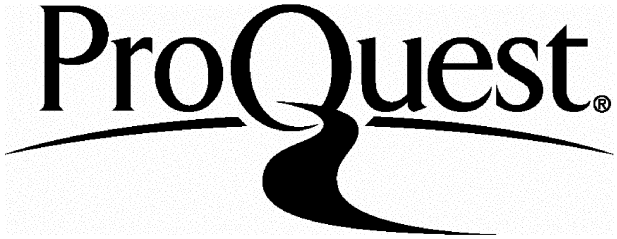
Post-Marketing Evaluation of ADHD Drug Treatment in Children and Young Adults

Suzanne McCarthy PhD Thesis

School of Pharmacy, University of London



Plagiarism Statement

This thesis describes research conducted in the School of Pharmacy, University of London between 2005 and 2008 under the supervision of Professor Ian Wong and Dr. Sarah Clifford. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

Suzanne M Carthy — 21/07/09

Signature — Date

To Geraldine and Richard McCarthy

Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder affecting 3-5% of children. In the UK, three drugs are licensed for its treatment; methylphenidate, dexamfetamine and atomoxetine. There is a lack of evidence on the prescribing of these to UK patients; however the common belief, particularly in the media, is that these drugs are over-prescribed. In addition, ADHD was once considered a condition of childhood alone; however increasing evidence suggests that the condition persists into adulthood in a significant number of patients. Again, there is little data on the use of these medications in older adolescents and young adults. Finally, in recent times, there has been much debate and concern over the safety of these drugs due to a number of spontaneous reports of sudden death in patients taking these medications. In light of these issues, this study had the following objectives: 1) to examine the utilisation of these drugs; 2) to examine prescribing of these medications to older patients; 3) to examine the safety of these medications, in particular the issue of sudden death. This was a pharmacoepidemiological study which mainly utilised data from the General Practice Research Database (GPRD), a computerised database of anonymised patient records from approximately 5% of the UK population.

The study showed that 1) prevalence of prescribing of these drugs has increased significantly over the last decade, however the prevalence of prescribing is much lower than prescribing rates reported in other countries; 2) prevalence of prescribing of these drugs decreases dramatically in older patients; 3) no increase in the rate of death or sudden death in patients taking these drugs was detected when compared to mortality rates from the general population.

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Publications

To date, the results of this thesis have been presented on the following occasions:

Peer review journals

McCarthy S, Asherson P, Coghill D, Hollis C, Murray M, Potts L, Sayal K, de Soysa R, Taylor E, Williams T and Wong I. Attention-deficit hyperactivity disorder: prescribing trends for adolescents and young adults. British Journal of Psychiatry, 2009 Mar;194(3):273-7.

McCarthy S, Cranswick N, Potts L, Taylor E and Wong I. Mortality Associated With ADHD Drug Treatment A retrospective cohort study of children, adolescents and young adults using the General Practice Research Database. Drug Safety (Accepted for Publication)

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McCarthy S, Murray M and Wong I. Drug Utilization Study of Methylphenidate, Dexamfetamine and Atomoxetine in Patients Aged 15-21 Years in UK Primary Care Using the General Practice Research Database (GPRD). Pharmacoepidemiology and Drug Safety, 15, S15, 31. (Oral Presentation)

Royal College of Paediatrics and Child Health; York, UK - April 2006

McCarthy S, Murray M and Wong I. Cessation of methylphenidate, dexamfetamine and atomoxetine in adolescents and young adults. Preliminary Results Using the General Practice Research Database. Archives of Disease in Childhood, 2006; 91; A41 (Oral Presentation)

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McCarthy S, Asherson P, Coghill D, Hollis C, Potts L, Sayal K, Taylor E and Wong I. Increasing UK prevalence of ADHD Drug Treatment with evidence of early discontinuation in adolescents and young adults. (Poster Presentation)

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McCarthy S, Murray M and Wong I. Drug Utilisation Study of Methylphenidate, Dexamfetamine and Atomoxetine in UK General Practice. (Oral Presentation)

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Glossary

ABPM	Ambulatory Blood Pressure Monitoring
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
AHRQ	Agency for Healthcare Research and Quality
ATC	Anatomical Therapeutic Chemical
ATM	Atomoxetine
BAP	British Association for Psychopharmacology
BNF	British National Formulary
BO	Business Objects
BORIS	Business Objects Replacement Information System
BP	Blood Pressure
BPM	Beats Per Minute
CADDY	Cessation of Attention deficit hyperactivity Disorder Drugs in the Young
CAMHS	Child and Adolescent Mental Health Services
CD	Conduct Disorder
CD-MDD	Major Depressive Disorder and co-morbid conduct disorder
CHM	Commission on Human Medicines
CI	Confidence Interval
CMR	Crude Mortality Rate

CNS	Central Nervous System
CSM	Committee on the Safety of Medicines
DAPs	Drug Analysis Prints
DAT1	Dopamine Transporter Gene
DEX	Dexamfetamine
DPA	Data Protection Act
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GDG	Guideline Development Group
GP	General Practitioner
GPASS	General Practice Administration System for Scotland
GPRD	General Practice Research Database
HKD	Hyperkinetic Disorder
ICD	International statistical Classification of Diseases and related health problems
IMD	Index of Multiple Deprivation
IMS	Intercontinental Medical Statistics
IMS-DA	IMS Disease Analyser – Mediplus
ISAC	Independent Scientific Advisory Committee
LQTS	Long QT Syndrome
MBD	Minimal Brain Dysfunction
MDD	Major Depressive Disorder

MedRA	Medical Dictionary for Regulatory Activities
MEMO	Medicines Monitoring Unit
MHRA	Medicines and Healthcare products Regulatory Authority
MIMS	Monthly Index of Medical Specialities
mmHg	Millimeters of Mercury
MPH	Methylphenidate
MPH-IR	Methylphenidate-Immediate Release
MPH-MR	Methylphenidate-Modified Release
MTA	Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder
NHS	National Health Service
NIC	Net Ingredient Cost
NICE	National Institute for Health and Clinical Excellence
NNT	Numbers Needed to Treat
NSF	National Service Framework
ODD	Oppositional Defiant Disorder
ODS	Operational Data Store
ONS	Office for National Statistics
OTC	Over the Counter
OXMIS	Oxford Medical Information System
PDD	Pervasive Developmental Disorder
POM	Prescription Only Medicine
PPA	Prescription Pricing Authority
PPD	Prescription Pricing Division

PUFA	Polyunsaturated Fatty Acids
QTc	Corrected QT interval
RCT	Randomised Controlled Trial
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES	Socio-Economic Status
SMR	Standardised Mortality Ratio
SNAP-25	Synaptosomal-Associated Protein
SoD	Statement of Death
SPC	Summary of Product Characteristics
SUD	Substance Use Disorder
THIN	The Health Improvement Network
UK	United Kingdom
US	United States (of America)
UTS	Up to Standard
VAMP	Value Added Medical Products
VAT	Value Added Tax
WHO	World Health Organization

1. Chapter ONE: Literature Review

1.1. Mental Health

As defined by the World Health Organization (WHO), mental health is a "state of well-being in which every individual realises his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" (WHO, 2007a).

Unfortunately, mental health problems are all too common, affecting all facets of society, from the rich to the poor, the old to the young.

Estimates from the WHO in 2002 showed that globally, 154 million people suffer from depression, 25 million people from schizophrenia and approximately 877,000 people die by suicide every year (WHO, 2007a). In addition to this, neuropsychiatric disorders are considered to contribute to 14% of the global burden of disease (Prince et al, 2007). It is believed that mental health disorders may affect morbidity and mortality through their association with risk factors for chronic diseases such as smoking, obesity and hypertension, through biological effects on serotonin, cortisol, inflammation and cell-mediated immunity, and through other factors such as delayed help-seeking behaviour and reduced medication adherence (Prince et al, 2007).

To experience mental health problems in adulthood can cause immense suffering, social isolation, poor quality of life and high morbidity and mortality, however to suffer from the same conditions in childhood and adolescence can be devastating to the individual and their family.

There is mounting evidence to suggest that antecedents of adult mental disorders can be detected in children and adolescents and therefore, it is imperative that mental health conditions in children do not go undiagnosed and untreated.

1.1.1. Mental Health in Children

(Source: WHO, 2003)

Reports from the WHO in 2000 and 2001 have estimated that worldwide, up to 20% of children and adolescents suffer from a disabling mental illness with suicide being the 3rd leading cause of death among adolescents (WHO, 2003).

In the UK in 2004, it was estimated that ten per cent of children and young people aged 5-16 years had a clinically diagnosed mental disorder including anxiety and depression; conduct disorder, hyperkinetic disorder (ADHD), autism and eating disorders (Department of Health, 2005a). As mentioned previously, it cannot be overestimated the impact that mental illness can have on the life of a child. Standard 9 of the National Service Framework for Children, Young People and Maternity Services 'The Mental Health and Psychological Well-being of Children and Young' published in 2004 recognised that "mental health problems in children are associated with educational failure, family disruption, disability, offending and antisocial behaviour, placing demands on social services, schools and the youth justice system. In addition, untreated mental health problems create distress not only in the children and young people, but also for their families and carers, continuing into adult life and affecting the next generation" (Department of Health, 2004).

All too often, in both the clinical and research settings, the mental health of the individual, both adults and children is not considered. Stigma, prejudice and a lack of recognition by society of the seriousness of mental health issues compared to physical conditions has as a result, led the area of mental health to be neglected in terms of training, funding, services and research. The focus of this study is a mental health condition, which is one of the most prevalent in childhood and adolescence and increasingly so in adulthood and one which is very controversial in the public arena, Attention Deficit Hyperactivity Disorder.

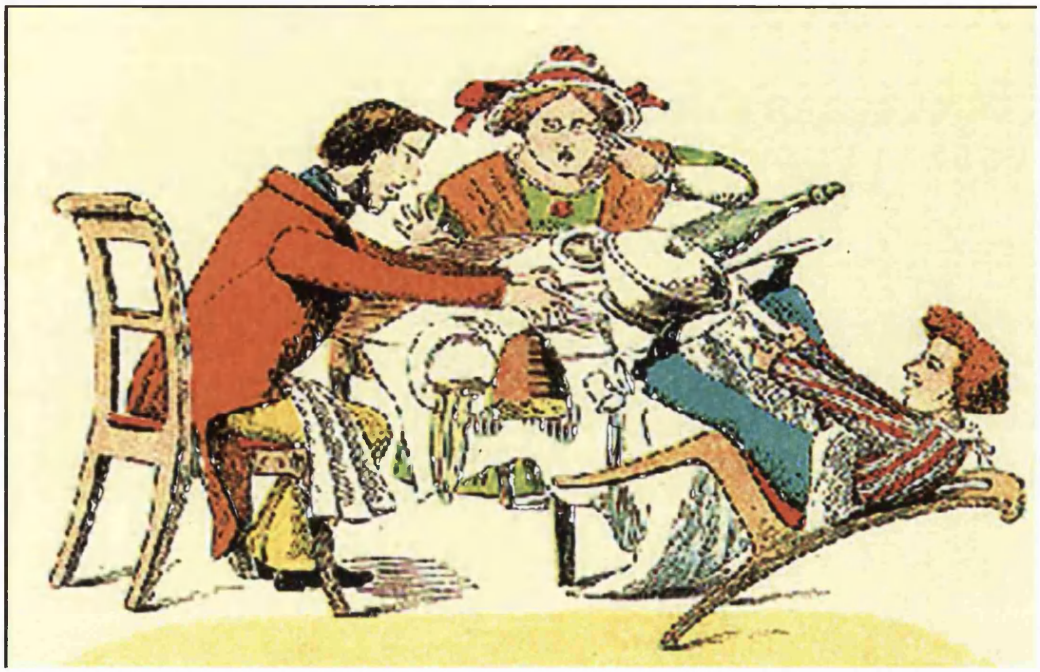
1.2. Attention Deficit Hyperactivity Disorder

1.2.1. History of ADHD

Attention deficit hyperactivity disorder or ADHD is a condition which has received much media coverage in recent times; however, it is not a new "trendy" label given to children in this hectic modern society. In fact, in contrast to many other child mental health disorders, ADHD as it is commonly known, has been studied and reported in the literature for many decades.

In 1845, a German physician called Heinrich Hoffman wrote a children's book as a Christmas gift for his 3 year old son. This book contained a number of short stories and pictures and it is thought that the tales contained within were drawn from his experiences with children suffering from psychiatric conditions. One of these stories was 'The Story of Fidgety Philip' from which an excerpt is given below:

"Let me see if Philip can be a little gentleman; let me see if he is able to sit still for once at table." Thus spoke, in earnest tone, the father to his son; and the mother looked very grave to see Philip so misbehave. But Philip he did not mind; his father who was so kind. See the naughty, restless child, growing still more rude and wild, till his chair falls over quite. Philip screams with all his might, catches at the cloth, but then, that makes matters worse again. Down upon the ground they fall, glasses, bread, knives forks and all. Poor Papa and poor Mamma look quite cross, and wonder how they shall make their dinner now."



(Source: http://www.adhdstrategies.com/FidgityPhillip.asp)

This is one of the earliest descriptions of many of the traits associated with ADHD including failure to sustain attention, hyperactivity and impulsivity (Thome & Jacobs, 2004).

The first description of the condition in the scientific literature was in The Lancet, by George Still, an English paediatrician, who in 1902 depicted a condition where patients had "marked inability to concentrate and sustain attention" (Swanson et al, 1998). He also proposed that this predisposition to behavioural problems was inherited for some children and as a result of pre- and postnatal injury for others.

Between 1917 and 1918, an outbreak of encephalitis occurred in North America resulting in children, who had survived this brain infection, presenting to clinicians with significant behavioural and cognitive deficits. This phenomenon led clinicians and researchers to believe that many behavioural problems such as those present in children with ADHD were as a result of brain damage. However, many other children presenting with behavioural disorders did not show any evidence of brain damage, and so the term given to the condition was modified to 'minimal brain damage' and later to 'minimal brain dysfunction' (MBD) in the 1950's and 1960's.

Researchers in the 1960s began to question the label of MBD, and shifted their focus from the aetiological to the behavioural symptoms displayed by these children leading to the concept of hyperactivity. In 1968, the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) was published by the American Psychiatric Association, and described the condition of Hyperkinetic Reaction of Childhood as a disorder which was characterised by overactivity, restlessness, distractibility, and short term attention span, especially in young children, behaviour which usually diminished by adolescence.

By the 1970s, additional features such as impulsivity and inattention were recognised as being equally as important to the condition as hyperactivity. Also during this time, a divergence in thought on the condition emerged between researchers and clinicians in North America and Europe.

In the US, the condition was believed to be an attention deficit which occurred more commonly, while in Europe, clinicians and researchers believed the condition was uncommon and defined by severe overactivity. In 1980, the 3rd Edition of the Diagnostic and Statistical Manual (DSM-III) publication described the condition ADD (with or without hyperactivity) as one in which the child displays signs of developmentally inappropriate inattention, impulsivity and hyperactivity. The diagnostic criteria proposed placed a much greater emphasis on inattention and impulsivity than had been previously described.

Meanwhile, the criteria used by European clinicians, the WHO International Classification of Diseases Version 9 (ICD-9) continued to emphasise pervasive hyperactivity as the defining feature of the condition.

The revised DSM-III criteria (DSM-III-R) renamed the condition, to what it is familiarly known as: Attention Deficit Hyperactivity Disorder or ADHD. The use of ICD-10 for the diagnosis of Hyperkinetic Disorder (HKD) and DSM-IV for Attention Deficit Hyperactivity Disorder (ADHD) will be discussed in further detail below.

1.2.2. Onset of ADHD

The symptoms of ADHD/HKD below are often apparent in the first few years of life. In particular, symptoms of hyperactivity and impulsivity can be easily identified by parents and teachers. The presentation of a child with the condition to a clinician depends on a number of factors including the degree to which the condition is impairing, the qualities of the child themselves and the tolerance of adults around them. It is often the case that children with the condition do not seek help as they are not aware of the problems or impairments it creates.

1.2.3. Symptoms and Diagnosis

Unfortunately, like many mental health conditions, there is no one definitive test that can confirm the presence of ADHD/HKD. The diagnostic criteria for ADHD are described in the American Psychiatric Association's DSM-IV (American Psychiatric Association, 1994) and those for HKD are in the ICD-10 manual published by the WHO (WHO, 1993). There are three symptom groups which constitute the condition of ADHD/HKD; inattention, hyperactivity and impulsivity.

Table 1-1 Symptom domains for ADHD in DSM-IV

Inattention
Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
Often has difficulty sustaining attention in tasks or play activities
Often does not seem to listen when spoken to directly
Often does not follow through on instructions, fails to finish schoolwork, chores or workplace duties (which is not due to oppositional behaviour or failure to understand instructions)
Often has difficulties organising tasks and activities
Often avoids, dislikes, or is reluctant to do tasks requiring sustained mental effort
Often loses things necessary for tasks or activities
Often easily distracted by extraneous stimuli
Is often forgetful in daily activities

Hyperactivity
Often fidgets with hands or feet or squirms in seat
Often leaves seat in classroom or in other situations where remaining seated is expected
Often runs or climbs excessively where inappropriate
Often has difficulty playing or engaging in leisure activities quietly
Is often 'on the go' or often acts as if 'driven by a motor'
Often talks excessively
Impulsivity
Often blurts out answers before questions have been completed
Difficulty awaiting turn
Interrupts or intrudes on others

Table 1-2: Symptom domains for HKD in ICD-10

Inattention
Often fails to give close attention to details, or makes careless errors in schoolwork, work or other activities
Often fails to sustain attention in tasks or play activities
Often appears not to listen to what is being said to him or her
Often fails to follow through on instructions or to finish schoolwork, chores or other duties in the workplace (not because of oppositional behaviour or failure to understand instructions)
Is often impaired in organising tasks and activities
Often avoids or strongly dislikes tasks, such as homework, that required sustained mental effort
Often loses things necessary for certain tasks and activities, such as school assignments, pencils, books or toys
Is often distracted by external stimuli
Is often forgetful in the course of daily activities

Hyperactivity
Often fidgets with hands or feet or squirms on seat
Leaves seat in classroom or in other situations in which remaining seated is expected
Often runs about or climbs excessively in situations in which it is inappropriate
If often unduly noisy in playing or has difficulty in engaging quietly in leisure activities
Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands
Impulsivity
Often blurts out answers before questions have been completed
Often fails to wait in lines or await turns in group situations
Often interrupts or intrudes on others
Often talks excessively without appropriate response to social constraints

The list of symptoms for ADHD and HKD are very similar which poses the question: what is the difference between the two conditions? The main differences between the diagnoses 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 (Rutter and Taylor, 2002).

A diagnosis of ADHD accommodates subtypes of the condition if symptoms are predominantly from one group. 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 such similar subtypes of HKD and a diagnosis requires the presence of all three core signs; six inattentive symptoms, three hyperactive symptoms and one impulsive symptom (Swanson et al, 1998). A diagnosis of HKD is therefore 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 only impairment arising from the condition present in another setting (Rutter and Taylor, 2002).

Many children with ADHD meet the criteria for another psychiatric disorder. These will be discussed in detail further on, however the commonly occurring co-morbid conditions include oppositional defiant disorder, conduct disorder, learning disorders, tic disorders and Tourette's syndrome.

The DSM-IV criteria for ADHD diagnosis recognise the co-existence of other conditions with the exception of schizophrenia, autism and pervasive developmental delay, although the symptoms must not be better accounted for by another mental illnesses such as affective and anxiety disorders. In general, the ICD-10 criteria do not allow co-morbid conditions to co-exist with the exception of conduct disorder (Swanson et al, 1998).

Common to both sets of criteria are the requirements for symptoms to persist for at least six months to a degree that is inconsistent with the development of the child, to significantly impair academic or social functioning and to be present before the age of seven.

For simplicity sake, from now onwards, the term ADHD will be used as an umbrella term to describe the condition unless specific distinctions are required.

A number of different approaches must be taken in order for a clinician to make a diagnosis of ADHD. Firstly, the trained and experienced clinician will undertake a clinical interview, usually with a number of informants, including the patient themselves, the parent(s) and if appropriate a teacher.

The purpose of such an interview is for the clinician to gain an insight into the range of problems of the patient and their level of impairment and to garner information on the patient's medical, social, family and educational history.

The clinician may also employ the use of rating scales to describe the patient's symptoms, such as the Strengths and Difficulties Questionnaire, the Connors Rating Scales, the Brown Attention Deficit Disorder Scales or the ADHD Rating Scale IV.

Medical and psychological assessments should also be conducted to either eliminate an undiagnosed condition mimicking the symptoms of ADHD, such as hearing impairment or epilepsy or to detect other co-morbid conditions such as tic disorders and learning difficulties. It should only be after a full and thorough evaluation that a diagnosis of ADHD be made by a clinician.

There are a number of questions which surround a diagnosis of ADHD/HKD.

1. How valid is the diagnosis?

The list of symptoms given in Tables 1.1 and 1.2 describes situations which can occur at some point in all children, adolescents and adults. This has led some clinicians and researchers to propose that ADHD does not exist and is "a modern version of the long-discredited 'science' of phrenology" (Timimi and Taylor, 2004).

It has been purported that the condition simply reflects a cultural change and has manifested due to conditions such as family-breakdown and a breakdown in moral authority of parents, busy family life and a time-poor society, loss of extended family support and pressures on schools (Timimi and Taylor, 2004). It has been suggested that a label of ADHD is a desirable one and medicating children has negated the responsibility on parents to raise children who are well-mannered and behaved.

Another explanation for the rise in ADHD is given in the book "Ritalin Nation: Rapid-Fire Culture and The Transformation of Human Consciousness" by DeGrandpre which explains how the "rapid-fire" culture in which we live, exposes children to more stimuli who then become more engaged in stimulus-seeking behaviour and as a result become unable to sustain attention during unstimulating activities such as school work (Shaywitz, 1999).

In addition to factors such as the breakdown in social cohesion and bad parenting, the drug companies who manufacture ADHD medications have been accused of being the driving force behind the increase in diagnoses and treatment of ADHD in order to generate huge profits.

The National Institute for Health and Clinical Excellence ADHD Guideline Development Group (GDG) undertook an evaluation of the evidence on the validity of the diagnosis of ADHD by addressing three questions:

- Do the phenomena of hyperactivity, impulsivity and inattention cluster together?
- Are the symptoms of ADHD distinguishable from other conditions?
- Are the phenomena of hyperactivity, impulsivity and inattention distinguishable from the normal spectrum?

Firstly, inattention, hyperactivity and impulsivity are continuous variables which are distributed throughout the population; however, there was strong evidence to suggest clustering of these characteristics in both population and clinical settings. Secondly, these symptoms are found to represent a separate condition to those of conduct or oppositional disorders. On the third point, they concluded that the condition is the extreme of a continuous trait distributed throughout the population such as hypertension or obesity.

On the basis of the review, the GDG summarised that ADHD is a valid clinical condition that can be distinguished from co-occurring disorders and the normal spectrum based on the occurrence of high levels of enduring ADHD symptoms which cause significant clinical, psychosocial and educational impairments and which pervade multiple settings (NICE, 2008).

2. Does it matter which of the two diagnostic systems are used and how strict are the conditions which define the diagnosis?

As previously mentioned, HKD represents a severe combined-type of ADHD. Therefore, if clinicians only use the ICD-10 criteria, it is possible that patients with impairment who do not fulfil the strict diagnostic criteria will go unrecognised. Also, much of the research into ADHD utilises the DSM-IV criteria (Mezzich J, 2002) and therefore, using ICD-10 criteria makes it difficult to conflate clinical and research findings.

In daily practice, there may be cases whereby a patient exhibits symptoms of ADHD, however does not fulfil all the necessary criteria, either by DSM-IV or ICD-10 and therefore in reality, clinicians may deviate from the diagnostic criteria using clinical judgement. Some of these issues, such as the diagnosis of a patient where age of onset is after 7 years, or where there is also evidence of Pervasive Developmental Disorder (PDD) have been raised by the NICE GDG (NICE, 2008). This guideline, which has recently been published, will be useful as a guide for clinicians who face these situations on a daily basis.

1.2.4. Co-existing Conditions

Co-morbidity refers to the presence of two or more separate and independent conditions in the same person (Rutter and Taylor, 2002). Many children with ADHD meet the criteria for a psychiatric co-morbid disorder, more commonly so in clinically-referred children than in the general population. This is largely due to referral bias especially when patients present with disruptive behaviours, as these tend to drive referrals. Approximately 50% of children with ADHD meet the criteria for two co-morbid conditions (Szatmari et al, 1989). Oppositional defiant disorder (ODD), characterised by a sustained pattern of argumentative, resentful, hostile and disobedient behaviour is observed in approximately 35 – 50% of patients with ADHD. Conduct disorder (CD), typified by a variety of antisocial behaviours such as aggression, destruction of property, theft, bullying and cruelty to animals occurs in around 25% of ADHD patients. Anxiety disorders and depressive disorders are thought to occur in 25% and 15% of patients respectively (Jensen et al, 1997; Kuhne et al, 1997). Diagnoses of ODD or CD should not be made unless behaviours have persisted for 6 months or more and occur significantly more frequently that the developmental norm (NICE, 2008).

Additional commonly occurring comorbid conditions include substance abuse, tic disorders and learning disorders (Kutcher et al, 2004).

Although the presence of co-morbid conditions complicates the diagnostic process, it is important that they are recognised early in order to improve patient management and outcome and to reduce the deleterious effect they can have on social and family functioning.

1.2.5. Associated Impairments

As described previously, the diagnosis of ADHD is based largely on symptomology however it is also a stipulation that impairment must be evident in at least one or two settings. What impairments are associated with ADHD and do they correlate with the symptoms of the condition?

Children with ADHD experience impairments in many areas of life. Children with ADHD are seen to possess low self-esteem and poor social functioning resulting in the development of fewer friendships (Mannuzza and Klein, 2000).

Impairments can also put a severe strain on the relationships within the family which in some cases can lead to family breakdown (Harpin, 2005).

In the area of education, these patients are likely to academically underachieve, complete fewer years in school, achieve poorer marks in exams and have more frequent disciplinary actions against them (Faraone et al, 2000; Young, 2001). Co-morbid disorders such as learning difficulties can also cause further impairment.

As they grow older, children with ADHD are at an increased risk of teenage pregnancy, developing substance use disorders (cigarettes, alcohol and drugs) and are more likely to become involved in crime and enter the criminal justice system (Young, 2001).

Gordon et al (2006) examined the results of four separate large-scale ADHD studies to determine the link between the number and intensity of ADHD symptoms and their impairment on daily functioning. The authors found only modest correlations between measures based on symptoms and on impairments and therefore suggest that while some patients displaying the full spectrum of ADHD symptoms will not necessarily be functionally impaired, others who do not meet the required level of symptomology may suffer significant maladjustment. They conclude that clinicians should not only focus on symptomology but also overall impairment when considering the diagnosis and management of the patient.

This reiterates the importance of a full and comprehensive evaluation of a patient, to enable the clinician to not only determine the symptoms displayed, but to diagnose other co-morbid conditions and to understand the impairments suffered by the patient, their family and those around them. This will in turn facilitate the appropriate and effective management of the condition.

