the DSM-IV ADHD diagnosis, were not getting access

to evidence-based treatment. Similar findings were reported by the NHS Quality Improvement Scotland review of ADHD treatment by NHS services across Scotland. They found that only 0.7% of children in Scotland are currently being treated for ADHD.[62] This problem appears to be further exacerbated in older adolescents and young adults.

Kessler *et al*.[64] conducted a retrospective assessment of childhood ADHD, childhood risk factors and a screen for adult ADHD in a sample of 3197 18 to 44-year-olds to determine patterns and predictors of ADHD persistence into adulthood. They examined age, sex, race/ethnicity, childhood ADHD severity (which included receiving treatment for ADHD, beginning as of age 15), childhood adversity, traumatic life experiences and comorbid DSM-IV child/adolescent disorders. The results of the study demonstrated that only childhood ADHD severity and childhood treatment significantly predicted persistence. Due to the constraints of the available data in the GPRD, we were unable to examine many of these predictors in our study, such as ethnicity, ADHD severity, other adversities and life experiences. The nature of our sample selection meant that all patients required treatment to be included in the study, and therefore this could not be examined. In contrast to the study by Kessler *et al*., the current study showed gender to be significant to persistence of treatment, as was the year when the patient entered the study. However, common to both studies was the identification of very few modifiable risk factors for persistence of ADHD or ADHD treatment into adulthood.

Reinitiating of treatment

Over the 6 years studied, the Kaplan–Meier analysis estimated that of those patients who stopped treatment, 18% restarted treatment. Again, there is an issue surrounding the varying follow-up periods and censoring of patients according to when they entered and subsequently stopped treatment. For example, a patient who stopped treatment at the end of 2005 only had 1 year of follow-up compared with a patient who stopped treatment at the end of 2001 who would have 5 years of follow-up.

The number of patients at risk has been documented at each time period in Figure 10. However, it can also be noted from this figure that the majority of those patients who did restart did so within the first year following treatment cessation and so most of the study cohort had sufficient follow-up data to record this. It may be the case that in those patients who do not restart treatment, the symptoms of ADHD have remitted and so they no longer require pharmacological treatment.

However, as discussed above, the rate of treatment cessation exceeds the expected rate of persistence, suggesting that many of the patients who have stopped treatment would have benefited from continued treatment. As the majority of patients who restarted treatment did so within 1 year of stopping treatment, this would suggest that the impairments of ADHD are noticed by patients quite soon after stopping treatment. It is also likely that patients may still be under the care of a clinician immediately after stopping treatment and thus it may be easier for patients to restart treatment.

Strengths and weaknesses of the study

The GPRD is one of the largest databases of anonymised longitudinal data from primary care in the world, capturing comprehensive information on treatments and outcomes of a 5% sample of British general practices. The use of the GPRD allowed us to capture what is actually happening under normal conditions of practice, rather than in selected samples of patients recruited into clinical trials.

However, there are a number of limitations in using the GPRD. The database does not record information concerning treatment indications, dispensing of prescriptions or treatment compliance. Factors which may predict persistence of the condition and the continued need for treatment such as ADHD severity, level of impairment and socioeconomic status are also not captured, which is a limitation of many automated databases. Although our study is a true reflection of primary care, it may underestimate the true prevalence of ADHD treatment in the UK, as some GPs are unwilling to prescribe treatments for ADHD for various reasons. This may include patients who are more severely impaired, to whom GPs do not wish to prescribe. Prescribing would then be done solely in secondary or tertiary care; however, there are no known data to show the proportion of patients in whom this occurs. Nevertheless, many patients will be prescribed treatment from their GP under a shared care protocol, following diagnosis and initiation of treatment from a child and adolescent psychiatrist or paediatrician. While this study shows discontinuation of prescribing to patients by GPs, we do not assume that the GPs alone are taking

the decision to stop medication. As recommended by the 2000 NICE guidance[3], treatment discontinuation should occur under specialist supervision. It is possible that young people no longer request prescriptions or attend follow-up for monitoring.

Unfortunately, from a methodological aspect there is no escaping the fact that informative censoring is a large problem in this survival analysis, and it is not known to what extent it has affected the analysis. There is no satisfactory way to compare covariates when informative censoring is present. Overall 52% of the data was censored, and of this, 65% was due to censoring under 2 years' follow-up, which may introduce bias into the analysis. Cut-offs were made to enable the model to fit the actual data better, as in 4–6 years of follow-up there were only 42 observations; of these, 36 (86%) were censored. Participants in the > 2004 group could only be followed up for a maximum of 3 years, so the model was also reduced in an attempt to allow a fairer comparison between ≥ 2004 and < 2004. In 2005 and 2006, 70% and 92% of the data respectively were censored, and therefore the years 2004–6 (and 1999–2003) were combined rather than excluding the data. The 2004 split also coincided with the release of atomoxetine. Gender was split on the basis of non-proportionality. When gender splitting was carried out, the model was shown to be proportional when applying the proportional-hazards assumption based on Schoenfeld residuals. In future research, it would be preferable to have longer follow-up periods for the more recent patients.

Finally, similar to other pharmacoepidemiological studies, this study was unable to identify the reasons for cessation or restart of treatments. Furthermore, it cannot describe the process of treatment cessation and restart. Therefore the Part 2 study was conducted and the results are discussed later in the report.

Conclusion

Since 1999, the prevalence of drug prescribing for adolescents and young adults with ADHD has increased rapidly, but the rise in prevalence over time has been smaller for older patients. There is a marked pattern of drug discontinuation between ages 15 and 21, with the most noticeable drop occurring between the ages of 16 and 17. Although it is not easy to determine which children with ADHD will continue to display symptoms and impairments in adulthood, clinicians need to be aware that the condition can persist as patients grow older, to varying degrees, with a significant proportion of patients requiring pharmacological treatment into adulthood. This study raises the possibility that treatment may be prematurely discontinued by or for some adolescents and young adults with ADHD and that overall the fall in treatment prevalence may be out of step with the numbers of people who still require treatment as young adults. Furthermore, it is estimated 18% of patients would restart the treatment after cessation, further supporting the view that some patients may be stopping their treatment prematurely. As there were very few risk factors that predicted successful treatment cessation, it is possible that it may simply be a lottery whether a patient has access to services to enable continuation with medication as they grow older. Therefore, further research should target reasons behind medication cessation and the appropriate management of these patients.

Chapter 3

Literature review on quality-of-life scales in ADHD

Introduction

The primary aim of CADDY is to conduct a scoping study to identify the current practice of the discontinuation of ADHD drug treatments in adolescents and young adults. The secondary aim of CADDY is to collect additional information on the reasons, processes and outcomes of treatment cessation. As mentioned previously, the information from this study will be used to inform development of a future randomised controlled trial (RCT) of a new protocol to manage treatment cessation in adolescents and young adults.

Health-related quality of life (HRQoL) is an increasingly important outcome measure for a range of clinical, research and policy purposes. It is crucial in assessing the quality of current care and in evaluating the success of interventions or changes to treatment plans (pharmacological and non-pharmacological) and would therefore be an important outcome measure for any possible future RCT. The US FDA and the European Medicines Agency (EMEA) have published guidance on the development and use of patient-related outcome measurements, including QoL.[65,66]

The concept of QoL can vary greatly between people. For some, QoL is about relationships with family and friends; others equate QoL with material wealth while for some people QoL is simply synonymous with happiness. Eiser and Morse[67] described five approaches to QoL: philosophical, economic, sociological, psychological and medical. In terms of the impact of illness and medical interventions on QoL, a number of definitions have been proposed. Leidy *et al*.[68] defined QoL as '…an individual's subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning… '. In addition to influences such as family, friends and socioeconomic status, illness has been identified as having a significant influence on QoL.[67]

Bullinger and Ravens-Sieberer[69] conducted a comprehensive search of the literature surrounding child QoL and identified, from over 20,000 publications related to QoL in medicine, 320 articles relevant to children. Most of these related to work in the areas of oncology and transplantation, asthma, epilepsy, diabetes and rheumatism. In addition to the effects of physical illness, mental illness has also been identified as having a major impact on QoL.[69] In fact, there is a school of thought that mental illness can have a greater impact on QoL than common physical conditions.[70,71] There is growing evidence that the presence of ADHD can impact on the QoL of children and young people.[72] Therefore, the CADDY team conducted a literature review to identify appropriate QoL questionnaires for patients with ADHD. Furthermore, a selected QoL questionnaire was subsequently used in the Part 2 study to test its feasibility for use in the future RCT.

Aim and objectives

The aim was to identify potentially appropriate QoL measures for patients with ADHD. The objectives were to:

1. search appropriate databases for QoL measures used with patients with ADHD
2. describe key characteristics of each measure
3. make a recommendation on the most appropriate scale to use with UK adolescent patients.

Methodology

ADHD is a condition frequently researched by medical, psychological and social investigators; therefore, medical, psychological and sociological databases were searched for relevant literature. The databases that were selected for use in the search are shown in *Table 5*.

Keywords and search strategy

In order to maximise the number of journal articles that could be identified on the subject of ADHD and QoL, previously published *Health Technology Assessment* literature reviews on ADHD[73] and QoL[67]

TABLE 5 *Electronic databases for literature search*

Database	Reason for choice
BIOSIS Previews®	Life sciences database containing literature on multidisciplinary life and medical sciences as well as general science[74]
CINAHL® database (Cumulative Index to Nursing and Allied Health Literature)	Literature for nursing and allied health disciplines[75]
EMBASE	Biomedical and pharmacological resource. Speciality subsets covered include paediatrics, pharmacy and psychiatry[76]
International Bibliography of the Social Sciences (IBSS)	Covers behavioural and social science subjects[77]
International Pharmaceutical Abstracts (IPA)	Provides worldwide coverage of pharmaceutical science and health-related literature[78]
Ovid Medline	Database on clinical medicine and nursing[79]
Ovid Medline In Process and other non-indexed citations	As above. Includes journals that are yet to be published[79]
PsycINFO	Database of psychological literature[80]
Social Sciences Citation Index – Web of Science	Database containing literature on social sciences[81]
Science Citation Index	Database containing literature on science in general[82]

were used to identify appropriate search terms. These terms were then modified by the CADDY team. The final search terms are listed in *Table 6*.

Databases search procedures

The following search terms listed in Table 6 were used on the databases listed Table 5 in order to identify relevant literature. The results of citations are shown in *Table 7*.

The identified scales were discussed within the study group. Any additional QoL scales that clinicians were aware of that had not been retrieved during the search were also included.

Inclusion and exclusion criteria

Inclusion criteria

Studies using scales to investigate the QoL for children, adolescents and/or adults with ADHD.

Exclusion criteria

1. Review articles relating to ADHD and QoL were excluded; however, they were searched for any additional scales not already identified.
2. Studies describing the general and non-specific QoL issues of patients with ADHD.

The method for this literature review is summarised in *Figure 11*.

Results

The database search was conducted in March 2007 and gave 368 citation results. The abstracts of the 368 articles were screened to see if they were relevant and the irrelevant articles were then categorised as shown in *Table 8*.

After the irrelevant abstracts were removed from the list, 55 articles remained and the full text for each article was screened to identify ADHD QoL scales that had been used in the ADHD population. Two articles were not written in English; however, information was obtained from the abstract, which was available in English. For these two articles, only the abstracts were used.

Of the 55 articles identified, 20 articles were excluded after further screening because they did not provide information on QoL scales used in patients with ADHD. This left 35 articles that used QoL scales in the ADHD population; 28 of the articles examined QoL in children and seven of the articles examined QoL in adults.

Twelve QoL scales were identified. Of the 12 scales, eight had been used in children and four in adults. *Table 9* lists the ADHD QoL scales used in children and *Table 10* the scales used in adults.

Discussion

The QoL scales used in children that were obtained from the relevant authors included the Child Health and Illness Profile – Child Edition (CHIP-CE), Pediatric Quality of Life Inventory™ version 4.0 (PedsQL), Youth Quality of Life Instrument-Research Version (YQOL-R), Munich Quality of Life Questionnaire for Children (KINDL),

TABLE 6 *Summary of search terms approved by the CADDY team*

Search number	Search term[a]
1	ADD-HD
2	ADDH
3	ADHD
4	Attention deficit disorder
5	Attention deficit disorder with hyperactivity
6	Attention deficit hyperactivity disorder
7	Brain dysfunction, minimal
8	Hyperactiv$
9	Hyperkine$
10	Inatten$
11	HRQoL
12	Health related Quality of Life
13	Health status indicators
14	QOL
15	Quality of Life
16	Quality of Life scales
17	Sickness impact profile
18	Health status
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21	19 and 20
22	(Measure$) or (scale$) or Index or (indicator$)
23	19 + 20 + 23

a Well-being and functional status were excluded as search terms as they were found to give unrelated articles in the preliminary search.

EuroQOL EQ-5D (Proxy version) and Weiss Functional Impairment Rating Scale (WFIRS). As discussed previously, two of the eight paediatric QoL scales were not obtained due to their high cost ($US5000). These scales, which are commercially available, are the Child Health Questionnaire 50-item parent form (CHQ-PF50) and the ADHD Impact Module-C (AIM-C). Of the children's QoL scales that were retrieved from the search, only the AIM-C was disease specific, all other QoL scales were generic.

Of the four QoL scales used in adults, two of the scales were obtained. The remaining two scales were unavailable at the time of analysing the results of this review. The available scales were the Adult Attention Deficit Hyperactivity Disorder Quality of Life Scale (AAQoL), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Both scales had been used solely in adults from the USA. The AAQoL is disease specific, whereas the Q-LES-Q is generic for the area of psychiatry and psychology.

From the review of the literature on QoL scales used in children, the CHIP-CE was the most frequently used QoL scale in the UK studies. Overall, it was the second most cited QoL scale used in ADHD. The CHIP-CE scale is a generic scale designed to assess QoL; however, it has been validated for use in children with ADHD in the UK. The Attention-deficit Hyperactivity Disorder Observational Research in Europe (ADORE) study examined the cross-sectional reliability and validity of the parent-report form of the CHIP-CE88. Parents of children with ADHD (aged 6–18 years) in 10 European countries (including the UK) completed the CHIP-CE at the baseline visit ($n = 1477$; data missing for one patient). Analyses included determination of internal consistency reliability, ceiling and floor effects, factor analysis, and Pearson's correlations between CHIP-CE

TABLE 7 *Search terms and results: date of search 22 March 2007*

Search number	Search term	A[a]	B[a]	C[a]	D[a]
1	ADD-HD	3	1	1	57
2	ADDH	269	2	129	84
3	ADHD	14,491	1232	8227	7258
4	Attention deficit disorder	28,414	169	10,334	10,132
5	Attention deficit disorder with hyperactivity	16,106	7	5552	8683
6	Attention deficit hyperactivity disorder	17,749	2501	8701	8683
7	Brain dysfunction, minimal	0	0	2	746
8	Hyperactiv$	60,871	2854	17,053	21,880
9	Hyperkine$	9936	126	6974	2110
10	Inatten$	5245	287	2751	2247
11	HRQoL	5025	479	620	2017
12	Health related Quality of Life	19,621	2116	2070	12,918
13	Health status indicators	11,046	3819	41	2704
14	QOL	17,479	1541	2163	6155
15	Quality of Life	21,763	22,522	17,595	89,277
16	Quality of Life scales	1265	151	348	11,220
17	Sickness impact profile	4872	630	258	1199
18	Health status	101,112	16,121	7155	51,608
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	79,634	3178	21,098	28,285
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	303,596	36,502	24,119	> 100,000
21	19 and 20	643	78	116	369
22	(Measure$) or (scale$) or Index or (indicator$)	4,896,787	170,536	511,414	> 100,000
23	19 and 20 and 22	252	38	55	171

A, BIOSIS Previews, EMBASE, International Bibliography of the Social Sciences, International Pharmaceutical Abstracts, Ovid Medline, Ovid Medline In Process and other non-indexed citations; B, CINAHL database; C, PsycINFO database; D, BIDS ISI Social Sciences Citation Index, Science Citation Index – web of science.
a Each column represents the number of citations found by the databases before combining them together.

and other scales used to measure ADHD severity, problems and family strain. ADORE has found that the internal consistency reliability was good to excellent (Chronbach's $\alpha > 0.70$) for all CHIP-CE domains and subdomains, and almost no ceiling and floor effects were observed. Furthermore, there were moderate to high correlations between the parent CHIP-CE scale and measures of ADHD and family factors. The QoL of children in ADORE was dramatically lower than that of community youth, with mean CHIP-CE scores almost 2 standard deviations below community norms.[72,86–89]

The CHQ-PF50 was the most cited QoL scale, although it is not commonly used in the UK. Its use in the UK was cited by two studies funded by the UK branch of an American pharmaceutical company.[97,98] It was not possible to obtain a copy of the QoL scale for the CHQ-PF50 due to its cost.

The other scales identified in the literature review had not been used in the UK at the time the review was performed. The PedsQL is a generic scale that has been used in the Netherlands, Thailand and the USA. The AIM is an ADHD-specific scale and was developed and tested in the USA; however, due to the cost, it was not obtained for evaluation. The YQOL-R is a generic scale and was also developed and tested in the USA. Finally, the KINDL questionnaire has been used in the USA and Japan.

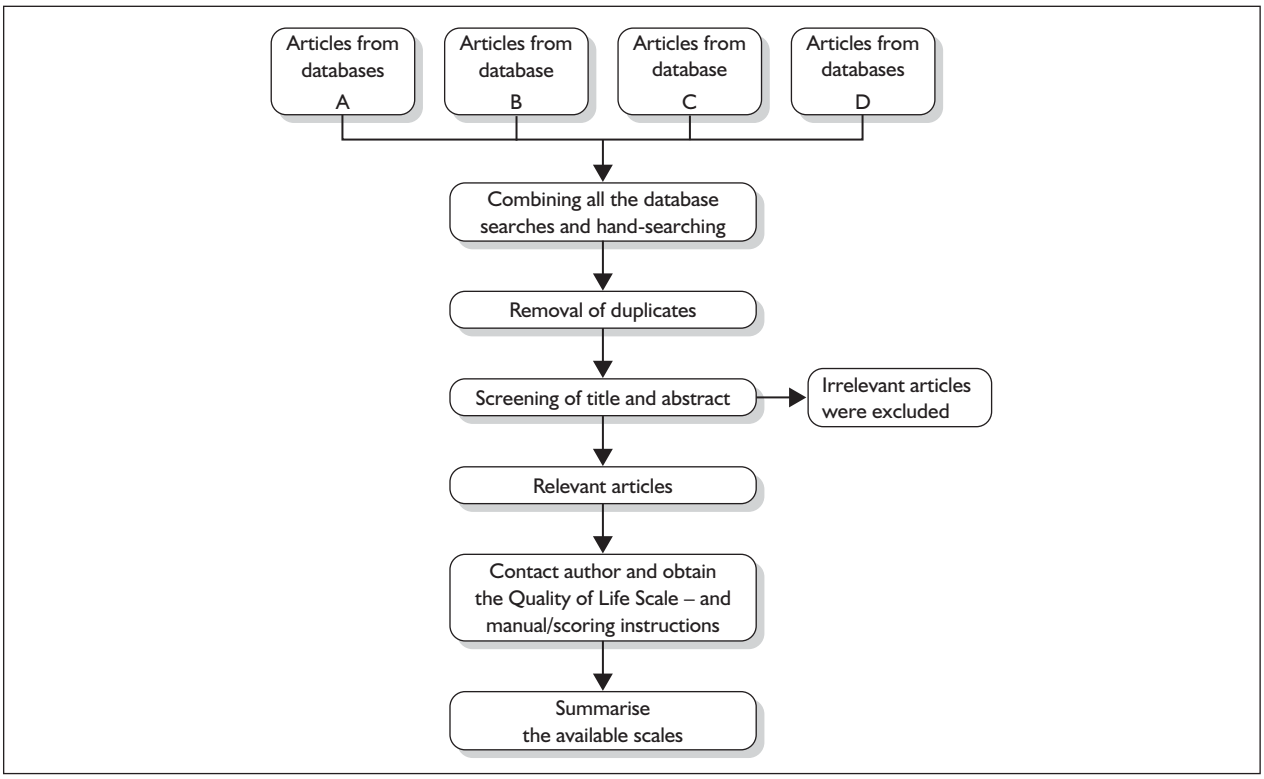

FIGURE 11 *Schematic summary of methods used for literature search.*

TABLE 8 *Irrelevant article categories and number of articles in each*

Category	Number of citations
QoL scales not used in an ADHD population	33
Review and non-primary research articles	46
Case studies	3
ADHD article without QoL scales	59
Articles that neither contained QoL scales nor were relevant to ADHD patients	172

ADHD, attention deficit hyperactivity disorder; QoL, quality of life.