1.2.6. Aetiology of ADHD

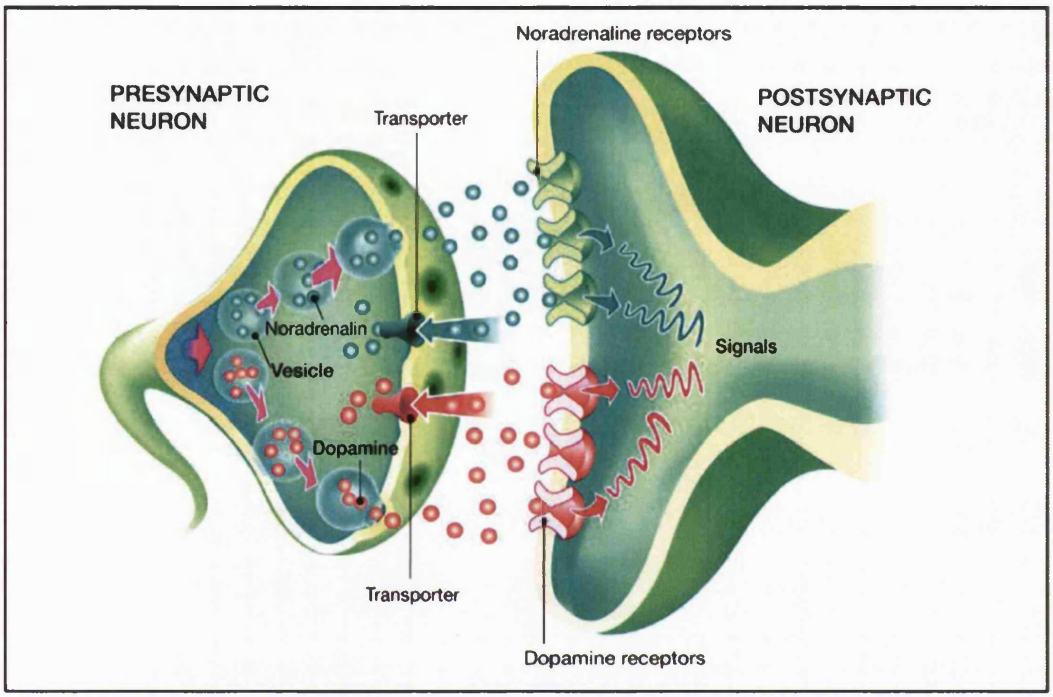
It is clear that ADHD is a clinically heterogeneous disorder which impacts in many ways on the life of the ADHD patient. However, do we know what causes ADHD? The aetiology of the condition is another area of debate. There is an assumption that mental disorders are discrete disease entities which occur due to a dysfunction of neuropsychological/biological mechanisms within the patient (Sonuga-Barke, 2005). As was seen throughout the history of the disorder, different theories, especially those concerning brain damage have been proposed as the cause of the condition. In the last few decades, with advances in biological and genetic research, it is recognised that ADHD is a heterogeneous condition with multiple causes; however the extent to which these exert their effect either alone or together is not known (Rutter and Taylor, 2002).

1.2.7. Neurobiological Influences

Figure 1.1 is a simplified diagram illustrating the neurotransmitters implicated with ADHD. Under usual conditions, noradrenaline and dopamine are released from vesicles in the pre-synaptic neurone into the synaptic cleft, where some will bind to the receptor molecules on the post-synaptic neurone. Others will undergo re-uptake into the pre-synaptic neurone by a number of transporters.

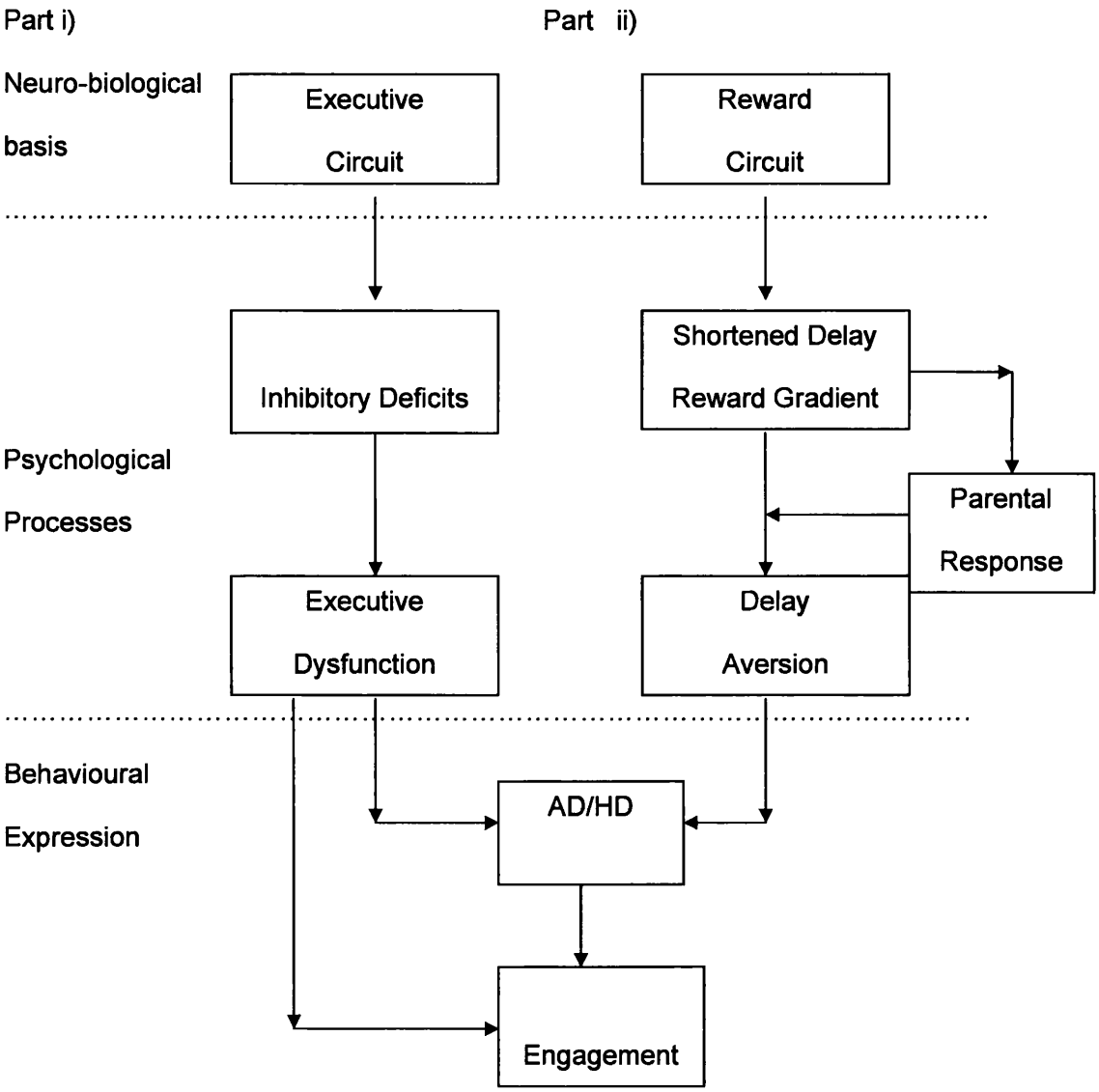
The first neurobiological theory of ADHD implicates a dysregulation in these monoamines, in particular dopamine and noradrenaline and to a lesser extent serotonin, in regions of the brain involved in executive control (Rutter and Taylor, 2002; Biederman and Faraone, 2005). Executive functions which are controlled by the frontal-subcortical circuits, include inhibition, planning and sustained-attention, symptoms which are often common in ADHD (Biederman and Faraone, 2005). Studies using structural and functional magnetic resonance imaging have also identified the area of the brain involved in executive function to been smaller and less symmetrical in patients with ADHD compared to matched controls (Rutter and Taylor, 2002). A schematic diagram given in Figure 1.2 Part i) present the executive dysfunction model underpinned by disturbances in the frontal-subcortical circuits.

Figure 1-1: Diagram of the neurotransmitters implicated in the aetiology of ADHD



Alternative neurobiological theories include Motivational Dysfunctional Models and the Delay Aversion Hypothesis in which it is proposed that disturbances in motivational processes result in impaired signalling of delay rewards, characterised by attempts to escape or avoid delay and difficulties in both waiting for desired outcomes and working effectively over extended periods of time (Sonuga-Barke, 2003; Sonuga-Barke, 2005). This model is presented in Figure 1.2 Part ii).

Figure 1-2: A Simplified Diagram of the Dual Pathway Model of ADHD showing the relationship between the biological, the psychological and the symptomatic levels of analysis (Adapted from Sonuga-Barke, 2003)



Results of trials which have studied both processes suggest that the two pathways provide distinctive and valuable contributions to the understanding of the disorder and it is likely that multiple neuropsychological pathways are involved in the development of ADHD (Sonuga-Barke, 2005).

1.2.8. Genetic Influences

Many studies have demonstrated a strong genetically inherited component to ADHD (Swanson et al, 1998; Biederman and Faraone, 2005; Faraone and Biederman, 1998). The possibility of a genetic link in ADHD originated with the observations that ADHD tended to cluster in families (Morrison and Stewart, 1971). Subsequent family, twin and adoption studies have estimated a heritability of ADHD of 0.80, highlighting the importance of the genetics in the aetiology of the condition (Faraone et al, 2005). (Heritability is the proportion of phenotypic variance attributable to genetic variance. Because heritability is a proportion, its numerical value will range from 0.0 where genes do not contribute at all to phenotypic individual differences to 1.0 where genes are the only reason for individual differences). A number of molecular genetic studies have identified several candidate genes associated with the development of ADHD.

The dopamine D4 receptor gene and the dopamine transporter gene (DAT1) have been identified by many studies to be associated with the condition, whilst others which have been suggested to be involved include the dopamine D5 receptor, the synaptosomal-associated protein (SNAP-25), dopamine α-hydroxylase, serotonin 1ß receptor, ß4-nicotinic receptor subunit, noradrenergic transporter gene and brain-derived neurotrophic factor (Asherson et al, 2005). Studies of candidate genes with significant associations have produced odds ratios of between 1.18 and 1.46, demonstrating that it is the overlapping effects of these multiple genes of small effect rather than their separate influences that are implicated in the development of the disorder (Faraone et al, 2005).

1.2.9. Environmental Influences

There is a debate in many areas of psychiatry, including ADHD as to whether the condition manifests itself through nature or nurture. The idea that there may be a component of each involved was postulated even as far back as the early 20th century by Still. There are a number of environmental factors which have been identified as influential to the development of ADHD.

Biological factors, through their effect on the developing brain during the periods of perinatal and early childhood, have been identified as increasing the risk of ADHD development.

These factors include maternal smoking, drug and alcohol consumption during pregnancy (Mick et al, 2002); foetal hypoxia and very low birth weight (Biederman and Faraone, 2005).

There are also a range of psychosocial factors which are associated with the development of ADHD. A study examining mental disorders in children living in the Isle of Wight and the inner boroughs of London identified six risk factors within the family environment including i) severe marital discord; ii) low social class; iii) large family size; iv) paternal criminality; v) maternal mental disorder; vi) foster placement. However, it was the combination of these rather than any single factor that was implicated with impairment (Biederman and Faraone, 2005).

Other studies have found a higher incidence of ADHD in patients exposed to "chronic conflict, reduced family cohesion, and maternal psychopathology" compared to control families (Faraone and Biederman, 1998) although many of these discordant relationships may be due to having a child with ADHD as opposed to them being risk factors for its development.

It has long been suggested, particularly in the media, that elements of diet can affect behaviour in children. This ranges from the elimination of substances such as artificial food colourings and preservatives to the supplementation with fish oils. In general, much of the research in this area has been hampered by methodological and feasibility issues.

A community-based, randomised, double-blind, placebo-controlled trial by McCann et al (2007) tested the effects of artificial food additives on children's behaviour. The findings suggested that artificial food colourings or a sodium benzoate preservative (or both) in the diet resulted in increased hyperactivity, with an average effect size of 0.18. They did however record substantial individual differences in the responses to additives suggesting that some children may be more susceptible to the effects of one or more food substances leading to exacerbation of hyperactive behaviour. Other studies have failed to show a difference between additives and placebo on the behaviour of hyperactive children (NICE, 2008). Supplementation diets, especially those involving the long-chain polyunsaturated fatty acids (PUFA) Omega-3 and Omega-6 have become popular in treating patients with ADHD. There is a paucity of quality research into the effectiveness of these preparations; however the few studies which have been published including studies by Stevens et al (2003) and Hirayama et al (2004) showed little or no benefit with the use of PUFA formulations on the behaviour of children.

1.2.10. Epidemiological Data on ADHD

The prevalence of ADHD/HKD reported in the scientific literature varies immensely from reports of 1% in Chinese boys (Leung et al, 1996) to *27%* in American boys (Satin et al, 1985). Disparity in the rates of prevalence reported, in particular the higher rates in the US led to a hypothesis that ADHD was a culturally-based construct particularly associated with US society (Polanczyk et al, 2007). Polanczyk et al (2007) conduced a systematic review and metaregression analysis of the prevalence of ADHD rates in the literature in order to explain the heterogeneity of values reported. Metaregression is a tool which can formally test whether there is evidence of different effects in different subgroups of trials. There are certain disadvantages of metaregression however which should be noted. While the studies included in a metaregression may be randomised trials, the analysis itself is observational and so suffers the same disadvantages as other observational studies including bias by confounding. As a consequence of their observational nature, one also cannot draw any causal conclusions. Metaregression can also be difficult to conduct due to a lack of data available from original studies such as treatment effect, variance and covariate values. Finally, one of the most important disadvantages of metaregression is that exploring heterogeneity in studies through post-hoc analysis may lead to false-positive conclusions (Thompson and Higgins, 2002). The study by Polanczyk et al (2007) reported a pooled prevalence of ADHD of 5.29% and concluded that once methodological differences had been adjusted for, the prevalence rates varied little between countries.

These methodological factors which differ from study to study and country to country include diagnostic criteria used (use of DSM-IV criteria producing higher prevalence rates compare to those made using ICD-10 criteria), the diagnostic measures used (such as rating scales for parents/ teachers or interviews), the number of people involved in the diagnosis process (parents only, teachers only or both), the age range of the population (school-aged children or adolescents/adults) and the area from which the population was sampled (inner city or rural areas) (Rutter and Taylor, 2002).

In addition to these, the prevalence rates reported are influenced by the extent of recognition of the condition. The rate of recognition of the condition in clinical practice underestimates the epidemiological prevalence due to factors such as the nature of the impairment, the tolerance of key adult figures to the presence of symptoms, the referral of patients and the ability to access services (Swanson et al, 1998).

In the UK, the prevalence of ADHD in school-aged children is estimated at 3 – 5% (Ford et al, 2003; NICE, 2000) whereas the prevalence of HKD in the same population is approximately 1.5% (Green et al, 2005).

1.3. Treatment of ADHD

There are various modes of treatment used in the management of ADHD, which can be broadly categorised into two categories; non-pharmacological and pharmacological treatments. The non-pharmacological treatments are largely outside the scope of this study; however they will be described briefly for completeness.

1.3.1. Non-Pharmacological Therapy

There are many reasons why non-pharmacological therapies are preferred in the treatment of ADHD. Firstly, for some patients, it will be considered the most appropriate first-line treatment for the condition. Secondly, some parents are uneasy with the thought of giving psychotropic drugs to children, especially to younger children. Thirdly, patients who do take drug treatment may either not respond to it or may experience intolerable side-effects warranting discontinuation. Finally, while drug therapy may improve certain aspects of the condition, other associated impairments such as poor self-esteem and co-morbid conditions will not improve with medication alone. The aims of psychological therapies are to improve the daily functioning of the patient by improving their behaviour and their relationships with peers and family. The most common forms of psychological therapies are behaviour therapy, cognitive therapy, social skills training, parent training and family therapy.

Behaviour therapy involves the reinforcement of positive behaviour and academic accomplishment and may involve either the provision of a reward in response to positive changes in motor, impulse or attentional control or by the withholding of rewards when inappropriate behaviour occurs (Rutter and Taylor, 2002).

Cognitive therapy attempts to enhance the young person's sense of self-control and to develop a more planned and reflective way of thinking and behaving through self-instructional strategies (Kendall and Panichelli-Mindel, 1995).

Social skills training aims to improve the behaviours and skills which are necessary for the child to develop and maintain social relationships. This is done using many of the techniques acquired during cognitive and behaviour therapy (NICE, 2008).

The aim of parent training is to increase parental competence and confidence and to improve communication and relations between parents and their children. Parent training is usually conducted in the group setting following a structured approach and involves teaching parents the principles of child behaviour management and how to manage stubborn and inappropriate actions (Rutter and Taylor, 2002).

There are many forms of family therapy; however they all aim to help families learn how best to support a child with this type of disability and how to avoid parenting practices, cycles of interactions, and other environmental factors that might exacerbate the problem (Bjornstad and Montgomery, 2005).

1.3.2. Pharmacological Therapy

There are three medications currently licensed in the UK for the treatment of ADHD, the stimulants (methylphenidate and dexamfetamine) and atomoxetine.

1.4. Stimulants

1.4.1. History

As ADHD is not a "new" condition, nor is the use of stimulants in the treatment of behavioural disorders. In 1937, Charles Bradley, a paediatrician in the US reported a "spectacular change in behaviour" and "remarkably improved school performance" in children receiving Benzedrine at a residential hospital in Rhode Island. He made his serendipitous discovery when treating children suffering from postpneumoencephalography headaches. He presumed that these headaches were due to spinal fluid loss and Benzedrine being a stimulant was given in the hope that it would stimulate the choroids plexus to produce spinal fluid. The Benzedrine did not provide any relief for the headaches, however teachers at the hospital noticed striking improvements in the patients' schoolwork.

He published a paper titled "The Behaviour of Children Receiving Benzedrine" in which he described his observations that stimulant medications could ameliorate a range of symptoms that we now recognise as the core symptoms of ADHD (Bradley, 1937).

Methylphenidate, usually used as first-line therapy has been used for over 50 years for the treatment of ADHD. Ritalin ® (Novartis Pharmaceuticals UK), an immediate release form of methylphenidate was only available in the UK on a named-patient basis until it was changed to a Schedule 2 Prescription Only Medicine (POM) in 1995.

Dexamfetamine (or dexamphetamine) is available in the UK as Dexedrine ® (UCB Pharma Limited). A stereoisomer of amphetamine, it was introduced by Smith, Kline and French (or GlaxoSmithKline as it is now known) in the early 1950's and is available also as a Schedule 2 POM.

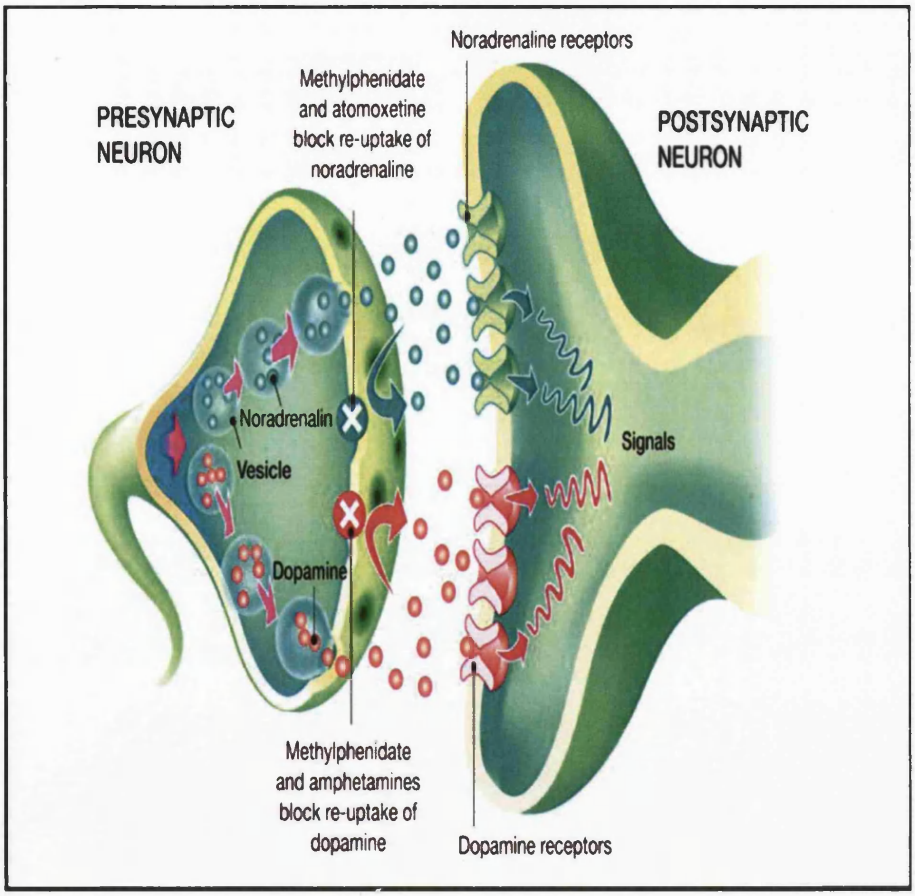
1.4.2. Mode of Action

Methylphenidate and dexamfetamine are mild central nervous system (CNS) stimulants which have more prominent effects on mental activities than motor activities. 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 neuron and increase their release into extraneuronal space thus increasing intrasynaptic concentrations.

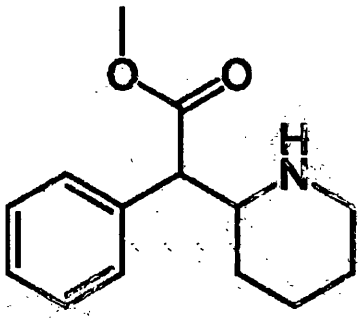
Methylphenidate is a potent inhibitor of dopamine reuptake by binding to the dopamine transporter. In vitro data on reuptake inhibition suggests that it also has a very high affinity for the noradrenaline transporter.

Dexamfetamine both inhibits dopamine reuptake and directly releases dopamine from pre-synaptic neurones (Faraone and Biederman, 1998). Figure 1.3 illustrates the presumed mechanism of action of the stimulants.

Figure 1-3: Mode of Action of the Stimulants



1.4.3. Methylphenidate



Methylphenidate is licensed in children aged 6 years and above, as a part of a comprehensive treatment programme for ADHD where remedial measures alone prove insufficient (Ritalin SPC, 2007).

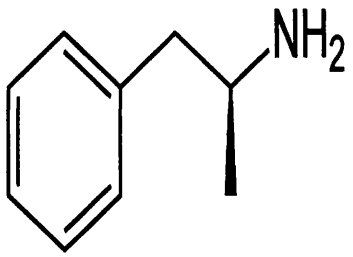
Methylphenidate is available as three immediate-release products in the UK; Ritalin ® (Novartis), Equasym ® (UCB Pharma) and Medikinet ® (Flynn Pharma). Immediate release methylphenidate is normally started at a dose of 5mg once or twice a day at breakfast and lunchtime. With a half-life of approximately 2 hours and duration of action of approximately 4 hours, multiple dosage regimens are often necessary. Dosage and frequency are titrated slowly over time according to symptom response to a maximum recommended daily dose of 60mg (Ritalin SPC, 2007).

The use of immediate release methylphenidate is associated with a number of advantages and disadvantages. It is useful in that smaller doses can be initiated, and dosage can be titrated easily to the desired level. However, it also has a number of difficulties associated with its use. Firstly, the occurrence of plasma peaks and troughs can lead to corresponding fluctuations in behaviour which can be especially problematic where drug levels and effects tend to be at their lowest during the most unstructured times of the school day such as break time and travelling home from school. Secondly, multiple doses can lead to intentional and non-intentional adherence issues. Thirdly, school-aged children will require the administration of medication during school which in itself causes other problems such as storage of a controlled drug, stigmatisation of the child and the potential diversion of medication.

These factors were integral to the development by the pharmaceutical industry of sustained release preparations of methylphenidate; Concerta XL ® (Janssen-Cilag Ltd), Equasym XL ® (UCB Pharma Limited) and Medikinet XL (Flynn Pharma). 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 of drug over several hours. The three medications vary in terms of their releasing properties and so it is imperative that brands are not interchanged once a child is stabilised on a particular preparation.

Side-effects experienced with methylphenidate, for both immediate and modified-release preparations include nervousness and sleeplessness (occurring in ≥ 10% of patients), reduced appetite, headache and dizziness (occurring in ≥ 1% of patients) (Ritalin SPC, 2007). Many of these are transient, can be reduced by a reduction in dose and only lead to drug discontinuation in approximately 5% of children (Vitiello, 2008). Methylphenidate has also been reported to cause suppression in growth, and although there is conflicting information on the subject, current evidence indicates that stimulant treatment does not, on average, influence final height (Vitiello, 2008). Serious adverse effects such as tachycardia, changes in blood pressure and heart rate have also been reported, however these will be described in further detail in Chapter 7 and 8.

1.4.4. Dexamfetamine



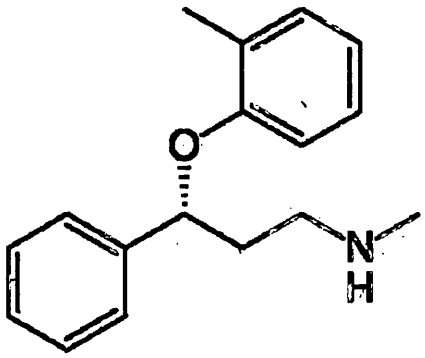
Dexamfetamine is licensed for use in children with 'refractory hyperkinetic states' (Dexamfetamine SPC, 2005). Dexamfetamine is a more potent stimulant than methylphenidate and with a longer duration can be administered as a once-daily dose. Whereas methylphenidate is only licensed for use in children 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 2.5mg daily whereas patients aged over 6 can be treated with an initial dose of 5-10mg daily (Dexamfetamine SPC, 2005). The common adverse effects of dexamfetamine are similar to those experienced with methylphenidate.

1.4.5. Efficacy of the Stimulants

Short-term studies (most often of 12 weeks duration or less) have reported that stimulants are effective in treating the symptoms of ADHD (Greenhill et al, 1999). Effect sizes, used as a method to standardise the magnitude of difference between drug and placebo across studies, have been calculated for both immediate and modified-release preparations of stimulants. With a 1-point difference indicating a difference of 1 standard deviation on a particular outcome, the stimulants (both immediate and modified-release) have been reported to have a mean effect size ranging from 0.8 to 1.0 on the core symptoms of ADHD (Banaschewski et al, 2006). Stimulants produce significant improvements in classroom performance, short-term memory, sustained attention and 'on-task' behaviour, while at home, stimulants improve compliance and parent interactions (Santosh and Taylor, 2000). In a comparison of the various immediate and modified-release methylphenidate preparations, the number of patients needed to be treated (NNT) in order to see a patient 'normalised' (defined as having no problems more than mild) ranged from 1.9 to 4.8.

1.5. Atomoxetine



Atomoxetine was originally called Tomoxetine; however the name was changed to avoid any potential confusion with Tamoxifen, a drug used in the treatment of cancer. Atomoxetine, available as Strattera ® (Eli Lilly and Company) in the UK, is a non-stimulant drug licensed for use in the treatment of ADHD in children over 6 years and in adults when treatment is initiated in childhood or in adolescence. It is thought to act through the highly selective inhibition of the pre-synaptic noradrenaline transporter thus inhibiting noradrenaline reuptake (as displayed in Figure 1.3). It has little or no affinity for other neurotransmitter transporters or receptors (Barton, 2005). 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 (Atomoxetine SPC, 2008).

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 70kg or less starting on an initial dose of 0.5mg/kg/day. The maintenance dose for these patients is normally approximately 1.2mg/kg/day. For patients weighing over 70kg, doses of 40mg should be initiated with a recommended maintenance dose of 80mg daily.

Atomoxetine has been developed in an era when regulations and surveillance of new drug entities is far more strict, leading to increased reporting of uncommon adverse effects. Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin has been reported, with the risk of serious hepatic disorders estimated at below 1 in 50,000 patients treated (Department of Health, 2005b). Nevertheless, this led to the issuing of a 'Dear Doctor' letter by the Food and Drug Administration (FDA) in the US and a 'Dear Healthcare Professional' letter by the Chairman of the Committee on the Safety of Medicines (CSM). Another rarely reported effect possibly linked to the use of atomoxetine is suicide-related behaviour (suicide attempts and suicidal ideation). In double-blind clinical trials, suicide-related behaviours occurred at a frequency of 0.44% in atomoxetine-treated patients (6 out of 1,357 patients treated, one case of suicide attempt and five of suicidal ideation) whereas no events were observed in the placebo group (n = 851).

The age range of children experiencing these events was 7 to 12 years. It should also be noted that the number of adolescent patients included in the clinical trials was low (Atomoxetine SPC, 2008).

Placebo-controlled trials in paediatrics have reported commonly occurring adverse effects associated with atomoxetine to include headache (19% of patients), abdominal pain (18% of patients) and decreased appetite (16% of patients) (Atomoxetine SPC, 2008). These effects are normally transient and do not usually require discontinuation of treatment. Cardiovascular adverse effects have also been reported, however as before, these will be described further in Chapter 7.

1.5.1. Efficacy of Atomoxetine

In short-term randomised, placebo-controlled trials, atomoxetine has been demonstrated to be clinically and statistically superior to placebo. Effect sizes range from 0.6 to 0.84 based on parent and teacher reports (Michelson et al, 2001; Michelson et al, 2002; Weiss et al, 2005; Gau et al, 2007; Bangs et al, 2007; Kelsey et al, 2004).

1.5.2. Issues in ADHD Treatment

From both the literature and clinical practice, there are a number of issues which surround the treatment of ADHD such as:

- Safety of drug treatment and risk of substance abuse
- Long-term efficacy of treatment
- ADHD Treatment for Younger Children, Older Adolescents and Adults
- Pharmacological vs. Non-pharmacological therapy
- Methylphenidate vs. Dexamfetamine vs. Atomoxetine
- Immediate vs. Modified-Release Methylphenidate

1.5.3. Safety of drug treatment and risk of substance abuse

The commonly occurring side-effects of various drug treatments have been discussed previously. In summary, many of the adverse effects including nausea, loss of appetite, headache and insomnia tend to be transient in nature and rarely require termination of treatment.

More serious adverse events such as sudden death with the stimulants and atomoxetine have been reported very rarely and rates are often no higher than are seen in the general population. These will be detailed in further detail in Chapters 7 and 8.

There has been a long-standing concern that stimulants may be abused by patients and that the administration of stimulant drugs to children will increase their risk of substance abuse in later life. Similarities between the stimulants and cocaine have been made. Dopamine transporter blocking drugs such as cocaine and methylphenidate raise the extracellular concentration of dopamine in various areas in the brain, including the nucleus accumbens, an area of the brain which is associated with the reinforcing effects of drugs of abuse (Koob and Bloom, 1988). Studies have demonstrated that oral methylphenidate is very effective in blocking dopamine transporters however its slow absorption and rate of occupancy of the transporters means that it does not induce euphoria, unlike drugs of abuse such as cocaine. In addition to this, the development of modified-release preparations has lessened the abuse potential of stimulants even more.

As has been discussed previously, ADHD itself is known to be a risk factor for later substance abuse including tobacco, alcohol and drug substances.

The evidence on whether ADHD medication is linked to later substance abuse is not as clear.

Many studies including a meta-analysis have demonstrated that prior treatment with stimulants was associated with a subsequent decreased risk for Substance Use Disorder (SUD) and cigarette smoking compared to non-medicated ADHD patients (Wilens et al, 2008, Wilens et al, 2003) thus suggesting that the use of medication in the treatment of ADHD may have a protective effect against later substance abuse.

This finding was not replicated in further studies by Biederman et al (2008) and Mannuzza et al (2008) who found neither an increased nor a decreased risk of SUD in patients treated with stimulants. Furthermore, the follow-up Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA) (Molina et al, 2007) found that stimulant treatment had neither a protective nor harmful effect on future SUD, however it should be noted that at the post-treatment follow-up at 22 months the mean age of participants was still relatively young (most were between 11 and 13 years of age). Although the protective effect of ADHD medication has not been consistently replicated, concerns about a negative effect of stimulants on later SUD should be alleviated by the available evidence.

1.5.4. Long-term efficacy of treatment

Many studies which have demonstrated the efficacy of the stimulants and atomoxetine have been over the short-term only. However, a number of longer-term trials, of various designs, have been conduced in this area.

1.5.4.1. Randomised Placebo-Controlled Trials

Gillberg et al (1997) conducted a parallel-design, randomised, double-blind, placebo-controlled study of amphetamine in 62 children aged 6 – 11 years, over a period of 15 months.

Participants were initially openly titrated with amphetamine for 3 months at which point they were randomly assigned to amphetamine or placebo for 12 months. Of the total cohort (n=30 placebo, n=32 amphetamine), only 32 children (8 placebo, 24 amphetamine) completed the 15 months of randomized treatment.

The study end-point occurred when the participant had to be removed from the protocol and given open treatment. Over the study period, amphetamine was superior to placebo in improving behaviour and on time to treatment failure, however the results of this study need to be interpreted with caution. The initial size of the sample was small and this was further decreased by the significant number of treatment failures, the reasons for which were not clearly explained. In addition, patients were openly titrated with amphetamine prior to randomisation and so it is likely that only those patients who initially responded to treatment were included in the second phase of the study thereby introducing a selection bias. Overall however, the study showed that amphetamine, over a long period resulted in a reduction in overactivity and other behaviour problems, both at home and in school.

A study by Buitelaar et al (2007) examined the efficacy of atomoxetine in maintaining symptom response. Participants were aged between 6 and 15 years and had previously responded to atomoxetine acutely, during an open-label phase and had also completed one year of double-blind atomoxetine treatment. Participants were then re-randomised to atomoxetine or placebo for a further six months.

One hundred and sixty three participants entered the continuation phase of the trial (n=81 atomoxetine, n=82 placebo), although efficacy analyses were performed on 79 participants in the atomoxetine group and 81 in the placebo group. Subjects who continued on atomoxetine were less likely to relapse or experience the return of partial symptoms than those taking placebo. There are a number of limitations to this study including the fact that all patients entering the continuation phase had already demonstrated excellent response to treatment, and thus selection bias at this stage may limit the generalisability of the results.

However, this study supports the long-term use of atomoxetine in patients who have initially responded to treatment for 1 year.

1.5.4.2. Multimodal Studies

The MTA study was designed as a large, multisite study in the US (n=579 children) where children, aged 7 to 9.9 years were randomised to a 14 month treatment of either intensive medication management (involving careful medication titration and monthly visits), intensive behavioural therapy (parent, school and child components), a combination of both or standard community care (where treatment was provided as normal by community clinicians. This resulted in approximately two-thirds of children taking medication). The 14-month MTA study demonstrated that well-titrated, carefully monitored stimulant treatment was very effective for reducing ADHD symptoms and the effect lasted with no tolerance or serious side-effects for the 14 months of the study (MTA Cooperative Group, 1999).

After the 14-month period, treatment was no longer delivered by MTA staff, randomisation ended and the study became an observational study where children were allowed to select the most appropriate treatment strategy for them. At this point, the groups were followed onwards in a naturalistic manner, and literature has been published on the outcomes at 24 and 36 months post-randomisation.

Of the 579 children participating in the initial study, 540 children were followed up for the subsequent 10 months (24 month period). The medication strategy group showed persisting significant superiority over the behavioural and community treated groups for ADHD symptoms, however the size of effect was half that observed at the end of the 14-month study (0.6 compared to 0.3) (MTA Cooperative Group, 2004).

Four hundred and eighty five of the original cohort (485/579, 83.8%) were again evaluated at 36 months post-randomisation. At this stage, the significant differences seen at 14 months and the modest advantages seen at 24 months had dissipated, and no differences between the four groups were observed. However, compared to baseline, patients in all groups demonstrated significant improvement in symptoms and overall functioning, with 1.6 – 1.7 SD units of change in ADHD symptoms, 0.9 – 1.0 SD in global impairment and 0.8 – 1.9 SD in social skills (Jensen et al, 2007).

Abikoff et al (2004) performed a 2 year multimodal intervention study whereby 103 children with ADHD, who had previously responded to short-term methylphenidate, were randomised to i) methylphenidate alone, ii) methylphenidate combined with psychosocial treatment including parent training and counselling, social skills therapy, psychotherapy and academic assessments or iii) methylphenidate plus attention psychosocial control treatment. Significant improvement occurred over all treatment groups and continued over the 2 years, however, similar to the MTA study, combination treatment did not lead to superior functioning.

1.5.4.3. Naturalistic Follow-Up Studies

Charach et al (2004) performed a follow-up study of children, aged 6 – 12 years who had previously undergone a 12 month randomised, placebo controlled study of methylphenidate. Of the original 91 participants, 79 were systematically followed on an annual basis at 2 (n=79), 3 (n=78), 4 (n=73) and 5 years (n=69). The results of the study showed that children who were taking stimulant medication at consecutive annual assessments continued to derive ongoing benefits.

Those children who adhered to medication (defined as taking medication for 5 or more days per week for at least 2 months prior to the assessment) were likely to have more severe symptoms at baseline and while still symptomatic, continued to show greater treatment response at 5 years compared to nonadherents.

Despite some of the limitations of the study's methodology, such as small sample size, risk of type 2 errors (missing an effect where one exists), decrease in participant continuation over time and potential recruitment bias, this study indicated that children with ADHD continued to derive benefit from ongoing stimulant use.

Weiss et al (1975) examined the long-term effect of treatment by comparing three groups of hyperactive children: i) 24 children who were treated with methylphenidate for 3 – 5 years, ii) 22 children treated with chlorpromazine for 18 months – 5 years and iii) 20 children who received no medication during the study period. Matching for factors such as gender, age, IQ and socioeconomic status, the authors found that at adolescence, no significant differences were observed in emotional adjustment, delinquency or academic performance. Similar to data reported by the MTA study, a significant reduction in hyperactivity was seen over the 5 years; however the difference between the three groups was not significant. The study did observe that in the methylphenidate-treated group, a well-functioning family was significantly correlated with a good outcome in terms of academic achievement, emotional adjustment and absence of delinquency.

Charles and Schain (1981) conducted a 4-year follow-up study of the effects of methylphenidate on the behaviour and academic achievement of 62 hyperactive children aged 10 – 16 years at follow-up.

Children were divided into three categories according to the length of time they had received stimulant treatment: i) children who had not received stimulants or had received them for less than 6 months, primarily consisting of drug failures or placebo responders ii) children who had received treatment for more than 6 months but less than 2 years iii) children who had been on stimulants for 2 – 3 years iv) children who had received stimulant treatment for 3 – 4 years, but had discontinued treatment at least one month before the follow-up assessment v) children still taking treatment at follow-up. At follow-up, symptoms of hyperactivity had decreased significantly although still remained higher than normal peers. Behavioural and social problems were less pervasive than academic underachievement. Differences in duration of stimulant treatment however failed to produce a statistically significant difference in the groups on any of the outcomes tested.

Paternite et al (1999) evaluated 97 young adults aged 21 – 23 years who had been treated for ADHD as children with methylphenidate for an average duration of 30.4 months (1 – 76 months). Childhood predictors (childhood inattention and overactivity; childhood aggression and treatment with methylphenidate) were assessed against various adult outcomes (schizotypic features, mania, alcoholism, drug abuse, psychiatric hospital admission, suicide attempts, not graduating from school, less tertiary education and unemployment).

Overall, treatment with methylphenidate in childhood had no effect on adult outcome in 63% of the sample. Of those in whom it did have positive effects in adulthood, longer duration of treatment with methylphenidate was associated with fewer schizotypic features and lower mania scores, whereas higher doses of methylphenidate were associated with less alcoholism and fewer suicide attempts. The presence of childhood aggression was likely to predict more adverse outcomes thus leading the authors to conclude that the variability of the condition, in particular the presence of childhood aggression was more likely than any treatment effect of medication to influence adult functioning.

1.5.4.4. Other Studies

Wilens et al (2005a) examined the effectiveness of OROS ® methylphenidate over 21 to 24 months as part of an open-label multisite study involving 407 children aged 6 – 13 years. Assessment of effectiveness was made by parents, teachers and investigator reports. Eighty five per cent of parents and 92% of investigators reported treatment as good or excellent and remained relatively constant throughout the study period. As this study was an open-label study, the level of response to placebo or observer bias cannot be determined. In addition, patients had previously responded positively to methylphenidate which may have exaggerated the positive response seen.

However, the results of the study suggest that for children who initially respond to stimulants, treatment benefits of OROS ® methylphenidate on ADHD symptoms are maintained in the majority of subjects for prolonged periods of up to 2 years.

A meta-analysis of 13 studies (7 double-blind, placebo controlled & 6 open-label) was conducted by Kratochvil et al (2006) to determine the effectiveness of long-term atomoxetine treatment among young children with ADHD. Data was pooled from 97 subjects, aged 6 and 7 years, who had received treatment for 24 months. Analysis over time showed that there was a marked improvement in ADHD symptoms one month after treatment initiation, which continued to increase until the 12-month time point and was maintained for the remainder of the 24 months. Again, because some of the studies were not placebo-controlled, the results may have been biased by patient, parent or investigator expectation. However, the results suggest that atomoxetine is effective in the longer-term in younger children with ADHD.

Wilens et al (2006a) conducted a similar meta-analysis on the long-term efficacy of atomoxetine for subjects aged 12 to 18 years. Again using results from 13 atomoxetine studies, data on 219 subjects who had completed 24 months of treatment was pooled. Significant improvement had been observed in the initial 3 months of treatment which remained improved at 24 months. Although many of the same limitations apply as above, this study also suggests sustained efficacy of atomoxetine treatment in adolescents over a period of 24 months.

1.5.4.5. Summary of long-term efficacy of treatment

Determining the long-term efficacy of ADHD medication is inherently difficult for the researcher. The ideal method of conducting a truly long-term trial would be to design a randomised, double-blind, placebo-controlled study whereby children would be assigned to active or placebo from diagnosis and followed-up on a regular basis into adulthood, to measure ADHD symptoms, impairments and compliance. However, this style of design poses many methodological and ethical challenges. Studies comparing placebo and active treatment frequently have high attrition rates, particularly in placebo groups, which increase with increased duration of study (Poulton, 2006). There are also ethical considerations of maintaining children with significant problems on placebo treatment for long durations of time, potentially increasing their risk of future psychological, social, functional and educational impairments. These points suggest that the RCT design is not an appropriate method for determining long-term efficacy over a period of years. However, those studies which did maintain a controlled design demonstrated continued benefit of treatment throughout the study, with the longest available being 2 years.

Data from open-label trials of both methylphenidate and atomoxetine demonstrated continued benefit from ongoing treatment at a 2-year period. However as noted before, the lack of controls, together with selection bias and potential expectations of patients, parents and investigators limit the interpretation of this data.

Naturalistic studies have provided conflicting data as to the long-term efficacy of ADHD drug treatment. However, these studies have a number of significant limitations when evaluating long-term outcome. Those who receive treatment in childhood may constitute a more significantly impaired cohort than those who don't and so the long-term outcomes of these patients may be negatively biased. Also in naturalistic studies, length of treatment can vary significantly as can dosages of medication used. It is often not determined or reported whether patients were receiving optimal doses of medication and in addition, the adherence of patients to medication during long-term studies is rarely considered, which may also impact significantly on the results obtained.

Many researchers and clinicians have interpreted the findings of the 24 and 36 month follow-up studies of the MTA to mean that medication is not effective in the long-term. While this cannot be discounted, there are other explanations which need to be considered.

Firstly, it is often not emphasized that the MTA as a controlled study ended at 14 months as which point the efficacy and superiority of medication was maintained. At this stage, the study became observational and so as patients were free to select the intervention which suited them best; it is not unexpected that all interventions would have reasonably good outcomes.

Also, because intensive therapy ended at 14 months, all treatment arms became similar to the community care group and so any additional effects with the intensive intervention would be lost. Finally, the outcome of the study did not suggest that treatment had no effect rather that all treatments showed benefit.

Although the true long-term efficacy of ADHD drug treatment has not be demonstrated in the literature, this does not necessarily mean that both medical and behavioural therapy should be seen as short-term treatments only.

Following an adequate response to treatment, therapy should be maintained for as long as it remains clinically effective and should be reviewed on a regular basis (NICE, 2008).

1.5.5. ADHD Drug Treatment for Younger Children, Older Adolescents and Adults

The importance of long-term efficacy of treatments is even more apparent as ADHD is now considered not only one of childhood, but one which is seen across the lifespan.

1.5.5.1. Pre-School Children

The symptoms of ADHD are often seen in the first few years in life however, concerns over the difficulty of distinguishing them from normal developmental variations can hinder the diagnosis of the condition.

According to NICE, once a pre-school child has received a diagnosis of ADHD, the parents of the child should be offered a referral to a parent-training programme, normally as part of a group-based approach (NICE, 2008).

If overall treatment including parent-training programmes is not effective in treating the symptoms of ADHD, patients should be referred to tertiary services for further management.

Drug treatment for the management of ADHD in pre-school children is not considered first-line therapy. In addition, literature on the use of drug treatment in pre-schoolers is sparse.

The Preschool ADHD Treatment Study (PATS) (Greenhill et al, 2006) was a multicentre, randomised efficacy trial to evaluate the short-term efficacy of methylphenidate in children aged 3 to 5.5 years who continued to meet ADHD severity criteria despite 10 weeks of parent training. One hundred and sixty five children were randomised to placebo or one of four methylphenidate doses (1.25 mg, 2.5mg, 5mg or 7.5mg) given three times daily. Compared to placebo, significant decreases in ADHD symptoms were seen at doses of 2.5mg, 5mg and 7.5mg given three times daily. No difference was observed at the lowest dose. Effect sizes observed were lower than those seen in school-aged children, with a range of between 0.4 – 0.8. The mean optimal total daily dose of methylphenidate for pre-schoolers was 14.2 + 8.1mg/day. The authors concluded that treatment with methylphenidate at doses of 2.5mg, 5mg and 7.5mg three times a day produced significant reductions on ADHD symptom scales compared to placebo, although effect sizes were smaller than those seen in school-aged children.

As part of the same study, Wigal et al (2006) examined the safety and tolerability of methylphenidate in this young population. Thirty per cent of children reported moderate to severe adverse events during all phases of the study including emotional outbursts, difficulty falling asleep, repetitive behaviours/thoughts, appetite decrease and irritability. Eleven per cent of children discontinued treatment due to a drug-related adverse event. These included cases of emotionality/irritability, tics, formication, possible seizure, rash, insomnia, appetite loss, weight loss, depression, anxiety, social isolation and scalding self.

Of the serious adverse events reported, one (suspected seizure) was thought to be possibly related to methylphenidate therapy. Compared to studies in school-aged children, the number of pre-schoolers discontinuing treatment was much higher and the pattern of moderate to severe adverse events reported differed. In school-aged children, the most commonly reported adverse events, significantly different to placebo, include decreased appetite, delay in sleep-onset, headaches and stomach aches (Barkley et al, 1990a), however pre-schoolers tended to display more signs of irritability, emotional outbursts, difficulty falling asleep, repetitive behaviours and thoughts and decreased appetite. Tolerability of this patient group to stimulants was lower than expected and although some adverse events may diminish over time, pre-school children taking stimulant treatment should be closely monitored.

1.5.5.2. 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% (Asherson et al, 2005). 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 (Faraone et al, 2000). These patients may then present to medical services when they are older enabling the condition to be diagnosed.

Compared to younger patients, adults with ADHD are more likely to exhibit inattentive symptoms as hyperactive symptoms tend to diminish throughout the course of the condition (Faraone et al, 2000). 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 a few. As with younger patients, ADHD also impairs on many functional, social and personal aspects of adult daily life. Many of these patients will have performed poorly in the area of education and continue to face problems in the workplace with poor performance, frequent job changes, lower rates of professional employment and lower socioeconomic status (Faraone et al, 2000; Wilens et al, 2004a).

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 (Faraone et al, 2000; Wilens et al, 2004a).

Adults with ADHD are at an increased risk of substance use disorders (alcohol and drugs) and are more likely to become involved in crime and entering the criminal justice system (Young, 2001).

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 (Faraone et al, 2000; Wilens et al, 2004a).

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

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 (Nahlik, 2004).

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 identified that this cohort is at an increased risk of the condition compared to parents of non-ADHD children (Faraone et al, 2000; Wilens et al, 2004a).

The second group is composed of patients who have not outgrown the condition in childhood and continue to show impairment in later life. A number of follow-up studies have examined the persistence of ADHD in adolescents and young adults.

Weiss et al (1985) 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. Eighty eight per cent of patients were followed-up at 5 years, 73% at 10 years and 61% seen at 15 years. A control group was 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 to 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 (1985) and Mannuzza et al (1993) 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 (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 (1985) with 11% of patients exhibiting symptoms in later years.

Mannuzza et al (1998) also conducted a prospective follow-up of clinically-diagnosed ADHD boys and at the mean age of 24 years, of the 85 patients interviewed (82% of the original cohort) only 4% of patients had the full ADHD syndrome.

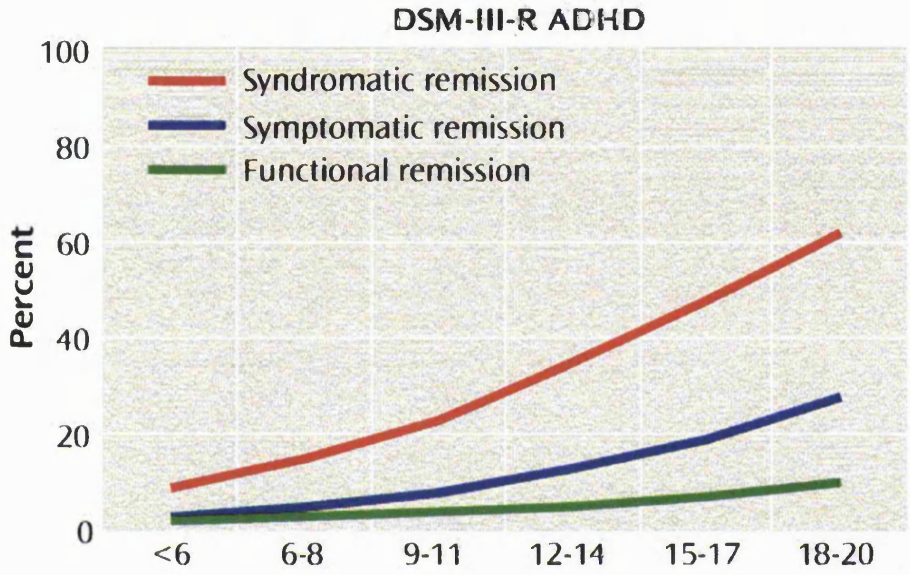
Barkley et al (1990b) conducted an 8-year follow-up of 123 hyperactive patients and 66 controls and observed a persistence of the condition in 80% of patients with ADHD. Rates of antisocial acts were considerably higher among hyperactives than normals, as were cigarette and marijuana use and negative 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.

This differentiation between definitions of persistence was examined by Keck et al (1998) who 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 (2000) examined these three patterns of remission in relation 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 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 four 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. Symptoms occurring two 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% (See Figure 1.4). This would suggest that a significant number of patients continue to exhibit ADHD symptoms and suffer the impairment associated with these symptoms.

Figure 1-4: Syndromatic, symptomatic and functional remission of adolescents and young adults with ADHD



(From Biederman et al, 2000)

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 the 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.

Use of syndromatic persistence only may provide an overly optimistic view of the long-term outcome and so knowledge of the symptomatic persistence gives both clinicians and patients a better idea of the prognosis of the condition.

A meta-analysis of follow-up studies in patients with ADHD by Faraone et al (2006) found that persistence was low when the syndromatic definition was used to define persistence, with a figure of ~15% at age 25. However, the use of the symptomatic definition of remission resulted in a persistence rate of between 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.

In 2006, the British Association for Psychopharmacology (BAP) produced guidelines for the management of adolescents with attention deficit hyperactivity disorder in transition to adult services and for the management of ADHD in adults (Nutt et al, 2006). A summary of the recommendations and guidance have been made.

As ADHD is currently understood to be a life-long condition, 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 is the case in children with ADHD, co-morbidity 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 of 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. 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 seven. 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 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.

Whilst 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 not licensed for the treatment of ADHD in adults. If drug therapy is considered, it should only be initiated under the guidance of a psychiatrist or clinician trained in the diagnosis and management of ADHD (NICE, 2008).

Although not licensed in the UK for the treatment of ADHD in adults, the first-line drug treatment is methylphenidate. If patients do not respond to an adequate trial of methylphenidate, then atomoxetine or dexamfetamine may be considered (NICE, 2008). For adults stabilised on medication who continue to suffer persistent functional impairment, group or individual cognitive behaviour therapy should be considered (NICE, 2008).

In terms of efficacy, a growing number of studies suggest that the stimulants and atomoxetine show significant improvements in ADHD in adult patients. A meta-analysis of the efficacy of methylphenidate in adult ADHD was conducted by Faraone et al (2004).

Six double-blind placebo-controlled methylphenidate studies were included contributing data on 140 methylphenidate patients and 113 placebo-treated patients. The mean effect size of 0.9 was statistically significant, and this rose to 1.3 when treatment was optimised to higher doses.

More limited information is available on the efficacy of dexamfetamine in adults however similar findings are reported. Paterson et al (1999) conducted a randomised double-blind, placebo-controlled study of dexamfetamine in 45 adults with ADHD. This 6-week study showed a significant reduction in total mean ADHD symptom scores in both placebo and active group, although the treatment group displayed significantly lower scores. In terms of clinical global impressions, a significant difference was seen between the two groups. 90.5% of the placebo group was rated as unchanged or minimally worse at the end of the study whereas 58% of the dexamfetamine patients were assessed as being much improved or very much improved. The authors concluded that in the short-term, dexamfetamine appeared to be efficacious in treating adult ADHD.

Michelson et al (2003) performed two identical randomised, double-blind, placebo-controlled studies in adults with ADHD to determine the efficacy of atomoxetine in this patient group. Two hundred and eighty adults participated in study 1 and 256 participated in Study 2, both of which were conducted over a period of 10 weeks. In both studies, atomoxetine was superior to placebo in reducing ADHD symptoms, in both attention and hyperactive/impulsive domains. The treatment effect size was 0.35 for Study 1 and 0.40 for Study 2.

The authors concluded that atomoxetine appears to be an efficacious treatment for ADHD, and with its lower abuse potential, may be an attractive choice of treatment for many patients.

As is the case in children, there is a lack of evidence comparing these three medications in terms of efficacy and tolerability and therefore a number of factors including patient choice and comorbid conditions such as substance misuse need to be taken into consideration when selecting the most appropriate drug preparation.

Older patients also require regular follow-up in order 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. This will be discussed in greater detail in Chapters 7 and 8.

1.5.6. Pharmacological vs. Non-pharmacological treatment

The indications for those drugs licensed for the treatment of ADHD include the statement that they should be used as part of a comprehensive treatment programme, including psychological, educational and social measures.

From the literature, there has been little evidence to suggest which treatment strategies (pharmacological, non-pharmacological or both) work best for which children and what impact they have on the function and impairment of children. It was for these reasons that the MTA was designed and conducted (Richters et al, 1995).

At the end of the 14-month study, patients in all four groups (intensive medication management, intensive behavioural therapy, a combination of both or standard community care) showed sizable reductions in symptoms, however significant differences were observed between the groups. For ADHD symptoms, medication management was superior to behavioural treatment which in turn was superior to community care. There were no significant differences between the medication management and the combined medication and behavioural groups although behavioural management may have conferred additional benefits for non-ADHD symptoms and positive functioning outcomes (MTA Cooperative Group, 1999). In summary, the 14-month study showed combined behavioural and medication management ~ medication management > behavioural treatment > community care.

1.5.7. Immediate vs. Modified-Release Methylphenidate

Data from studies on the efficacy of immediate and modified-release methylphenidate show no significant difference in the effect sizes observed (Banaschewski et al, 2006). In addition, no statistically significant differences in the incidence of adverse effects between immediate and modified-release methylphenidate were observed (NICE, 2006a).

1.5.8. Methylphenidate vs. Dexamfetamine vs. Atomoxetine

The NICE Technology Appraisal in 2006 examined the evidence comparing the three drugs licensed for the treatment of ADHD (NICE, 2006a). Four studies were retrieved comparing methylphenidate with dexamfetamine (Efron et al, 1997; Arnold et al, 1978; Elia et al, 1991; Pelham 1990). Although the results from these studies suggested no difference in efficacy between methylphenidate and dexamfetamine, none of the studies met the basic requirements for quality. No studies were retrieved which had directly compared dexamfetamine and atomoxetine, while only three studies were found comparing atomoxetine and methylphenidate, of which only one was published (Kratochvil et al, 2002). The study by Kratochvil et al (2002) was an open-label study and showed no significant difference between methylphenidate and atomoxetine. The other two studies, one open-label and one randomised, double-blind placebo-controlled study reported a significant difference between the two, in favour of methylphenidate.