The review identified that generic QoL scales were cited more often than ADHD-specific scales. There is an issue as to which is the more appropriate to use when assessing QoL in patients with ADHD. ADHD-specific scales can focus on particular areas of concern in relation to the disorder and are useful when measuring the effects of an intervention. However, generic scales are designed to be more comprehensive and are therefore less likely to be sensitive to treatment-related change. The use of a generic measure would be more appropriate in circumstances where one wishes to compare different patient groups or when describing the QoL of individuals who are suffering from more than one condition.

Limitations of the literature review

The review of the literature involved searching published journals that were indexed in the selected databases, which precluded the inclusion of unpublished material and those from sources such as pharmaceutical companies and specialist research. It may be the case that pharmaceutical companies develop their own QoL scales to

TABLE 9 *Quality-of-life scales used in children with ADHD*

Name of scale	Additions available	Reporter	Type (specific or generic)	Domains covered in the scale	(i) Source (company/author who devised the scale) (ii) Source of identification
1. Child Health and Illness Profile (CHIP)	Child Health and Illness Profile – Child Edition (CHIP-CE). For children aged 6–11 years	Self-report	Generic	Satisfaction with health and self: 9 items Discomfort: 12 items Resilence: 8 items Risk avoidance: 8 items Achievement: 8 items	(i) Riley *et al.*[83] (ii) Preuss *et al.*[72]; Dopfner *et al.*[84]; Prasad *et al.*[85]; Ralston *et al.*[86]; Riley *et al.*[87,88]; Steinhausen *et al.*[89]; Matza *et al.*[90]; Secnik *et al.*[91]
	Child Health and Illness Profile – Adolescent Edition (CHIP-AE). For adolescents aged 11–17 years	Self-report			
	Child Health and Illness Profile – Parent Report Form (CHIP-PRF)	Parent report			
2. Child Health Questionnaire (CHQ)	Child Health Questionnaire – Child Form (CHQ-CF-87). For children aged 5–18 years	Self-report	Generic	Physical functioning Role limitations: emotional/ behavioural, physical Bodily pain Mental health Self-esteem General health perceptions Parental impact: emotional, time Family activities Family cohesion	(i) Landgraf *et al.*[92] (ii) Sawyer *et al.*[70]; Prasad *et al.*[85]; Klassen *et al.*[93]; Matza *et al.*[90,94,96]; Graetz *et al.*[95]; Perwien *et al.*[97,98]; Rentz *et al.*[99]
	Child Health Questionnaire – Parent Form. Available in three formats according to the number of questions (CHQ-28, -50, -98)	Parent report			
3. Pediatric Quality of Life Inventory™ version 4.0. (PedsQL)	Pediatric Quality of Life PedsQL Child Self-Report. Adapted for different ages: age 5–7 years, 8–12 years, 13–18 years	Self-report	Generic	Physical functioning Emotional functioning Social functioning School functioning	(i) Varni *et al.*[100] (ii) Bastiaansen *et al.*[101]; Pongwilairat *et al.*[102]; Varni *et al.*[103]; Sallee *et al.*[104,105]

DOI: 10.3310/hta13500

Name of scale	Additions available	Reporter	Type (specific or generic)	Domains covered in the scale	(i) Source (company/author who devised the scale) (ii) Source of identification
	Pediatric Quality of Life PedsQL Parent-Proxy Report. Parallel versions available for various child versions	Parent/proxy report			
4. ADHD Impact Module (AIM)	ADHD Impact Module – Child (AIM-C)	Parent report	Specific	Two core multi-item scales: child scale (QoL of child); home scale (QoL at home)	(i) www.healthact.com/aim_c.html[106] (ii) Landgraf *et al.*[107]
	ADHD Impact Module – Adult (AIM-A)	Self-report			
5. Youth Quality of Life Instrument (YQOL)	Youth quality of life Instrument – Research version (YQOL-R). For adolescents aged 11–18 years	Self-report	Generic	Self Relationship Environment General quality of life	(i) http://depts.washington. edu/yqol/instruments/YQOL-R.htm[108] (ii) Patrick *et al.*[109]; Topolski *et al.*[110,111]
	Youth Quality of Life Instrument – Surveillance Version (YQOL-S)				
	Youth Quality of Life Instrument – Facial Differences Version Instrument (YQOL-FD)				
6. Munich Quality of Life Questionnaire for Children (KINDL)	Kiddy-KINDL. For ages 4–7 years	Self-report	Generic	Physical functioning Psychological functioning Social functioning	(i) http://www.kindl.org/indexE.html[112] (ii) Patrick *et al.*[109]; Japanese version: Furusho *et al.*[113]
	Kid-KINDL. For ages 8–11 years	Self-report			
	Kiddo-KINDL. For ages 12–16 years	Self-report			
	Parent versions are also available for Kiddy and Kid-KINDL	Parent report			

continued

TABLE 9 *Quality-of-life scales used in children with ADHD (continued)*

Name of scale	Additions available	Reporter	Type (specific or generic)	Domains covered in the scale	(i) Source (company/author who devised the scale) (ii) Source of identification
7. EuroQOL EQ-5D	EuroQOL EQ-5D (Proxy version)	Parent report	Generic	Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	(i) http://www.euroqol.org/[114] (ii) Matza *et al.*[90]; Secnik *et al.*[115]
8. Weiss Functional Impairment Rating Scale (WFIRS)	Weiss Functional Impairment Rating Scale-Self (WFIRS-S)	Self-report	Specific	Family Learning and school Life skills Child's self-concept Social activities Risky activities	(i) Weiss[116] (ii) Coghill *et al.*[117]
	Weiss Functional Impairment Rating Scale (WFIRS-P) Parent Report	Parent report			

TABLE 10 *Quality-of-life scales used in adults with ADHD*

Name of scale	Type (specific or generic)	Domains covered in the scale	Source of QoL scale	Number of citations (from results list)
1. Adult Attention Deficit Hyperactivity Disorder Quality of Life Scale (AAQoL)	Specific	Life productivity Psychological health Relationships Life outlook	The BROD GROUP, 219 Julia Avenue, Mill Valley, California 94941, USA mbrod@thebrodgroup.net	Brod *et al.*[118,120]; Able *et al.*[119]
2. Medical Outcomes Study 36 item short-form health survey (SF-36)	Generic	Eight health domains: Physical functioning Bodily pain Role limitations due to physical problems Role limitations due to emotional problems General health perceptions Mental health Social functioning Vitality	Ware *et al.*[121] http://www.outcomes-trust.org/instruments.htm#SF-36 Website: http://www.sf-36.org/wantsf.aspx?id=1	Adler *et al.*[122]; Goodman *et al.*[123]
3. Quality of Life Enjoyment and Satisfaction (Q-LES-Q)	Generic for psychiatry and psychology	Physical health Subjective feelings Leisure time activities Social relationships General activities	Endicott *et al.*[124]	Biederman *et al.*[125]
4. Quality of Life Questionnaire (QLQ)	Not available	Not available	Evans *et al.*[126]	Grenwald-Mayes[127]

monitor the QoL of patients, although most companies would use recognised validated scales such as those described above.

Conclusion

From the results of this review, it can be concluded that few QoL scales have been validated in the UK ADHD population. Of the eight scales that were used in children, three had been used in the UK: CHIP-CE, EuroQOL EQ-5D and CHQ-PF50. CHIP-CE was the most commonly used QoL scale in ADHD patients in the UK, had been validated for use in UK patients aged 6–18, and is accompanied by clear instructions regarding its administration, scoring and processing of data. On this basis, the CHIP scale was determined to be the most appropriate scale for use in the CADDY study; taking into consideration the age range of the study cohort, the CHIP-Adult Edition (AE) was the scale chosen to be tested in the Part 2 study.

Chapter 4

Part 2 Study

In-depth interview study with participants from specialist ADHD clinics and clinicians who work with ADHD participants

Objectives

Part 2 aimed to explore the process and outcome of cessation in order to understand how cessation can be appropriately managed as follows:

- 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 QoL.
- 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).

Methodology

Background

For future research, it is anticipated that a randomised withdrawal study could be used to trial a new protocol for managing treatment cessation for young people with ADHD; this study would likely be similar to a previous study in antiepileptic drug withdrawal.[128] However, to develop an appropriate protocol for managing treatment cessation for young people with ADHD, it is crucial to first understand the processes contributing to this and outcomes associated with treatment cessation from the perspectives of the key stakeholders involved.

The GPRD provides pharmacoepidemiological data from general practice. However, it does not record the reasons for medication cessation or any detail about the clinical and social outcomes of cessation or patients' experience of the process of cessation.

Understanding patients' and clinicians' views on the processes and outcomes of cessation could inform the development of appropriate ways to manage treatment cessation in young adults. Therefore, the aim of Part 2 was to explore patients and clinicians views on cessation of ADHD medication.

Methods

Data collection: patients

Patient recruitment and sample size considerations

Eligible patients were recruited from the four clinical collaboration sites: London, Nottingham, Dundee and Liverpool. Local researchers identified all active and discharged patients at their site. An active patient was defined as a patient who was under the care of the collaborating clinics for management of ADHD. A discharged patient was defined as a patient who was no longer under the care of the collaborating clinics (including patients who stopped treatment, transferred to adult psychiatric care or primary care or who moved away). All patients had to be aged 15–21 years after 1 January 1999[3] and 31 December 2006 (in line with Part 1 inclusion criteria). Collaborators contacted discharged patients in writing to establish whether or not treatment had been stopped.

A structured data capture form was designed to allow systematic case-note review of eligible patients at the collaborating clinics. The primary purpose was for the data to serve as the sampling frame for selecting patients for interview. In order to explore a diverse range of experiences of ADHD treatment from the perspective of patients, we used the case-note data to stratify patients according to the following three categories:

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

Although the team recognise the difficulty in defining what is meant by 'successful' and 'unsuccessful' treatment cessation, consensus was obtained from discussion among team members. A patient was defined as having stopped treatment if there was a period of 6 months from their last prescription when no further prescriptions were issued. In line with Part 1 of the study, it was agreed that 'successful' cessation could be applied to patients who had stopped treatment for 6 months or more and 'unsuccessful' treatment could be applied to patients who had to restart their treatment after 6 months of stopping. Furthermore, we wanted to use the case-note data to obtain information on the potential recruitment rate in the centres likely to take part in a future randomised withdrawal trial. Finally, we wanted to estimate the proportion within each stratum that consented to participate in the interviews and to explore any differences between those who consent and those who do not.

The goal was to recruit 15 patients in total, five from each of the three categories above. Fifteen was deemed a reasonable number of patients to recruit within the time and resource constraints. Sample sizes in qualitative research are necessarily small due to the complexity of the data, and the time and resources taken for in-depth analysis.[129] An alternative approach would be to continue recruiting patients and clinicians until theoretical saturation was reached, but this was beyond the scope of the present study. We originally anticipated the response rate to be approximately 50%, so we first attempted to over-sample by 100%, i.e. inviting a random sample of 30 patients to participate (10 from each strata). However, as response rate was so poor, 75% of total number of case notes reviewed were sampled.

Initially, patients were invited via letter to participate in a face-to-face interview with the researcher. For patients aged 15–17 years, parental consent was obtained. The invitation pack was sent via the local collaborator to parents directly and contained an invitation letter, patient information sheet (one aimed at parents and the other at patients) and a consent form (Appendices 5–12). A reminder was sent after 2 weeks. For patients aged 18 years and over, the invitation pack was sent to them directly and contained all the documents detailed above (minus the parent information sheet).

After several months of recruitment, the response rate was very low. Therefore (as specified a priori in the event of a low response rate) we sought and received ethics approval for a change in recruitment strategy. Instead of recruiting via post, the local collaborators approached patients face-to-face in clinic or over the telephone to explain the study and obtain initial verbal consent. Patients and/or parents were still given time to decide whether or not they wanted to participate as they were later followed up by telephone by the researcher and, if they wished to participate, a convenient date was set for the interview. The researcher ensured that a signed consent form was received via post or on the day of the interview before proceeding with the patient interview.

Patient topic guide and interview development

The patient interviews aimed to explore patients' experience and attitudes towards the process and outcomes of cessation (in both clinical and social terms). A face-to-face interview was deemed the most appropriate method as questions are focused, in that a topic guide is used to guide questioning, yet also open-ended, which allows interviewees to respond in their own words. This form of interviewing gives the interviewer flexibility in following up unanticipated ideas of relevance to the interviewee. It also permits a more natural, less restricted discussion between the interviewer and interviewee than would be the case with a very structured form of interviewing. Prompts were used to gain greater detail about participants' responses.

The topic guide (Appendix 15) was developed by members of the research team, which included two psychologists, clinicians and a patient representative, according to steps recommended by Bowling.[129] The interview sought to explore patients' unique experiences with their medication and therefore the topics covered included:

- adherence to medication
- beliefs about medication
- medication-related problems
- QoL 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.

With participants' consent, the interviews were digitally recorded and transcribed verbatim. Field notes were also written up after each interview

to record the interviewer's thoughts, feelings and reflections about the interview, any marked non-verbal behaviour from the interviewee and to note anything discussed after the digital recorder was switched off. Some answers were read back to interviewees to check the researcher's understanding of what had been said in the interview.

Patient questionnaire administration

At the end of the interview, the CHIP-AE™ QoL questionnaire was administered to patients to assess attitudes towards their perceived QoL.[130] A QoL scale was included because HRQoL is an important outcome measure when assessing the quality of current care and in evaluating the success of interventions or changes to treatment plans (pharmacological and non-pharmacological). HRQoL refers to the impact of health status (including disease and treatment) on physical, psychological and social functioning. As it would be crucial to use HRQoL in the evaluation of a future protocol to manage treatment cessation in young adults with ADHD, it was included here so we could explore participants' views on the scale (e.g. relevance, ease of completion, time taken to complete).

After discussion and review of the available literature (as detailed in Chapter 3), the team selected the CHIP-AE because it was specifically developed for use in the adolescent population. Furthermore, previous research suggested that the CHIP-CE (the related scale for younger children) was suitable for use with the UK population. The CHIP-AE measures six broad domains: satisfaction, discomfort, resilience, risks, disorders and achievements; each domain has two or more subdomain scales. The scale has been validated and shown to have robust psychometric properties.[130]

Ethical considerations

The study was approved by the South East Research Ethics Committee (REC reference 06/MRE01/53). At the start of the interview, the interviewer ensured that an appropriate consent form had been signed and received. After a brief introduction to the study, interviewees were reassured that their responses were confidential and that the interview could be stopped at any time if they felt uncomfortable. The researcher was an experienced interviewer and had a sound understanding of ADHD and common difficulties associated with the condition (e.g. family conflict, difficulty holding attention for long periods of time). If any evidence of family tension or patient distress became apparent during the interview, the researcher was prepared to stop the interview and to provide the interviewee with the opportunity to speak to medical staff involved (or previously involved) in their care. Alternatively, the Patient Advice and Liaison Service would have been recommended to patients. In the event of disclosure of child protection issues, Medical Research Council (MRC) guidelines would have been followed in order to bring it to the attention of the relevant authorities.

Data collection: clinicians

Clinician recruitment and sample size considerations

Interviews were also conducted with clinicians involved in the treatment of young people with ADHD to explore their perceptions of the issues relating to cessation of ADHD treatment in our target population. Clinicians were defined as community paediatricians (associated with mental health clinics), child and adolescent psychiatrists or adult psychiatrists and were recruited from our collaborating centres (London, Nottingham, Dundee and Liverpool). Eligible clinicians were contacted via the local collaborator or details were sent to the researcher and an email then sent to each clinician with an explanation of the study and an invitation to participate (Appendices 13 and 14). A reminder was sent if no response was received after 2 weeks. Ten interviews were deemed feasible within the time and resource constraints for this study.

Clinician topic guide

The research team also developed a topic guide to elicit clinicians' perspectives of the process of patients' stopping medication for ADHD. A face-to-face interview was chosen as the most appropriate method. The topic guide (Appendix 16) covered the same areas identified for the patient interviews. With participants' consent, the interviews were digitally recorded and transcribed verbatim. Field notes were also written up after each interview.

Data analysis

General approach

The digital recordings from each interview were transcribed verbatim and anonymised. The transcripts and field notes were then analysed using a grounded theory approach. Grounded theory is an inductive methodology that allows theory to be developed from the systematic gathering and analysis of data.[131] Two researchers (SC and CP) independently read and coded the first half of the transcripts from the clinician interviews and

the first half of the transcripts within each of the three categories from the patient interviews. One researcher has a background in health psychology (SC) and the other in psychology and social research methods (CP).

Regular meetings were held to discuss emerging themes, unusual cases and anything that needed to be followed up in subsequent interviews. The remaining transcripts were read by both researchers but coded by the main researcher (CP).

Computer-assisted data coding and retrieval

Transcripts and field notes were coded using MAXQDA™, a computer software package that allows a corpus of text to be organised and managed in preparation for interpretive analysis. MAXQDA™ also supports search and retrieval operations that facilitate the comparison of text segments within a transcript and between different transcripts. During the first phase of the analysis, process codes were attached to sections of text using an open coding approach and memos were used to track interpretive reflection. In contrast to using a predefined scheme, this approach allows a coding scheme to emerge from the data.

Secondly, text segments to which the same codes had been attached were compared. Thematically heterogeneous codes were divided into subcategories and the data recoded using these subcategories. Memos were attached to these codes to document the decision-making process underlying changes to the coding scheme. The final coding scheme (Appendices 17 and 18) was used to assist in text retrieval so that text segments with the same codes could be identified and compared. Furthermore, those participants with certain characteristics in common, for example current treatment status, were compared.

There has been much debate about the methodological benefits and pitfalls of using computer software for qualitative research[132,133] and, in particular, concern that computer-assisted qualitative data analysis software can alienate the researcher from the data. However, in line with the distinction made by Seidel and Kelle,[133] in this instance, codes performed a referential function in signposting the researchers to certain text passages that were considered interesting rather than to simply denote facts. For this purpose, the software enabled the data to be organised and managed efficiently and allowed for a more systematic and transparent process.

Interview participants

Summary of details from case-note review

A total of 120 case notes were reviewed at the start of the Part 2 study and came from the following clinical settings in the UK:

- South London and Maudsley: 30 (25%).
- Dundee: 30 (25%).
- Liverpool: 30 (25%).
- Nottingham QMC: 17 (14%).
- Nottingham Thorneywood: 13 (11%).

Of these patients, 50 (42%) were still on medication and had never attempted treatment cessation. A further 18 (15%) were on medication, but had at least one unsuccessful attempt at treatment cessation in the past; 17 patients (14%) had successfully stopped treatment and 16 (13%) were deemed as lapsed from treatment. Data were missing from the case records for the remaining 19 (16%) patients. *Table 11* contains a summary of patient demographics.

Table 12 contains details about the ADHD diagnosis, comorbidities and family history of mental illness. A total of 58 patients (48%) had at least one comorbid disorder; Table 12 shows the nature and extent of these different disorders. Because of the gaps in information on the patient case notes, it is not possible to determine whether the remaining 62 patients had no comorbidities or if this information was not recorded in the notes.

Table 13 shows the identifying codes and stratification of patient interviewees. *Table 14* shows the clinician identifying codes (participants: six child and adolescent psychiatrists, two general adult psychiatrists, one consultant paediatrician and one community paediatrician).