In terms of adverse effects, one of the unpublished studies reported no difference in the occurrence of adverse events whilst the other reported a higher incidence of reduced appetite and insomnia in the methylphenidate group, but no differences in headache or stomach ache.

The Technology Appraisal Committee acknowledged that the lack of clear evidence comparing the preparations precluded any determination of superiority. Therefore, the decision on which drug to use in treatment will be dependent on a number of factors:

- The dosage required and the need for titration
- Adverse effect profiles of the different preparations
- Presence of comorbid conditions
- Potential for drug diversion or misuse
- Issues surrounding adherence
- Patient and Family Preference
- Cost

The use of medication will not always be appropriate in the treatment of ADHD; this may be particularly the case in younger children and patients with more mild symptoms and impairments. When drug therapy is considered appropriate, methylphenidate is normally used as the first-line treatment (NICE, 2008).

Patients may be initiated on immediate-release methylphenidate which allows lower doses and more flexible dosing. Alternatively, patients may be started directly on modified-release preparations for the reasons already outlined above in Section 1.4.3. Atomoxetine is considered to be the second-line of treatment, in cases where the maximum dose of methylphenidate is not effective or where patients need to discontinue methylphenidate due to adverse effects. In some cases, such as in patients with comorbid tic or Tourette's syndrome, patients with comorbid anxiety or where drug misuse or abuse may be suspected, atomoxetine may be favoured for use as first-line treatment (NICE, 2008).

NICE, in their recent guidance, found no trials on dexamfetamine that met the quality criteria and therefore had no evidence on its efficacy. They concluded that dexamfetamine should be considered for use in patients who do not respond to the maximum doses of methylphenidate or atomoxetine (NICE, 2008).

The NICE Technology Appraisal also performed a comparison of the three licensed drugs in terms of cost effectiveness. In terms of actual cost, the following table lists the various products and prices excluding VAT, according to British National Formulary (BNF 49th Edition) prices (NICE, 2006a)

Table 1-3: Annual Costs of ADHD Drug Treatment according to BNF costs

Drug	Annual Cost
Ritalin ®	£34 - £407
Equasym ®	£34 - £364
Concerta XL ®	£329 - £776
Equasym XL ®	£304 - £730
Dexedrine ®	£20 - £313
Strattera ®	£712 - £1424

The economic evidence on the pharmacological treatments demonstrated that all three are cost-effective compared to no-treatment in children with ADHD. The manufacturers of the three different drugs all adopted different approaches to the estimation of treatment effectiveness and associated utility values, and coupled with the lack of data on the relative clinical efficacy, cost-effectiveness of the different medications could not be compared (NICE, 2006a).

1.6. Summary of the Literature on ADHD

ADHD is a prevalent neurodevelopmental disorder which can cause significant impairments in the lives of those affected by the condition. It is no longer seen as disorder exclusive to school-aged children, and is now recognised as a condition which can begin in very early childhood and can persist in some patients into adolescence and adulthood.

The condition can be treated using various modes of therapy from cognitive behaviour therapy and family therapy to the use of stimulant and non-stimulant drugs. ADHD is one of the most widely studied childhood psychiatric conditions; however this review has identified a number of gaps in the literature.

Firstly, many of the studies reporting on the use of medication for the treatment of ADHD have been conducted in the US or mainland Europe with very little information on their use in the UK. Data from the US and other European countries cannot easily be extrapolated to UK data due to differences in diagnostic criteria, approaches to treatment and the healthcare structure of the various countries. Information on prescribing practices is therefore essential to establish patterns of prescribing and to the extent of prescribing to patients with ADHD.

Secondly, although ADHD is now considered to be a condition which can be chronic in nature, there is a paucity of data on the transition of patients from child to adult services and the extent to which they continue to receive medication treatment.

Thirdly, although the medications used in the treatment of ADHD have been studied in many short and longer-term trials, there remains controversy over their safety. As safety is of paramount concern with drug treatment, it is imperative that further information on the adverse effects of these medications is garnered.

2. Chapter TWO: Aims

The overall aim of this pharmacoepidemiological study is to conduct a post-marketing evaluation of methylphenidate, dexamfetamine and atomoxetine; drugs used to treat ADHD in children and young adults.

To achieve this aim, four main research questions were proposed:

1. How are ADHD drugs utilised in the UK and how has this changed over the last decade?
2. What are the patterns of drug use when children transition to older adolescence and adulthood?
3. What is the evidence in the literature concerning the serious adverse effects of the ADHD drugs?
4. Are methylphenidate, dexamfetamine and atomoxetine associated with an increased risk of mortality in patients treated for ADHD?

3. Chapter THREE: Objectives

To answer the research questions, the following objectives were undertaken:

- To conduct a drug utilisation study using data from a number of UK databases to determine patient demographics, prescribing patterns and prevalence and incidence of methylphenidate, dexamfetamine and atomoxetine prescribing. Data would be stratified to enable analysis by age group; pre-school children, school-aged children, adolescents and young adults.
- To examine the prescribing trends in a cohort of patients aged 15 – 21 years to determine prevalence of drug prescribing and continuation of treatment as patients become older. Survival analysis and Cox regression would be undertaken to determine discontinuation of treatment and factors affecting this.
- To conduct a systematic literature review on the cardiovascular safety of the ADHD drugs.
- To determine the incidence of mortality in a cohort of patients who have been prescribed methylphenidate, dexamfetamine and atomoxetine and to determine the likelihood of an association.

4. Chapter FOUR: Methods

Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people (Strom, 2003). The pharmacoepidemiological studies contained in this thesis can largely be divided into two groups: drug utilisation studies and pharmacovigilance studies.

4.1. Introduction

4.1.1. Drug Utilisation Studies

Drug utilisation studies are increasingly being used in the field of pharmacoepidemiology. Drug utilisation is defined by WHO as the "marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences" (WHO, 2000). During the pre-marketing phase of drug trials, it is not possible to predict patterns of drug prescribing and utilisation and so post-marketing drug utilisation studies are necessary to see how drugs are being used and to identify any determinants of changes in usage patterns. Drug utilisation studies can be divided into two types: quantitative and qualitative. Quantitative drug utilisation studies are used to quantify the present state, developmental trends and the time course of drug usage in the population in question.

This data is 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.

The focus of qualitative drug utilisation studies is to examine the appropriateness of medicine use, by linking prescriptions to indications. This method is used for example in the area of infection control to identify issues such as the prescribing of antibiotics for self-limiting viral infections. The drug utilisation studies contained in subsequent chapters are mainly concerned with quantitative methods.

4.1.2. Pharmacovigilance Studies

A number of tragedies in history have led to the development of medicines regulation in the UK; the most famous of these was the "thalidomide disaster" (Silverman, 2002). This tragic event set in motion the regulation of medicines in the UK, with the development of the Committee on Safety of Drugs in 1963. The remit of this committee was to scrutinise the safety of new drugs. This subsequently became the Committee on Safety of Medicines (CSM) under the terms of the Medicines Act of 1968, which provided the legal framework for the control of medicines in the UK. The Medicines Act required that the quality, safety and efficacy of medicines be determined before being licensed and allowed onto the UK market (Cartwright & Matthews, 1991). Many of the provisions of the Act have now been superseded by regulations implementing European legislation on medicines.

In 2005, the CSM amalgamated with the Medicines Commission to become the Commission on Human Medicines (CHM), a committee of the UK Medicines and Healthcare products Regulatory Authority (MHRA). The roles of the CHM include advising UK government ministers on matters relating to human medicinal products, giving advice in relation to the safety, quality and efficacy of human medicinal products, and promoting the collection and investigation of information relating to adverse reactions for human medicines (MHRA, 2008a). The Medicines Control Agency was created in 1989, and merged with the Medical Devices Agency to become the MHRA in 2003 (MHRA, 2007). The MHRA is the UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. The roles of the MHRA are numerous and include the assessment and authorization of medicinal products for sale and supply in the UK, the regulation of clinical trials of medicines, and the post-marketing surveillance of adverse drug reactions.

When developing new medicines, pharmaceutical companies are required to undertake rigorous clinical trials to demonstrate clinical efficacy and risk-benefit ratio. They are also required to submit safety data; however clinical trials, due to their limited sample size and controlled nature are only able to detect common adverse effects. Post-marketing pharmacovigilance studies are therefore necessary to monitor medicines long-term in order to identify and evaluate possible safety hazards not previously highlighted. This may be undertaken in a number of ways, including spontaneous reporting systems and the use of databases.

4.2. Data Sources

4.2.1. Introduction

Prior to the development of automated databases, difficulties in 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 complex process. Now, the use of automated databases allows researchers to conduct studies with large sample sizes and more complete and accurate follow-up data. The use of databases also facilitates pharmacovigilance studies as the large patient sample enables the detection of uncommon adverse events. 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 a number of factors including the size of the database, how representative it is of the population, and cost.

In the UK, there are many databases which contain patient and prescription data. They include the General Practice Administration System for Scotland (GPASS), the Medicines Monitoring Unit (MEMO), QResearch, The Health Improvement Network (THIN), the General Practice Research Database (GPRD), IMS Health Databases, the Prescription Pricing Division (PPD) and the Yellow Card System.

4.2.2. General Practice Administration System for Scotland (GPASS)

GPASS is a primary care IT system which is used by almost 80% of practices in Scotland. GPASS manages four million Scottish patients' primary care records; which facilitates the effective collection and analysis of national morbidity and prescribing data for the NHS and Scottish Executive Health Department. (GPASS, 2008)

4.2.3. Medicines Monitoring Unit (MEMO)

MEMO is a University-based organisation that uses record-linkage techniques to construct an observational database for the population of Tayside, Scotland. The population of Tayside is approximately 400,000 people. The database contains information including all prescriptions dispensed in Tayside; data on morbidity including inpatient hospital admissions, and cancer registration; results from biochemical tests and diagnostic procedure and death certification. Linkage to national Scottish data can also be performed. (MEMO, 2004)

Both of these databases provide useful data, however because they are focused on the Scottish population, they may not be representative of the UK population as a whole.

4.2.4. QResearch

QResearch is a new emerging national database derived from the anonymised health records of over 10 million patients. The data currently comes from approximately 550 general practices using the EMIS clinical computer system. The practices are spread throughout the UK and include data from patients who are currently registered with the practices as well as historical patients who may have died or left their practice (QResearch, 2007). In recent years, more studies using data from QResearch have been published and it is likely that its use in primary care research will continue to grow (QResearch, 2007).

4.2.5. The Health Improvement Network (THIN)

THIN is a medical research database of anonymised patient records derived from information entered by GPs using the Vision computer system. THIN is a collaboration between EPIC (who provide primary care patient data to medical researchers) and In Practice Systems (InPS) (who develop and supply Vision general practice computer systems). Data available from THIN includes patient demographics, medical records, therapy and dosage data. The THIN database contains data from 308 practices comprising of over 5 million patient records and the number of publications using the THIN database is continuing to grow (THIN, 2008).

There is some overlap between data from THIN and GPRD as both databases receive data from EPIC and so both sources cannot be used in conjunction.

Whilst these four databases all have their own unique advantages for performing pharmacoepidemiological research, the work conducted in this project primarily utilised data from the GPRD, with validation from the IMS database, the PPD and the Yellow Card System. These will now be discussed in turn.

4.3. General Practice Research Database (GPRD)

4.3.1. History

The General Practice Research Database (GPRD) was established in 1987 as the Value Added Medical Products (VAMP) Research Databank. VAMP, a commercial company, provided computerised general practice software that allowed for the comprehensive recording of anonymised medical information. The system provided for computer recording of patient demographics, all prescriptions and all clinical diagnoses along with other additional information such as test results. When VAMP was taken over by Reuters Health Information in 1994, Reuters retained the practice software business, but donated the research database to the UK Department of Health. It was at this time that the database was given its current name (Strom, 2003).

In 1995, it was decided by UK Health Ministers that the database should be self-financing and as a result, a licensing system was developed whereby licensees were required to pay a fee to access the data. Until 1999, the database was managed by the Office for National Statistics (ONS) (GPRD, 2005).

Control was then transferred to the Medicines Control Agency, now known as the MHRA, where it exists as a self-financing, not-for-profit, multi-disciplinary division, separate to the Agency's regulatory obligations.

4.3.2. Facts and Figures

The GPRD is one of the world's largest databases of anonymised longitudinal medical records from primary care. As of April 2008, the GPRD contained data from 433 Up-To-Standard (UTS) practices on a total of 6.42 million patients with 43.12 million patient years. This figure comprised of 3.66 million active patients (31.55 million person years) and 2.76 million patients who had transferred out of the practice or had died (11.57 million person years) (GPRD, 2008). Active patients are defined as patients who are alive and registered with a GP practice that is Up-to-Standard. The definition does not include patients who have died, transferred out of a practice or are temporarily registered with a practice. The demographic distribution of the GPRD is similar to the general UK population.

Although the Vision software is primarily designed to create electronic medical records for the purpose of managing patient data, the GPRD is considered by many to be the gold standard of longitudinal anonymised patient databases from primary care. Over 600 research papers have been published in peer-reviewed journals.

There have also been many unpublished studies that have been helpful to drug licensing authorities when handling issues arising from spontaneous adverse reaction reporting schemes (Walley and Mantgani, 1997; GPRD, 2008).

4.3.3. Data Source and Quality

Data for the GPRD are collected from GPs using practice management software. Initially, this included DOS VAMP Medical ("VM") software only, but in 1995, the Microsoft Windows-based Vision software was introduced (GPRD, 2005). Participating GPs from over 400 practices in the UK currently contribute data to the database. GPs are required to enter the patient data in a standardised manner into their clinical computing systems and in return receive a small fee for their services. GPs must record all patient demographic data, including date of birth, date of registration and gender. Patient registration details including registration status, transferred out reason and date must also be recorded.

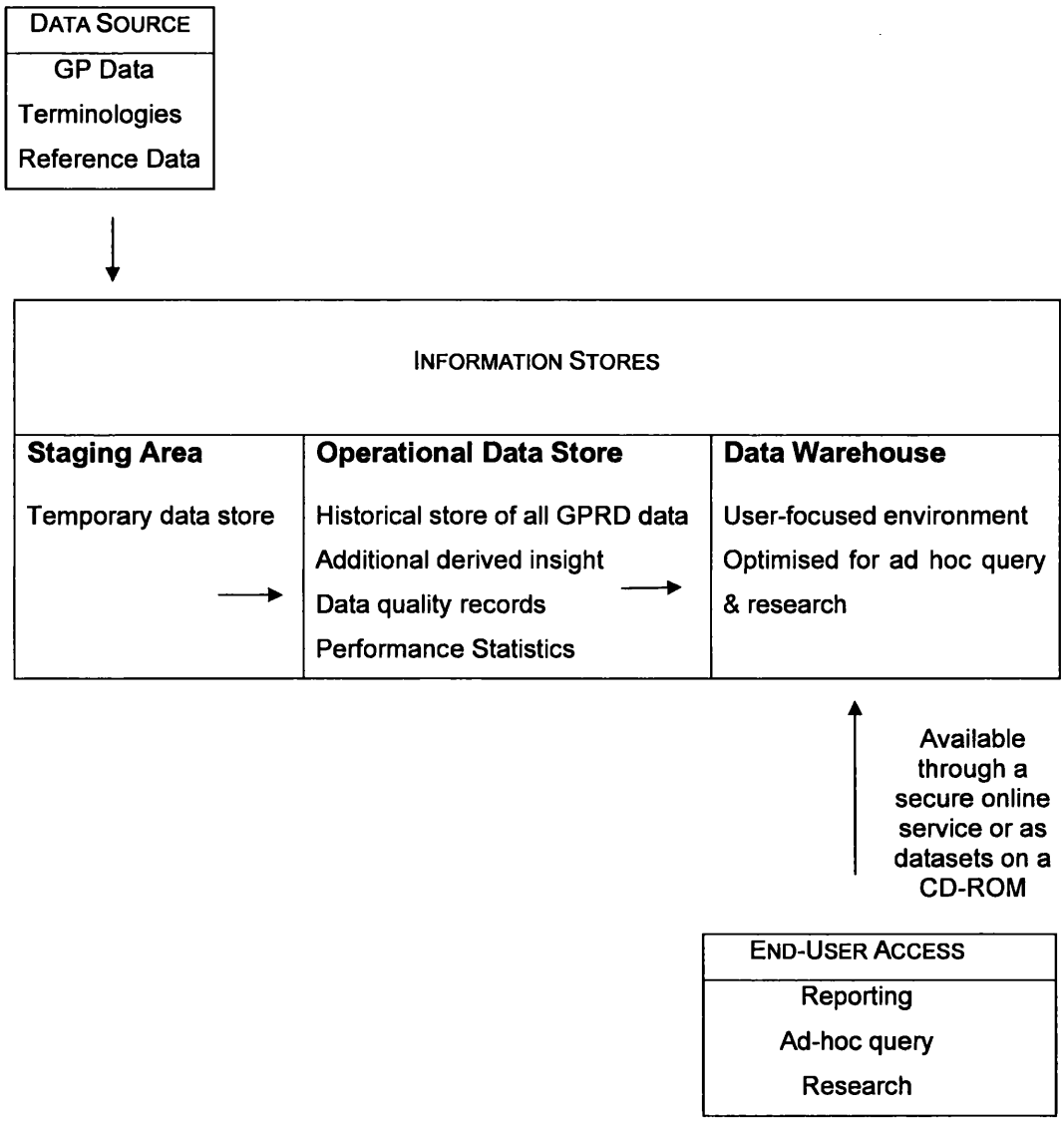
The six types of records entered onto the database by GPs include:

- Clinical Records – these contain the medical diagnoses of patients and are coded by either Oxford Medical Information System codes (OXMIS) or Read codes (adopted by the UK Department of Health for use in general practice). Additional comments may be added using free text, however this is not readily available on the database due to issues of confidentiality. They are available through the GPRD verification scheme.
- Referral Records – GPs can input information on secondary or tertiary referrals including reason for referral and referral department.
- Test Records – these include results from pathology, laboratory and X-ray.
- Immunisation Records – all components of vaccines are listed
- Therapy Records – medicines and devices prescribed by the drug substance (generic) and product name (brand). Formulation, route of administration, daily quantity, number of packs and dose can all be recorded.
- Repetition Records – repeated prescriptions for medicines

In addition to the above information, GPs can record information on patient lifestyle records include alcohol consumption and smoking status, along with patient factors such as height and weight.

The GPRD also contains medical and product dictionaries. The medical dictionary contains a hierarchical system of Read/OXMIS codes with corresponding Medical Dictionary for Regulatory Activities (MedDRA) preferred and lower level terms. Figure 4.1 is a schematic diagram to illustrate the process whereby data is entered by GPs and is extracted by the researcher. Data from the GP is entered on the VM or Vision software and loaded into the Operational Data Store (ODS) where quality checks are performed.

Figure 4-1: Schematic diagram of data processing in the GPRD



In terms of quality control, internal checks are performed on a patient and practice level. For a patient to be deemed by the GPRD as an "acceptable patient", their data must fulfil a number of criteria.

- Patients should not have an event record which precedes their year of birth i.e. 'Acceptable event record flag' should be set to yes.
- The patient's age should be less than 115 years i.e. 'Acceptable patient age flag' should be set to yes
- The patient's gender should be recorded as 'male', 'female' or 'indeterminate' i.e. 'Acceptable patient gender flag' should be set to yes
- The patient's registration to the practice is recorded as 'applied', 'permanent' or 'transferred out' i.e. 'Acceptable registration details' should be set to yes.

Additionally, patient's year of registration must not be before the year of birth, patients who are registered as 'permanent' or 'applied' must not have a transferred out reason or date, and patients who have transferred out of a practice must have a valid transferred out reason and a transferred out date which is after the date of registration. Once the above requirements have been satisfied, the patient is included as an 'acceptable' patient (GPRD, 2005).

At a practice level, a quality measure referred to as the Up To Standard (UTS) date is employed. The UTS date is generated by an automated audit and assesses the extent to which data complies with the recording guidelines in the areas of completeness, continuity and plausibility of data.

Measures which require fulfilment for a UTS date to be generated include:

- Percentage of 'acceptable' patients
- Percentage of patients with acceptable registration status
- Monthly prescription rate
- Percentage of new prescriptions with a medical indication
- Death rates
- Recording of cause of death
- Outcome of pregnancy
- Contraception events
- Referral rate
- Recording of clinical speciality for referrals.

A number of other validation measures are performed, including checking the referential integrity of the data (e.g. an event recorded must refer to a valid patient already existing in the database), ensuring that there is no gaps in the data collected from practices (i.e. that data from the GP has not been lost due to any technical difficulties) and to ensure there are no duplicate records in the database.

Validation studies show that the quality and completeness of the data is high (Hollowell, 1997; Walley and Mantgani, 1997).

4.3.4. Patient Profiles

Individual patient profiles can be downloaded from the database. These profiles contain the full history (all types of records) of the patient and are useful during case verification and causality assessment. Each patient profile displays the following information:

- Patient Identification Number
- General Practice Identification Number
- Family Identification Number
- UTS date of the practice
- Registration date of the patient
- Gender
- Year of birth (and month of birth for children under 15 years)
- Marital status
- Age of the patient in the current year (i.e. the year the data was extracted from the database)
- Transferred out date
- Transferred out reason

4.3.5. Verification Service

The GPRD offers a verification service to provide more detailed information on patients. The researcher, having identified a particular cohort of patients of interest, can request copies of hospital letters, discharge summaries, death certificates and post-mortem reports. Questionnaires can be sent to GPs in order to obtain additional patient data. All data returned to the researcher from the GPRD verification service is anonymised in order to protect patient confidentiality. Each verification service is subject to a fee paid by the researcher to the GPRD.

4.3.6. Strengths and Limitations of the GPRD

4.3.6.1. Strengths

It is possible to study rare diseases and rare events using the GPRD due to its large size. These outcomes may not be detectable in clinical trials, especially in the case of paediatric patients where clinical trial is limited. The GPRD contains population data which is representative of the UK population and studies have demonstrated that the quality and completeness of the data is high (Walley and Mantgani, 1997). In addition, the ability, through the verification service, to access original patient data provides an additional advantage over other databases. The data is available on a live online database which is accessible to research centres with individual password-protected log-ins.

4.3.6.2. Limitations

As the GPRD contains primary care data, there is limited data available on any secondary care activities pertinent to the patient. There is no information on hospital tests, length of stay or drug exposure during any inpatient episode. Also, the database does not facilitate the collection of data relevant to Over-the-Counter (OTC), herbal or homeopathic remedies. The GPRD does not directly link prescriptions to clinical diagnoses which is a recognised limitation of not only the GPRD but also many other databases (Wong and Murray, 2005). There is a small proportion of patients who due to their personal circumstances may not be registered with a GP and therefore would not be captured on the database. These include prisoners, homeless people and members of the armed forces (Wood and Martinez, 2004). Finally, a limitation of the database that is relevant particularly to this study is the fact that the stimulants methylphenidate and dexamfetamine, being controlled drugs, were required by law up until November 2005 to be hand-written. There is a possibility that these prescriptions would not also be entered electronically on the database and therefore captured as part of this study. For the last year of the study periods (2006) used, prescriptions for controlled drugs could be generated electronically like any other prescription and so this should not be a problem.

Prior to 2006, although prescriptions had to be hand-written, the Vision practice guidelines (GPRD, 2005) for GPs stated that:

"What prescriptions to record: All drugs and appliances prescribed by, or on behalf of, doctors in the practice should be entered in the Therapy History, including:

- Drugs prescribed by partners, locums, registrars, assistants, Pros and deputising doctors
- Drugs prescribed by a doctor in the practice on the advice of another doctor, e.g. a hospital doctor
- Drugs prescribed on home visits or elsewhere away from the surgery. These should be recorded retrospectively in the Therapy History against the actual dates on which the drugs were prescribed (i.e. not against the default "today's" date generated by the system which should be overwritten)
- Controlled drugs should be entered in the Therapy History, although the script will need to be hand-written.
- Contraception prescribed in the surgery and in family planning sessions run by the practice."

As previously mentioned, each practice undergoes rigorous quality checks before the data they submit is uploaded onto the database. Therefore, although it is possible that there is a degree of under-reporting of controlled drugs, it should not be a significant problem as to preclude the study of these drugs using the GPRD.

4.3.7. GPRD Summary

The GPRD is one of the world's largest computerised databases of anonymised longitudinal patient records from UK primary care. The database has an international reputation in the areas of drug utilisation and safety. This database will provide the majority of the data presented in this body of work looking at the use and safety of methylphenidate, dexamfetamine and atomoxetine in the treatment of ADHD in children, adolescents and young adults in the UK.

4.4. IMS Health Databases

4.4.1. Introduction

IMS, formally known as Intercontinental Medical Statistics Ltd, is an international healthcare company providing information to the pharmaceutical and healthcare industries. IMS provide a number of health-related databases including IMS Prescribing Insights, IMS Hospital Pharmacy Audit and IMS Disease Analyser-Mediplus.

4.4.2. IMS MIDAS Prescribing Insights

IMS MIDAS Prescribing Insights provides comprehensive medical data from 46 countries worldwide, with in-depth information for 11 countries including the US, Canada, Japan, UK, Germany, France, Italy, Spain, Brazil, Mexico and Argentina, representing over 75% of the world prescription market (IMS Health, 2008).

The detailed information provided by IMS MIDAS Prescribing Insights includes:

- Diagnoses and Therapies
- Age and Gender of the Patient
- Type of visit and type of drug (first or subsequent visit; first prescription, change or repeat)
- Cost of treatments prescribed

This information is provided by over 14,000 doctors worldwide.

4.4.3. IMS HEALTH: Hospital Pharmacy Audit

There is no NHS collation of information on medicines used and issued in NHS hospitals similar to those in primary care. IMS HEALTH Hospital Pharmacy Audit collects information on a commercial basis from pharmacies in hospital trusts in England. Ninety seven per cent of acute English hospitals supply data to IMS about all medicines dispensed in hospitals (NICE, 2006b).

The IMS Hospital Pharmacy Audit database is based on issues of medicines recorded on hospital pharmacy systems and each month, this data is sent electronically to IMS Health. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; discharge etc. IMS data also includes all drugs dispensed in NHS hospital regardless of the patient, and so will include drugs dispensed to private patients in private wards within NHS hospitals as long as they have been dispensed via the hospital pharmacy. Information on cost and volume/quantity of medication used is available from the IMS Hospital Pharmacy Audit. Estimated costs are calculated by IMS using the drug tariff and other standard price lists and so because many hospitals receive discounts from suppliers, this cost does not represent the true price paid by the NHS on medicines.

However, these costs are used as a proxy for utilisation and allow comparisons of prescribing data from different sources. The volume/quantity data refers to the number of packs used. This cannot be used across various preparations due to differences in dosages and pack sizes.

The disadvantage of the IMS Hospital Pharmacy Audit is that it does not link to demographic or to diagnosis information on patients and therefore, cannot be used to provide prescribing information on age and sex.

4.4.4. IMS Disease Analyser-Mediplus

IMS Disease Analyser-Mediplus (IMS-DA) collects practice records from over 500 GPs in the UK, equating to over 3 million active patients (Wong and Murray, 2005). The database is broadly representative of the UK population in terms of age, gender and contributing GPs although smaller GP practices and those from Scotland and Northern Ireland tend to be under-represented, while younger GPs tend to be over-represented (Wong and Murray, 2005). Information held on the database includes patient demographics, prescription details and indications for treatment. Prescribed drugs are coded based on the Anatomical Therapeutic Chemical (ATC) classification, issued by the European Pharmaceutical Market Research Association (2008) while therapy indications are coded using the Read Code system which can be linked to the International Classification of Disease (ICD) version 10 codes (ICD, 2006).

The database is also subject to internal validation and quality checks and studies of the database have concluded that the information from IMS-DA is generally consistent and complete (Langman et al, 2001).

For validation of the data obtained from the GPRD, the IMS-DA was utilised to examine prescribing patterns of methylphenidate, dexamfetamine and atomoxetine in the UK. Data from the IMS Hospital Pharmacy Audit, was obtained from the Prescription Pricing Division (PPD) with permission from IMS Health and was used to investigate utilisation of the study drugs in secondary care.