Findings

The topics explored during interviews with participants and clinicians included reasons underpinning cessation, the decision-making process prior to cessation, communication with health-care professionals at the time of cessation, and support available at the time of cessation. Patient and clinician views are presented together to facilitate the comparison and contrast between the different perspectives of those involved in the process.

TABLE 11 *Results of case-record review: basic patient demographic details (number of cases for each variable varies because of missing information in the case notes)*

Variable		Results
Gender (*n* = 116)	Male	107 (92%)
	Female	9 (8%)
Age (*n* = 115)	Mean (standard deviation)	18 (2.4)
	Range	14–24
Ethnicity (*n* = 85)	White British	79 (93%)
	White: other	1 (1%)
	Mixed: white and black Caribbean	1 (1%)
	Mixed: other	1 (1%)
	Other	3 (4%)
Educational level achieved (*n* = 82)	Secondary school	42 (51%)
	Special educational needs (SEN) school	23 (28%)
	College/sixth form	16 (20%)
	University	1 (1%)
Employment status (*n* = 57)	Student	39 (69%)
	Employed	11 (19%)
	Unemployed	7 (12%)

Other, more general topics surrounding ADHD and treatment that were covered included attitudes towards ADHD and ADHD medication, medication-related problems and treatment adherence. These are discussed in the first instance as they set the context for later discussion of medication cessation.

Understanding of ADHD

Interviews opened with general questions about current education and/or employment and favourite pastimes and social activities. These questions were used as a way of building rapport with the participant before moving onto more topic-specific questions. During the first part of the interview participants were asked what they understood ADHD to be and the perceived effect the condition has on their daily life.

The majority of patients spoke about ADHD in terms of symptomology and attributed a number of behaviours to their ADHD. The behaviours most commonly talked about can be characterised as: inattentiveness, impulsiveness, hyperactivity and interpersonal conflicts with peers and family. The impact of these behaviours on daily life was most often talked about in relation to school or work, but also in terms of relationships with peers, employers/teachers and family. The following are examples:

- interrupting in class
- going missing for days
- getting into trouble with the law
- difficulty getting homework finished especially in the evenings when medication wears off
- difficulties holding down a job
- difficulties socialising
- getting into fights
- suspension from school
- skipping lessons
- easily distracted
- difficulty expressing ideas and executing tasks
- difficulties with interpersonal relationships were attributed to quick temperedness, getting into arguments and talking back.

One young person described the perceived cause, although was confused as to how ADHD differed from depression:

> S7: ADHD is a chemical imbalance in the brain and something about synapses not firing enough or not getting where they are supposed to. Which to me sounds exactly like what depression is.

Others described it as:

> S8: … something you get when you are young …

> S9: … behavioural problems …

TABLE 12 *Results of case-record review: clinical details (number of cases for each variable varies because of missing information in the case notes)*

Variable		Results
Age when symptoms first recognised (*n* = 75)	> 3 years	23 (31%)
	4–7 years	28 (37%)
	8–11 years	15 (20%)
	12–15 years	9 (12%)
ADHD classification according to DSM-IV (*n* = 24)	Combined	12 (50%)
	Inattentive	7 (29%)
	Hyperactivity/impulsive	5 (21%)
ADHD classification according to ICD-10 (*n* = 21)	Hyperkinetic disorder	15 (71%)
	Hyperkinetic disorder associated with conduct disorder	6 (29%)
Comorbid disorders (*n* = 58)[a]	Oppositional defiant disorder	19 (33%)
	Dyslexia	8 (14%)
	Conduct disorder	7 (12%)
	Autistic spectrum disorder	6 (10%)
	Deliberate self-harm	6 (10%)
	Tics	6 (10%)
	Anxiety	6 (10%)
	Obsessive compulsive disorder	4 (7%)
	Dyspraxia	4 (7%)
Use of psychotherapy (*n* = 63)	Yes	30 (48%)
	No	33 (52%)
Family history of mental illness (*n* = 63)	Yes	50 (79%)
	No	13 (21%)

ADHD, attention deficit hyperactivity disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision; ICD-10, *International Classification of Diseases*, 10th edition.
a Many patients had more than one comorbidity, hence percentages add up to more than 100.

TABLE 13 *Patient interviewee identifying codes and stratification category*

Participant	Age (years)	Gender	Site	Treatment category	Education/ employment
C1	20	Female	London	Continuing	College
C2	17	Male	Liverpool	Continuing	College
C3	16	Male	Nottingham	Continuing	School
C4	18	Male	Dundee	Continuing	College
C5	21	Male	London	Continuing	Employed
S6	17	Male	Liverpool	Discontinued	College
S7	17	Female	Liverpool	Discontinued	College
S8	19	Male	Nottingham	Discontinued	Unemployed
S9	17	Male	Dundee	Discontinued	College
S10	15	Male	Dundee	Discontinued	School
R11	18	Male	Liverpool	Restarter	Unemployed
R12	24	Male	London	Restarter	Unemployed
R13	20	Male	London	Restarter	Employed
R14	17	Female	London	Restarter	Employed
R15	17	Male	London	Restarter	College

TABLE 14 *Clinician interviewee identifying codes*

Participant	Site
L1	London
V2	Liverpool
L3	London
L4	London
N5	Nottingham
N6	Nottingham
D7	Dundee
N8	Nottingham
V9	Liverpool
N10	Nottingham

> S7: A different learning style … the question for me is, ADHD? What does that mean. Everybody thinks it needs to be solved, oh you have ADHD, therefore you have a problem. But I think along with people who are dyslexic, is they [people with ADHD] just have an extreme learning style.

Some felt that they did not really understand the condition:

> C5: I don't know a lot about it. I haven't read up on it or nothing. I just know it keeps me high and that, very high.

> R11: How can I get rid of it … they [clinicians] weren't that good at telling me what it was. They tell you it's a problem in your head. But they still haven't explained it properly to me.

> R14: To tell the truth I don't really know that much about it. I only got diagnosed when I was fifteen as well. That was by a private psychiatrist who thought that I didn't need to know what it was. So even now I am not that sure what it is.

Three participants talked about the positive aspects of ADHD:

> S7: I think people with ADHD have a great sense of humour, are very creative, amazing, fabulous people.

> R12: The impulsive side of it is hilarious when you're a kid, because you can get away with things when you are a kid.

Most patients did not consider themselves as different from other people of their own age:

> C3: I don't feel different as such, but I was generally the person who would cause the most disruption in class.

With the exception of one, patients felt comfortable telling close friends about their ADHD and that they took medication for it.

Beliefs about ADHD medication

Participants described both positive and negative aspects of taking medication for their ADHD. All the participants interviewed had been prescribed at least one stimulant medication during the course of their treatment. The perceived positive effects of stimulants were described in terms of symptom improvement and included improved concentration and ability to focus on tasks:

> S6: You can just sit there and concentrate in lessons, you can get on with the work.

Others felt less impulsive, for example being able to:

> S9: … think things through before acting …

Others mentioned how the medication made them feel calmer, and how it improved relationships with other family members:

> R12: The good thing is not so much how it affects me, but everyone around me. It is not my life that seems to feel better, it is theirs that gets better.

Some found it difficult to notice any difference when they were on medication:

> S9: Mum said they worked, but I don't think they worked because I didn't feel any different.

> S8: It was more in class that I noticed the difference. When I was out with my mates I didn't really feel any difference. It was only when I thinking about work and stuff that I could feel a difference.

> C1: Yeah, I came off it for a week, and the school could see a huge difference but I couldn't.

Clinicians also spoke about the difficulties some patient's have recognising any change in behaviour:

> N6: Some children with ADHD are quite unaware of their difficulties. They say that they are okay and they really think they are OK. They tell a very different story about their behaviour. They think they behave the way they behave because they are reacting to people being unfair to them, picking on them. This is the case for about 20% patients.

> V9: I say how does it make you feel? Do you feel any better on them? Do you notice a difference? I think the patients that are easier to work with are the ones that recognise a difference and recognise that their medication changes them. There are still significant numbers that sit in front of me and say, I can't tell any difference and the only reason I know there is a difference is because of my teachers or my mum tells me.

Clinicians often talked about medication as a tool rather than a solution, whereas sometimes parents have unrealistic expectations of what medication is for and can achieve:

> N5: Parents expect everything to be improved with medication.

> V2: When we start someone on ADHD medication a lot of families judge how well they are doing on the wrong criteria, they judge them on whether somebody has suddenly turned into an angel instead of whether someone is concentrating better.

The perceived negative aspects were side effects. The most commonly reported were appetite suppression and sleep disturbance. Also mentioned were feeling spaced out, grouchy, nervous, tense and fidgety, and an inability to daydream.

Three of the participants interviewed had been prescribed antidepressants for their ADHD. All three reported having a serious and negative experience on antidepressants. Side effects reported were feeling spaced out, drowsy, suicidal ideation and self-harming. Particular stress was felt by the two participants who were prescribed antidepressants because of a lack of adult service provision. Both felt that antidepressants were the wrong type of medication for the condition, following in one instance self-harming leading to hospitalisation and in the second case to repeated and deliberate non-adherence because of side effects.

> R12: They put me on antidepressants and they had huge side effects. Being on antidepressants made me more depressed.

Many patients felt that taking medication on a daily basis was an inconvenience:

> R12: The downside is I have to take ninety tablets a month, just so I don't argue with people, and to me that seems a lot to be considered normal. I am going to, but I don't like the idea of it. I have never really been a big fan of tablets.

> S7: On some level I feel that relying on medication is a bad thing, but on the other hand, it worked.

Although consultations were sometimes seen as a hassle, the majority who were still attending clinical consultations were reasonably happy to attend:

> C2: Well he is alright with me. He understands. He explains everything to me, but he's not like a walking dictionary, like the others that use all the technical words and all that. Like the other doctor, he used to explain it in these complex words and I used to sit there with my head tilted on one side going, what? He'd make it like a half hour conversation and then sum it up in a short sentence the next minute and you'd think, why didn't you say that at the beginning, simple.

> R14: I don't mind coming. At first it used to be like, I can't be bothered. But now it is just routine, and I just do it.

Other patients also described their negative experiences:

> R12: They don't seem to know about ADHD, but they don't want to hear what I know. One of the doctors told me it was dangerous to give Ritalin to adults, but I am taking them now.

Information about ADHD and medication mainly came from clinicians during consultation and mum, who normally (but not always) took the lead in obtaining and disseminating information to their child:

> C5: She [mum] knows a lot. Studies it. Uses the internet. Reads the books and watches all the programmes.

> C1: I am not well informed, but my mum knows about it. She knows more than me and I'm taking it … she finds out from the internet, telly, family friends.

> S8: At the time I didn't really read into it a lot. My mum and dad did. My mum definitely did, she's like that. She used to be a nurse and would let me know if anything was going really wrong. Many people didn't know a lot about it at the time. It wasn't a trial but more of a case study if you know what I mean. That is as much as I knew.

One participant was given a pamphlet, one attended a course on ADHD (however, not completed as he got into conflict with another boy on the course) and one carried out his own independent research using the internet:

> R12: Yeah I had to, because no-one was listening. I had to prove I knew more than they did, to show them.

Those clinicians that reported giving out written information (developed in-house or by pharmaceutical companies) normally did so at the time of diagnosis:

> V9: … it's difficult, we're probably not as good at that as we should be because children are normally diagnosed at six, seven and eight and are still on medication at fourteen and the information is given to their parents and we don't make a conscious decision to repeat that information. We've got lots of leaflets and we've got information sheets which are really good, but we tend not to give that information out again in teenage years.

In terms of understanding how the medication works, the majority of patients tended to have quite a limited understanding and unresolved queries:

> C2: Yeah, why did they give me 36 mls? I understand that they changed the medication but why put me on a higher dose?

> R11: I would like to know if there is a medication that can get me back to normal … just wish they could find a tablet or any form of medication that would get me back into normal life.

One clinician felt it was important to give certain information, but also tailored to the individual:

> N6: Depends on how much they want to know and ability to understand, some patients will want to know how it works, some people may want to know how it influences substances in the brain, they may ask what are the reasons for ADHD. It is important to give information about genetic influence, side effects and what to do if they occur, and what changes to expect. Also, the fact that it will be necessary to increase the dose as part of dose titration not because they depend on it more and more.

Treatment adherence

To explore the issue of adherence, participants were asked to talk about their medication regimen, whether they had missed doses, and if they had missed doses, the frequency with which they were missed, whether it was intentional or unintentional, and the reasons. Finally, participants were asked about the strategies they used to help to remember to take their medication.

All the participants interviewed had missed a dose of their medication at some point during the course of their treatment. The reasons underpinning non-adherence can be characterised as intentional and unintentional. Unintentional non-adherence consisted of doses missed and delayed due to forgetting; the length of delay was variable.

Intentional non-adherence to medication during weekends and school holidays was common. Two clinicians preferred to initiate a drug holiday during term time in order to obtain feedback from teachers. Drug holidays were mostly initiated by a clinician or the participants' parents/guardians.

The decision to intentionally miss a dose(s), not as part of a routine drug holiday, was in most instances the choice of the patient. The reasons underpinning this form of non-adherence can be characterised as patient related and drug related.

Patient-related factors included a dislike of taking medication:

> R11: Just not wanting to take them. Just wanting to be normal on my own.

R12: It will be sitting right in front of me but it is like part of me is saying, you don't need it. But I know I do.

The most common drug-related factor mentioned was side effects from the medication. The commonly reported side effects are detailed in the section above. Participants also talked about the size of tablet, the taste and the inconvenience of taking multiple daily doses.

Of the participants that spoke of intentional non-adherence, a number spoke of hiding, stashing and disposing of medication. One girl told her clinician that she was missing doses because of a side effect which in fact she was not experiencing. To clinician she said:

S7: … it made my heart race. And they asked, 'Does it?' And I said, yes I swear. They said, 'Let's run some tests' and I was like, damn. They said, 'It doesn't seem to be making your heart race', and I was like yeah you got me on that one.

This was echoed by one of the clinicians:

V2: I've met one or two [participants] where the side effects are an excuse to avoid the discussion about why they don't want to take their medication.

When patients were asked if anyone else was aware of the occasions when they had missed a dose, participants said:

S8: When I got brought home because I was suspended. She [mum] knew then.

S6: I told my mum. But she said I had to take them if I wanted to stay in school. Because they wanted to kick me out. Because of being naughty. I was shouting at teachers and stuff like that, giving them abuse. They wanted to kick me out, everyday but they kept ringing my doctor and he kept telling them I was on tablets so they couldn't as long as I was taking them.

S9: He was always saying you have got to take them, but he didn't know what they did himself. So I took no notice of him.

When clinicians were asked about their patients' adherence, nearly all said that they felt their patients did adhere to their medication regimen for the most part, although there were exceptions. A couple noted that they may not have the complete picture:

V9: I think doctors always think they do and I think research shows that probably they don't.

V2: I suspect that often you don't find out until somewhere down the road where someone will come in and say I've been throwing them in the bin or mum will say he's not taken them for the last 6 weeks and we haven't told you yet.

Clinicians identified the following as barriers to adherence:

- side effects
- negative view of medication and/or medication taking
- disorganised and chaotic family life
- frequency of pill-taking for the non-slow-release formulations
- lack of awareness of condition and medication efficacy
- stigma attached to taking medication
- medication has not fulfilled expectations
- comorbid oppositional behaviour.

V9: I think they often see themselves as being different. I think it often goes back to when they were first started on Ritalin and there may be some teasing … we diagnose them when they're young and their parents have always said you need to take these tablets but I think some of them [participants] never quite agree with that.

A couple of clinicians felt that the development of slow-release formulations had helped patients to adhere and one mentioned that this also helped to reduce stigmatisation at school. One clinician spoke of the clinical impact of non-adherence:

N6: If you believe they are taking the medication you may increase the dose because you think they need a higher does when the problem is they are not taking the dose you are giving them.

Parents play an important role in reminding their child to take their doses. The patients that were more autonomous in their medication taking or living away from the family home took a stronger role in self-management:

C2: It is one of those things, do you wake up in the morning and think, oh God, I have to

take pills. Or are you gonna be like, I have to take pills. I get into a routine of when I get up I have a shower and take my meds to go to college and stuff.

R12: The first thing I do when I go into the kitchen is instantly go to the box [of medication].

R14: I get on my bus every morning, it comes at like five to eight, so I know I have got to take it then. And at four I take it at the same time as my contraceptive pill. That's more or less how I remember.

In one case, lack of medication management by the school was a factor:

S6: I stopped going to the teacher [for medication] and she didn't come and get me, so I could get away with it.

Reasons for treatment cessation

Participants who had stopped taking medication and those that had attempted to stop but subsequently restarted were asked to talk about the reasons underpinning their decision to stop. For 7 of the 10 patients in these two categories the decision to stop was their own and was often influenced by more than one factor. The weight given to each factor varied depending on the individual, but most commonly reported was of a developing sense of control over the disorder or a desire not to take medication any more:

S10: As I got older I didn't really need them as much as I had done, even though they were more effective [Concerta as opposed to Ritalin]. I didn't really need them … I was able to handle situations when I needed to be calm, and was able to differentiate between situations when I needed to be calm or not, and with age was able to control myself more than when I was younger. So I didn't need the tablets any more.

S7: … not that I outgrew it [ADHD] but I have outgrown needing medication. That if I do badly it is because I am doing badly and I don't have anything to blame. And if I do well, I am doing well on my own accord and not because of some meds.

S8: Because I had some days when I forgot to take it and I felt just the same when I didn't have it to when I had it, and because when I was on it I couldn't sleep very easily I decided to stop. That was the main reason, actually, lack of sleep … I don't know if I grew out of it. I don't know if that happens, but that is what it felt like.

The inconvenience of taking medication on a daily basis and side effects were also seen as contributing factors. These factors also influenced intentional non-adherence (as discussed in section above).

R15: I just didn't take them one day. And I thought, you know what, I don't like this one, it's not agreeing with me.

One patient described his unease when he learned that the medication he was taking had similar properties to amphetamines:

R12: I found out that the ingredients in it were similar to the ones used in Speed, I didn't like the idea and thought I knew better and stopped.

For the remaining three patients, cessation was due to a lack of adult service provision at the point that child and adolescent services were no longer available for them:

R13: My mum had to find me another doctor because I got chucked off the list and then I was off medication for about a year. A doctor from [clinic X] came out to prescribe me with medication, tried to help me and I had to go to hospital to see if they could help me. My dad rung the police to see if someone could help me and no-one could … I didn't have any [tablets] at all. I didn't have a doctor to prescribe them … I felt really ill.

Patients in the continuing treatment category, who had not attempted cessation, were asked to talk about how they felt about the prospect of stopping in the future. All the participants considered it an option, but there was some apprehension, as the following quotes illustrate:

C4: I'm a bit wary of that … well, maybe a plus side might come out of it, that I'm not really needing it any more … there's not much point staying on it the whole time because it might not be doing anything.

C2: I don't know. It is just a scary thought. Like, you take me off something that I've been

on for ages, and am I going to be the same? Or am I going to be the same as when I was younger? I don't want to be that. I know I have got more than that.

C3: Well, the only reason is because my mum says I can't stay on medication forever and you've got to try and get better, but apart from that the only potential one is probably the issue of appetite, but I think to be honest, even though I feel a bit lethargic because I'm not eating and my blood sugar levels are low the positives far outweigh the negatives. Obviously I will eat at some point, I just get hungry a lot later on but the not being able to concentrate is so so much worse.

From a clinical perspective, the reasons that patients decided to stop treatment were again broad-ranging and included:

- patient symptomology
- side effects
- inconvenience or dislike of taking medication
- being labelled and concomitant stigma attached to having a label.
  N5: They feel stigmatised because they are taking medication and if people find out they are taking medication they are called names. Previously, there was a problem before long-acting preparations came along that they had to take a lunchtime dose and that was an issue for a lot, especially secondary school children, that did not want to do that.

This was the experience of one patient, although it had not caused him to stop taking medication:

C5: When I was on the original Ritalin, which I used to have to take in the morning and then the afternoon … erm a lot of people were like, being at that age, 'Aw he's taking pills, he's going a wee bit daft'.

Clinician-initiated cessation was attributed to:

- lack of beneficial effect
- side effects (all clinicians stopped medication immediately if serious side effects occurred)
- non-attendance at appointments
- age of patient or length of time patient had been on medication
  V2: I'm uncomfortable leaving a child on medication for more than about 18 months without broaching the idea of seeing what happens if we discontinue or reduce the medication a little bit.
- those approaching the age where CAMHS are finishing where there is a lack of adult services.

All the clinicians interviewed spoke of the difficulties that arise once an adolescent reaches the age where child and adolescent services are no longer available:

L3: Lots of people just fall off the end of a cliff really if you like, and adult services won't take them. You get no care. All the medication is stopped.

Provision of care to patients beyond the age limit set by CAMHS was described as very limited. Where there are no services commissioned for adult ADHD treatment, one option for clinicians is to continue to monitor patients within CAMHS. In most cases, but not all, this was carried out without Trust knowledge:

V2: We are resourcing facilities to have young people monitored when they are way past our age range. You can't send someone out into the community and say 'Right, well I don't know where you're going to be getting your next prescription from, I don't know who's going to be checking your blood pressure, if you have a problem I don't know who you should call but it's not me any more'.

N10: There isn't a service for them. I don't know what will happen if we get caught … I haven't come to that stage yet, whereas a couple of my colleagues have and they've tried to persuade the GPs to continue, and they won't. I don't think that's true across the board. I think there are a couple of GPs that would, but the two cases I've been involved with discussing, have been where GPs won't.

For some patients, clinicians decide that cessation will be attempted:

V2: You have to start thinking about whether you can get someone to monitor the medication from here (CAMHS), you maybe approach GPs, you maybe approach the adult psychiatrists, and people say no. You sometimes find yourself in a position of having to cut back on medication and see if a child can do without it.

> L1: A common experience of our patients is that once they reach 17, 18, they finish with Child Psychiatry and GPs stop prescribing without any preparation, without taking into account the state of their lives and for some of them they experience that as quite traumatic because suddenly they couldn't take medication.

Two clinicians felt that some patients were relabelled:

> N5: At the moment transfer is very variable and pot luck. If they are referred to me, I will carry on treating them. If they go to my colleagues, most of them are given a different label, taken off their medication and sent out into the community and goodbye.

The reasons why transfer was seen as problematic were twofold. The first is the issue of Trusts not commissioning services due to a lack of resources and guidelines:

> N5: There aren't any NICE guidelines and unfortunately other colleagues say it is not recognised, the products aren't licensed, so why should we? We are prescribing something that isn't licensed. We do this all the time in Child Psychiatry but they are not used to it and commissioners do not commission services for adults, so that is another fall off point'.

The second contributing factor was the issue of adult psychiatrists and GPs not understanding or not having appropriate training in ADHD diagnosis and management, having competing priorities and an unwillingness to prescribe unlicensed medications, or a belief that the condition does not exist in adulthood:

> L3: I don't think there is a huge impetus for adult clinicians to want to develop the expertise in these services. They have competing demands and I think those are met more often than thinking about ADHD service delivery.

> V2: Adult mental health services are much more geared towards what they call severe mental illness.

> N8: Colleagues in General Psychiatry are usually not too keen on diagnosing ADHD because if you diagnose it you need to treat it and the treatment is unlicensed. In spite of that I treat patients because I am quite quite confident with the diagnosis. But I wouldn't be surprised if I am criticised by colleagues because they tend not to treat, not to diagnose.

The two adult psychiatrists treating ADHD (not as part of the National ADHD Clinic service) were each treating two patients. Both felt the number of referrals they received was low. One commented:

> D7: I have a feeling it is far lower than it should be, if you look at the incidence of ADHD in the progressional and teenage years. It seems very low. I don't know why, but it doesn't seem quite right.

Referrals to Adult Psychiatry were received via two pathways. The first, through GPs:

> N8: The patient will probably first be seen by his GP and then the GP may or may not have detailed knowledge of ADHD. I don't think the majority of GPs will have ADHD [as a possible diagnosis] in mind, but if a person complains of lack of attention etc. and they think they may have ADHD the GP can refer the patient to Mental Health Services.

The second pathway involved transfer from local Child and Adolescent Services to the National ADHD Clinic. The transfer process was reported to involve preparation and discussions with those clinicians involved in the patient's care to ensure a smooth transition.

The National ADHD Clinic also takes referrals from GPs for adults diagnosed in childhood who need this diagnosis confirmed in adulthood or adults referred for a new assessment.

Process of cessation

Decision-making

Seven of the ten that had either stopped medication or attempted to stop said that the decision to stop was their own. Family involvement in the decision-making process varied from no involvement to full involvement.

In some cases parents disagreed with their child's decision to stop because of the perceived impact of non-medicated ADHD on their child's behaviour, in particular the implications for schoolwork and relationships with family at home:

> S7: My dad was kind of annoyed with me at first. He was like, 'You do whatever you want.

> You do anyway'. My mum tried to coerce me into taking them … She was like, 'Don't you think you do better when you are on medication. You haven't been doing your essays lately. Don't you think you did your essays when you were on medication?'

The majority of clinicians had experience of divergence between patients and their families on the issue of cessation:

> N5: The patient doesn't want to take it and the family want them to, but the patient doesn't think they are any different but the family and school say that symptoms are different if they take medication compared to if they don't. So the pressure is on the patient to conform to what the family and school want, and we as clinicians give advice. We cannot say that they must take it.

A less common scenario was a parent wanting their child to stop while their child wishes to remain on medication:

> L4: Occasionally you have parents who are keen to discontinue and children who want to continue. That is far less common than the other way round, where parents feel it is beneficial and children don't want to take medication.

Level of clinical involvement in the decision-making process varied. Where the clinician was involved prior to cessation there tended to be a triadic discussion between patient, family and clinician, with a period of follow-up and progress monitoring. Where clinicians were not involved, there was either no follow-up or limited follow-up, and this was mainly because the patient had broken contact with the service.

All the clinicians spoke about the need for shared care decision-making when deciding whether cessation is the right course to take, and saw this process as an integral part of preparing for cessation:

> L4: You work to a joint decision but you do sometimes get cases where the kids just refuse, even though both parents and I think it is beneficial. That happens occasionally. But I would say in the majority of cases, actually to stop medication is a mutual decision. I am always trying to have an agreed set of objectives. What we are all trying to achieve and have a discussion about is whether we are achieving it or not. So it is always about trying to have a partnership.

> N6: If it is done with a common decision with the children it can give the person a good feeling because now they can manage without the medication so they feel more confident in their own abilities.

For older patients, who may be living independently or are no longer attending appointments with their parents, the family may be less involved, but this was not always the case.

Planned versus unplanned cessation

Clinicians distinguished between unplanned and planned cessation. Unplanned cessation is where the patient and/or parent makes the decision to stop treatment prior to any clinical consultation and initiates cessation without clinical input or only subsequent to cessation. Unplanned cessation was characteristic of patients who described persistent and intentional non-adherence to medication. Clinicians also recognised this link:

> V9: They're more likely to stop if they're not adhering. I think they're voting with their feet.

None of the clinicians interviewed had any formal guidelines or protocols in place for cessation. Care was more tailored to individual needs, although the process characteristically involved four key stages: preparation, choosing an appropriate time, commencing cessation, and a period of monitoring and follow-up. Each of these is discussed in turn.

Preparation

Preparation was carried out during normal consultation (some clinicians began preparations at the onset of treatment) in which the possible outcomes to cessation were explained and any questions and/or anxieties that the patient and family might have would be discussed:

> N5: We discuss it, plan it and then implement it. It takes a few weeks and they can ask any questions, and they can change their mind if they wish to. What they finally decide we implement and then we follow them up after to see whether it has gone okay or whether they want to ask any more questions, do anything else or go back on it.

Timing

Clinicians had different ideas about what constituted an appropriate time to attempt cessation, be it the patient's age, whether they were

still in full-time education, or the length of time they had been on medication.

Commencing cessation
Although some clinicians preferred to reduce doses gradually, the majority decided on a specific time (with the patient and their family) when the patient would stop taking all doses.

Both clinicians and patients used drug holidays as a way of seeing how patients would get on. Patients felt that this provided them with an opportunity to see how they would manage without medication and had given them the confidence to attempt a more prolonged period of cessation.

Follow-up
Timing of follow-ups and frequency varied, but most clinicians would offer a follow-up session shortly after cessation was initiated, with another follow-up consultation further down the line. Support during this time was mainly provided by the patient's main clinician, although some had access to community psychiatric nurses, a family support worker, a family coach, educational services and cognitive-behaviour therapists.

Outcome of cessation

The outcome of cessation varied:

> L3: I have seen a huge variety where clearly it just doesn't work at all. Parents are giving up too early, like two days in they are giving up. So I try and encourage them to continue. I have seen people who clearly go downhill and who never manage to discontinue. Or the symptoms abate. I have also seen a much commoner group, where the symptoms come back but aren't as bad as they used to be. And people need to think about the balance of whether they continue or not, and what it means to continue, and really thinking about what the potential long-term side effects are, what is known about that. And I try and do that, but they have a sense that they are deciding to continue, rather than me recommending. I recommend that they try discontinuing, but I hope they will feel ownership of whether they discontinue or not.

Successful cessation
Successful cessation is hard to define, but those participants who had stopped taking medication for a period of 6 months or more felt that they were managing adequately enough to prevent them having to restart, even if they were experiencing residual symptoms:

> S6: When I was on medication I was concentrating a lot better. But I would still rather not take them.

None had any plans to go back on medication, although it was not something that was ruled out if in the future they perceived a need to restart, for example to improve concentration at work:

> S8: Maybe if I change to a different career or something that involved a lot of paperwork and concentration, then I might think about it. But I would have to see how I felt when I got to that point, see if I felt I needed it. I wouldn't go back on the stuff unless I really needed it.

Clinician's identified the following as factors that can help improve outcome:

- supportive interpersonal relationships
- structured home and school life
- support from home and school
- stable and interesting employment
- patient's level of maturity
- patient motivation.

Clinicians did not consider there to be any difference in outcome when stopping a modified-release preparation compared with an immediate-release preparation.

Unsuccessful cessation
For three of the five in the restarter group, the distress they described during the period they were not on medication was twofold. Firstly, the distress caused by the untreated ADHD:

> R12: I went through, as I put it, seven years of hell trying everything that people asked me to do, and not one, in seven years, tried what I asked and I wish they had. I could have missed out on a hell of a lot of problems.

Secondly, the distress caused by the inability to engage with and access appropriate services at the point at which it was felt they were required:

> R12: I had to shove every shred of information under my GPs nose before they referred me and that took a long time. I think once they said they were going to refer me, it took eight months before I heard anything.

None of the clinicians felt that an unsuccessful attempt at cessation had any implications in terms of future pharmacological treatment. However, two talked about the possible psychological impact:

> V2: I think if you have a failed attempt to come off medication it makes families more nervous about stopping it a second time. I think you then get into the supporting work that often goes alongside ADHD which is about self-esteem and confidence, because it's not a good belief for a young person to be going out into the world thinking the only reason I can cope is because I've got Ritalin inside me … if you do go through this cycle of stopping and then it goes haywire you risk the person getting into that mind set.

> L1: I have an example of somebody who was discontinued on Ritalin at 16 and between 16 and 19 he was very depressed, he made a lot of suicide attempts and was involved with the law. Now he is back and doing really fine, but of course, he had a number of bad experiences. It is not the outcome of the treatment per se and the effectiveness, but what happens in the period when they are not taking it.

Some thought that having to restart could have a positive effect, improving a patient's awareness of the condition and subsequent compliance to treatment:

> D7: I think they have learned that their treatment is helpful and it allows them to take control over their treatment. They are not taking it because they have to, they are taking it because they choose to, because they see the benefits of it.

The factors identified by clinicians as influencing a patient's need to restart medication were diverse:

- difficulties with interpersonal relationships
- poor parental support (e.g. parents who also have ADHD, chaotic family life)
- recurrence of symptoms
- pressure from family and school to restart
- negative impact on schooling or at work
- comorbidities or learning disabilities
- getting into trouble at school
- getting in trouble with the law
- alcohol and substance abuse
- lack of alternative interventions.

One clinician felt that a late diagnosis had an impact on outcome:

> N10: The other children that do really poorly are the ones that I feel we have caught late and have already got to a position of defiance and conduct disorders and I really worry about what we're going to do with them because actually medication isn't the whole answer.

The long-term outcomes of cessation were more difficult to determine as none of the clinicians were in a position to follow up patients long term once they were discharged from their service:

> N5: Unfortunately I haven't seen them too much after they discontinue. They just seem to disappear. Most of them will discontinue when they leave school, and they leave the service and they don't come back so I haven't got feedback. Very few I will see again, that have come back.

Beliefs about ideal conditions for treatment cessation

When asked what advice they would have for someone wishing to stop, participants talked about the need to think it through and feeling equipped to manage without medication:

> S8: Make sure you are confident without them. Make sure you feel you can deal with things exactly the same as if you were using them [medication] as if you weren't.

> S7: You will have to learn to deal with ADHD or with your problems. You still have the problems even if you might have outgrown them slightly. You have to bear with yourself. Don't get impatient if you don't get things right, or when you start daydreaming too much or when things take too long. It is like the same thing with someone that has a limp. Don't try not to limp if you have a limp. Take your time and learn to deal with it and learn what is right for you.

> S10: I would say if they really think it's going to positively benefit them, then they should go for it, and it's their right to stop medication if they wish.

> R14: Think about it before you do it. That is the only thing I would say really. Just make sure it is what you want.

One of the participants spoke of developing individualised systems:

> S7: Systems are really important, if you have a pre-inclination to not having them, or being disorganised … A lot of people will be like, 'Oh you want to develop a system, try mine!' You just have to work out what system works for you. Even if you think no system works for you, there will be one, so keep trying.

There was variation in the level of support that was considered necessary. One participant felt that with encouragement he would have stayed on medication:

> S6: Just tell them to stay on it really. It will make them get somewhere. I had a job and stuff but I left because I couldn't be bothered with it. I couldn't concentrate, but if I had carried on I would probably still be there now. But I didn't want to take them any more … If they [clinicians] had encouraged me to stay on it then I probably would have. It was just my mum asking me to stay on them, but in the end she said I didn't have to take them if I didn't want to.

Other participants talked about the need for parents and clinicians to support their decision to stop, provide information about the possible outcomes, and to be accessible if medication was once again needed. The following participants said it would be important to consider the following:

> C2: How are you going to stop it? Are you going to stop it full stop? Can I go back on it afterwards?

> C5: How would I react, would I be able to keep calm and that?

> C3: Is it alright to go back on it if I am not really operating well without it? Or is there anything else I could take if I couldn't take the one I'm currently on any more. I would probably want to know how well I will be able to operate without medication.

None of the clinicians had any formal guidelines in place for the cessation of ADHD medication. Therefore, discussion centred on what should be incorporated into best practice guidelines. The points below illustrate the diverse range of answers given:

- check patient history and previous response/non-response to medication
- identify any comorbidities
- discuss the potential advantages and disadvantages of cessation and what might happen once they have stopped
- ensure patient has developed appropriate coping skills
- assess progress either at consultations or using measurement tools which should be completed by the patient, parents and school
- use trial periods to see how the patient gets on
- select an appropriate time
- offer support to the patient and their family if required
- close monitoring and timely follow-up
- long-term follow-up
- develop a 'correction plan' to identify symptoms of relapse and strategies to be put in place in the event of deterioration
- some written information to give to patients and families
- inter-agency collaboration
- alternative interventions, for example family support, coaching, psychoeducational support
- dedicated transitional service bridging CAMHS and Adult Psychiatry.

For all clinicians, timely follow-up was seen as key:

> N5: We follow them up when they are on medication. Even if they have discontinued there should be a period of time, 6 months to a year, where there needs to be follow-up rather than discontinue and goodbye, that is it. And that is what tends to happen.

Quality of life

The CHIP-AE was administered to patients after the interview and in accordance with the instructions outlined in the user manual. Of the 15, a total of nine patients completed the questionnaire; the time it took to complete ranged from 12 to 25 minutes. Four participants had difficulties with reading and comprehension and so took the questionnaire home so they could have more time and support from parents; only one was returned. Two participants did not have time to complete the questionnaire during the session because of the time taken to conduct the interviews, but were given the questionnaire to take home; neither were returned.

Of those that completed the questionnaire, all described it as easy to work through, but considered it lengthy. The majority of patients asked for clarification of questions that would be more appropriate for young people in the USA.

Discussion

Overall, the results of the Part 2 study provide a unique insight into patients' and clinicians' perspectives about treatment cessation for young people with ADHD. Reasons for cessation varied between individuals and usually involved a combination of factors. There were differences in the way that patients managed the process of treatment cessation; some planned it in advance, whereas for others the cessation process appeared to be more ad hoc. Clinicians reported the stages of cessation and the support available to patients who planned their treatment cessation. Outcomes of cessation also varied and were dependent on a range of factors, including recurrence of symptoms, access to services and patient circumstances (e.g. family, school, work). These results are discussed in detail below and recommendations made about how the results could inform practice or further research in this area.

Beliefs about ADHD and ADHD medication

The majority of patients described ADHD in terms of the behaviours they attribute to the condition; these behaviours map onto the symptoms associated with the three core signs of ADHD: inattentiveness, hyperactivity and impulsiveness. These behaviours were most commonly described in terms of their impact at school or workplace and, to a lesser extent, relationships with family at home and with peers. Young people tended not to raise the issue of cause and for some there was confusion about this issue. Patients often reported that they did not feel any different while on medication compared with when they were not taking it so they often relied on feedback about their behaviour from other people, especially peers, parents, clinicians and teachers. Many recognised that their behaviour while on medication produced more positive responses from friends and family compared with times when they were not taking the medication.

Many patients reported perceived side effects from their ADHD medication. The most commonly reported side effects were sleep disturbance and appetite suppression, which is consistent with previous research. Of the three patients that had tried antidepressants, all reported a negative experience. Although patients reported that the antidepressants were prescribed for their ADHD, it is unclear, without clinical corroboration, whether this was indeed the reason why treatment with antidepressants was initiated. ADHD, especially in clinical samples, is often comorbid with other disorders including depression.[134,135] Evidence of inappropriate prescribing of antidepressants for children with HKD was found to be less than 1%.[134] The majority of patients did not have a clear understanding of how their medication works and when treatment was more complex and changeable there was confusion as to why medicines had been changed.

Recommendations
As understanding of ADHD and its treatment was relatively low, patients may benefit from additional education/support from their clinical team (e.g. checking understanding of what the medication is for, how it works, possible side effects). This may be particularly important for patients diagnosed early in childhood and clinicians should check understanding and provide age-appropriate information at various points as the child gets older. In between usual clinic appointments, patients and families could be asked to write questions/queries down as they think of them and bring them to consultations for discussion. There is also a need to develop standardised educational materials for children, young people, and their carers.

Adherence to medication

All the young people interviewed in this study had missed doses at some point during the course of their treatment. The non-adherence described can be characterised as either unintentional or intentional. Accounts of unintentional non-adherence involved the accidental missing of doses or doses taken later than recommended. Reports of intentional non-adherence were common and often involved drug holidays (at weekends or during school holidays), most often initiated at the suggestion of clinicians and/or parents with agreement from the young person. Clinicians were, on the whole, more inclined to suggest that drug holidays take place outside of term time to reduce any potential problems occurring at school or work.

The most commonly reported reasons for intentional non-adherence were side effects and a dislike of taking medication on a daily basis, and was more often described by the group of participants no longer taking medication and the restarter group. For some patients, intentional non-adherence was a precursor to unplanned cessation. Non-adherence was more commonly reported as

occurring in adolescence and young adulthood as opposed to childhood, when the mother, and to a lesser extent the father, played an important role in helping their children manage their medication taking. Clinicians generally reported good adherence to medication regimens, although acknowledged that this may not be the reality.