4.4.5. IMS Summary

IMS Health databases contain a rich source of medical information from both primary and secondary care, and from the UK, Europe and the US. Those used in this study will include the IMS Disease Analyser-Mediplus which provides data on patients, prescribing and diagnoses from primary care and the IMS Hospital Pharmacy Audit which captures data on drug use from the hospital sector.

4.5. Prescription Pricing Division (PPD)

All NHS prescriptions written by GPs and dispensed by community pharmacies in England are sent to the Prescription Pricing Division (PPD) (formerly known as the Prescription Pricing Authority (PPA)) to determine reimbursement and remuneration levels. As a result, the PPD maintains the largest drug database of its kind in Europe containing over 576 million prescriptions per year (PPD, 2008). The PPD provide data to NHS organisations and legitimate research organisations once specific criteria are met (Wong and Murray, 2005). As the data from the PPD database does not stratify age, it is often not a useful source of data when conducting paediatric research. However, the drugs used in the treatment of ADHD are mainly used in children and young people and so it may be assumed that the majority of those prescriptions presented to the PPD are for the paediatric population.

There are a number of different prescription data available from the PPD including:

- Net Ingredient Cost (NIC): the basic price of a drug i.e. the price listed in the Drug Tariff or the Monthly Index of Medical Specialities (MIMS). As mentioned previously with the IMS Hospital Pharmacy Audit, this cost does not take into consideration any discounts pharmacies may have received from suppliers.
- Volume: this can be expressed in terms of number of items, number of tablets etc.; however these can only be used when the use of one drug type is being examined.

In addition to data from prescriptions written by GPs, data is also obtained by the PPD on prescriptions written by hospital prescribers that are dispensed in the community (FP10HP prescriptions).

4.5.1. PPD Summary

The PPD contains a vast amount of information on drug dispensing in primary care. It has the advantage over databases such as the GPRD and IMS-DA in that it contains data on drugs dispensed and not those prescribed. It can also provide individual level data to certain research organisations such as the Drug Safety Research Unit (DSRU). This study utilises the PPD data to examine trends in the dispensing of methylphenidate, dexamfetamine and atomoxetine in primary care.

4.6. Yellow Card Scheme

As a result of the thalidomide disaster, the Yellow Card Scheme was introduced in 1964 with the aim of providing 'a straightforward route for a doctor or dentist to report a suspicion that a medicine could have harmed a patient' (MHRA, 2004). Nowadays, the Yellow Card Scheme is maintained by MHRA and the Commission on Human Medicines (CHM), and allows the reporting of suspected adverse drug reactions (ADRs) from healthcare professionals including doctors, nurses, dentists and pharmacists and more recently has been extended to include direct reporting by patients. The Yellow Card Scheme contains over half a million reports of adverse drug reactions (ADRs) experienced by patients. Each report details an ADR or ADRs that the reporter suspects may be associated with the patient's use of a drug and the data are coded according to the internationally accepted Medical Dictionary for Regulatory Activities (MedDRA) (MHRA, 2008b). Proof of a causal link is not required. Reports may be submitted relating to prescription medicines, herbal medicines and OTC medicines. In 2004, the Independent Review of Access to the Yellow Card Scheme recognised the research potential of the Yellow Card/ADROIT database, as one of the largest single source of suspected adverse drug reactions in Europe (MHRA, 2004).

Under the Freedom of Information Act (FOIA, 2000) data from the Yellow Card Scheme is available to researchers whilst at the same time protecting the confidentiality of individuals and their personal data as specified in the Data Protection Act (DPA, 1998).

The detail of information required by researchers dictates the level of scientific and ethical scrutiny they will undergo before any data is provided.

Category Ia data consists of anonymised aggregated ADR data. This data does not identify the patient or reporter. Category 1a data is available on the MHRA website in the format of Drug Analysis Prints (DAPs) which are regularly updated.
Category Ib data can provide information from individual Yellow Cards, on the provision that any information which may identify either the reporter or the patient is omitted. Additional data available, which is not available from DAPs include the age categories of the patients; the proportion of males and/or females who experienced the reaction; the drug or drugs involved; the dose and duration of drug therapy; the route of drug administration and the suspected adverse drug reaction(s) that the patient experienced. These data are generally releasable under the FOIA, without consideration by the MHRA's Independent Scientific Advisory Committee (ISAC), although provision of these data will depend on the number of cases held by the Agency. Data will only be released if there are at least five cases in any data subsets. Requests for data that have less than five cases in any one cell will be aggregated with adjacent cells prior to release.

Category II Data may indirectly identify either the reporter or the patient in the form of inclusion of patient's medical history, the date of drug administration and reaction or the specific test results relevant to the suspected adverse reaction.

Requests for data that relate to a small number of ADR cases may also identify the reporter or patient and these requests will have to be considered by the Committee. Researchers may also request to contact the patient or reporter directly and so require their personal details. A number of safeguards have been established to ensure that release of these data would follow scientific and ethical approval and that reporter and patient consent would be obtained prior to release of any of their identifiable data. These include requests in which the reporter would need to be approached in the first instance so that the reporter could decide whether the patient should be asked for his/her consent. Consent from both the reporter and the patient must be obtained before their contact details are disclosed to the researcher. All Category II data requests are reviewed by the ISAC. The Yellow Card System was used as part of the pharmacovigilance study conducted into the safety of methylphenidate, dexamfetamine and atomoxetine. Category 1b data was obtained, the details of which will be discussed in Chapter 8.

4.6.1. Yellow Card Scheme Summary

The Yellow Card Scheme provides a system for early detection of emerging drug safety hazards and routine monitoring for all medicines in clinical use. It has the benefit in that it contains an immense amount of information on potential adverse drug reactions for both newly marketed medicines and those already existing on the market. The disadvantage of the system is that it neither captures the total number of reactions occurring, nor the number of patients using the drug.

Therefore, the incidence of the adverse drug reactions cannot be calculated. It is also not known the extent to which external factors such as media influence can affect the reporting of adverse reactions.

4.7. Methods Summary

The National Health Service is a unique healthcare system which by its establishment and its structure facilitates the collection and analysis of medical data through the utilisation of large automated databases. These databases provide a wealth of patient and medical information which, while protecting the anonymity of patients, enables researchers to examine various aspects of disease and drug epidemiology.

To attempt to answer the research questions proposed in this study, it was felt that the GPRD, one of the world's largest databases of primary care data and considered by many to be the gold standard, was the most appropriate source of data. As validation of the GPRD, another well-used and validated general practice database, the IMS-Disease Analyser-Mediplus was utilised. To complement the data obtained from these sources, data was obtained from the Prescription Pricing Division on medication dispensed from secondary and primary care.

Although they have many limitations, spontaneous reporting systems have also been used as the cornerstone of pharmacovigilance, and so data on the adverse effects of the stimulants and atomoxetine was obtained from the Yellow Card Database.

The use of databases in this study has provided us with large cohort of patients receiving methylphenidate, dexamfetamine and atomoxetine to enable us to examine trends in utilisation in the UK, particularly in specific patient groups such as pre-school children and older adolescents and young adults and to identify whether there are any serious adverse effects associated with the use of these drugs. Without the facility of these databases, it would have been logistically very difficult to locate, consent and research the use of these drugs in patients with ADHD. Various methods of data manipulation and analyses will be used throughout this study and will be described in detail in each of the chapters.

5. Chapter FIVE: Drug Utilisation of ADHD medications in the UK

5.1. Introduction

ADHD and its drug treatment have been studied and reported widely in the medical literature for many decades; however in the last few years, the condition and in particular the use of stimulants has attracted mass media interest. A search of some of the UK's popular media revealed that while some articles present a more balanced scientific view on the use of stimulants 'Ritalin, does it work?' (Ahuja, 2007), others are less objective in their approach to the topic with articles such as 'Ritalin made my son a demon' (Browne, 2000), 'Pills for everything' (Petit-Zeman, 2003) and 'Ritalin: The scandal of kiddy coke' (Davies, 2007). These dramatic headlines attract larger audiences and are likely to bias perceptions of ADHD and its treatment. Indeed, there have been suggestions both in the media and in some of the medical literature that ADHD is over-diagnosed and over-treated.

However, apart from anecdotal evidence, where is the evidence to support the perceptions that ADHD is not a 'real' medical condition, that it is over-diagnosed and that it is over-treated?

The scientific evidence supporting the validity of ADHD as an impairing neurodevelopmental disorder has been described previously in Section 1.2.3.

Those who believe that ADHD is an invalid diagnosis will determine any level of diagnosis as excessive, however Sciutto and Eisenberg (2007) state that to conclude that ADHD is over-diagnosed, the overall number of false positives (i.e. those who receive a diagnosis of ADHD but should not) must substantially exceed the number of false negatives (i.e. children with ADHD who are unidentified or undiagnosed). To determine whether this was the case, they reviewed studies where ADHD prevalence rates were quoted and studies documenting factors that contribute to the identification of false positives such as comorbidity and diagnostic inaccuracies and false negatives such as gender differences and barriers to accessing treatment. They concluded that it is possible that in some cases, ADHD is misdiagnosed; however there is insufficient evidence to determine that it is systematically over-diagnosed. Much of the evidence in this review was based on US data, so is there any data in the literature to suggest that ADHD/HKD disorder is over-diagnosed in the UK? In the UK, it is believed that ADHD is under-diagnosed, with children displaying marked behavioural impairments remaining unidentified and at risk (Timimi and Taylor, 2004).

The third issue, which pertains to this study, is that concerning the treatment of ADHD and whether doctors are dishing out stimulants "like smarties" (Oliver, 2000). It is recognised that the use of stimulant medications has increased in the last decade or so, however, it is not known to what extent this occurred. There is a dearth of information from the literature on the use of medications in the treatment of ADHD in the UK.

A study by Jick et al (2004) used the GPRD to report the incidence and prevalence of drug-treated ADD in boys aged 5-14 in the UK from 1996-2001 and found that the level of drug treatment was substantially lower than that in the US. A national survey conducted by Green et al (2005) found that all children (aged 5-16) receiving stimulant treatment had evidence of pervasive hyperactivity (overactivity, impulsiveness and inattention). This study also found that a large proportion of children (~57%) with hyperkinetic disorders, were not getting access to an evidence-based treatment suggesting that concerns about over-prescribing of stimulant medications were unfounded. This limited evidence from the early part of this decade suggests that ADHD is not over-treated in children in the UK, however, it is not known how the increase in medication use has manifested in recent years, especially in under-studied groups such as females, younger children and young adults.

5.2. Aim

The overall aim of this study was to examine the utilisation of methylphenidate, dexamfetamine and atomoxetine in children, adolescents and young adults in the UK.

5.3. Studies

To achieve this aim, three individual studies were undertaken:

1. To report on the prescribing patterns of methylphenidate, dexamfetamine and atomoxetine, the demographics of the patients prescribed these medications, and the incidence and prevalence of prescribing in both males and females with ADHD/HKD aged between 2 and 21 years from 1996 to 2006 using the GPRD.
2. To report on the prescribing patterns, incidence and prevalence of methylphenidate, dexamfetamine and atomoxetine in males and females aged between 3 and 18 years from 1996 to 2006 using data from the IMS Disease Analyser-Mediplus Database
3. To report on hospital and primary care dispensing data from 2001 to 2006 using data from the Prescription Pricing Division.

Each of these individual studies is detailed below; however the results will be discussed together in Section 5.7.

5.4. Drug Utilisation Study using the General Practice Research Database

5.4.1. Method

5.4.2. Data Source

The GPRD as a data source has been described previously. The database has previously been used to investigate paediatric psychotropic medication prescribing in the UK (Murray et al, 2004; Ackers et al, 2007; Rani et al, 2008).

5.4.3. Data Extraction

A paediatric cohort of the GPRD (online Full Feature version) was made available for the study. The online data extraction tools, Business Objects and Business Objects Information Systems (BORIS) are software provided by the GPRD which act as an interface between the user and the database and allow users to create queries to ask specific questions relevant to their research area.

In order to create queries and retrieve relevant information, the user must define criteria in terms of which areas of the GPRD database they wish to examine. In this study, a number of steps were undertaken in order to extract data on the use of ADHD drugs in the UK.

Step 1: As the objectives of this study were to examine the prescribing of ADHD drugs, the study cohort was defined by the use of methylphenidate, dexamfetamine and atomoxetine. Therefore the first step was to formulate a comprehensive list of study drug codes. The GPRD's Product Dictionary was searched for individual ADHD drugs in the following search fields: 'Drug Substance Name' (i.e. the active drug e.g. methylphenidate) and 'Product Name' (i.e. brand names e.g. Ritalin). The search history is contained in Table 5.1.

Table 5-1: Search history for ADHD drugs in GPRD Product Dictionary

Search_Field	Search_Value
Drug Substance Name	*methylphe*
Product Name	*methylphe*
Product Name	*ritalin*
Product Name	*equasym*
Product Name	*concerta*
Drug Substance Name	*dexamphe*
Drug Substance Name	*dexamfetamine*
Drug Substance Name	*dexamphetamine*
Product Name	*dexedrine*
Drug Substance Name	*atomoxetine*
Product Name	*strattera*

In addition to these fields, the 'BNF Code' field was searched using the 'CNS Stimulants and drugs used for attention deficit hyperactivity disorder' section code of the BNF. This search strategy enabled a comprehensive list of ADHD drugs to be compiled which is contained in Appendix 1.

Step 2: Once the list of drug codes was collated, the next step was to enter these codes into a BO query in order to retrieve all the relevant information on the patients who had ever received these drugs. This Patient Data file contained information on: Patient Identification Number, Practice Identification Number, Gender, Year and Month of Birth, Date which a patient transferred out of a GP practice (if relevant) and Reason for transferring out of the practice (if relevant). Details of the BO query are given in Figure 5.1.

Figure 5-1 Business Objects Report for Retrieving Patient Records from GPRD for ADHD drugs

Business Objects Patient Report

BO Report created: 25/05/07 (Data run in GPRD 25/05/2007) **by** Suzanne McCarthy

Objects

Practice Eid (Current), Patient Eid (Current), Current Gender (Current), Current Reg. Status (Current), Birth Year (Current), Birth Month (Current), Patient Currently Reg Flag (Current), Current Transfd Out Reason (Current), First Registration Date (Current), Current Transfd Out Date (Current), Event Type

Conditions

Event Type In List 'Therapy', Age at Event Less Than 24, Event Date Between 01/01/1992 and 31/12/2006, Patient Record Deleted Flag Equal to 'N', Standard Patient Criteria.

GPRD Product/Medical Codes

(36 Methylphenidate, Daxamfetamine, Dexamphetamine, Atomoxetine)

4013832,4013833,4063247,4080748,4086659,4089329,4089330,4090953,4092593,4092635,4093143,4096580,4096581,4110981,4110982,4110983,4110984,4110985,4111897,4111898,4111899,M03577001,M07558001,M08155001,M08551001,M08551002,M08551003,M10450001,M12516001,M12517001,M12518001,M12519001,M12520001,M13050001,M13051001,M13066001,

Step 3: The next step was to collect information on all of the practices in the GPRD. This was again retrieved using a BO query and the Practice data file contained information on: Practice Identification Number, Practice Status, the date the practice was up-to-standard, the last date which data was collected from the practice. Details of the BO report are given in Figure 5.2

Figure 5-2 Business Objects Report for Retrieving GP Practice Data from GPRD

Business Objects Practice Report

BO Report created: 25/05/07 (Data run in GPRD 25/05/2007) **by** Suzanne McCarthy

Objects

Practice Eid, Practice Status, Up to Standard Date, Practice Last Collection Date

Conditions

None

GPRD Product/Medical Codes

None.

Step 4: The next step was to get data on all the prescriptions issued for the study drugs. This was done using a BO query (Figure 5.3). The prescription data included information on: GPRD drug code, Drug name, Drug dose, Quantity of drug prescribed, Pack size and Date when the prescription was issued.

Figure 5-3 Business Objects Report for Retrieving Prescription Data from GPRD

Business Objects Therapy Report

BO Report created: 25/05/07 (Data run in GPRD 25/05/2007) **by** Suzanne McCarthy

Objects

Practice Eid (Events), Patient EID (Events), Birth Year (Current), Current Gender (Current), Age at Event, Event Type, Event EID, Event Text UID, Event Date, GPRD Product Code (Events), GP Product Name (Therapy), Associated Consultation EID, Dose (Therapy), Product Total Quantity (Therapy), Number of Packs (Therapy), Pack Type/Size (Therapy), Prescription Duration (Therapy).

Conditions

Event Type in List 'Therapy', Age at Event less than 24, Event Date Between 01/01/1992 and 31/12/2006, Event Deleted Flag Equal to 'N', Patient Record Deleted Flag Equal to 'N', Standard Patient Criteria.

GPRD Product/Medical Codes

(36 Methylphenidate, Daxamfetamine, Dexamphetamine, Atomoxetine)

4013832,4013833,4063247,4080748,4086659,4089329,4089330,4090953,4092593,4092635,4093143,4096580,4096581,4110981,4110982,4110983,4110984,4110985,4111897,4111898,4111899,M03577001,M07558001,M08155001,M08551001,M08551002,M08551003,M10450001,M12516001,M12517001,M12518001,M12519001,M12520001,M13050001,M13051001,M13066001,

Step 5: Although the study cohort was defined by those who had received a prescription for a study drug, it was also necessary to extract all the clinical details of these patients for a number of reasons including determining whether patients had a diagnosis of ADHD and whether patients had records suggesting an adverse event relating to the use of these drugs. These clinical records were extracted using BORIS. Details of the BORIS query is given in Figure 5.4.

Figure 5-4 BORIS Report for Retrieving Medical Data from GPRD

BORIS report

BORIS Report created: 25/05/07 (Data run in GPRD 25/05/2007) by Suzanne McCarthy

Objects

Event EID, Patient EID, Event Date, Event Text UID, Consultation Type, Associated Consultation EID, GPRD Medical Codes, Clinical Episodes

User File

20070525_therapy

Step 6: As the data from BORIS only contains medical codes, the final step was to link these BORIS records by the GPRD medical code with medical terms in the GPRD's Medical Dictionary. The GPRD medical dictionary was used to identify all Read and OXMIS codes related to ADHD. Related search terms were entered in 'Read/OXMIS Term' and 'MedDRA Preferred Term' fields.

The corresponding Read/OXMIS codes were then used to search the hierarchical system of Read/OXMIS codes for any further related ADHD codes. The search terms used for identifying ADHD codes are contained in Table 5.2

Table 5-2: Search history for ADHD codes in GPRD Medical Dictionary

MedDRA Preferred Term	*attention*
MedDRA Lower Level Term	*attention*
Read or OXMIS Term	*attention*
MedDRA Preferred Term	*hyperkin*
MedDRA Lower Level Term	*hyperkin*
Read or OXMIS Term	*hyperkin*
Read or OXMIS Code	*E2E*
Read or OXMIS Code	*Eu9*
Read or OXMIS Code	*30*
Read or OXMIS Code	*ZV*
Read or OXMIS Code	*13Z*
Read or OXMIS Code	*307*
Read or OXMIS Code	*Ry*
Read or OXMIS Code	*1BR*
Read or OXMIS Code	*ZS*
Read or OXMIS Code	*Z7*
Read or OXMIS Code	*1BW*
Read or OXMIS Code	*1B1*

Read or OXMIS Code	*ZR*
Read or OXMIS Code	*1P*

The list of ADHD/HKD codes contained in the Medical Dictionary is given in Appendix 2. The list of codes used in the pharmacovigilance study is given in Appendix 3. This list of codes is a standard and verified list of codes for identifying death which is compiled by the GPRD.

Figure 5.5 provides an overall view of how data was obtained and processed from the database. As the GPRD is a relational database, it was necessary to link all the datasets in order to produce a complete patient dataset. This was done by importing all the datasets onto a local server at the School of Pharmacy, where the data was cleaned and merged (Figure 5.6).

Figure 5-5: Flow chart of obtaining data from the GPRD

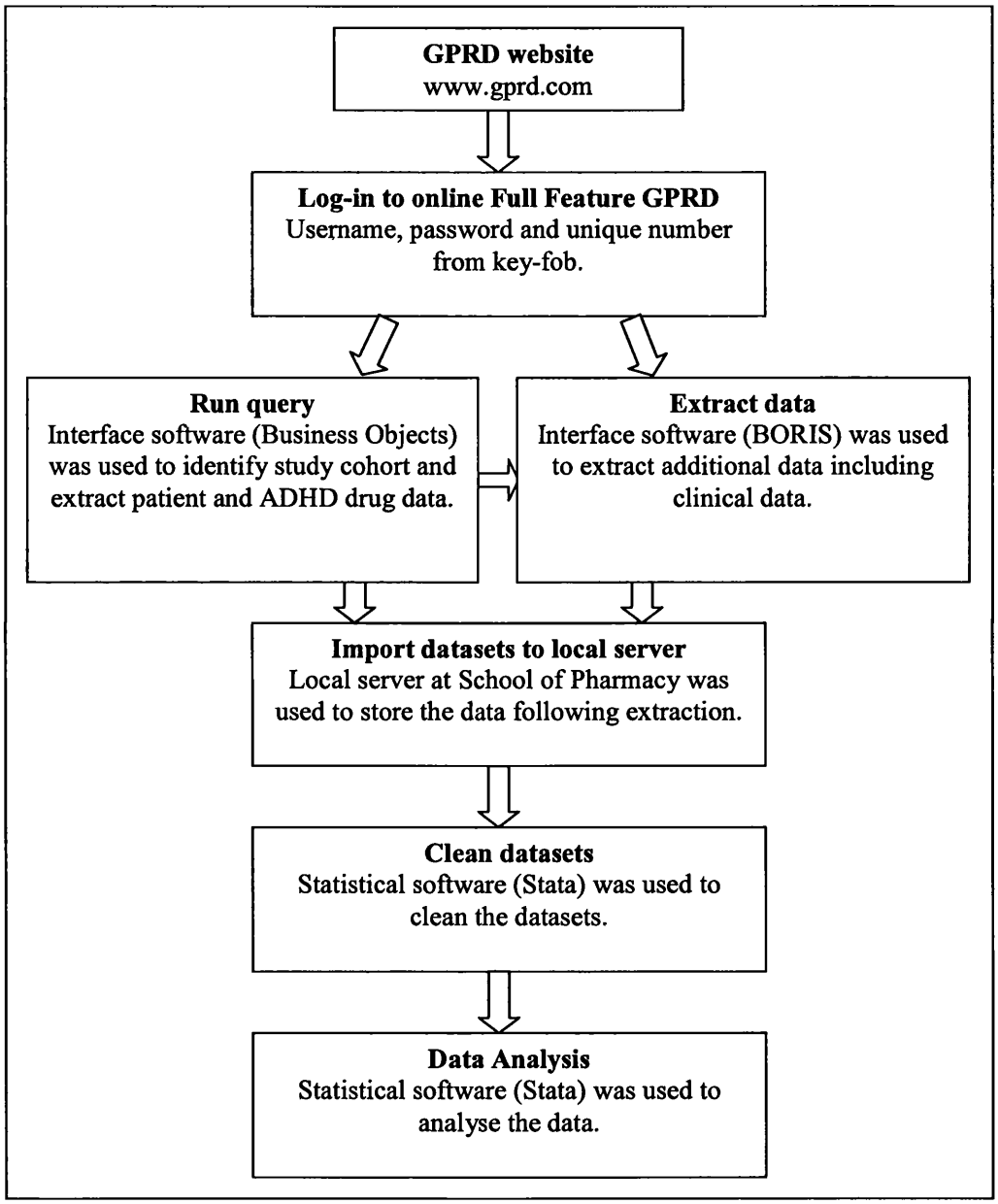
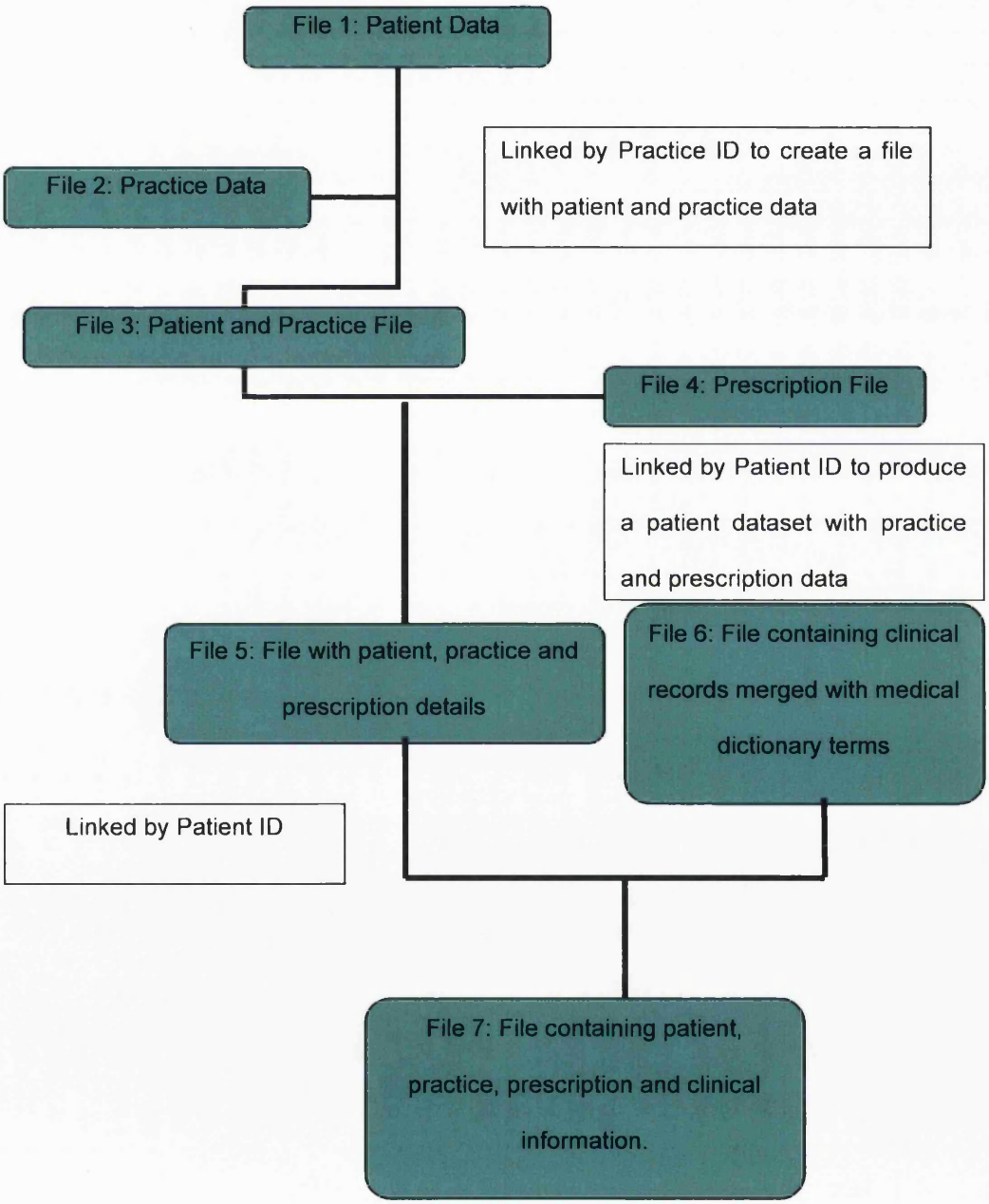


Figure 5-6: Schematic diagram to illustrate the linking of data files to produce a master dataset.



5.4.4. Study Period

The study period for this utilisation study was 1st January 1996 to the 31st December 2006. This period was chosen to enable specific comparisons with other studies conducted in this area. Although data is available from 1992 onwards, and has been used further on in the study on medication safety, the low numbers of patients using these drugs in the early part of the 1990's would not make significant changes to the utilisation patterns or rate calculations.

5.4.5. Eligibility Criteria

The study population encompassed all patients in the GPRD aged 2 to 21 years. Following the approach described in Section 5.4.3, all prescriptions from this study population were screened for a study drug; methylphenidate, dexamfetamine and atomoxetine. Patients who received at least one prescription for a study drug during the defined study period and who had a diagnostic code indicative of ADHD or HKD were classified as cases in the study. Patients were required to have at least one year of research standard data available, a known gender, and an acceptable patient registration status. Subjects who were temporarily registered with a practice were excluded.