The barriers to adherence identified by both patients and clinicians are broadly similar to the reasons underpinning non-adherence discussed in the extensive literature on non-adherence to medication used to treat other chronic conditions. A recent US review of the diagnosis, treatment and clinical implications for ADHD among adolescents summarised the factors associated with better adherence in other adolescent illness groups and strategies that may be useful in tackling non-adherence.[136] Factors associated with better adherence include:

- self-concept[137,138]
- family stability[139–142]
- internal locus of control[138,140,143]
- increased motivation[144,145]
- simplified medication regimens[146]
- lack of adverse effects[140,147–149]
- good doctor–patient relationship.[150]

Recommendations

A less than optimal outcome from treatment may be the result of either persistent unintentional or intentional non-adherence. In consultation with patients and their families, exploring reasons for non-adherence while on medication may give clinicians insight into patients' medication-taking behaviour and ways in which they can be supported appropriately. For some, the notion that ADHD may persist beyond childhood and that long-term medication use might be necessary will be difficult to accept and these patients may need extra support coming to terms with this. Evidence suggests that some patients may recognise the positive aspects of medication-taking on behaviour, but will still refuse to adhere. It is important that these patients are identified and a planned discontinuation initiated in which they are given the appropriate support and follow-up.

In previous studies, various brief interventions and motivational techniques have been found to improve adherence in paediatric health-care settings.[151,152] A recent review suggested that these findings on successful strategies to improve adolescents' adherence in other chronic conditions could be useful in adolescents with ADHD (although they require further evaluation).[146] Motivational techniques in particular have been found to help adolescents make decisions and feel in control about their medication.[153–157] It has been suggested that these techniques could help overcome the resistance to medication commonly found in adolescents with ADHD and increase motivation towards treatment.[158] Further research is needed to evaluate the effectiveness of these strategies in adolescents and young people with ADHD in the UK.

The literature on how adolescents and young adults make decisions about their health could also be drawn on for a better understanding of medication-taking behaviour in this population. Work in this area contains discussion of issues to consider involving adolescents and young people in medical decision-making.[159,160] However, further research is needed to assess how best to facilitate this in UK adolescents and young adults with ADHD.

Medication cessation

Reasons for and process of cessation

Reasons for cessation varied between individuals and normally involved a combination of factors, most commonly side effects, a dislike of taking medication and feeling equipped to manage without medication. There were three distinct groups of patients who had attempted cessation: patients who planned their cessation and involved parents and clinicians in decision-making and the process of cessation; those who did not plan their cessation; and those who fell into the gap between CAMHS and adult services.

Adolescents and young people in this study ultimately felt that the decision to stop was theirs. In cases where parents and clinicians agreed with the patient's decision to stop, there normally followed a more planned attempt at cessation, involving discussion of outcomes and follow-up. Where patients reported that there had been disagreement about cessation between themselves and their parent or clinician, intentional non-adherence characterised the period leading up to cessation and a more unplanned cessation followed; patients spoke of using the last of their tablets, then deciding not to renew their prescription or just waking up and deciding that they were no longer going to take them. In these cases, clinicians were often not informed until after the patient had already stopped.

Recommendations

These findings suggest that patients should be encouraged to talk to clinicians before attempting cessation, or to notify them very soon after so that appropriate preparation can be organised and follow-up sessions arranged. Additional work may also be needed with patients and families when there is divergence on the issue of cessation. Many patients at this age, but not all, are becoming more autonomous in making decisions about their health and medication-taking, so to avoid tension and conflict this may form an important part of the preparatory work necessary to ensure a successful outcome from cessation. Patients want to feel supported in their decision to stop, to understand possible outcomes and to be able to reaccess medication if it is needed.

Outcome of cessation

The outcome of cessation was dependent on several factors: recurrence of symptoms, residual symptoms and ability to re-engage with services, family circumstances, educational/work circumstances. For some patients, the outcome could be deemed successful as they reported being able to continue coping without medication. For others, the outcome was not so successful and patients reported difficulties in being able to regain access to medication. Follow-up of patients varied; some were monitored by their clinical team to track whether cessation was appropriate whereas others reported very little or no follow-up.

Recommendations

The patients who reported the most satisfactory outcomes from cessation tended to be those who had planned the process. Therefore, patients and families need to be encouraged to engage in planned cessation and outcomes assessed at follow-up. The type and number of follow-up sessions will be dependent on the individual and should, where possible, be tailored to the individual. Patients who experience recurrence of symptoms that are impacting on daily life, but who do not want to restart medication may need alternative non-pharmacological treatment where available.

Ability to reaccess services is very important as change in symptomology and/or circumstance (e.g. family or school/work circumstances) may mean that a patient needs to restart treatment quickly. Therefore, evidence suggests that adult services need to be made available for patients whose symptoms persist into adulthood and should be consistent with the care they receive in CAMHS. Previous researchers have highlighted the challenges involved in transition of care between paediatric and adult health care, the main challenge being the difference at organisational level between the two service areas.[161] Others have suggested that the differences are likely to be particularly problematic in mental health services due to diagnostic difficulties, difficulty accessing psychotherapy in adult services and poor liaison between the different professions and agencies involved.[162] Continuity of care between paediatric and adult services for ADHD is crucial to ensure patients have timely and appropriate access to medication and other non-pharmacological treatments required for them to manage their condition and daily activities. Considerable distress could be caused if patients cannot access services they feel they need.

Implications for future studies

As discussed in the introduction, findings from this study could help inform a future randomised withdrawal study. In particular, they inform about the mechanisms that might mediate the outcomes that result from interventions. Insight from the interviews into the process and outcomes of cessation can help with the development of guidelines for managing the withdrawal process. Furthermore, reflection on the research methods used here can help inform appropriate methodology for the trial to assess the effectiveness of the withdrawal guidelines.

Implications for the development of guidelines for treatment cessation

In terms of the process of cessation, a key to successful outcome will be to ensure a triadic dialogue between patient, family and clinician in deciding whether cessation is appropriate. Although parents were not interviewed in this study, when patients were asked how their parents felt about their decision to stop they quite often reported that there was some disagreement on the issue. Patients feel that ultimately the decision to stop is their own; hence clinicians can explore this through discussion with both patients and parents about appropriate strategies to use during the cessation process.

To facilitate treatment cessation, evidence from the interviews suggest that a comprehensive plan for preparation could be helpful and should include the following:

- Baseline assessment of symptomatology.

- Post-cessation assessment of symptomatology with some longer-term assessment, ideally with patient, parent, clinician and, where appropriate, teachers. However, for anyone who has already left school or college this will not be possible. Therefore, patient self-report and parent and clinical assessment would be important, as evidence suggests that compared with parents and teachers, adolescents with ADHD tend to under-report their symptoms and level of impairment.[163]
- Assessment of patient treatment history and other factors that may influence outcomes, for example family structure, comorbidities, alcohol/substance abuse and adherence issues.
- A comprehensive discussion of the potential advantages and disadvantages of cessation and what might happen once cessation is initiated (backed up by a written information pack for patients to take away and reflect on).
- Close initial monitoring and long-term follow-up. For some patients a change in situation (work/school/times of chaos) may mean that they need to restart.
- Use of an algorithm for restarting treatment.

Patients who had never attempted cessation all spoke of being willing to attempt it at some stage in the future, but were concerned about outcomes and the need to be able to restart medication if they felt it was necessary. This highlights the need to ensure appropriate provision of services for those restarting. This will be particularly important for those living in areas where adult services for ADHD are not available. Services should be made available for patients who need to remain on medication.

Patients with a more complex treatment history, or those who have experienced difficulties engaging with services in the past, may be more wary about attempting cessation. This should be taken into consideration when deciding appropriate inclusion and exclusion criteria for any trial that aims to evaluate a protocol for discontinuation.

Implications for study design to evaluate future guidelines

In terms of methodology, the poor response rate encountered in this study strongly suggests there may be difficulties recruiting patients to an RCT. The initial recruitment strategy of contacting patients by post (as recommended by the ethics committee) was ineffective in this patient group. Recruitment rate improved once ethics approval was obtained for patients to be contacted by their local collaborator, either face-to-face in clinic or over the telephone. Therefore, for a future RCT and other research in this area, we recommend that patients are, in the first instance, approached face-to-face or by telephone. It is important that patient and parent are both approached and that study information (invitation letter, patient information sheet, etc.) is targeted at each group appropriately.

Qualitative interviews worked well with this group of patients and clinicians and this method could be used to assess acceptability of the withdrawal process in the future trial. Acceptability among patients, parents and clinicians could be assessed via qualitative interviews conducted at the same time as the initial outcome measures. The interviews would also permit the exploration of barriers and facilitating factors to uptake of the service. Information on the extent of uptake and attrition would provide further insight into the acceptability of the process. If the future randomised withdrawal trial is designed to incorporate an economic evaluation, it will be important to assess a range of health service costs associated with cessation, for example how often patients engage with services once cessation begins, subsequent clinic attendance, amount of contact with other specialists, as well as taking a whole-society perspective.

Strengths and weaknesses of the study

As agreed by the HTA commissioning panel, interviews were deemed an appropriate method for the Part 2 study because they allowed depth of enquiry on a topic we previously knew little about. Furthermore, it allowed the researcher to clarify any misunderstandings and to prompt and encourage participants to expand on their responses where appropriate. Interviewees were generally receptive and communicative with the interviewer. The limitation of the in-depth interview approach is that it relies on participants responding honestly. The interviewer attempted to deal with the issue by spending time on rapport building at the start of the interview (e.g. talking about hobbies, interests) before moving on to discuss issues on the topic guide.

The participants interviewed were asked to recall retrospectively their experiences of discontinuation. The time from discontinuation to the interview taking place varied but in some instances was as long as 7 years. This may have implications for accuracy of recall. Some patients struggled to remember the timing of events in the

past. Parents were not interviewed in this study so we were not able to explore their perceptions of and/or experience with the cessation process. In instances where there was discussion with parents before and/or after interview, there was often contextual information extracted that patients had been unable or unwilling to discuss during their interview. Further exploration of convergence and divergence on issues surrounding discontinuation are needed. Most patients in the restarter category were sourced from London rather than the other collaborating sites. This is most likely to be because there is a National ADHD Clinic for adults based in London. Recruiting restarters and stoppers was extremely difficult. The interviews that we did with patients in these categories suggest that this was because they are often not followed up long term after discontinuation so once they are disengaged with the service it is hard to locate them.

Given the nature of ADHD symptoms it is not surprising that it was challenging to recruit participants to the study and that the initial approach recommended by the HTA to recruitment was inadequate. The initial approach aimed to give potential participants sufficient time to review the invitation pack; unfortunately, it was unable to engage with the potential participants. It could be due to their underlying conditions or simply that they were not interested in the research. Recruitment improved significantly after consent or assent was taken in person; this allowed an opportunity to engage with the young person, explain the study and answer questions.

The team attempted to avoid participation bias through the stratification of participants into three categories: patients who remain on treatment and have not attempted to stop; patients who have successfully stopped treatment; and, patients who were unsuccessful in stopping treatment. This was important for ensuring that a range of experiences of medication continuation and cessation was explored. Furthermore, participants were selected from four sites across the UK, again to limit bias. However, given the difficulties experienced during the recruitment phase and the possibility that the study was affected to some extent by participation bias, there is a need to refrain from making across-the-board generalisations. Nevertheless, the replies given by the participants have provided an interesting insight into the views of some young people and clinicians working with young people with ADHD. It is now important to build on this research and try to assess the extent to which the issues raised are affecting young people across the UK.

Conclusion

Some patients were able to stop medication despite some residual symptoms persisting. Conversely, other patients were unable to cope with the symptoms and felt the need to restart treatment. Ability to re-engage with services and obtain medication was difficult in some cases due to a lack of adult services.

The interviews highlighted variation in the process of managing treatment cessation and patient outcomes from this process. This is perhaps not surprising as no guidelines currently exist in this area. Individual patient symptomatology and other factors in patients' lives at the time of cessation and the period before and after may also have an effect.

Issues raised by patients and clinicians in the interviews can be useful for informing future guidelines and research into management of treatment cessation in young people with ADHD.

Chapter 5
Overall discussion

This project combined quantitative and qualitative approaches using a retrospective cohort study with a large automated database and an interview study to investigate current practice in treating adolescents and young adults with ADHD in the UK, during the period 1999–2008.

Extensive discussion of the results has been provided in the individual sections and so the overall discussion aims to draw together and summarise the main findings and to conclude by making recommendations for future research.

Key findings

- The rate of treatment discontinuation largely exceeded the estimated rate of persistence of ADHD.
- The reduction in prescribing was most noticeable between the ages of 16 and 17 years.
- Approximately 18% of patients restarted treatment if they had stopped treatment after the age of 15. For those patients who restarted treatment, they were more likely to restart within the first year following treatment cessation.
- Patients continuing on treatment consider cessation as an option for the future, although were often concerned about the process and the impact of not taking medication on their behaviour.
- Young people who have stopped taking medication often feel able to cope adequately even if residual symptoms still exist. The majority would consider restarting if their circumstances changed and it was considered necessary.
- Some young people found that they still required treatment after attempting cessation.
- Some clinicians and patients feel there is a lack of services for adults with ADHD. Some patients have their treatment stopped for this reason.
- For some patients restarting treatment, engaging appropriate adult services is a lengthy and difficult process.

One of the most important findings from this study, and previously unreported in the literature, is the large number of young people who stop medication between the ages of 16 and 17. The following factors could have contributed to the earlier than expected discontinuation of medication.

- Between the ages of 16 and 17, the proportion of patients who stopped treatment was twice that which would be expected. This is the age when adolescents complete their GCSE and may leave school.
- Poor provision of diagnostic and treatment services for older adolescents and young adults.
- Neither methylphenidate nor dexamfetamine is licensed for the treatment of ADHD in patients over 18 years and atomoxetine is only licensed to individuals over the age of 18 years who started their treatment before that age.
- Condition not persisting into adulthood.

The Part 2 study has provided some useful information in relation to these suggestions. To our knowledge, this is the first qualitative study that has explored in depth the issue of cessation in young people with diverse treatment trajectories.

Education system and cessation of treatment

Most interviewees spoke about ADHD in terms of the impact the condition has on schooling or work and described how treatment improved concentration and ability to focus on tasks. Clinicians spoke of the need to choose an appropriate time to attempt cessation, with schooling and academic performance a factor taken into consideration when making that decision. The structured nature of the education system can help make adolescents aware of the potential benefit of the right treatment. However, after leaving education, young people may perceive less need for sustained attention and focus to complete tasks and this may explain the large proportion of patients that stopped treatment at school-leaving age.

Poor provision of diagnostic and treatment services for older adolescents and young adults

All the clinicians interviewed in the Part 2 study discussed the difficulties that arise once an adolescent reaches the age when child and adolescent mental health services are no longer

available; this was echoed in the accounts given by some of the patients. Clinicians offered a range of reasons to account for this, including a lack of education and expertise in diagnosing and treating ADHD in adults, and perception of the priority and clinical significance of ADHD in relation to other mental health conditions.

Effects of licensing status on the discontinuation of the treatment

Unlike the majority of other medicines, ADHD treatments are currently licensed for children and adolescents only. The exception is atomoxetine, which is licensed for adults who start treatment before the age of 18. The off-label use of ADHD treatments may deter prescribers from continuing treatment beyond adolescence, similar to the off-label prescribing of adult medicines to children. Findings from clinician interviews suggest that adult psychiatrists may be reluctant to prescribe for this reason.

Condition not persisting into adulthood

All the participants who had stopped taking medication felt they were managing adequately, even if they were still experiencing residual symptoms. Therefore for this group of young people, cessation was appropriate. However, some patients reported the need to restart treatment because of the impairment from continuing symptoms. For some young people symptoms clearly persist into late adolescence and adulthood.

Chapter 6
Overall conclusion

For the majority of adolescents and young adults taking medication for acute or chronic conditions, the decision to stop is their own. To date the evidence base for the outcomes of cessation of treatment in ADHD patients is scarce. This study raises the possibility that treatment may be prematurely stopped by or for some adolescents and young adults with ADHD and that overall the fall in treatment prevalence may be out of step with the numbers of people who still require treatment as young adults. It has been highlighted in the literature and by some of the respondents in this study that ADHD services within adult mental health services are poorly developed. Factors in adult services such as poor transition arrangements from child services, lack of resources, poor training of adult psychiatrists in the diagnosis and management of ADHD, competing priorities, unwillingness to prescribe unlicensed medications and beliefs that the condition does not exist in adulthood are all likely to contribute to patients failing to be identified for initiation or continuation of treatment for ADHD, even where this is clinically indicated. Guidelines and further research are needed to aid patients, families and clinicians in making an informed and evidence-based decision about whether cessation is appropriate. The research priorities identified based on the study results and the latest data from the MTA trial and the NICE guideline include investigating whether stimulants, particularly methylphenidate, are still effective after long-term treatment, i.e. by conducting a placebo-controlled trial. Once the aforementioned study is conducted, then a further study optimising the cessation and/or continuation process is needed to guide clinicians on future practice.

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Contributions of authors

Ian Wong, chief investigator of the project, contributed to study design, data analysis, interpretation of results and writing of the report. Philip Asherson contributed to the study design, patient recruitment, interpretation of results and commenting on the report. Andrea Bilbow contributed to the study design, interpretation of results and commenting on the report. Sarah Clifford contributed to the study design, data analysis, interpretation of results and writing of the report. David Coghill contributed to the study design, patient recruitment, interpretation of results and commenting on the report. Ruwan DeSoysa contributed to data analysis, patient recruitment, interpretation of results and commenting on the report. Chris Hollis contributed to the study design, patient recruitment, interpretation of results and commenting on the report. Suzanne McCarthy contributed to the data collection, data analysis, interpretation of results and writing of the report. Macey Murray contributed to the study design, data analysis, interpretation of results and commenting on the report. Claire Planner conducted interviews with patients and clinicians, analysis of the qualitative data and interpretation of results and writing of the report. Laura Potts contributed to data analysis and writing of the report. Kapil Sayal contributed to the study design, patient recruitment, interpretation of results and commenting on the report. Eric Taylor contributed to the study design, patient recruitment, interpretation of results and commenting on the report.

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Appendix 1

GPRD product codes for methylphenidate, dexamfetamine and atomoxetine

GPRD product code	GPRD product name	Strength	Unit
M13066001	Dexamfetamine oral liquid 1 mg/ml	Null	Null
4013832	Dexamphetamine sulphate 10 mg CAP	10	mg
4013833	Dexamphetamine sulphate 15 mg SPA	15	mg
4063247	Dexedrine tablets 5 mg	5	mg
M03577001	Dexamfetamine tablets 5 mg	5	mg
4086659	Equasym tablets 10 mg	10	mg
4089329	Equasym tablets 5 mg	5	mg
4089330	Equasym tablets 20 mg	20	mg
4090953	Tranquilyn tablets 10 mg	10	mg
4092593	Equasym XL capsules 20 mg	20	mg
4092635	Tranquilyn tablets 5 mg	5	mg
4093143	Tranquilyn tablets 20 mg	20	mg
4096580	Concerta XL tablets 18 mg	18	mg
4096581	Concerta XL tablets 36 mg	36	mg
4111897	Equasym XL capsules 10 mg	9.98	mg
4111898	Equasym XL capsules 20 mg	20	mg
4111899	Equasym XL capsules 30 mg	29.94	mg
4111897	Equasym XL capsules 10 mg	9.98	mg
4080748	Ritalin tablets 10 mg	10	mg
M08155001	Methylphenidate modified-release capsule 20 mg	20	mg
M08551001	Methylphenidate tablets 10 mg	10	mg
M08551002	Methylphenidate tablets 5 mg	5	mg
M08551003	Methylphenidate tablets 20 mg	20	mg
M10450001	Methylphenidate modified-release tablet 18 mg	18	mg
M13050001	Methylphenidate modified-release capsule 10 mg	9.98	mg
M13051001	Methylphenidate modified-release capsule 30 mg	29.94	mg
M12516001	Atomoxetine capsules 10 mg	11.43	mg
M12517001	Atomoxetine capsules 18 mg	20.57	mg
M12518001	Atomoxetine capsules 25 mg	28.57	mg
M12519001	Atomoxetine capsules 40 mg	45.71	mg
M12520001	Atomoxetine capsules 60 mg	68.56	mg
4110981	Strattera capsules 10 mg	11.43	mg
4110982	Strattera capsules 18 mg	20.57	mg
4110983	Strattera capsules 25 mg	28.57	mg
4110984	Strattera capsules 40 mg	45.71	mg
4110985	Strattera capsules 60 mg	68.56	mg

Appendix 2

GPRD medical codes for attention deficit hyperactivity disorder

GPRD medical code	Read/OXMIS term
206685	Childhood hyperkinetic syndrome
206686	Child attention deficit disorder NOS
206761	[X]Attention deficit hyperactivity disorder
206762	[X]Hyperkinetic conduct disorder
219266	[V]Other behavioural problems
224711	Child attention deficit disorder
224790	[X]Behavioural/emotional disords onset childhood/adolescence
228338	[V]Behavioural problems
233837	Hyperkinesis with developmental delay
233838	Other hyperkinetic manifestation
233918	[X]Hyperkinetic disorder associated with conduct disorder
233919	[X]Other hyperkinetic disorders
233920	[X]Hyperkinetic disorder, unspecified
242886	Behaviour disorder
242896	Hyperkinetic conduct disorder
242973	[X]Hyperkinetic reaction of childhood or adolescence NOS
247275	Overactivity
248592	Behavioural problems at school
252105	[X]Attention deficit disorder
263159	[D]Overactivity
270501	Attention deficit with hyperactivity
270502	Hyperkinetic syndrome NOS
279567	Overactive child syndrome
279650	[X]Hyperkinetic disorders
288785	[X]Childhood behavioural disorder NOS
292335	[X]Personal history/other mental and behavioural disorders
297952	Attention deficit without hyperactivity
298026	[X]Disturbance of activity and attention
298027	[X]Hyperkinetic syndrome NOS
303416	Poor concentration
303485	Behaviour problem
303491	Hyperactivity
303499	Disorder behaviour childhood
303503	Overactivity (childhood)
309168	Reduced concentration
310028	[X]Attention deficit disorder

continued

GPRD medical code	Read/OXMIS term
310044	ADD – Attention deficit disorder
331605	Attention deficit disorder
331683	Short attention span
333051	Hyperactive behaviour
339951	Poor concentration
340570	Behavioural problem
340608	Disorders of attention and motor control
340623	Short attention span
341494	Reduced concentration span
341515	Minimal brain dysfunction
341765	Rating scale of attentional behaviour
342347	Behavioural inattention test
342478	Test of everyday attention – child
342538	MBD – Minimal brain dysfunction
346520	Test of everyday attention – adult

NOS, not otherwise specified.

Appendix 3

GPRD ethics application for drug utilisation study

Background

Attention deficit hyperactivity disorder (ADHD) is one of the commonest causes of mental health problems in childhood.[1] Longitudinal studies indicate that it is a major developmental risk, persisting into adult life, and is one of the strongest risk factors for mental health problems and social exclusion in young adult life. ADHD is usually markedly improved by pharmacological treatment such as methylphenidate, dexamfetamine and atomoxetine. The National Institute of Clinical Excellence (NICE) produced guidelines on the use of methylphenidate in ADHD in October 2000 and identified 'current patterns of treatment and prescribing for ADHD' as an area for further research.[2] It also drew attention to the almost complete lack of evidence about long-term outcomes. Therefore there is no clear guidance to as to the amount of specialist services that are required for children, the extent to which affected adults should receive treatment, the costs associated with treating and not treating, and the best advice to give to individual patients and their families. It is hoped in the future to conduct a RCT to compare the effects and costs of a programme of continuation of stimulant medication against one of discontinuation in young people who have previously been given short-term treatment with methylphenidate, dexamfetamine or atomoxetine. Firstly, however, it is necessary to establish current prescribing patterns in this group of patients.

1. Swanson JM, Sergeant J, Taylor E, Sonuga-Barke E, Cantwell D. Attention deficit hyperactivity disorder and hyperkinetic disorder. *Lancet* 1998;**351**:429–33.

2. National Institute of Clinical Excellence. *Guidance on the use of methylphenidate (Ritalin, Equasym) for attention deficit/hyperactivity disorder (ADHD) in childhood*. Technology Appraisal Guidance No. 13. London: NICE; 2000.

Purpose

1. To estimate the incidence and prevalence of ADHD treatments in the target population.
2. To describe the demographic and clinical details of patients in the target population who received ADHD pharmacological treatment including age, gender, duration of treatment and dosage.
3. To estimate the percentage of patients in the target group who stopped the ADHD treatment, and investigate possible factors affecting the continuation or cessation of pharmacological treatments.

Study population

Inclusion criteria

- The study population will include all children and young adults aged less than 22 years who received one or more prescriptions for methylphenidate (MPH), dexamfetamine (DEX) or atomoxetine (ATM) between 01/01/1992 and 31/12/2005.
- Patients must have a diagnosis of ADHD associated with the first prescription of MPH, DEX or ATM (whichever was issued first).
- Patients must have a known gender.
- Patients must have at least 6 months of research-standard data in the database.
- Patients must have permanent or applied registration, or transferred-out status with the GP practice.
- Preliminary data identified 675 patients receiving 6113 prescriptions for the study drugs between 01/01/2001 and 31/12/2004.

Exclusion criteria

- Patients prescribed MPH, DEX or ATM for other conditions such as narcolepsy or epilepsy will be excluded.
- Patients who have temporary registration with a general practice will be excluded.

Study design

Descriptive cohort study; drug utilisation study specifically looking into trends of prescribing, prevalence and incidence, duration and cessation of treatment.

Selection of controls

Not applicable.

Clinical outcome of interest

This is a descriptive utilisation study and so there is no specific clinical outcome of interest. However, associated consultation codes will be examined to investigate possible reasons for prescribing and to eliminate prescriptions prescribed for indications other than ADHD.

Non-clinical outcome of interest

The prescribing trends of MPH, DEX and ATM will be examined.

Exposure of interest

The study looks at prescribing of MPH, DEX and ATM.

Data analysis

Data will be extracted using standard GPRD data tools. STATA version 9 will be used for data management and analysis. It will be used to calculate 95% confidence intervals.

Incidence and prevalence

Incidence will be defined as:

$$\frac{\text{Number of patients with a new prescription for MPH, DEX or ATM}}{\text{Patient years at risk in the GPRD population}}$$

Prevalence will be defined as:

$$\frac{\text{Number of patients with a prescription for MPH, DEX or ATM}}{\text{Patient years at risk in the GPRD population}}$$

Incidence and prevalence will be stratified according to age, year of event and drug group.

This method will only identify patients who were prescribed one of the study drugs by the GP and so will exclude patients who only receive treatment in secondary care. However, these patients may have a diagnosis of ADHD recorded in the GPRD. To identify these patients, the records of patients with an ADHD diagnosis but without a therapy record for one of the study drugs will be screened to see whether any free text records of secondary care prescriptions are attached.

To identify ADHD diagnoses

The associated consultation code will be used to link diagnosis and first prescription for the study drug.

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 diagnosis of ADHD. The medical records will be screened in the 6-month period before and after the first prescription for a diagnosis of ADHD.

Free-text fields will also be screened for ADHD diagnoses.

Duration of treatment

To gain a complete picture of drug treatment in this population, data will be gathered and analysed on all patients who received a prescription for one of the study drugs. A subanalysis will also be conducted on patients who have had good response to treatment. This will include patients with at least 1 year's duration of treatment with MPH, DEX or ATM.

Prescription durations will be estimated from the number of tablets taken per day and the total prescribed quantity. Treatment duration mapping will be estimated by concatenation of overlapping prescriptions for products involving the same active drug substance.

Cessation of treatment

A minimum gap of 6 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 who stopped treatment. This method will also be used to examine the percentage of patients restarting treatment. Possible factors affecting cessation and treatment restart such as age, gender and dose will be identified.

Study period

1 January 1992 to 31 December 2005.

Appendix 4

Number of male patients receiving prescriptions for ADHD medications (numerator), corresponding GPRD population (denominator) and prevalence figures by age and year

Year	Numerator	Denominator	Prevalence (per 1000 patients)
Age 15			
1999	21	15,932	1.32
2000	48	17,940	2.68
2001	51	19,216	2.65
2002	80	20,025	4.00
2003	106	21,223	4.99
2004	138	21,661	6.37
2005	170	22,468	7.57
2006	177	21,299	8.31
Age 16			
1999	17	15,546	1.09
2000	21	17,543	1.20
2001	43	19,285	2.23
2002	48	19,324	2.48
2003	69	20,348	3.39
2004	100	21,689	4.61
2005	132	22,183	5.95
2006	151	21,694	6.96
Age 17			
1999	6	15,752	0.38
2000	13	17,188	0.76
2001	10	18,804	0.53
2002	36	19,221	1.87
2003	38	19,683	1.93
2004	57	20,689	2.76
2005	73	22,211	3.29
2006	89	21,442	4.15

continued

Year	Numerator	Denominator	Prevalence (per 1000 patients)
Age 18			
1999	7	15,721	0.45
2000	5	17,593	0.28
2001	8	18,791	0.43
2002	7	19,098	0.37
2003	27	19,797	1.36
2004	28	20,265	1.38
2005	41	21,412	1.91
2006	49	21,399	2.29
Age 19			
1999	1	15,941	0.06
2000	6	17,392	0.34
2001	1	19,100	0.05
2002	6	18,722	0.32
2003	6	19,271	0.31
2004	15	20,017	0.75
2005	21	20,384	1.03
2006	30	19,759	1.52
Age 20			
1999	1	15,524	0.06
2000	1	17,814	0.06
2001	4	19,020	0.21
2002	2	19,193	0.10
2003	5	18,949	0.26
2004	6	19,367	0.31
2005	12	20,012	0.60
2006	15	18,639	0.80
Age 21			
1999	0	14,642	0.00
2000	1	17,468	0.06
2001	1	19,594	0.05
2002	3	19,307	0.16
2003	3	19,583	0.15
2004	3	19,373	0.15
2005	5	19,793	0.25
2006	8	18,793	0.43

Appendix 5

Participant invitation letter (parents of patients 15–17)

To be printed on site-specific headed paper

[Name of potential participant]

[Address line 1]

[Address line 2]

[Address line 3]

[Postcode]

Date

Dear [name of potential participant]

Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

I am writing to follow up on a conversation you had with [enter clinician/nurse name who spoke to the parent previously] about a study that we are carrying out to understand how ADHD in adolescents and young adults is currently treated. As [X] explained, we are therefore inviting your child to take part in an interview to discuss the medication(s) they currently take or have taken in the past; what they think about ADHD medication; any problems they may have experienced with their treatment and, if they have attempted to stop taking medication, their experience of stopping. The project is being conducted by a team of researchers and doctors from universities and hospitals across the UK.

If [name of child] is interested in participating in this study, it is important for you both to understand why the research is being done and what it will involve. Please take time to read the parent and participant information leaflets enclosed for further details. If [name of child] decides they would like to take part and you are also happy for them to do so, then please could you both complete the consent form and questionnaire and return them in the freepost envelope provided. As [name of child] is under 18 we need consent from you both in order to go ahead with the interview.

I will telephone you in a few days time to follow up and answer any queries you may have and to arrange a convenient time to meet your child for the interview. The talk will be conducted at the clinic that your child attends or previously attended for treatment.

We estimate that the interview will take approximately 55 minutes, depending on how much [name of child] has to say. The travel expenses for your child (as well as yourself if you want to accompany your child) will be reimbursed by the research team.

If you or [name of child] have any questions about the study please do not hesitate to contact either myself or [clinician details].

[Clinician details]

Claire Planner

Researcher

Centre for Paediatric Pharmacy Research

The School of Pharmacy

University of London

E-mail:

Tel: 020 0000 0000

Fax: 020 0000 0000

Appendix 6

Participant invitation letter (patients 15–17)

To be printed on site-specific headed paper

[Name of potential participant]

[Address line 1]

[Address line 2]

[Address line 3]

[Postcode]

Date

Dear [name of potential participant]

Cessation of Attention deficit hyperactivity Disorder Drugs in Young (CADDY)

We are carrying out a study to understand how ADHD in adolescents and young adults is currently treated. Therefore we are inviting you to take part by talking to us about the medication(s) you currently take or have taken in the past; what you think about ADHD medication; any problems you may have experienced with your treatment and, if you have attempted to stop taking medication, your experience of stopping. The project is being conducted by a team of researchers and doctors from universities and hospitals across the UK.

If you are interested in helping us with this study, it is important for you to understand what it will involve. Please take time to read the information leaflet enclosed and discuss it with your family or friends if you wish. As you are under 18, we are required to tell your parents that we have asked you to take part in this study and they must also say 'yes'. Therefore we have sent them a version of this letter along with a parent information leaflet and a consent form. A member of staff from your current or previous hospital team will also have already spoken to your parent or guardian about this study to ensure they understand why it is being conducted and what it would involve to take part.

If you decide you would like to take part then please could you *and* your parent or guardian fill out the two consent forms enclosed. Please return one copy to us in the freepost envelope provided and keep the other copy for yourself. If you decide you want to say 'no' but your parent or guardian wants you to take part, then your decision will overrule theirs.

Once the researcher has received your completed consent form, she will telephone you to arrange a convenient time for you to meet.

The talk will be conducted at the clinic that you attend or previously attended for treatment. The questions will take approximately 55 minutes, depending on how much you want to talk. We will pay you back the money it costs you to travel to the clinic to talk to us.

If you or have any questions about the study please do not hesitate to contact either myself or [clinician details].

[Clinician details]

Claire Planner

Researcher

Centre for Paediatric Pharmacy Research

The School of Pharmacy

University of London

E-mail:

Tel: 020 0000 0000

Fax: 020 0000 0000

Appendix 7

Participant invitation letter (patients 18+)

To be printed on site-specific headed paper

[Name of potential participant]

[Address line 1]

[Address line 2]

[Address line 3]

[Postcode]

Date

Dear [Name of potential participant]

Cessation of Attention deficit hyperactivity Disorder Drugs in Young (CADDY)

I am writing to follow up on a conversation you had with [enter clinician/nurse name who spoke to the patient previously] about a study that we are carrying out to understand how ADHD in adolescents and young adults is currently treated. As [X] explained, we are therefore inviting you to take part in an interview to discuss the medication(s) you currently take or have taken in the past; what you think about ADHD medication; any problems you may have experienced with your treatment and, if you have attempted to stop taking medication, your experience of stopping. The project is being conducted by a team of researchers and doctors from universities and hospitals across the UK.

If you are interested in helping us with this study, it is important for you to understand why the research is being done and what it will involve. Please take time to read the participant information leaflet enclosed and discuss it with others if you wish. If you decide you would like to take part then please could you sign both of the consent forms enclosed with this letter. Please return one copy to us in the freepost envelope provided and keep the other copy for yourself. I will telephone you in a few days time to follow up and answer any queries you may have.

The talk will be conducted at the clinic that you attend or previously attended for treatment. We estimate that the interview will take approximately 55 minutes, depending on how much you want to talk. Your travel expenses will be reimbursed by the research team.

If you have any questions about the study please do not hesitate to contact either myself or [clinician details].

[Clinician details]

Claire Planner

Researcher

Centre for Paediatric Pharmacy Research

The School of Pharmacy

University of London

E-mail:

Tel: 020 0000 0000

Fax: 020 0000 0000

Appendix 8

Participant information sheet (parents of patients 15–17) V6 (4 May 2007)

To be printed on site-specific headed paper

Cessation of Attention deficit hyperactivity Disorder Drugs in Young (CADDY)

Participant Information Leaflet

The School of Pharmacy is taking part in a project involving adolescents and young adults who are either taking medication for the treatment of ADHD or have done so in the past. We would like to invite your child to take part in this project. Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish your child to participate. Please contact us if there is anything that is not clear or if you would like more information.

The HTA (Health Technology Assessment) are funding the project. It was approved by the [South East Multicentre Research Ethics Committee/06/MRE01/53].

Sarah Clifford: Researcher
Email: Tel. 020 0000 0000

Claire Planner: Researcher
Email: Tel. 020 0000 0000

1. The aim of the project

The aim of the project is to understand how ADHD in adolescents and young adults is currently treated. We will ask your child questions about the medication(s) they currently take or have taken in the past; what s/he thinks about ADHD medication; any problems they may have experienced with their treatment and if they have attempted to stop taking medication, their experience of stopping.

2. Why has your child been chosen?

We will be inviting 15 young people to take part in the project. We will also interview 10 clinicians.

3. Does your child have to take part in this project?

No. If you and/or your child decide not to take part in this project, it is entirely your right and will not in any way affect your child's present or future treatment. If you do decide that your child can participate, they are still free to withdraw at any time and without giving a reason.

4. How will the project be done?

If you decide your child can take part, a researcher called Claire will talk to your child about their experience of taking medication for ADHD. The talk will be conducted at the clinic that your child attends or previously attended for treatment. Your child's travel expenses will be reimbursed (and your own if you

decide to accompany them to the interview). The talk will last approximately 55 minutes but it may be slightly more or less depending on how much they want to talk. We will ask your child's permission to tape record the interview and to write down their responses from the tape recording. Your child will also be asked to complete a few short questionnaires which explore attitudes and feelings towards treatment and quality of life issues. Any information from the interview will be kept strictly confidential and your child's name will be removed so that s/he cannot be identified from the final report.

We are also interested in your opinion of how your child's ADHD affects their behaviour, and have included a questionnaire for you to complete. Please return the completed questionnaire in the freepost envelope.

5. How will the results be used?

The information given to us, along with the information from our other study participants, will be used to write a report about ADHD treatment in adolescents and young adults. This report will be published in one of the medical journals. We may use quotations from your child's interview but they will not contain any information which will allow others to identify your child. Furthermore, the tape-recording will never be played to anybody outside of the research team.

Your clinic doctor [add name] will not have access to any of the personal information that your child gives to Claire. This is to ensure that everything s/he says is kept confidential. Results from the study will be available from December 2007; if you would like a copy then please let Claire know.

6. Who do I speak to if I have further questions or worries?

If you would like more information about the study please contact Claire Planner, Researcher at the School of Pharmacy, on 020 0000 0000. If you have any complaints about the study, in the first instance please discuss them with Sarah Clifford on 020 0000 0000. If the problem is not resolved, or you wish to comment in any other way about the project you can contact the Chief Investigator for the study, Professor Ian Wong, on 020 0000 0000.

7. How do I agree for my child to take part in the project?

If you have understood the information contained in this leaflet and have no further questions, please sign, along with your child, the enclosed consent form and return one of the copies to Claire Planner in the freepost envelope provided. Please keep the other copy of the consent form and this information leaflet for future reference.

Thank you for reading this leaflet

Appendix 9

Participant information sheet (patients 15–17) V6 (4 May 2007)

To be printed on site-specific headed paper

Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

Please will you help us with our research?

We are interested in talking to young people with ADHD who are taking medication or have done so in the past. We have set out the questions you might want to ask, with our answers. Please contact us, Claire or Sarah, if you want more details.

Claire Planner 020 0000 0000 [email address]

Sarah Clifford 020 0000 0000 [email address]

Why is the project being done?
Researchers have not asked young people much about the treatment they receive or have received in the past for ADHD. We plan to listen to young people and health staff and write a report about their views. The aim is to help families and health staff know more about how you feel about the treatment you receive(d) and what you think about stopping treatment.

What will happen to me if I take part?
If you agree, Claire will meet you at the clinic where you receive treatment or have received treatment in the past, to talk to you. If it is OK with you she will tape record what you say so she can remember it better. She will talk with you for approximately 55 minutes.

We will also ask you to complete a short questionnaire which will ask you about quality of life and your thoughts and feelings towards treatment. You won't be asked to take any treatment. If you are living at home we will ask your parent or carer to complete a questionnaire before you come to the clinic as it will be useful to get their opinion on how ADHD affects your day to day activities.

We will refund the cost of your trip to the clinic to meet with Claire.