5.4.6. Data analysis

Once the imported patient data was cleaned and merged to produce a master dataset, analysis was undertaken using STATA Stata/SE version 9.1 (StataCorp, College Station, Texas, United States).

When quantifying utilisation of a drug, it is essential to know not only the quantity of the drug prescribed or the number of patients who received the drug (the numerator), but also the size of the population from which it was drawn (the denominator). This allows estimates of drug use in the population to be calculated and comparisons to be made between different populations.

The populations used in this study were represented in two ways; as the number of patients in the GPRD population and also the number of person-years at risk in the GPRD population. These populations have the same patient characteristics as the study sample i.e. same age group during the same time period, but differ in their exposure to the study drug.

5.4.6.1. Person-Years

Person-years at risk is the sum of the number of years contributed by each subject at risk of being prescribed an ADHD drug during the study period in the study population (children and young people aged 2 – 21 years). For example if 100 'acceptable' subjects are registered in the database for one full year, this equate to 100 person-years.

If the same 100 subjects were only present on the database for 6 months, this would equate to 50 person-years. For each subject in the GPRD study population (2 – 21 years), an 'xstart' data was generated by using the maximum of the start date of the study period, Up-to-Standard date of the GP practice or the date of registration to the practice. A date for 'xend' was determined by using the minimum of the end date of the study period, the last collection date, the date the patient transferred out of a practice or the date of death. The 'xstart' and 'xend' dates were then used to calculate the number of person-years contributed by each subject to each calendar year and age stratum. This is illustrated in Table for 5.3 for five hypothetical patients.

Table 5-3: Calculation of person-years for 5 hypothetical subjects

	Study Starts	GP Practice UTS Date	Patient Registers with Practice	**Xstart**	Study Ends	Date of death of patient	Patient Transfers Out of Practice	**Xend**	**Person-Years (Xend-Xstart)**
Subject A	01/01/96	10/02/92	30/06/98	**30/06/98**	31/12/06	N/A	N/A	**31/12/06**	**8.5 years**
Subject B	01/01/96	15/08/90	23/01/92	**01/01/96**	31/12/06	N/A	30/04/00	**30/04/00**	**4.3 years**
Subject C	01/01/96	31/08/01	08/09/98	**31/08/01**	31/12/06	N/A	N/A	**31/12/06**	**5.3 years**
Subject D	01/01/96	20/5/93	01/01/99	**01/01/99**	31/12/06	30/06/05	30/06/05	**30/06/05**	**6.5 years**
Subject E	01/01/96	25/08/90	19/03/92	**01/01/96**	31/12/06	N/A	N/A	**31/12/06**	**11 years**

Total Person-Years at risk: 35.6 years

5.4.6.2. Prevalence

Prevalence measures the proportion of subjects in a population who have the disease at a specific time (Hennekens & Buring, 1987). This analysis examined the proportion of the *number of patients* in the GPRD population who were receiving treatment with methylphenidate, dexamfetamine or atomoxetine at a particular time during the study period. The age-specific and gender-specific annual prevalence was calculated for each calendar year. Prevalence was calculated by the number of subjects prescribed an ADHD drug divided by the GPRD population (aged 2 – 21 years) in a particular year.

$$\text{Prevalence} = \frac{\text{All subjects prescribed the drug in a particular year}}{\text{Total population in GPRD aged between 2 and 21 years in a particular year}}$$

5.4.6.3. Incidence

The second method of analysis used was to examine the incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine in the GPRD. In epidemiological research incidence normally refers to the rate of development of a new illness in a certain population during a specified period of time (Hennekens & Buring, 1987). For this study looking at prescribing, incidence referred to the rate at which patients started treatment with medication i.e. new starters of medication.

The first 12 months of data for each subject was used as a screening period. Subjects who did not receive a prescription for an ADHD drug but did thereafter were classified as incident (new starters). The age-specific and gender-specific annual incidence was calculated for each calendar year in the study period. Incidence was defined as the number of subjects classified as incident divided by the person-years at risk in the GPRD population (age 2 – 21 years) in a particular year.

The calculation for incidence can be expressed as:

$$\text{Incidence} = \frac{\text{All subjects classified as incident in a particular year}}{\text{Total person-years at risk in GPRD population aged 2 – 21 in a particular year}}$$

5.4.6.4. Statistical Analysis

Prevalence and incidence were stratified into three age bands (2 to 4 years, 5 to 14 years and 15 to 21 years). Although these age categories differ from those recommended in the International Committee for Harmonization (2001) guidelines for paediatric research (children categorised into 2 – 11 years, 12 – 16/18 years), they were chosen so as to allow comparisons with previous published studies in the area. Ninety-five per cent Confidence Intervals (95% CI) were generated using Poisson approximation. Chi-squared tests for trend were used to see if changes in prevalence and incidence were significant. A p-value of less than or equal to 0.05 was considered statistically significant.

5.4.7. Ethical Approval

Ethical approval was granted by ISAC – Protocol Reference No. 779 (See Appendix 4).

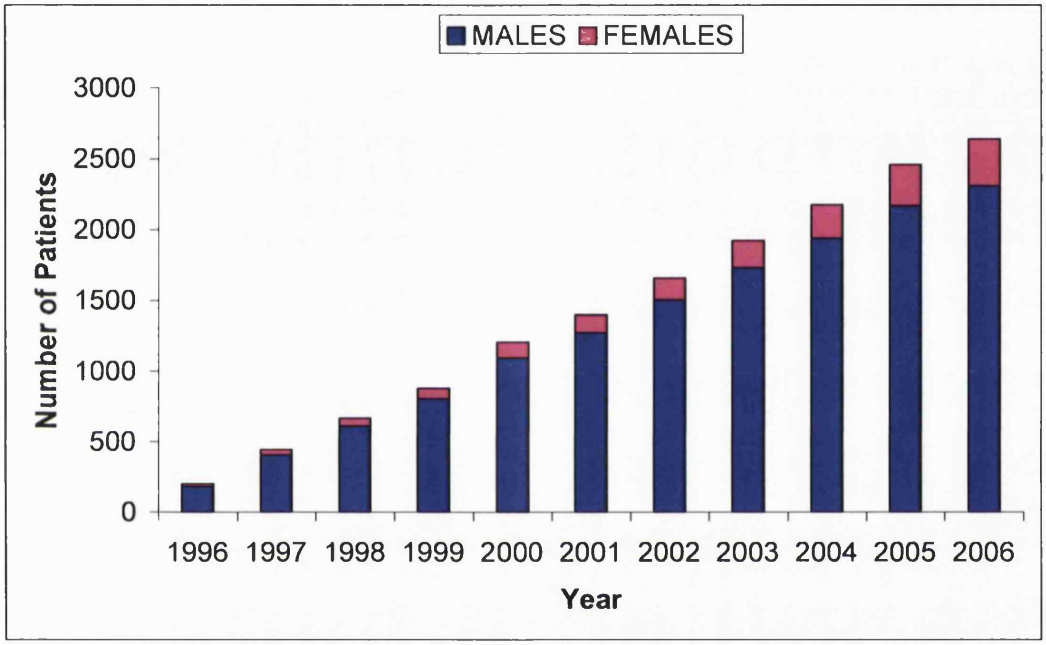
5.5. Results

Between 1996 and 2006, 4,877 patients were identified who fulfilled the inclusion criteria. This study cohort received a total of 115,723 prescriptions.

5.5.1. Patient Demographics

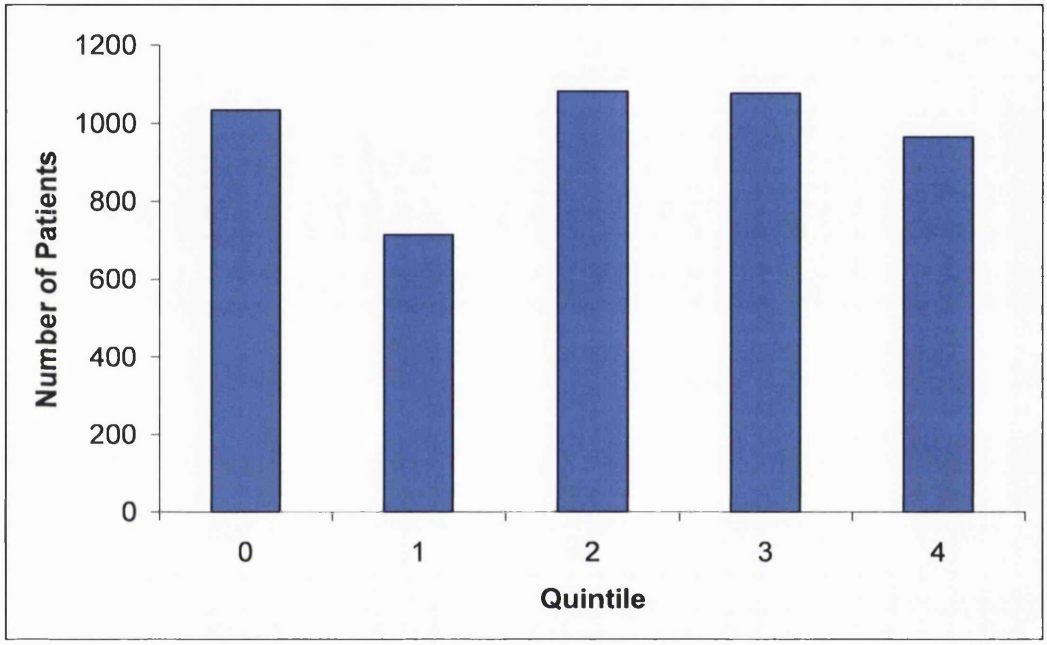
Of the 4,877 patients, 4,310 (88%) were male. Figure 5.7 shows how the ratio of male to female patients changed over the study period. Although the overall number of patients receiving prescriptions increased over 13-fold during the study period, the ratio of males to females decreased only slightly from 9.1: 1 (male: female) in 1996 to 7.03: 1 in 2006.

Figure 5-7: Number of male and female patients aged 2 - 21 years receiving ADHD drug treatment from 1996 to 2006



A proxy for the socio-economic status (SES) of patients receiving prescriptions for ADHD medications was calculated. The GPRD does not at present provide a direct link between individual patients and SES but does have a practice-based score, derived from the Index of Multiple Deprivation (IMD) which can be used as a proxy marker for SES. Quintile 0 is the least deprived, quintile 4 is the most deprived. The scores for the 4,877 patients are presented in Figure 5.8.

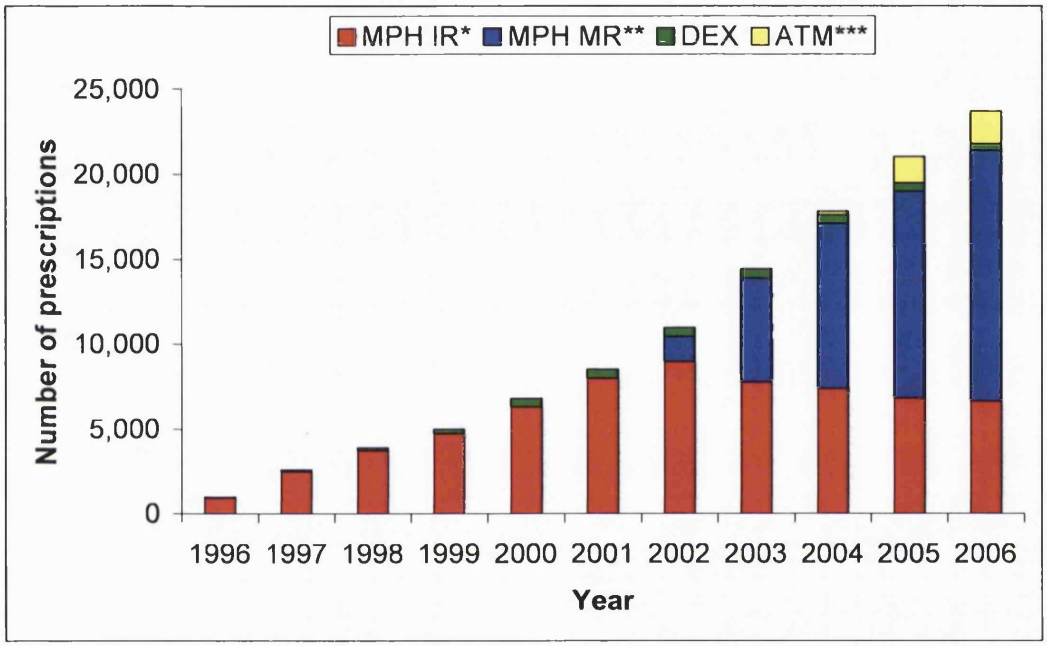
Figure 5-8: Number of patients receiving ADHD drug treatment by socio-economic status (n=4,877)



5.5.2. Prescriptions Patterns

The median number of prescriptions issued per patient was 15 (inter quartile range 5-33). The median duration of a prescription, regardless of stimulant type or strength was 30 days. The drug prescribing patterns by year are further illustrated in Figure 5.9.

Figure 5-9: Proportion of ADHD drug use (methylphenidate, dexamfetamine and atomoxetine) by year



* Immediate-release

** Modified-release preparations first authorised in 2002

*** First authorisation in 2004.

5.5.3. Prevalence and Incidence of Prescribing of ADHD/HKD medications

5.5.3.1. Prevalence

The overall prevalence of the cohort (males and females aged 2-21 years) increased 8-fold over the 10 years studied. The prevalence was 0.43 per 1000 patients (95% CI: 0.37 to 0.49) aged 2 – 21 years in 1996, whereas in 2006, the prevalence had risen to 3.44 per 1000 patients (95% CI: 3.31 to 3.58).

Figure 5.10 illustrates the prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine for patients aged 5 – 14 years and 15 – 21 years. For both males and females across all age bands, there was a significant linear trend ($p<0.001$ for trend) demonstrating a strong association between increasing treatment prevalence and time. The prevalence of prescribing increased 6.75-fold in males aged 5 – 14 years, 21.91-fold in males aged 15 – 21 years, 7.88-fold in females aged 5 – 14 years and 69-fold in females aged 15 – 21 years.

Figure 5.11 illustrates the prevalence of prescribing for patients aged 2 – 4 years. During the ten years studied, only three female patients between the ages of 2 – 4 years received a prescription for a study drug. Therefore, as the number of females in this age category was too low to make a meaningful description, only prevalence figures for males were reported. For this age group, though the absolute number of patients receiving treatment was low, there was a significant decrease in treatment prevalence over the study period ($p=0.001$) from 0.20 per 1000 patients in 1996 (95% CI: 0.09 to 0.40) to 0.04 per 1000 patients in 2006 (95% CI: 0.004 to 0.13).

Figure 5-10: Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine by age and sex from 1996 to 2006

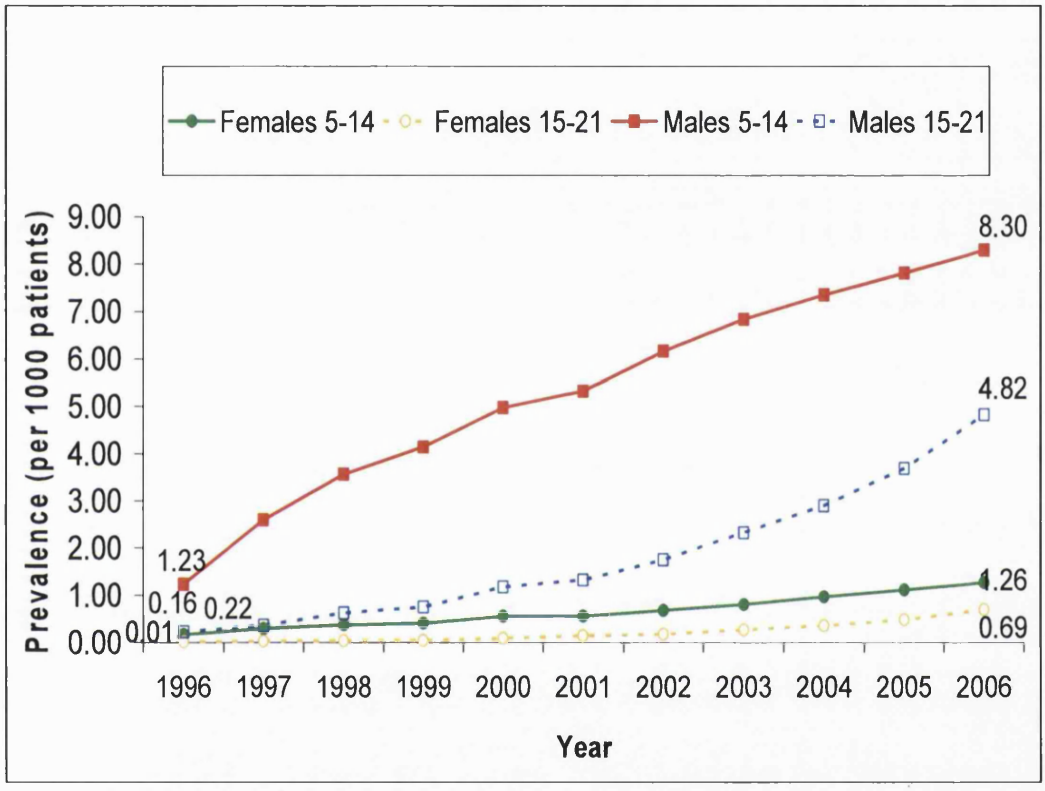
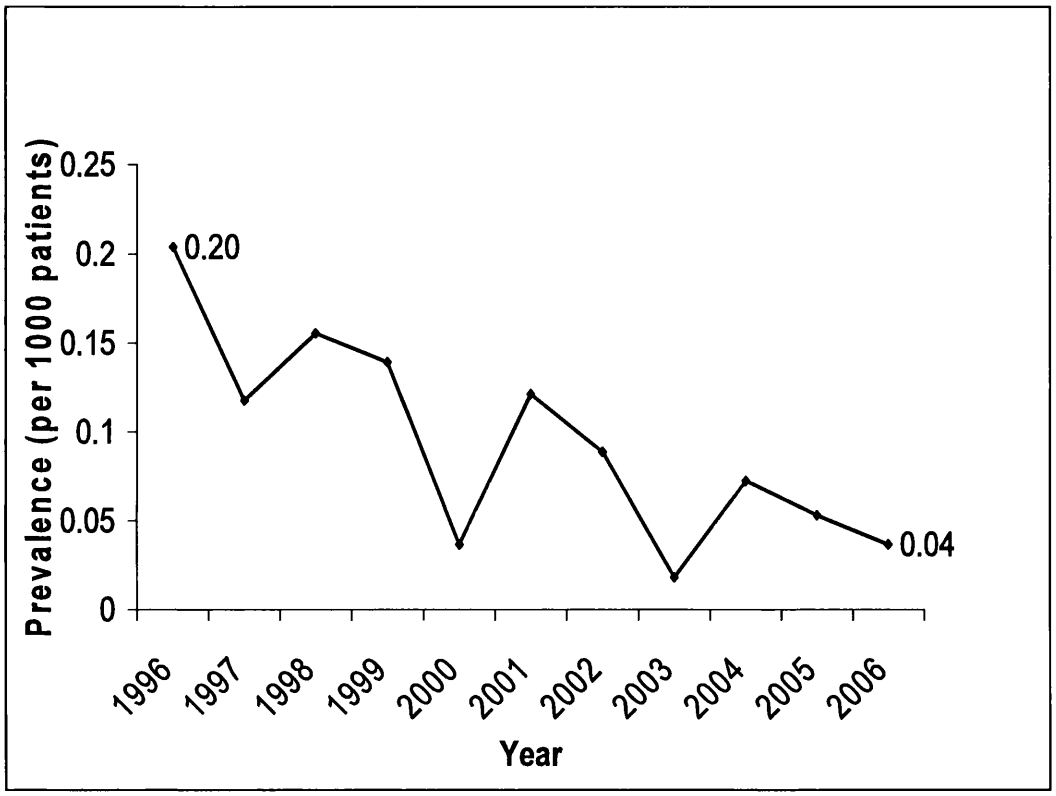


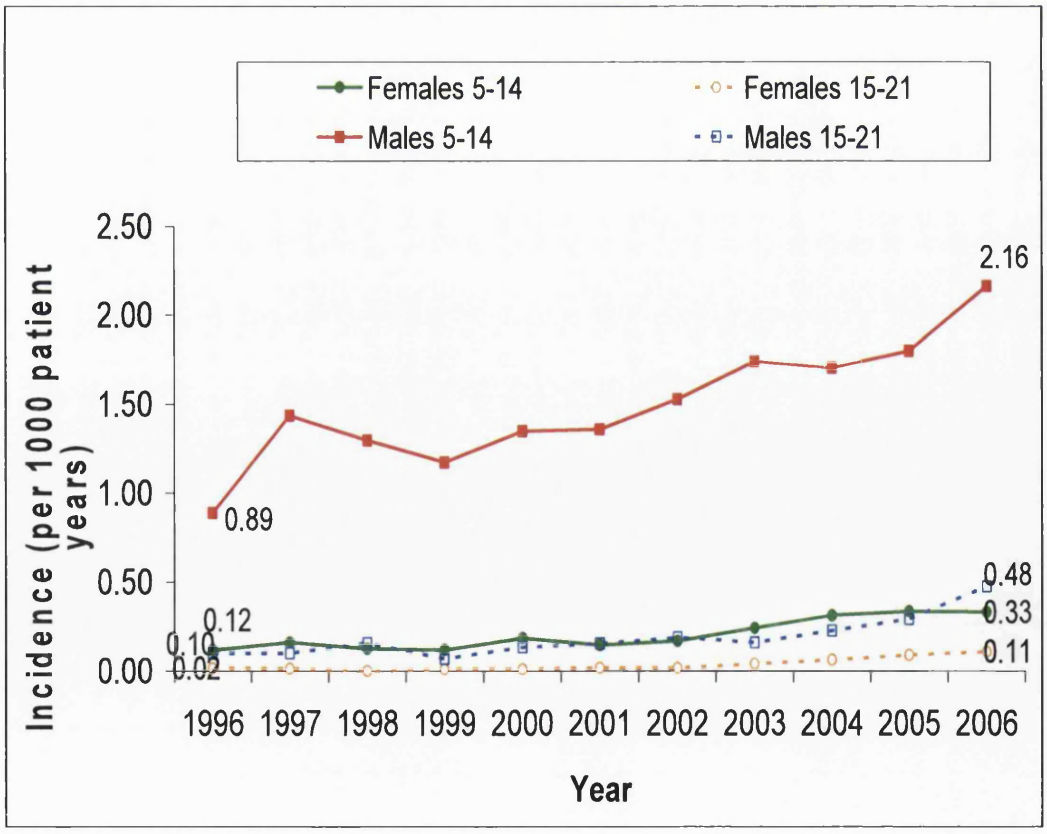
Figure 5-11: Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males aged 2-4 years from 1996 to 2006



5.5.3.2. Incidence

The overall incidence of prescription of ADHD/HKD medication within the cohort increased over the study period, from 0.30 per 1000 patient years (95% CI: 0.25 to 0.36) in 1996 to 0.74 per 1000 patient years (95% CI: 0.68 to 0.81) in 2006, a 2.47-fold increase. The incidence (new starters) of prescribing for patients aged 5-14 years and 15-21 years is illustrated in Figure 5.12.

Figure 5-12: Incidence of methylphenidate, dexamfetamine and atomoxetine by age and gender from 1996 to 2006



Mirroring the trends in Figure 5.10, there was an overall increase in incidence from 1996 to 2006 ($p<0.001$). Incidence of prescribing to males aged 2-4 years is illustrated in Figure 5.13. Similar to the prevalence of prescribing to these pre-school children, the incidence of prescribing has dropped over the study period; however this decrease was not significant ($p=0.06$).

Figure 5-13: Incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males aged 2 - 4 years

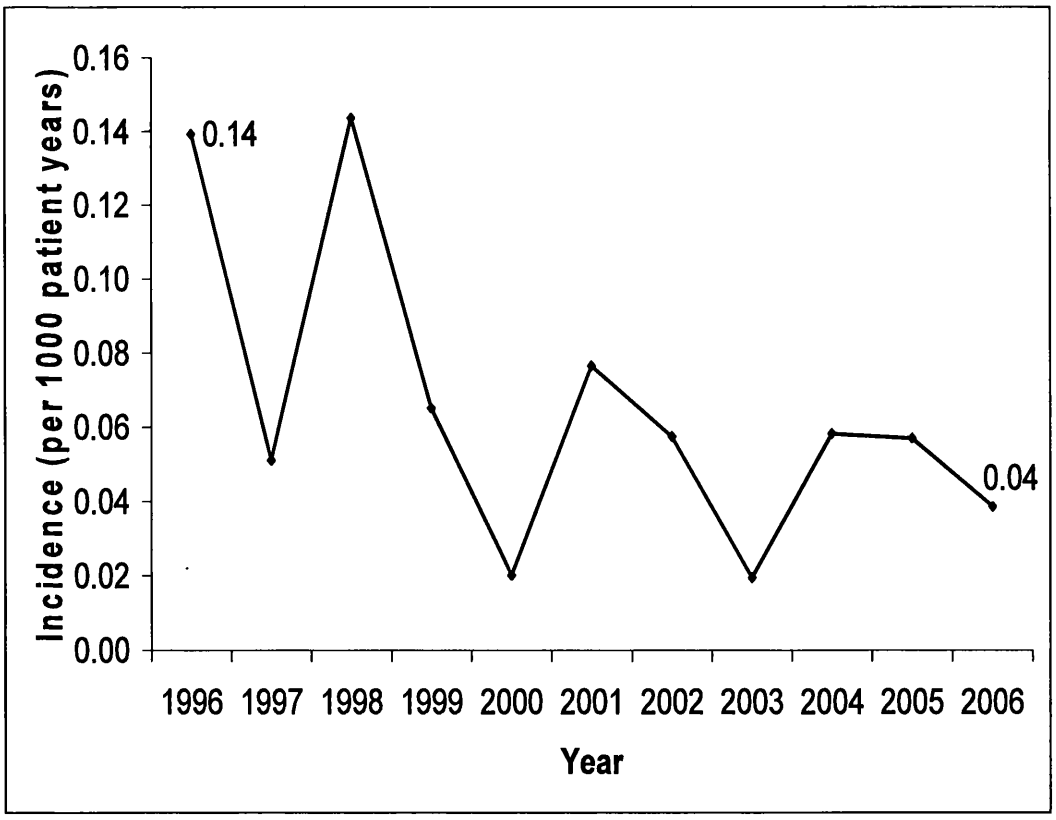
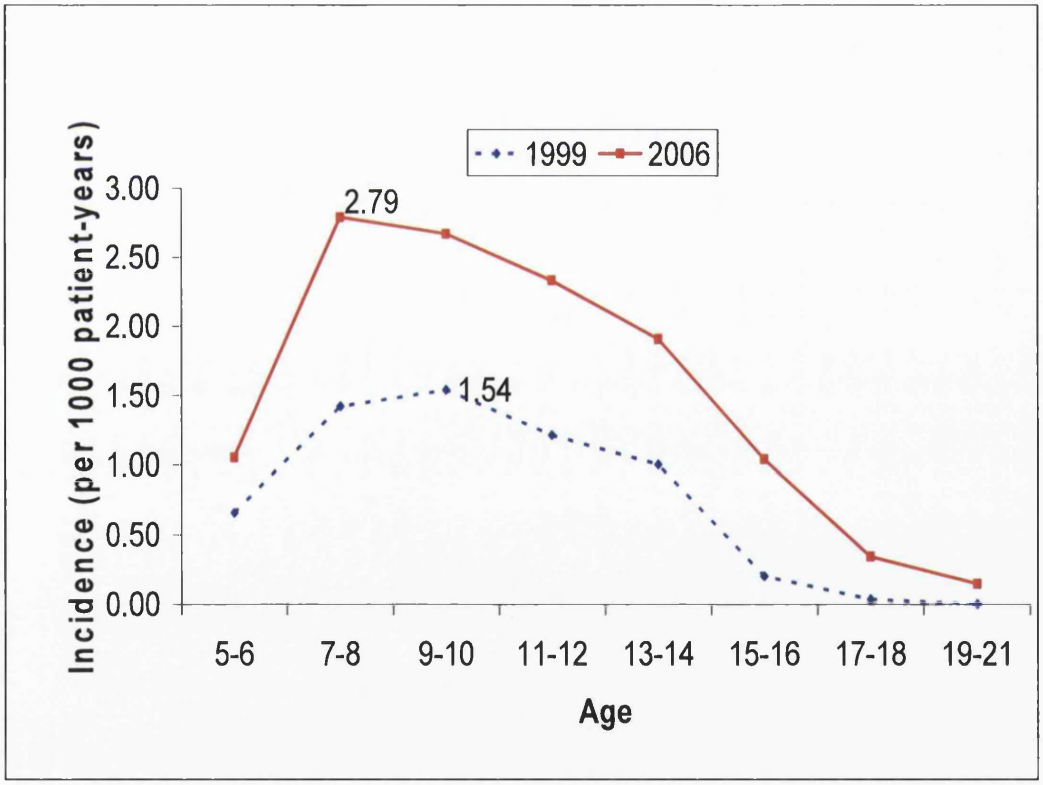


Figure 5.14 illustrates the age distribution of incident cases in males. This information is presented for the years 1999 and 2006 to allow for comparison with other published studies. This graph shows an increase from age 5 to a peak incidence in the 7-8 year old category, after which the incident rate decreases.