Who will be in the project?
We'll be talking to 15 young people and 10 doctors from four different areas in the UK.

Do I have to take part?
No. It's your choice. If you say 'yes', you can still drop out at any time. If you don't want to answer some questions, just say 'pass'. You do not have to tell us anything unless you want to. Even if your mum/dad/carer wants you to, you can still say no and you won't have to take part. Whether you help us or not, you will still go on having just the same care at your clinic (if you still attend one).

Will there be any problems for me if I take part?
We hope you will enjoy talking to us. A few people get upset when talking about their lives, and if you don't want to talk about something and/or stop that's OK. We can put you in touch with someone to help you, if you wish. If you are unhappy about anything that happens in the project, please tell us. You can also tell your mum or dad, or your doctor.

Will doing the research help me?

We hope you will like helping us. We will write a report about what you and other young people say, as well as doctors. We hope that when people read the report it might help people understand ADHD treatment better. You too may find the report useful.

Who will know if I am in the research and what I have talked about?

Doctors in the clinic and your mum or dad will know if you are taking part in the project, but we will not tell them or anyone else what you have said. The only time we might have to break this promise is if we think you or someone else might be at risk of being hurt. If so, we will talk to you first about the best thing to do.

We will keep our tapes in a safe lockable place and delete your name from the tape at the end of the project.

When we write reports about your views, we will change your name, so no one will know what you said.

Will I know about the results?

We will send you a short report.

The HTA (Health Technology Assessment) are funding the project. It was approved by the [South East Multicentre Research Ethics Committee/06/MRE01/53].

If you take part, please keep this leaflet with the copy of your consent form.

Thank you for reading this leaflet!

Appendix 10

Participant information sheet (patients 18+) V6 (4 May 2007)

To be printed on site-specific headed paper

Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

Please will you help us with our research?

We are interested in talking to young people with ADHD who are taking medication or have done so in the past. We have set out the questions you might want to ask, with our answers. Please contact us, Claire or Sarah, if you would like more details.

Claire Planner 020 0000 0000 [email address]

Sarah Clifford 020 0000 0000 [email address]

Why is the project being done?

Researchers have not asked young people much about the treatment they receive or have received for ADHD. We plan to ask you about the medication you currently take or have taken in the past; what you think about ADHD medication; any problems you may have experienced with your treatment and if you have attempted to stop taking medication, your experience of stopping.

We will then write a report about the views of young people. The aim is to help families and health staff know more about how you feel about the treatment you receive(d), if treatment should be stopped and, if so, when and how it can be stopped.

What will happen to me if I take part?

If you agree, Claire will meet you at the clinic where you receive treatment/have received treatment in the past, and talk with you for approximately 55 minutes depending on how much you want to talk. If it is OK with you she will tape record what you say so she can remember it better. We will also ask you to complete a few short questionnaires which will ask you about your feelings towards treatment and quality of life issues. You won't be asked to take any treatment.

If you are living at home we will ask for your permission to allow us to send a questionnaire to your parent or carer as it will be useful to get their opinion on how ADHD affects your day to day activities.

We will refund the cost of your trip to the clinic to meet with Claire.

Who will be in the project?

We'll be talking to 15 young people and 10 doctors from four different areas in the UK.

Do I have to take part?

No. If you decide not to take part in the project, this is entirely your right and will not in any way affect your present or future treatment. If you do decide to take part you are still free to withdraw at any time and without giving a reason. Whether you help us or not, you will still go on having just the same care at your clinic (if you still attend one).

Will there be any problems for me if I take part?

We hope you will enjoy talking to us. A few people get upset when talking about their lives, and if you don't want to talk about something that's OK. We can put you in touch with someone to help you, if you

wish. If you are unhappy about anything that happens to you in the project, please tell us. You can also inform your mum, dad, or your doctor.

Will doing the research help me?
We will write a report about what you and other young people say, as well as doctors. We hope that when people read the report it might help people to understand ADHD treatment better. You too may find the report useful.

Who will know if I am in the research and what I have talked about?
Doctors in the clinic will know if you are in the project, but we will not tell them or anyone else what you have said. We will keep our tapes in a safe lockable place and delete your name from the tape at the end of the project. When we write reports about your views, we will delete your name, so no one will know what you said.

Will I know about the results?
We will send you a short report.

The HTA (Health Technology Assessment) are funding the project. It was approved by the [South East Multicentre Centre Research Ethics Committee/06/MRE01/53].

If you take part, please keep this leaflet with your copy of the consent form.

Thank you for reading this leaflet!

Appendix 11

Consent form (patients/parents 15–17)

To be printed on site-specific headed paper

Centre number:
Patient identification number for this study:

Consent Form

Title of project: Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

Name of Chief Investigator: Professor Ian Wong

Please read each of the statements below and tick each box if you *both* agree.

		I agree
1.1	confirm that we have read and understood the information sheet (Version 6) dated 04/05/2007 for the above study and we have had the opportunity to ask questions	❑
2.1	understand that participation is voluntary and that my child is free to withdraw at any time, without giving any reason and without medical care or legal rights being affected	❑
3.1	understand that sections of my child's medical notes may be looked at by responsible individuals from the School of Pharmacy or from the clinic attended by my child when it is relevant to the research. I give permission for these individuals to have access to my child's records	❑
4.1	give my consent for my child to take part in the above study	❑

Please write your name, today's date and sign below.

_____	_____	_____
Name of parent	Date	Signature
_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of researcher	Date	Signature

Appendix 12

Consent form (patients 18+)

To be printed on site-specific headed paper

Consent Form

Title of project: Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

Name of Chief Investigator: Professor Ian Wong

Please read each of the statements below and tick each box if you agree.

		I agree
1.1	confirm that I have read and understood the information sheet (Version 6) dated 04/05/2007 for the above study and have had the opportunity to ask questions	❑
2.1	understand that participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected	❑
3.1	understand that sections of my medical records may be looked at by responsible individuals from the School of Pharmacy or from [*place/clinic]* when it is relevant to the research. I give permission for these individuals to have access to my records	❑
4.1	give my consent to take part in the above study	❑

Please write your name, today's date and sign below.

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of researcher	Date	Signature

Appendix 13

Clinician information sheet V 0.7 (4 May 2007)

To be printed on site-specific headed paper

Cessation of Attention deficit hyperactivity Disorder Drugs in Young (CADDY)

Participant Information Leaflet

The School of Pharmacy is taking part in a project involving adolescents and young adults who are either taking medication for the treatment of ADHD, or have done so in the past, and clinicians. We would like to invite you to take part in this project. Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish to participate. Please contact us if there is anything that is not clear or if you would like more information.

Sarah Clifford: Researcher
Email: Tel. 020 0000 0000

Claire Planner: Researcher
Email: Tel. 020 0000 0000

1. The aim of the project

The aim of the project is to understand how ADHD in adolescents and young adults is currently treated. Recent evidence has shown that ADHD persists into adulthood in at least one-third of patients; however there is little information on the treatment of these patients. 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). Therefore to gain an insight into current practice it is vital for patients and clinicians to express their views on the process of cessation of ADHD treatment. Topics to be explored include adherence to medication, medication-related problems and decisions surrounding medication cessation.

The project is taking place between October 2006 and December 2007 and is funded by the Health Technology Assessment (HTA).

2. Why have I been chosen?

You are being invited to take part in the project because we would like to interview community paediatricians, child and adolescent psychiatrists and adult psychiatrists. In total we will interview 10 clinicians. We will also be inviting approximately 15 patients to take part in the project.

3. How will the project be conducted?

If you decide to take part, a researcher called Claire Planner will interview you. The interview will be conducted at your clinic and will last a maximum of 1 hour. We will ask your permission to tape record the interview and to write down your responses from the tape recording. Any information from the interview will be kept strictly confidential and your name removed so that you cannot be identified from the final report.

4. How will the results be used?

The information you give us in the interview, along with the information from our other study participants, will be used to write a report about ADHD treatment in adolescents and young adults. This report will be published in one of the medical journals. We may use quotations from your interview but they will not contain any information which will allow others to identify you. Furthermore, the tape-recording will never be played to anybody outside of the research team. If you wish to read a copy of the questions and answers you gave in the interview, we will send you a copy.

Results from the study will be available from December 2007; if you would like a copy then please let Claire Planner know.

5. Who do I speak to if I have further questions?

If you would like more information about the study please contact Claire Planner, Researcher at the School of Pharmacy, on 020 0000 0000. If you have any complaints about the study, in the first instance please discuss them with Sarah Clifford on 020 0000 0000. If the problem is not resolved, or you wish to comment in any other way about the project, you can contact the Chief Investigator for the study, Professor Ian Wong, on 020 0000 0000.

6. How do I agree to take part in the project?

If you have understood the information contained in this leaflet and have no further questions, please sign the enclosed consent form and return one of the copies to Claire Planner in the freepost envelope provided. You will then be contacted by a member of the CADDY team to arrange a convenient time for the interview. Please keep the other consent form and this information leaflet for future reference.

Thank you for reading this leaflet

Appendix 14

Clinician consent form

To be printed on site-specific headed paper

Consent Form

Title of project: Cessation of Attention deficit hyperactivity Disorder Drugs in the Young (CADDY)

Name of Chief Investigator: Professor Ian Wong

Please read each of the statements below and tick each box if you agree.

		I agree
1.1	confirm that I have read and understood the information sheet (Version 0.7) dated 04/05/2007 for the above study and have had the opportunity to ask questions	❑
2.1	understand that participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected	❑
3.	I give my consent to take part in the above study	❑

Please write your name, today's date and sign below.

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of researcher	Date	Signature

Appendix 15

Interview topic guide: patients (modified according to treatment category)

Introductions
Background to project
Actions before interview

- Complete consent form and give participant a copy.
- Request permission to record the interview.
- Explain confidentiality.
- Interview can be stopped at any time if they wish (breaks).
- There are no right or wrong answers: it's important to find out what people really feel and how they really deal with things.
- Check whether participant has any further questions.

Participant

1. Age.
2. Daily routine (during the week/weekend).
3. School/college/work.

ADHD and quality of life

1. What do you know about ADHD?
2. How does ADHD affect your daily routine/school, college, work? Experienced any difficulties because of condition?
3. Do you feel different to other people your age? If yes, in what ways?
4. Do other people, such as friends, or family members, or teachers understand about your ADHD?
5. Do other people understand about ADHD medication?

ADHD medication

1. Medication taken for ADHD (type; dose; other types; doses at school; support from school).
2. Medications taken in the past (why stopped/changed; medication-related problems?)
3. Who prescribes medication (consultant/GP; regularity of appointments).
4. Appointments with other clinicians/services (role).
5. How do you feel about these appointments?

Beliefs about medication

6. How do you feel about taking medication? Positive, negative?
7. Effect of medication on ADHD (improvements; if medication makes your ADHD worse in any way, in what ways?)
8. Knowledge and understanding of the medication you take. (Imagine a 10-point scale.)
9. Who provides you with information about your medication? (Adequate; easy to understand.)
10. Anything you don't understand/questions about medication?
11. Age at which could/did understand about what ADHD medication was and its effects.
12. If you have queries or concerns about the medication, who do you talk to?

Adherence

- Are doses of medication missed? (If yes, how often miss; why; discuss this with anyone; anything that would help with remembering; do other people know when a dose is missed? If no, strategies to remember.)

Medication cessation (adapt depending on treatment category)

- Ever stopped taking medication? (For how long; age when stopped; taken medication since.)

Reasons for medication cessation

- Who decided that you would stop taking medication? [Patient themselves, parent(s), clinician.]

If patient:

1. Can you tell me the reason(s) why you decided to stop taking medication?
2. What did your parent(s)/clinician think about your decision to stop? Were they informed; how any issues were resolved?

If parent/clinician:

- Can you tell me the reason(s) why your parent/clinician decided that you should stop taking medication? How did you feel about the reasons they gave?

The process of cessation

- Who decided when you would stop taking medication? [Patient; parent(s); clinician; how did you choose a time.]

If parent(s)/clinicians

1. Why do you think they chose that time? What did you think about it?
2. Can you talk me through what happened next? (Discuss process.)

Medication cessation: communication with HCPs/ families

1. Did anyone talk to you about what would happen when you stopped? Information adequate?
2. Did you have any questions/concerns about stopping?

Medication cessation: the outcome

1. How did you feel when you stopped taking your medication/how do you feel now? If positive, why do you think you were able to stop? If negative, what made you want to restart? Effect on day to day life?
2. Did you have appointments with [clinician X] after you stopped? How often?
3. Did anyone else provide help/support at that time/now?
4. Had you ever stopping medication before? (Drug holidays; outcomes.)
5. How do you feel about medication now?
6. Who would you contact if you decided to restart?

Restarting

1. What made you want to restart?
2. Experience and process of restarting?
3. Re-engaging with services.

Advice to others

1. What advice would you give to someone thinking of stopping?
2. How can clinicians help someone who is stopping?
3. How can parents help someone who is stopping?

Future cessation

1. How would you feel about stopping medication in the future?
2. What factors would make you consider stopping?
3. Who would you talk to about stopping if you decided it was something you would like to try?
4. If you were going to stop what sort of information would you want to know before deciding whether or not to go ahead? (Extra support.)
5. Do you have any concerns about stopping?

Transition to adult services [if not covered]

1. What happens/happened when you turned 18?
2. Process of transfer.

Is there anything else important about your life, your ADHD, or taking medication that you would like to say?

Appendix 16

Interview topic guide: clinicians

Introductions
Background to project
Summary sheet for interviews
Actions before interview

1. Ask participant if he/she would like some time to read the participant information leaflet again.
2. Complete consent form and give participant a copy.
3. Request permission to record the interview.
4. Explain confidentiality.
5. Check whether participant has any further questions.

Participant

1. Role within the Trust (length of service).
2. Other roles.
3. Who else is involved in providing services? (Structure: role of GPs, role of other services such as voluntary organisations; psychosocial services available.)
4. Experience of patients with ADHD.
5. Local services.
6. ADHD population you treat (number of cases; age range; gender ratio; types of cases; comorbidities).
7. Traffic light system.
8. Treatments (protocols).

Medication cessation

If we can start by firstly talking about discontinuing ADHD medication treatment and then move onto more general issues regarding medication-taking.

Reasons for medication cessation

1. Key factors that determine whether or not a patient will stop treatment for their ADHD (age/timing; family dynamics/anxiety: how resolved).
2. Who makes the decision to stop treatment? (Extent of involvement; shared decision-making; conflicts: resolved.)
3. What are the reasons patients give for wanting to stop treatment? (Any different from the reasons of parents; patients.)
4. Who decides when to stop, what factors affect choosing a time to stop? What is the most common time during the year/at what age?

Process and communication

1. The process of cessation (decision-making; preparing parents; parents preparing their child; medication holidays).
2. Discussing the issue of treatment cessation.
3. Information provided to patients and parents on cessation (what form that information takes). Do you collect feedback?

If not covered above

1. Follow-up of patients (how often).
2. Possible to stop treatment to see how things go, for example during a school holiday?
3. Do you ever stop during term time? If not, why? If yes, why?
4. Do the wishes of parents and patients diverge? How are issues resolved?
5. Who is involved with the patient and family at the time of discontinuation (clinician, parent, school)? How much involvement do schools and teachers have in both ADHD treatment and discontinuation, other services?
6. Support offered to patients/parents (specific support: who provides it; other therapies such as psychotherapy; impact on decision-making process) at the time of cessation/follow-up. Is support needed?

Outcomes of cessation

1. Outcomes when patients stop (lifestyle: peers/family).
2. What do you consider successful cessation? (Length of time without medication.)
3. How many of your patients, approximately, have successfully stopped?
4. Cases where cessation has been successful and the factors that facilitate success.
5. Cases where cessation has been unsuccessful and barriers to success.
6. Other factors that affect the outcome of cessation (family, education, support, access to other services).

Restarting treatment if stopping is unsuccessful

1. Factors affecting whether a patient has to restart treatment once they have stopped (level of agreement between patient and parent; how any issues are resolved).

If not covered above

1. Reasons for you wanting a patient to restart.
2. Reasons for patients wanting to restart.
3. Reasons for parents wanting to restart.
4. If a patient has to restart treatment, any impact on future treatment? (Adherence; beliefs about medications; quality of life.) How long would you wait before trying again?
5. Assessing if medication is still needed (scales; parents; patient).
6. Any problems with patients stopping modified-release preparations, compared to immediate release?

Best practice cessation

1. Recommendations for best practice guidelines to cessation: what would go in them to help patients achieve the best outcomes? (Systems; future research; support; best age.)
2. Are such guidelines needed?

Quality of life issues

1. Aspects of quality of life patients perceive as most important.
2. Aspects of their child's quality of life parents perceive as most important.
3. Effect ADHD has on quality of life of patients.
4. Effect taking medication for ADHD has on quality of life of patients.

If not covered above

1. Other factors affecting quality of life (family; school; generic factors).
2. Impact cessation of treatment has on quality of life.
3. Is quality of life assessed? (Consultation; what scales are used; why that scale was chosen; used any scales that were not relevant/ inappropriate.)

Adherence to medication

1. Monitoring adherence (how often; use of rating scales; communication with HCPs, family, teachers).
2. Do patients adhere to their medication regimen? (Attending appointments; taking meds.)
3. Factors affecting adherence (improve adherence; barriers to adherence; gender differences).
4. Problems associated with non-adherence.
5. Are low or high adherers more likely to want to stop treatment (reasons)?

Beliefs about medication

1. Elicit patients' beliefs about their medication (do they talk about their medication, feedback at appointments/assessment scales).
2. How do patients feel about taking medication? (Positive/negative.)
3. Do patients perceive it is as necessary for them to take their medication?
4. Concerns/fears about taking meds. How do they feel the meds make them think, feel, behave? How easy is it to talk to patients about how they feel about their meds, use of other treatments (psychotherapies available)?
5. Type of information provided to patients/ families regarding their meds (form; at different stages of treatment).

Medication-related problems

1. Common medication-related problems for patients with ADHD (common adverse drug reactions).
2. Patients report of medication-related problems.

Other

1. Do you have any written guidelines/protocols for ADHD treatment cessation?
2. If no, what is current practice based on (research; information passed on by colleagues; experience)?

Appendix 17

Coding framework for patient interviews

Demographics

- Age.
- Date of diagnosis.
- Age left school.
- Current education/work status.
- Home life.
- Occupation (current and previous).
- Hobbies/social activities.

Impact of condition

- Problems at school ('trouble', disagreements with teachers, absenteeism from school, suspension).
- Problems at work (disagreements with employers, inability to concentrate, paperwork; edgy).
- Aggressive behaviour.
- Trouble with the law.
- Drug taking.
- Relationships with friends and family.
- Difficulties concentrating.
- Impulsivity.
- Easily distracted.
- Positive aspects.

Medication taking

- Treatment:
  - Medications.
  - Time of commencement.
  - Length of time on medications.
  - Understanding of/feelings towards changing medication.
- Initial referral process.
- Prescribers.
- Trust in parental expertise with meds/ADHD.

Impact of taking medication

- Increased concentration, attention, motivation.
- Increased consideration/forethought.
- Calming.
- Relationships with friends and families.
- Length of effect.
- Problems at school.
- Dislike of taking meds.
- Inconvenience of daily doses.
- Patient perceived lack of treatment effect.
- Need for additional treatment.
- Side effects.

Patient understanding of medication/ condition

- Lack of understanding.
- Perceived cause.
- Other beliefs about ADHD.
- Age when began to understand more.
- Perceived difference to friends.
- Questions/queries/concerns.
- Information given out by parents/clinicians.
- ADHD courses.
- Independent research.

Family, friends, teachers support/ understanding of medication

- Level of support from family/friends:
  - Telling friends.
  - Not telling friends.
- Other friends/family with ADHD or other problems.
- Level of support from school and teachers.
- Family/friends aware when not taken medication compared to when taken.
- Negative view of others.