Figure 5-14: Incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males in 1999 and 2006



5.6. Drug Utilisation Study using IMS Disease Analyser - Medipius Database

5.6.1. Method

5.6.2. Data Source

The data source for this study was the IMS Disease Analyser – Mediplus Database (IMS-DA) which has been described previously. This database has been previously used to examine the prescribing trends of non-steroidal anti-inflammatory drugs and anti-diabetic drugs in children in the UK (Langman et al, 2001; Hsia et al, 2008). A subset of the IMS-DA, containing all paediatric data was supplied to the School of Pharmacy from IMS Health. In a manner similar to the GPRD study, the study cohort was defined by the prescribing of a study drug. Therefore, the first step involved compiling a list of drug codes for methylphenidate, dexamfetamine and atomoxetine. Unlike the GPRD who use the GPRD product code classification system, the IMS-DA use the ATC coding system for drugs. The ATC codes relevant to the ADHD drugs were: Methylphenidate (N06BA04), Dexamfetamine (N06BA02) and Atomoxetine (N06BA09). The database was searched for all records relating to the above codes. All prescriptions for a study drug were extracted from the database along with information on the patients who received them and the indication for their use.

5.6.3. Study Period

The study period for this utilisation study was 1st January 1996 to the 31st December 2006. This period was chosen to enable specific comparisons with data derived from the GPRD and other studies in this area.

5.6.4. Eligibility Criteria

The study population encompassed all patients aged 3 to 18 years registered with a GP who contributed data to the IMS-DA (Data was not available on children less than 3 years) . All prescriptions from this study population were screened for a study drug; methylphenidate, dexamfetamine and atomoxetine, using ATC classification codes.

Patients who received at least one prescription for a study drug during the defined period were classified as cases in the study. Patients were required to have at least one year of research standard data available, a known gender, and an acceptable patient registration status. Subjects who were temporarily registered with a practice were excluded.

5.6.5. Data analysis

The data extracted from the IMS-DA was imported into Stata/SE version 9.1 (StataCorp, College Station, Texas, United States), where the data was cleaned, manipulated and analysed. Prevalence and incidence were calculated using the equations described in Sections 5.5.3.1 and 5.5.3.2 respectively.

Prevalence and incidence were stratified into three age bands (3 to 4 years, 5 to 14 years, and 15 to 18 years) to allow comparisons with previous published studies. Ninety five per cent Confidence Intervals (95% CI) were generated using Poisson approximation and trends in annual prevalence and incidence from 1996 to 2006 were examined using the chi-squared test for trend.

5.6.6. Ethical Approval

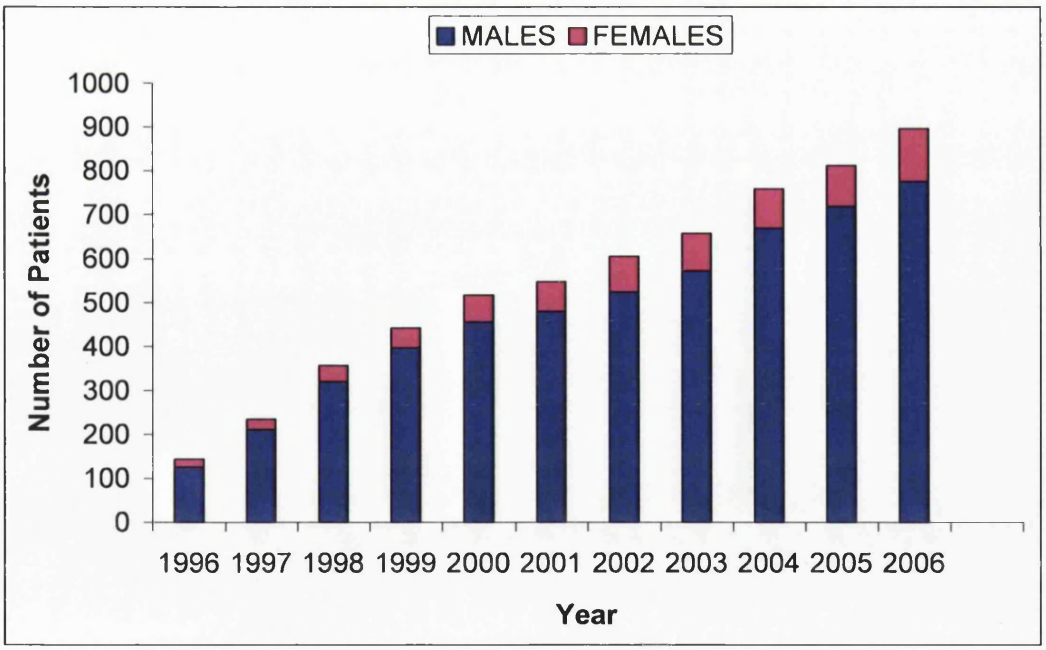
This study was covered by a generic ethical approval granted by the Independent Scientific and Ethical Advisory Committee for the conduct of drug utilisation studies in children and young adults in the UK using the IMS Disease Analyser – Mediplus (See Appendix 5).

5.6.7. Results

5.6.7.1. Patient Demographics

Between 1996 and 2006, 1,987 patients aged 3 – 18 years received a prescription for a study drug. The total number of prescriptions issued during this time was 41,848 prescriptions.

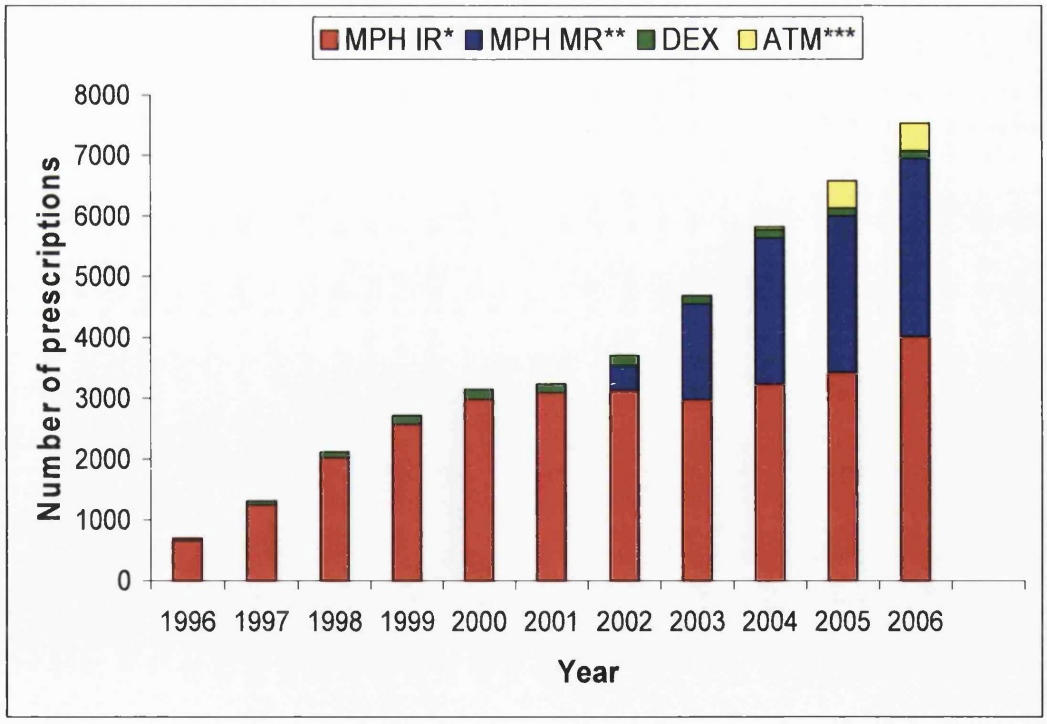
Figure 5-15: Number of male and female patients aged 3 - 18 years prescribed ADHD drug treatment from 1996 to 2006



The IMS data again shows a rise in the number of patients receiving ADHD drug treatment over the study period, with males comprising the majority of the study population. The ratio of males to females in the IMS database is 7:1 in 1996 dropping to 6.4:1 in 2006.

5.6.7.2. Prescribing Patterns

Figure 5-16: Proportion of ADHD drug use (methylphenidate, dexamfetamine and atomoxetine) by year



The changes in prescribing patterns presented here are similar to those observed from the GPRD data. The number of prescriptions issued for each of the drugs increased over the study period with the largest increase seen in atomoxetine prescribing (91% increase from 2004 when first licensed to 2006), followed by methylphenidate modified-release preparations (86% increase from 2002 when first licensed to 2006), immediate-release methylphenidate (83.5% increase from 1996 onwards) and dexamfetamine (66% increase from 1996).

One thousand six hundred and twenty five patients from the cohort of 1,987 (82%) had a diagnosis from Chapter V of ICD-10, Mental and behavioural disorders (F00-F99). These are listed according to ICD-10 code in Table 5.4.

Table 5-4: Indications for prescriptions as defined by WHO ICD-10 codes

ICD-10 code	Number of patients
Hyperkinetic Disorders (F90)	926
Conduct Disorders (F91)	408
Emotional Disorders with onset specific to childhood (F93)	4
Disorders of Social Functioning with onset specific to childhood and adolescence (F94)	1
Tic Disorders (F95)	7
Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence (F98)	18
Behavioural and emotional disorders with onset usually	**1364**

occurring in childhood and adolescence (F90-98)	
Mental Disorder, not otherwise specified (F99)	**127**
Receptive language disorder (F80.2)	3
Specific reading disorder (F81.0)	5
Developmental disorder of scholastic skills, unspecified (F81.9)	23
Specific developmental disorder of motor function (F82)	2
Mixed specific developmental disorders (F83)	1
Childhood autism (F84)	28
Asperger's syndrome (F84.5)	24
Pervasive developmental disorder, unspecified (F84.9)	1
Unspecified disorder of psychological development (F89)	6
Disorders of Psychological Development (F80-F89)	**94**
Unspecified mental retardation (F79)	1
Mental Retardation (F70-F79)	**1**
Emotionally unstable personality disorder (F60.3)	5
Disorders of adult personality and behaviour (F60-F69)	**5**
Behavioural syndromes associated with physiological	**2**

disturbances and physical factors (F50-F59)	
Neurotic, stress-related and somatoform disorders (f40-F48)	**26**
Mood (affective) disorders (F30-F39)	**4**
Mental and behavioural disorders due to psychoactive substance use (F10-F19)	**1**
Organic, including symptomatic, mental disorders (F00-F09)	**1**

5.6.7.3. Prevalence and Incidence of Prescribing

Prevalence

Figure 5.17 shows the prevalence of prescribing by age and gender from 1996 to 2006. As was demonstrated by the GPRD data, the prevalence of prescribing has increased across all ages and gender.

In 1996, the prevalence of prescribing for males aged 5-14 years was 1.21 per 1,000 patients, which increased to 7.96 per 1,000 patients in 2006, a 6.58-fold increase.

The prevalence for females of the same age increased from 0.19 per 1,000 patients in 1996 to 1.31 per 1,000 patients in 2006, a 6.89-fold rise. The prevalence of prescribing in young children is presented in Figure 5.18. Again, as seen with the GPRD data, there was a decrease seen in the overall prevalence of prescribing to males aged 3 – 4 years.

Figure 5-17: Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine by age and sex from 1996 to 2006

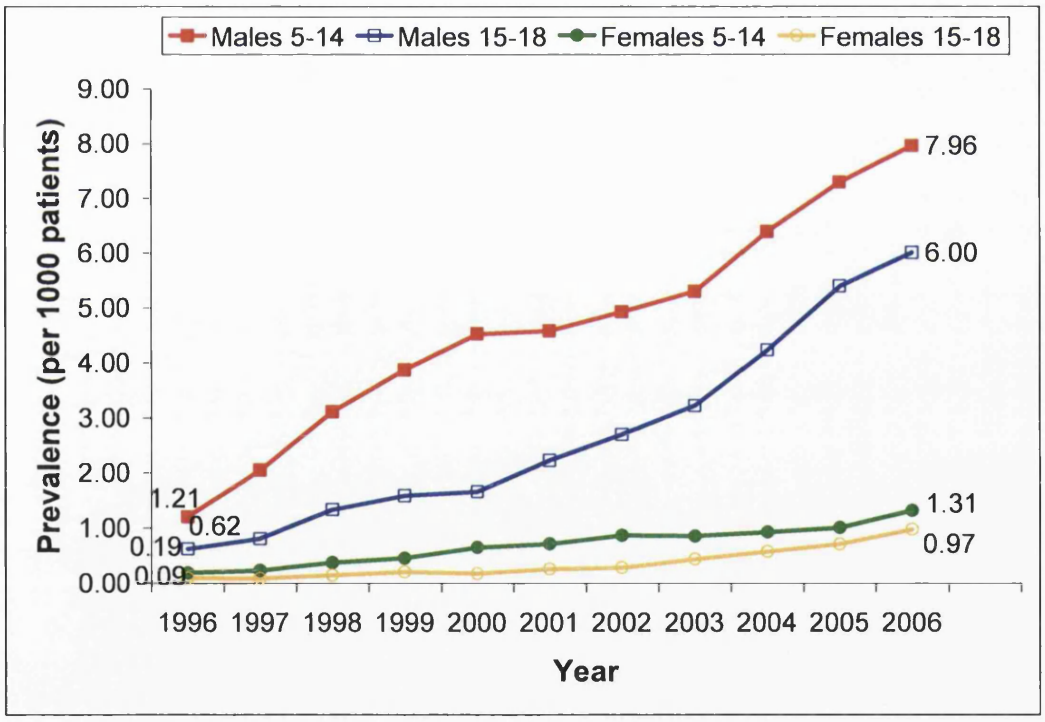
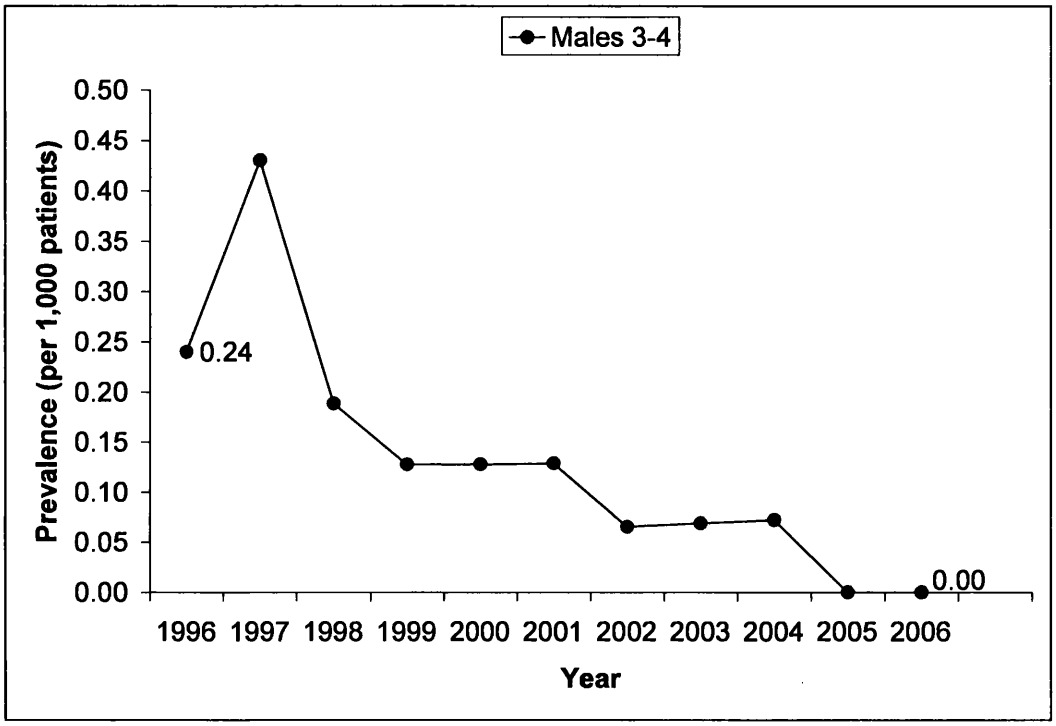


Figure 5-18: Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males aged 3 - 4 years from 1996 to 2006



Incidence

The incidence of prescribing by age and gender is illustrated in Figure 5.19. The incidence in males aged 5-14 years increased 1.88-fold over the study period. A 2.44-fold increase was seen in female patients aged 5-14 years.

The incidence of prescribing in younger males is presented in Figure 5.20. An overall decrease was also seen in these patients. In 1996, the incidence was 0.25 per 1,000 patient years which dropped to 0 per 1,000 patient years in 2006.

Figure 5-19: Incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine by age and sex from 1996 to 2006

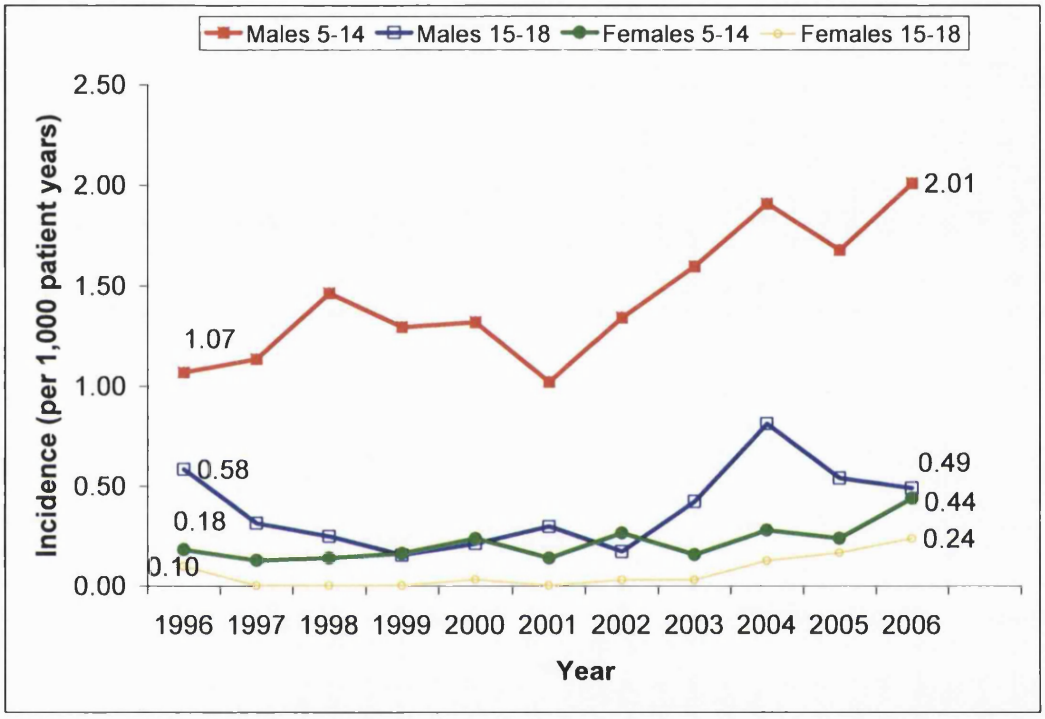
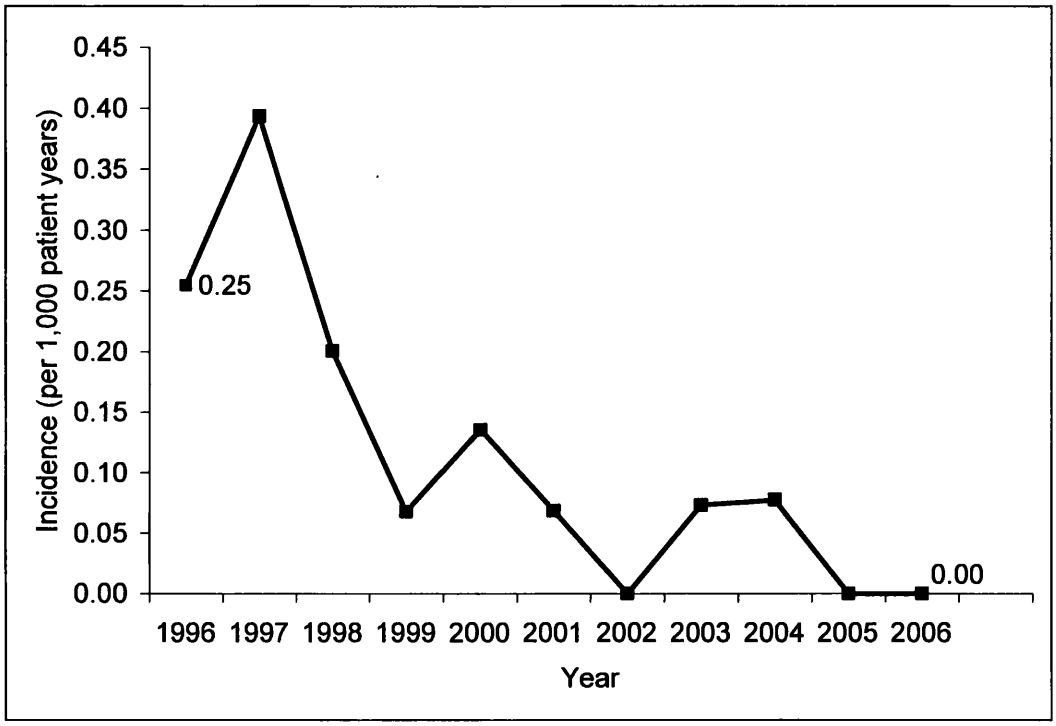


Figure 5-20: Incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males aged 3 - 4 years from 1996 to 2006



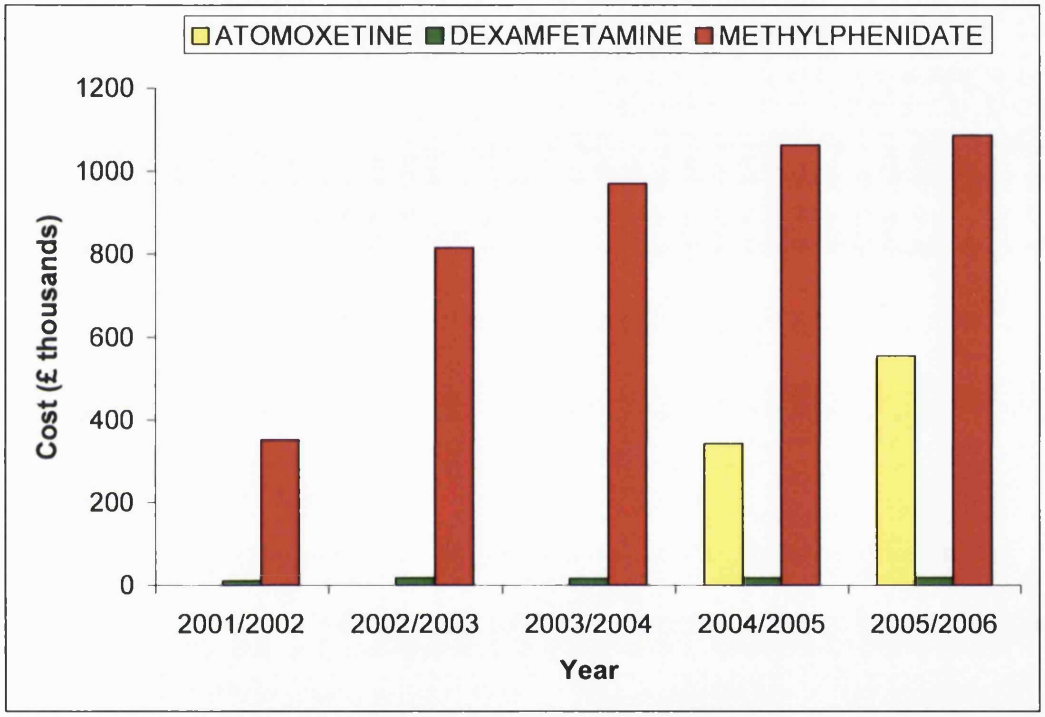
5.7. Prescription Pricing Division Data

Data was obtained from the Prescription Pricing Division (PPD), on the use of methylphenidate, dexamfetamine and atomoxetine from hospital and primary care dispensing records.

5.7.1. Hospital Data

One of the main limitations of the GPRD and IMS-DA is the fact that data is only obtained from primary care records. Therefore, to determine the extent of medication use in secondary care, hospital dispensing information was obtained from IMS Hospital Pharmacy Audit data.

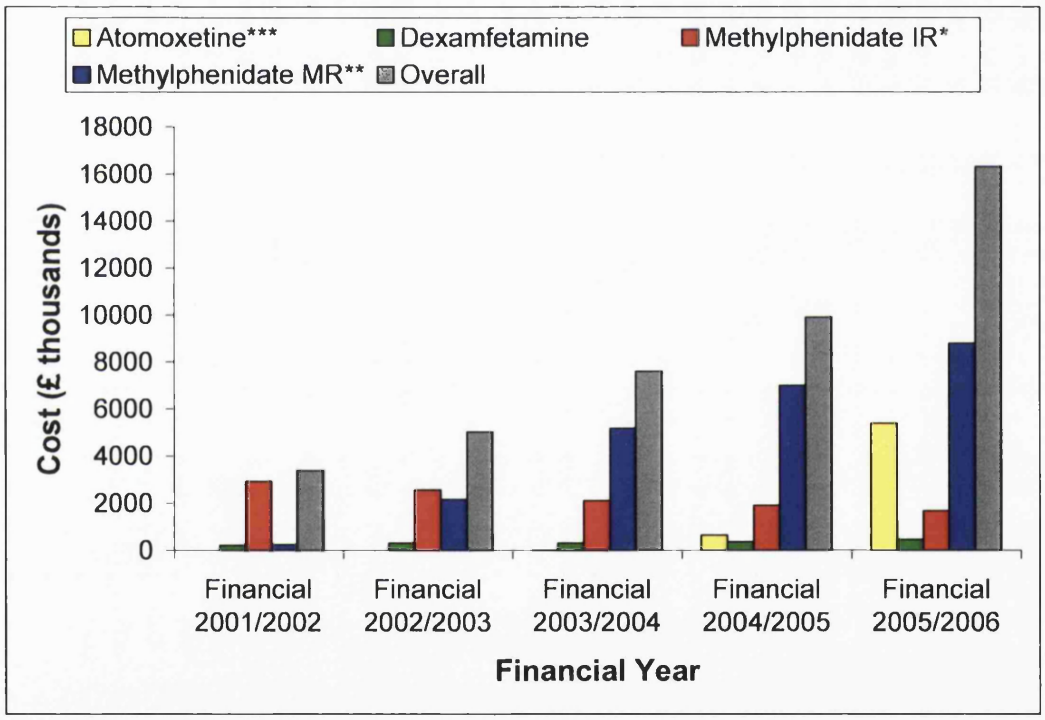
Figure 5-21: Cost of methylphenidate, dexamfetamine and atomoxetine at NHS Price List from 2001 to 2006 from IMS HEALTH Hospital Pharmacy Audit (HPAI) database



5.7.2. Primary Care Data

Data on methylphenidate, dexamfetamine and atomoxetine from primary care was also obtained from the PPD and is presented by financial year in Figure 5.22.