Beliefs about medication and medical care

- Concerns about medications.
- Perceptions of necessity of the medication.
- Dislike of ADHD medication.
- Dislike of all medication.
- Positive aspects of medication.
- Positive consultations/support with clinicians.
- Negative consultations/support with clinicians.
- Process of transferring to Adult services.
- Lack of Adult services.

Treatment cessation

- Dislike of ADHD medication.
- Dislike of medication in general.
- Hassle of taking the medication.
- Growing out of it.
- Other reasons for cessation.
- Stopping in the future is an option.
- Concerns about stopping.
- Adherence issues.
- Lack of perceived effect.
- Perceived side effects.
- No Adult services.

Process of cessation

- Age when stopped treatment.
- Preparation for stopping:
  - Talking with family and clinician.
  - Questions asked.
- Decision to stop:
  - Patient-initiated.
- Family involvement in decision:
  - Family agreement.
  - Family disagreement.
- Clinician involvement in decision:
  - Clinician agreement/disagreement about appropriateness of cessation.
  - Info from clinicians about how the meds were supposed to help may have changed patient's views about stopping.
- Method of stopping:
  - Planned.
  - Unplanned.
- Follow-up from clinicians.

Outcome of cessation

- Felt fine.
- Not much difference felt.
- Negative effects.
- Impact on education/work.
- Perceived facilitating factors.
- Follow-up from clinicians.
- View of medication now.

Beliefs about ideal conditions for treatment cessation

- Need for self-confidence.
- Stability in life.
- Beliefs about additional support required with cessation.
- Individual choice is of importance to patients.
- Level of support needed from others.
- Advice to other stoppers.

Restarting

- No perceived need for restarting treatment.
- Change depending on circumstances (e.g. work):
  - Improvements since restarting.
  - Weighing up pros and cons.
- Discussion with clinicians/parents if wanted to restart.
- Process of reassessment.
- Difficulties restarting (e.g. GPs, unlicensed drugs, pharmacy).
- Discussions with others about restarting.
- Outcome of restarting:
  - Improvements.
  - Problems/issues.
- Follow-up.

Adherence

- Non adherence: reasons
  - Dislike of taking meds.
  - Forgetting.
  - Delayed doses.
  - Taste.
  - Hassle.
  - Side effects.
- Pattern of missed doses:
  - Drug holidays taken when previously taking medication.
  - Trial stops.
- Informing others:
  - Hiding/stashing doses.
  - Telling parent(s)/clinicians.
- Remembering to take medication (adherence):
  - Strategies to remember.
  - Routine.
  - Other people give reminders.

Appendix 18

Coding framework for clinician interviews

Professional background

- Primary role.
- Other roles.
- Length of service.
- ADHD expertise/experience of treating.

Structure of services

- Providers.
- Shared-care protocols.
- Alternative therapies available.
- Adult services.

Patient demographics

- Number of cases.
- Age range.
- Gender ratio.
- Severity of cases.
- Comorbidities.

Patients' experience of ADHD/ medication

- Side effects.
- Understanding of ADHD:
  - Patients.
  - Variation between patients.
  - Parents.
  - Teachers/school.
  - Feedback patient gets from others (e.g. family, friends).
  - Information given to patients/parents (e.g. written/consultation).
- Adherence
  - High adherence: facilitators.
  - Low adherence: reasons.
  - Level of adherence (varies).
  - Perceived adherence among patients.
  - Clinical impact of non-adherence.
  - Adherence linked to likelihood of success/ failure of stopping.
- Patient/parents' beliefs about medication:
  - Patient/parents beliefs about necessity.
  - Patient/parents concerns about taking.
  - Patient's awareness of difference when on or off medication.
  - Clinician's perception of impact of medication.
  - Impact on symptomatology.
  - Interpersonal relationships.
  - Schooling/work.
  - Medication as a tool rather than a solution.
  - Information given to patients/parents (e.g. developed in-house/pharmaceutical companies/packs).
- Quality of life:
  - Variation between patients.
  - Increased severity linked to decreased quality of life.
  - Influence of comorbidities.
  - Family and peer relationships important.
  - Relationships with teachers.
  - Education/work circumstances.
  - Measuring quality of life.
  - Assessed through consultation.
  - Service provision on quality of life.
  - Impact of medication on quality of life.

Factors affecting decision to stop treatment

- Timing (end of school/no more than 18 months on meds/previous drug holidays).
- Individual patient symptoms (if doing well, will try stopping).
- Family dynamics.
- Family anxiety.
- Patient choice: reasons.
- Parent choice: reasons.
- Clinician choice: reasons.
- Lack of Adult services:
  - Competing priorities.
  - Lack of training/understanding of clinicians in ADHD.
  - Unlicensed medications.
  - Trust not commissioning services.
  - Lack of guidelines.
  - GPs unable (traffic light system)/unwilling to prescribe.

The process of cessation

- Decision-making:
  - Involve patient and family.
  - Patients' perspective crucial.
  - Potential conflict between the triad (clinician, patient, parents/carer).
  - Resolving divergence on issue of cessation.
- Preparation:
  - Raising issue of eventual treatment cessation before treatment even started.
  - Trial periods (weekends, school holidays,

  try for 1 month).
  - Timing.
  - Reassurance.
  - Information provision.
  - Discussion about expectations.
- Gradual reduction of doses/immediate stop.
- No difference between stopping shorter/longer-acting medications.
- Planned versus unplanned cessation.
- Follow-up periods:
  - Timing.
  - Additional support.
  - Long-term follow-up.

Factors affecting the outcome of treatment cessation
- Recurrence of symptoms.
- Symptom management.
- Family dynamics.
- Family communication.
- Impact on interpersonal relationships.
- Education circumstances.
- Patient/parent expectations.
- Financial circumstances.
- Appropriate support.
- Access to other services.
- Motivation of patient and family.
- Pressure from parents/school.
- Patient maturity.
- Comorbidities/learning disabilities.
- Substance and/or alcohol abuse.
- Prior experience of cessation.
- Level of agreement between patient and parent.
- Symptoms.
- Impact on school/work.
- Trouble with the law.

Restarting ADHD medication after stopping
- Positive impact on future medication-taking.
- Negative impact on future medication-taking.
- Reaccessing services/referral pathways.

Best practice cessation
- Patient treatment history.
- Appropriate preparation.
- Assessing progress.
- Follow-up.
- Trial stops.
- Choose an appropriate time.
- Support/alternative interventions.
- Written information/pack.
- Long-term follow-up.
- Inter-agency collaboration.
- Transitional service.

Perceptions of ADHD-related guidelines and services
- Awareness of guidelines.
- Variation in local and regional practice.
- Conflict between guidelines and clinicians' perceptions of best practice (non-adherence to guidelines).
- Lack of services for adult ADHD patients.
- Limited resources to support treatment cessation.

Appendix 19

HTA-approved protocol for funding (Version 20 December 2005)

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).

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:

1. 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.
2. Data from the case-note review will be used to identify patients who meet the following stratification criteria:
   i. Patients who remain on treatment and have not attempted stopping.
   ii. Patients who have successfully stopped treatment.
   iii. Patients who were unsuccessful in stopping treatment.
3. A random sample of five 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 2 weeks before the proposed time for interview.
4. 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.
5. 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 £2125. The total cost of the project has reduced by £6855 to £114,681.

Planned investigation

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 objectives was also included so that the data could be collected for the development of future clinical trials and 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).

Existing research

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 4–8% 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.[4–6] The discontinuation of methylphenidate for the treatment of ADHD is recommended during adolescence, although no firm guidelines for the withdrawal of treatment are given.[1] 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. and 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).

Unpublished pilot data

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 of 18 responders had guidelines, and even this clinician has suggested that 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.

Preliminary data analysis of General Practice Research Database

A number of pharmacoepidemiological studies have described the utilisation of stimulants, particularly methylphenidate in children.[8–10] Jick *et al*.[8] found the prevalence of methylphenidate-treated ADHD was 5.3 per 1000 UK boys aged 5–14 years in 1999. Pharmacotherapy for ADHD is more prevalent in the USA, where annual prevalence ranged from 25.4 to 38.4 per 1000 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 16 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 General Practice Research Database (GPRD) demonstrating that the number of patients receiving ADHD drug treatments rapidly declines by 45% between 16 and 17 years of age (Appendix 1 of the HTA-approved protocol). 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 of the HTA-approved protocol). 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 ADHD. All these factors urgently require investigation in order to support future research and practice.

Brief introduction to 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.

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 1–3. 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 4–6.

Setting

1. Primary care using the 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.

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]

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.

Selection of databases and data source

In the UK, there are five main databases which contain patients' longitudinal data. These are the GPRD, IMS Disease Analyzer-Mediplus (Mediplus), General Practice Administration System for Scotland (GPASS), Medicines Monitoring Unit (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 remain 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. In particular, 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 databases 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. The GPRD has been used to study the safety of the measles, mumps and rubella (MMR) vaccine in children, and selective serotonin reuptake inhibitor and suicide,[17,18] and a recent report published by the Royal College of Paediatrics and 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 huge potential in children's medicines research, the EU Commissioners have agreed to fund the lead applicant to access the GPRD for 5 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 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 hand-written, but a study has shown that over 80% of hand-written 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.

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. Data are collected regularly by the GPRD, so by the time the project is initiated, the study period may be extended to June 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.

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 2001 and 31 December 2004 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 1 year's duration of treatment with methylphenidate, dexamfetamine or atomoxetine, which 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).

Data synthesis and analysis to obtain information on current practice
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 the following.

- 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 6-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.

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 1000 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.

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 6 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
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 is 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.

Methods

Patient selection and data collection

Collaborators at London, Nottingham, Dundee and Liverpool will identify all active patients (aged 15–21 years after year 2000, 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. 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.

A structured data capture form will be designed to enable systematic case-note review of all patients at the collaborating clinics (estimated to be 150 patients in total) in order to identify appropriate patients for interview. The lead applicant has experience in case-note review of over 1000 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: five who remain on treatment, five who have successfully stopped treatment and a further five who were unsuccessful in stopping treatment. Each patient will be contacted by a member of NHS staff (face-to-face 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 patients aged between 15 and 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 these patients at least 2 weeks before the proposed time for interview. This allows for sufficient time to ask further questions and consider whether or not to participate. If patients do not reply after 2 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 are 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.

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 2 weeks before interview to allow them sufficient time to consider whether to take part or not. If these clinicians do not reply after 2 weeks, a reminder will be sent.

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.

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 no more than 30 minutes. 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 via MAPI (http://www.mapi-research.fr/). 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 us 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 this method.

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.[24] 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 by the research assistant and meetings will be held with 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.[25] 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 Rebecca Walwyn in order to identify the most appropriate quality of life measure to use in the future withdrawal trial.

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 are 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 (MREC) approval. 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.

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.

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 (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.

Dr 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 (GCP) trained 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 patient/clinician 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 runs the national adult ADHD clinic at the Maudsley Hospital. He will contribute to patient/clinician 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, and he will contribute to patient and clinician recruitment in Derby and Nottingham for the Part 2 study; furthermore, 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 patient/clinician 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 Alder Hey Hospital. He will contribute to patient/clinician 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 patient/clinician 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 patient/clinician recruitment and data collection in the Part 2 study in South London. He will also contribute to data interpretation of both Part 1 and 2 studies.

Ms Rebecca Walwyn 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 end points 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.

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 MHRN and MfCRN 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.

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, and (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 4 days in total.

Project timetable

See Appendix 3 of the HTA-approved protocol.

Justification of support

Our experience in conducting GPRD studies suggests that 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 adolescentsit 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:

- liaise with clinicians at individual clinics to review case notes to identify appropriate patients (estimated to be 150 patients)
- liaise with RA2 to stratify patients sample
- obtain consent from 15 patients, and make appointments for interviews
- obtain consent from 10 clinicians at the collaborating centres, and make appointments for interviews
- in order to streamline the financial arrangement, the team proposes to reimburse each clinic with £30 per case-note review and £100 per patient for consent, so that total cost will be £6000.

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 £1000 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 and RA2) 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 Rebecca Walwyn 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 × 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 £1500 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 access to 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 £2000. These two aspects have represented at least £17,000 saving, which is sufficient to cover the interview study proposed in Part 2.

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 and RA2) 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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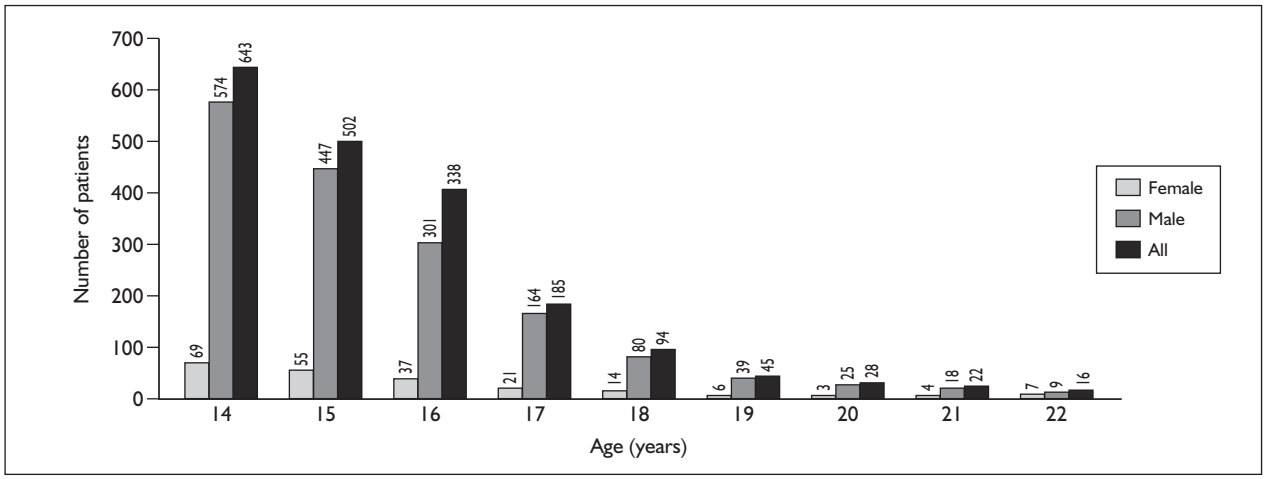
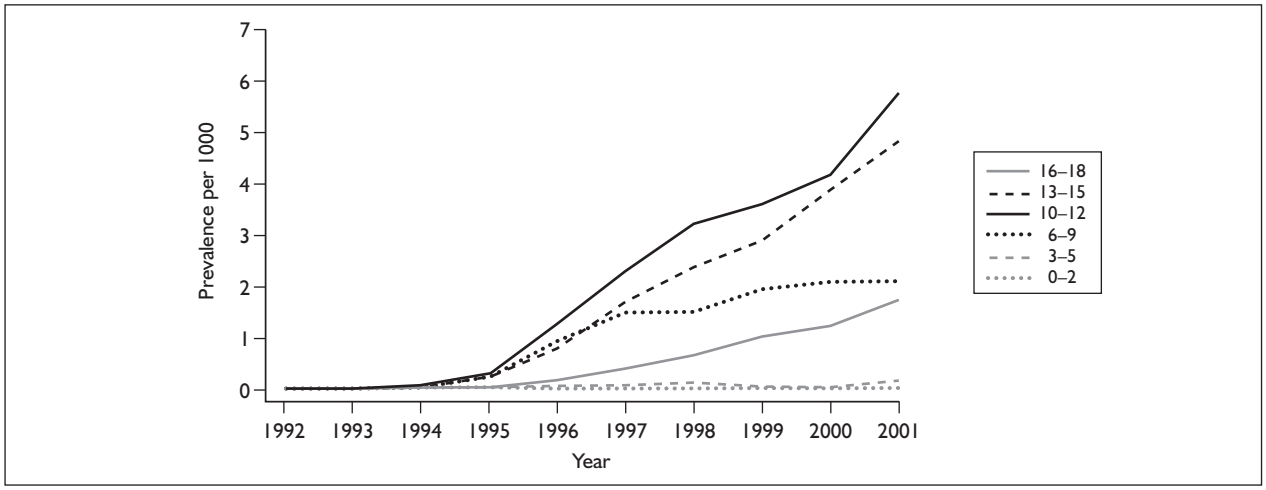
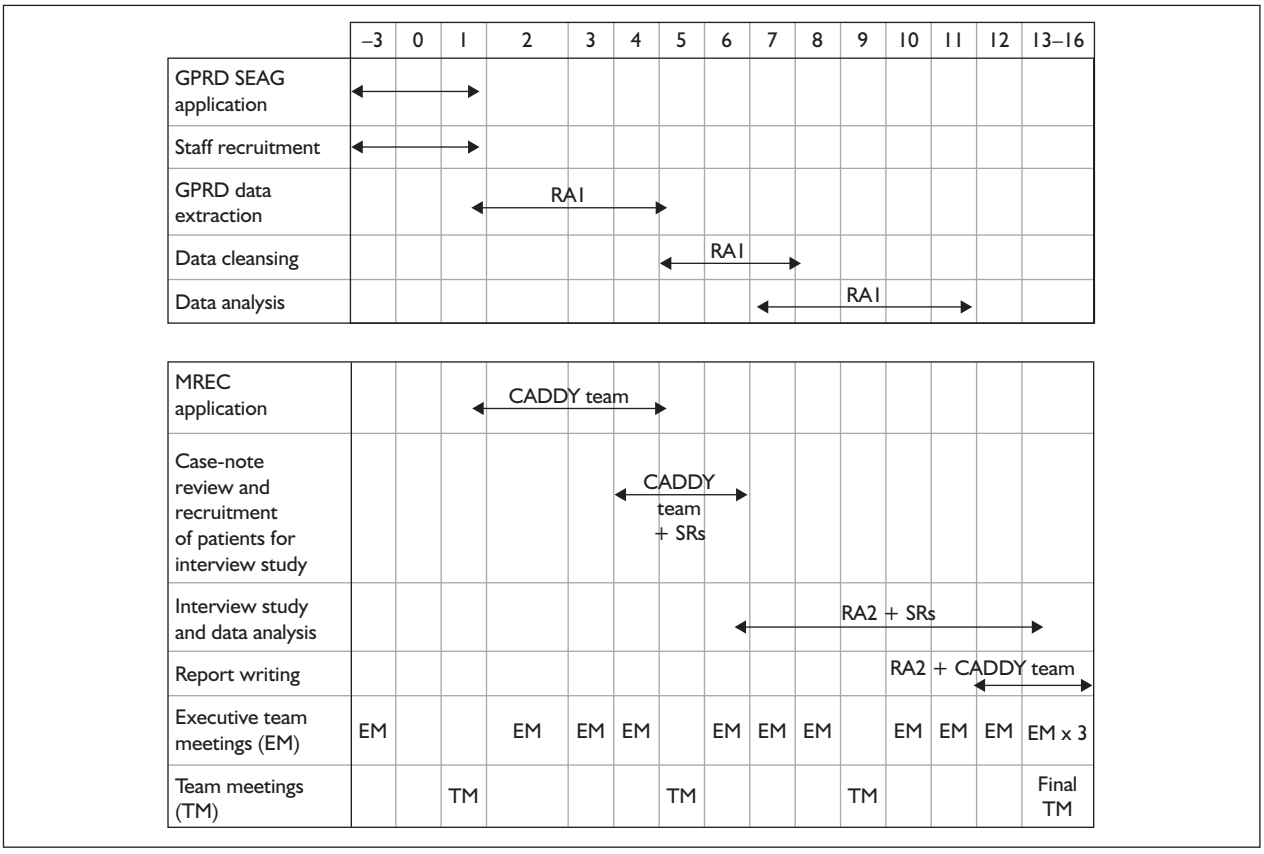
Appendix 1 of the HTA-approved protocol: distribution of patients on the GPRD prescribed methylphenidate, dexamfetamine and atomoxetine between 2001 and 2004 (unpublished GPRD data) (patients may be counted twice in this dataset by virtue of having different ages over the study period).



Appendix 2 of the HTA-approved protocol: annual prevalence of methylphenidate (unpublished GPRD data from Yingfen Hsia and Corinne de Vries, University of Surrey).



Appendix 3 of the HTA-approved protocol: timetable and milestones



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We look forward to hearing from you.

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