Figure 5-22: Net Ingredient Cost of methylphenidate, dexamfetamine and atomoxetine from 2001 to 2006 from primary care



* Immediate-release

** Modified-release preparations first authorised in 2002

*** First authorisation in 2004.

5.8. Overall Discussion

5.8.1. Patient Demographics

The prevalence of ADHD in children reported in the literature is much higher in males than females, ranging from a ratio of 2:1 to 9:1 (Biederman et al, 2004a). It is not known to what extent this is a true behavioural gender difference and how much is due to factors such as the under-diagnosis and under-reporting of the condition in females. The results from this utilisation study using both GPRD and IMS data show that although the overall number of patients receiving ADHD drug treatment has increased, there remains a significant gender difference. The data from the GPRD showed how the ratio of male to female patients in the cohort decreased only slightly, and in 2006, remained at approximately 7:1. The results from this study are similar to those found by Green et al (2005), who conducted a national survey in 2004 to examine the mental health of children and young people in Great Britain and found that 86% of children with HKD were boys. The issue of gender differences, particularly in older adolescents will be examined in further detail in Chapter 6.

A proxy for the socio-economic status of patients was examined. As mentioned, there is no direct link of patients and SES and so the practice post-code score which is derived from the Index of Multiple Deprivation was used. As the population of many practices spans the social spectrum, the use of the SES score may not be a reliable indicator of the social deprivation of a patient, and so needs to be interpreted with caution. Green et al (2005) found that children with hyperkinetic disorders (HKD) were more likely than other children to live in low income households and to have parents with no educational qualifications. Children with HKD were more likely to live in areas classified as 'Hard Pressed' and less likely to live in areas classified as 'Wealthy Achievers'. However, the data represented here demonstrates that the patients prescribed medications for ADHD were derived from populations of varying levels of deprivation, and no difference was seen in the proportion of patients receiving ADHD medications between the most and least affluent groups.

5.8.2. Patterns of drug selection

From 1996 to 2002, immediate-release methylphenidate and dexamfetamine were the only medications available for selection by clinicians. From 2002 onwards, with the introduction of extended release preparations such as modified-release methylphenidate and the non-stimulant atomoxetine (in 2004), there has been a shift in prescribing, particularly to the use of the modified-release methylphenidate. Similar trends in prescribing and dispensing were seen in the GPRD, the IMS database and the PPD, both from primary and hospital data.

The data from the GPRD showed that by 2006, modified-release methylphenidate preparations accounted for over 62% of the total usage of the study drugs; immediate-release methylphenidate was the next most prescribed medication with 28% of the total usage, followed by atomoxetine (8%) and lastly dexamfetamine (2%). The dramatic increase in use of longer acting preparations that has occurred since their introduction to the market is not surprising considering that they offer several key advantages over the immediate-release drugs. These have been discussed previously in Section 1.4.3.

A recent systematic review on the use of long-acting medications in ADHD and HKD (Banaschewski et al, 2006) examined the issue of choice of medication for the condition, and recommended that long-acting preparations of methylphenidate should be available and used and may be the preferred choice of patients. They do suggest however that these modified-release preparations should not replace the short-acting drugs, which will often be the preferred choice when initiating treatment due to their lower cost and the flexibility of dosing. The data from the GPRD suggests that the use of modified-release methylphenidate has largely replaced both immediate-release methylphenidate and dexamfetamine. More patients are also being prescribed atomoxetine, and though its overall use is still low, its use has increased significantly in the three years since its introduction.

5.8.3. Trends in prevalence and incidence

5.8.3.1. Pre-School Children

Because stimulants are drugs of potential abuse, controversy continues to surround their use, especially for preschool-age children. A study examining trends in the prescribing of psychotropic medications to children aged 2 – 4 years in the US from 1991 to 1995 showed an increase in the prevalence of methylphenidate to young children. This study by Zito et al (2000) used data from 2 state Medicaid programs and a health maintenance organisation. Over the study period, the prevalence figures increased 3-fold to 11.1 per 1000 patients, 1.7-fold to 7.5 per 1000 patients and 3.1-fold to 4.0 per 1000 patients for the three sites.

The data from the GPRD, 0.2 per 1000 patients in 1996 and 0.04 per 1000 patients in 2006, suggests that the numbers of pre-school children receiving medication for ADHD/HKD in the UK from their GP is very low. This trend was also replicated using data from the IMS data. As recommended by NICE (2008), if pre-school children require drug treatment for ADHD, then they should be referred to a clinician with specialist expertise in the area. It is therefore possible that a proportion of these very young patients may be solely under the care of a child psychiatrist or community/hospital paediatrician and therefore not receive prescriptions from a family doctor thus leading to the underestimation of the prevalence of prescribing to this cohort by the GPRD. Despite the low number of these patients, the data showed that in contrast to the other age categories, prevalence in preschool boys showed a significant decline over the study period.

5.8.3.2. School-Aged Children, Adolescents and Young Adults

The GPRD study shows that the prevalence of prescribing to boys aged 5-14 has risen from 1.23 per 1000 patients in 1996 to 8.30 in 2006, a 6.7-fold increase. The prevalence in adolescent males and in females of all ages has also increased over the 10 years studied. Similar increases were seen using data from the IMS database.

To our knowledge, only one previous study has examined the use of these drugs in the UK (Jick et al, 2004). The authors reported on the incidence and prevalence of methylphenidate in boys aged 5-14 from 1996-2001. This study reported a prevalence of 5.3 per 1000 boys in 1999.

A study from the Netherlands (Schirm et al, 2001) used computerised pharmacy dispensing records to examine the prevalence and incidence of psychotropic medications in children. The prevalence of stimulant use in patients aged 0-19 years increased from 1.5 per 1000 children in 1995 to 7.4 per 1000 children in 1999. The highest rate of prevalence was seen in children aged 5-9 years which in 1999, was 13.9 per 1000 children.

A study examining prescribing trends for stimulants from 1992 to 1998 using North Carolina Medicaid prescription claim files reported an increase in prevalence from 44 per 1000 patients in 1992 to 95 per 1000 patients in 1998 in children aged 6-14 years (Rushton and Whitmire, 2001). This study has acknowledged that the rates observed were much higher than other studies reported, however they do not speculate as to why this is the case.

Another study (Miller et al, 2001) examined prescription data from 1990 to 1996 using the British Columbia's Triplicate Prescription Program database for controlled drugs. They reported for children aged 19 years and less, the prevalence increased from 1.9 per 1000 in 1990 to 10.96 per 1000 children in 1996.

A more recent study from the US (Zuvekas et al, 2006) used the Medical Expenditure Panel Survey database to report prevalence of stimulant use from 1997 to 2002 in children aged less than 19 years. Unlike other reports, the authors did not find a statistically significant increase in prevalence during the study period. The prevalence increased from 27 per 1000 patients (95% CI: 23 – 31 per 1000) in 1997 to 29 per 1000 patients (95% CI: 25 – 33 per 1000) in 2002. They also reported the highest use of stimulants in children aged 6-12 years.

These utilisation studies suggest that especially in the US, the prevalence of stimulant use increased significantly during the last decade, however more recent studies suggest that this increase may have attenuated in more recent years. Our study has demonstrated a significant increase in prevalence rates in the UK, which have continued to rise throughout the study. As discussed previously, there has been concern reported in the media over the frequency and appropriateness of prescribing of these drugs. The highest prevalence figure reported in the GPRD study of 8.3 per 1000 patients (boys aged 5-14 years of age in 2006) is well below those reported from a decade ago in both the Netherlands and the US.

More importantly this figure is also far lower than the global prevalence of ADHD in children or hyperkinetic disorders in the UK, which were recently estimated to be 5% and 1.5% respectively (Polanczyk et al, 2007; Green et al, 2005). This is relevant as current European clinical guidelines recommend that for those with hyperkinetic disorder, medication will most often be the first choice treatment and that medication will also be appropriate for a proportion of those who whilst not meeting the criteria for hyperkinetic disorder do meet the criteria for the broader ADHD phenotype (Taylor et al, 2004).

An overall increase in the incidence rate of prescribing was observed in this study. The incidence in males aged 5-14 years increased from 0.89 per 1000 patient years in 1999, to 1.35 per 1000 patient years in 2001 (also reported by Jick et al, 2004) and to 2.16 per 1000 patient years in 2006, an overall 2.43-fold increase. For older boys aged 15-21 and females of all ages, the increase in incidence became significant from 2001 onwards. This coincided with the publication of the NICE guidelines on methylphenidate in October 2000 (NICE, 2000) which is likely to have prompted appropriate prescribing to the untreated ADHD patient. In line with data from Jick et al (2004), the peak incidence of prescribing in 1999 occurred in patients aged 9-10 years. In 2006 however, the peak incidence occurred in children aged 7-8 years, suggesting that patients may now be presenting to clinicians and receiving treatment at an earlier age.

5.8.4. Strengths and weaknesses of the study

The use of GPRD and IMS data allowed us to capture what is actually happening under normal conditions of practice, rather than in selected samples of patients recruited into clinical trials. There are however a number of limitations in using the GPRD and IMS databases.

Whilst the GPRD deems patients as being 'active' or not on the database, this was not verified and is a limitation of the study. One method which could have been employed to do this would be to review all patients' records over a defined period of time to see whether they had had any consultations or prescriptions issued, thereby ensuring their active status. However, to do this, one would have to determine an arbitrary period of time to define what an active patient is and as many children do not attend their GP on a regular basis, this method may have lead to an underestimation of the number of active patients on the database.

As previously mentioned, as it was a legal requirement prior to 2005 for controlled drugs to be hand-written, there is a possibility that the actual number of prescriptions prescribed is under-reported on the database. However, if this was the case, we would not expect the rate of under-reporting to differ from year to year or to affect any particular patient group, and so the trends in prescribing should not be significantly impacted by this limitation.

The databases do not record information concerning treatment dispensing of prescriptions or treatment compliance, which is a limitation of many automated databases.

In addition, some GPs are unwilling to prescribe treatments for ADHD for various reasons in which case prescribing continues solely in secondary or tertiary care. Unfortunately there is no known data to show the proportion of patients in whom this occurs and so the data presented may under-represent the true prescribing prevalence and incidence of ADHD treatment in the UK.
In an attempt to bridge this gap, data was obtained from the Prescription Pricing Division on the dispensing of these ADHD drugs in primary and secondary care.

Although the nature of the data available prevents calculations on prevalence or incidence, or indeed analysis by age group, the data in the form of drug cost displayed trends of increasing use, which mirror those seen using GPRD and IMS data.

5.8.5. Conclusion

The data presented here from the GPRD and the IMS database suggests that both the prevalence and incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine to school-aged children and young adults has increased over the last decade in the UK. Although the rates are well below the reported prevalence of the condition in the UK and are also lower than the prescribing rates reported in the Netherlands and the US, further work is required to determine whether levels of prescribing are appropriate to the level of the condition.

6. Chapter SIX: Cessation of Attention Deficit hyperactivity disorder Drugs in the Young (CADDY)

6.1. Introduction

Whilst there is evidence of persistence of ADHD from childhood into adulthood, there is limited data from the literature on the persistence of drug treatment in adolescents and young adults. Consequently, in 2006 the Health Technology Assessment (HTA) programme, as part of the National Institute for Health Research commissioned a scoping study "Cessation of Attention deficit hyperactivity Disorder Drugs in the Young" (CADDY). The CADDY team was a multidisciplinary team composed of pharmacists, consultant child and adolescent psychiatrists, an adult psychiatrist, paediatricians, psychologists, epidemiologists, a statistician and a representative from a national ADHD support group. My role in this multidisciplinary team was to conduct the Part 1 quantitative study. This involved refining the initial study protocol in line with reviewer comments from the HTA , extracting, manipulating and analysing data from the GPRD, interpreting the results obtained in the context of the available published literature and the qualitative data gathered from the Part 2 interview study and the final report writing.

6.2. Aim and Objectives

The overall aim of the CADDY project was to review the current practice of treatment of ADHD during transition from adolescence to young adulthood.

The objectives of the study in order to achieve this aim were:

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.

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 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 the feasibility of use with adolescents and young adults with ADHD.

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).

Objectives 1 to 3 were answered in Part 1 of the CADDY study, a pharmacoepidemiological study using general practice data. To achieve objectives 4 to 6, an in-depth interview study (Part 2) was conducted with ADHD patients and clinicians involved in the care of patients with ADHD. The Part 2 study was conducted by other collaborators in the CADDY team; however the results of the study will be discussed in light of the findings from the Part 1 study.

6.3. Method

6.3.1. Data Source

Data was extracted from the GPRD as described previously.

6.3.2. 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 1st January 1999 and 31st December 2006
- Have at least 1 year of research-standard data available in the database.
- Have a diagnosis of ADHD
- Have at least one year's duration of treatment with methylphenidate, dexamphetamine or atomoxetine. This will ensure only patients who have had good response to treatment will be included in the study.

Exclusion criteria included:

- Temporary registration with a general practices.
- A prescription for methylphenidate, dexamfetamine or atomoxetine for other reasons, such as narcolepsy, or epilepsy (to counter toxic effects of anticonvulsants).

6.3.3. Data synthesis and analysis to obtain information on current practice

Patients were initially identified using the methodology described in Section 5.4.3 From this drug cohort, only those patients meeting the eligibility criteria for the CADDY study were included. Patient characteristics, prescribing trends and prevalence rates were examined for this patient group over the study period.

6.3.4. Duration, cessation and restart of treatments

A number of steps were taken in order to calculate duration of treatment, and to identify treatment cessation and re-initiation.

Step 1: Initially, the duration of each prescription for each patient was calculated from the daily dosage and the quantity of medication prescribed. The daily dosage was calculated using the dosage converter tool supplied by the GPRD. This tool enables the conversion of a dosage instruction such as 'Take two tablets in the morning and one tablet at midday' to a daily dose of 3 tablets. This method was used to convert the dosage instructions of all prescriptions.

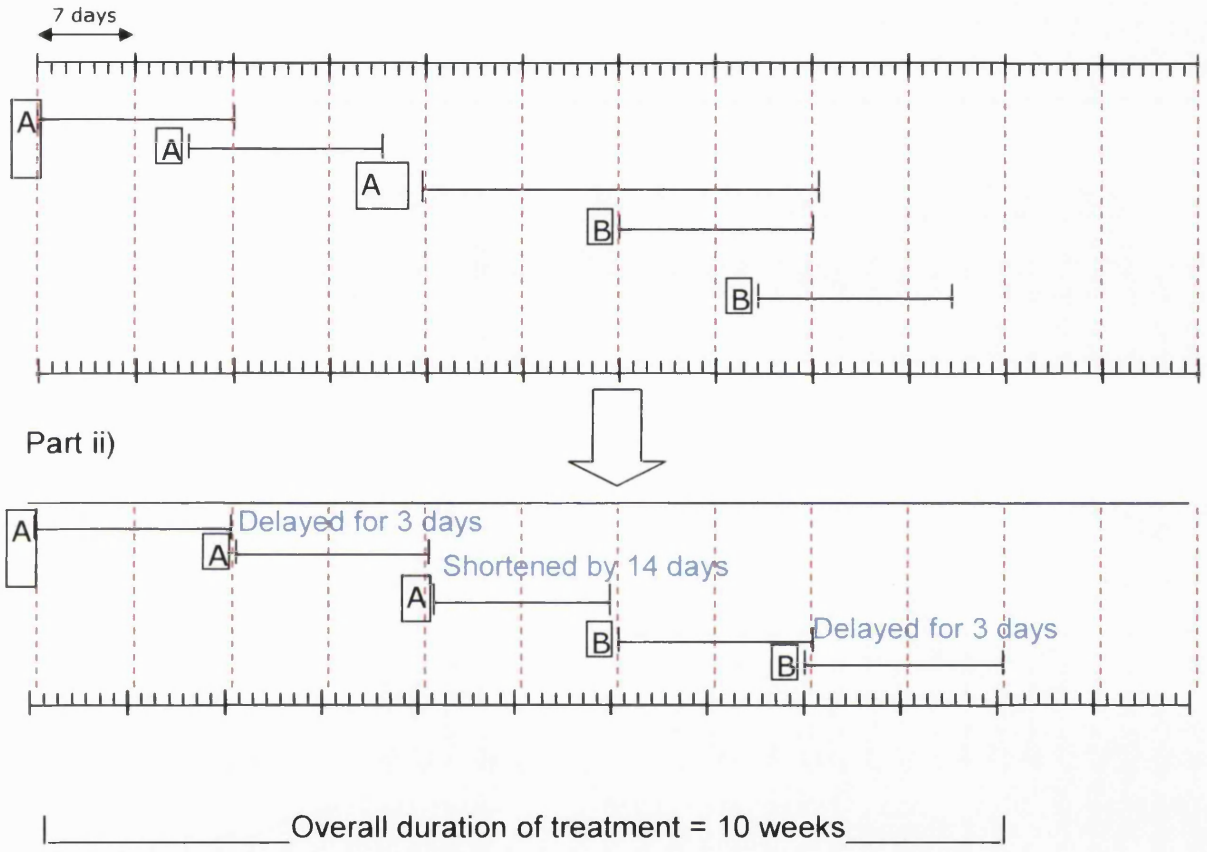
For any prescriptions where the dosage could not be determined, such as 'Take as directed', the daily dose for that prescription was replaced with the median daily dose for that drug type and strength.

Dividing the total quantity of tablets given in any one prescription by the daily dosage resulted in the prescription duration e.g. a prescription for sixty tablets of Ritalin ® with dosing instructions of 'Take one tablet twice a day' resulted in a prescription duration of 30 days.

Step 2: Following the calculation of all prescription durations, the prescriptions were then 'mapped' in order to determine overall treatment duration. Figure 6.1 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 in both prescriptions, it was assumed that the second overlapping prescription started the day after the previous one finished 'concatenation'.

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 'truncation'. In Figure 6.1, Part i) shows the prescriptions for Drug A and B as they were issued to a patient while Part ii) shows how the prescriptions are truncated and concatenated to determine the overall total duration of treatment.

Figure 6-1: Schematic diagram illustrating concatenation and truncation of prescriptions for Drug A & B



Step 3: Patients' data was screened for any records of treatment cessation. The consensus of the CADDY team was that a minimum gap of six months between prescriptions would constitute a stop in treatment. The team felt that patients receiving treatment for ADHD would be seen by the clinician at least every six months, and would not receive a prescription for a study drug that would last longer than 6 months. Therefore, anyone with a gap of more than 6 months between prescriptions was classified as having stopped treatment.

The date that the last prescription ended was used as the stop date of the treatment episode. 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 (i.e. treatment starting following a gap of six or more months without treatment) and possible factors affecting treatment restart were also investigated.

As detailed in Section 1.5.5.2, the rate of persistence of ADHD into adulthood was examined by Faraone et al (2006) by meta-analysis of follow-up studies. 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. We hypothesized that the rate of decline in prescriptions for ADHD should mirror this rate of decline in diagnostic prevalence. Using the conservative figure of 83% for each 1-year change in age (i.e. patients who retain the full ADHD diagnosis); we should expect to see an equivalent reduction in prescribing rates of around 17% each year.

6.3.5. Ethical Approval

Ethics approval was granted for the project by ISAC Protocol Reference No 779. (See Appendix 4)

6.4. Results

6.4.1. 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.

Tabie 6-1: Characteristics of the study population by year

Year	Total Prescriptions	MPH IR* (% of total)	MPH MR** (% of total)	DEX (% of total)	ATM*** (% of total)	Total Patients	Ratio of Males/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	1,194	964 (80.7)	162 (13.6)	68 (5.7)	-	197	182 / 15
2003	2,180	977 (44.8)	1,123 (51.5)	80 (3.7)	-	284	254 / 30
2004	3,211	1,022 (31.8)	2,038 (63.5)	123 (3.8)	28 (0.9)	386	347 / 39
2005	4,571	1,075 (23.5)	3,031 (66.3)	173 (3.8)	292 (6.4)	505	454 / 51
2006	5,517	1,116 (20.2)	3,932 (71.3)	88 (1.6)	381 (6.9)	577	519 / 58

* * Immediate-release ** Modified-release preparations first authorised in 2002

*** First authorisation in 2004.

Table 6.1 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 accounted for approximately 95% of the total usage. From 2002 onwards, there has been a shift in prescribing in this patient cohort, particularly to the use of the modified-release methylphenidate. This mirrors the trends seen in younger children in Chapter 5.

6.4.2. 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 (95% CI: 0.19 to 0.33) in 1999 to 2.07 per 1000 patients (95% CI: 1.90 to 2.25) in 2006.

Figure 6.2 demonstrates the increase in prevalence stratified by gender. In 1999, the prevalence of drug prescribing for males aged between 15 and 21 was 0.49 per 1000 patients (95% CI: 0.36 to 0.64) whereas in 2006, the prevalence per 1000 patients was 3.63 (95% CI: 3.32 to 3.95). This was an overall 7.41-fold increase in prevalence over the 8-year period ($p<0.001$ for trend). In females in 1999, the prevalence was 0.02 per 1000 patients (95% CI: 0.002 to 0.07); however, in 2006, this figure rose to 0.43 (95% CI 0.32 to 0.55), a 21.5-fold increase ($p<0.001$ for trend).

Figure 6-2: Prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine to patients aged 15 - 21 years from 1999 to 2006

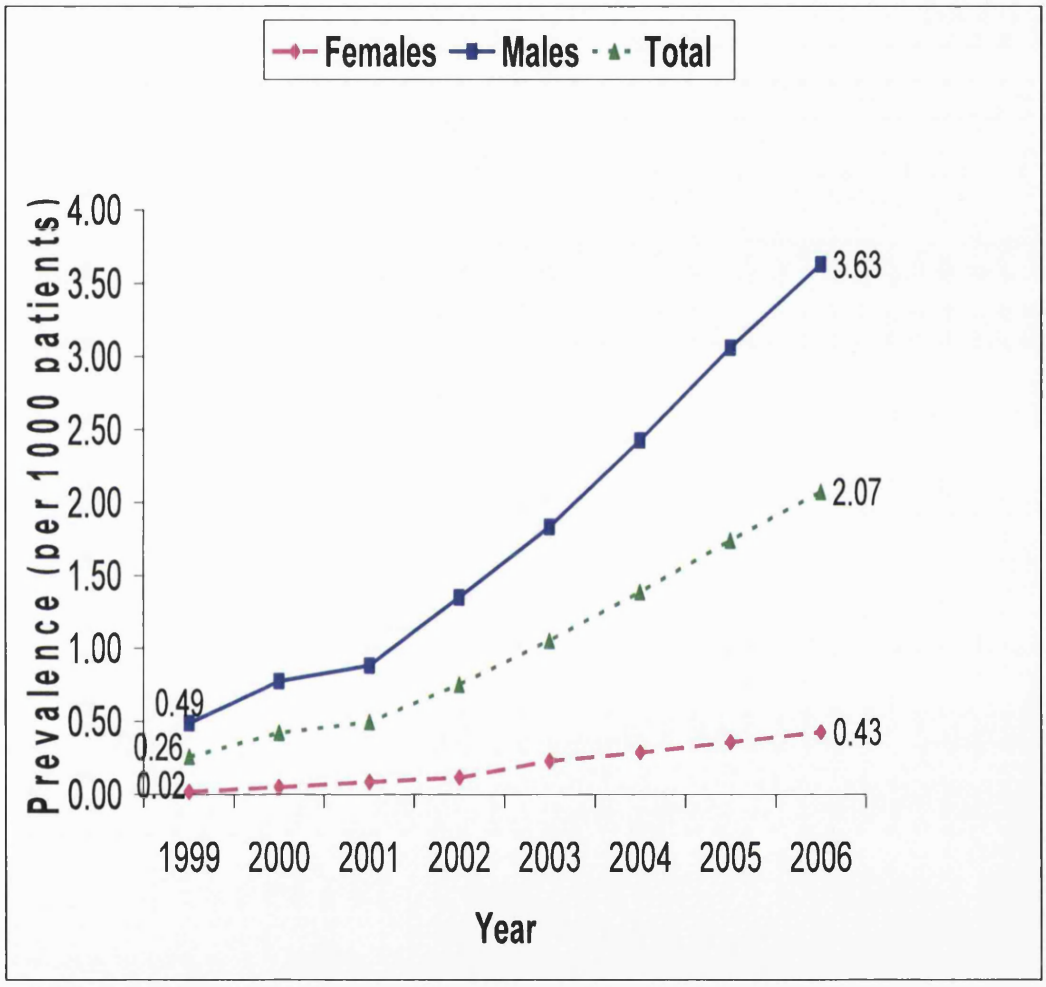


Figure 6-3: Increasing prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine by year in males aged 15 to 21 years

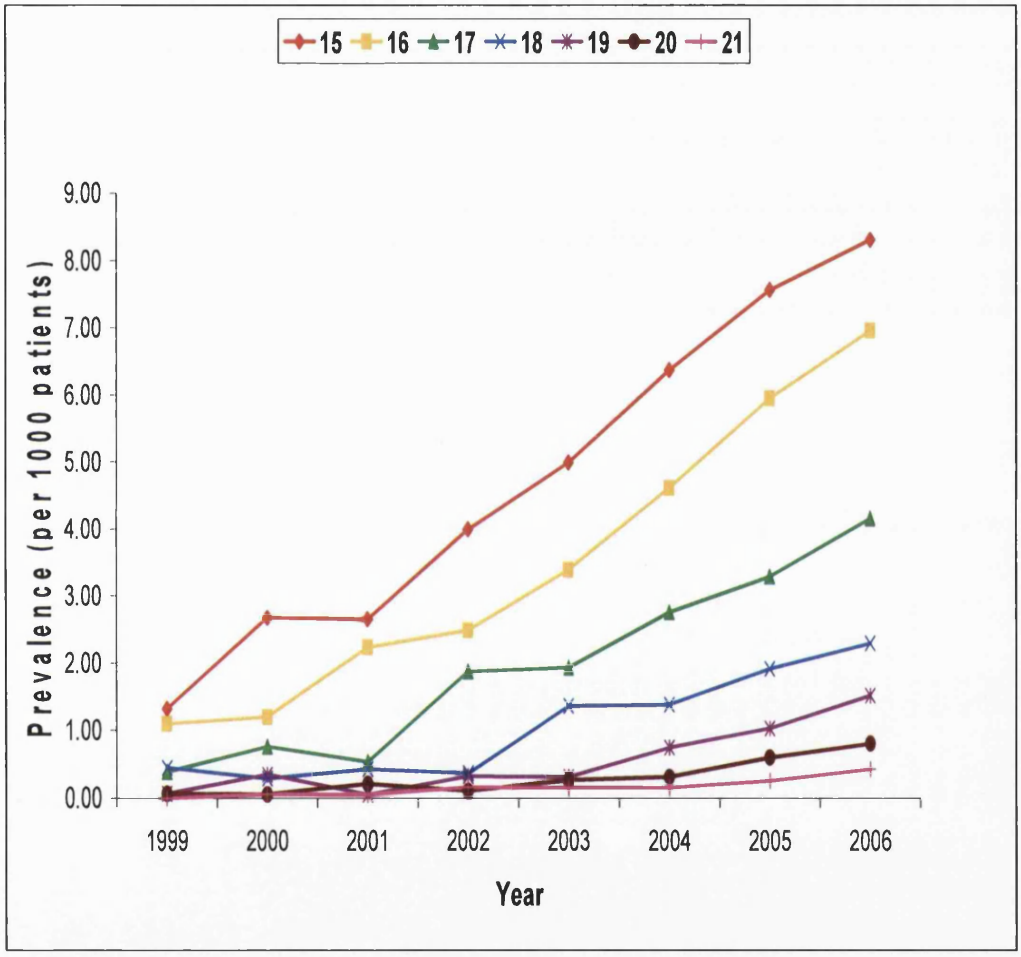


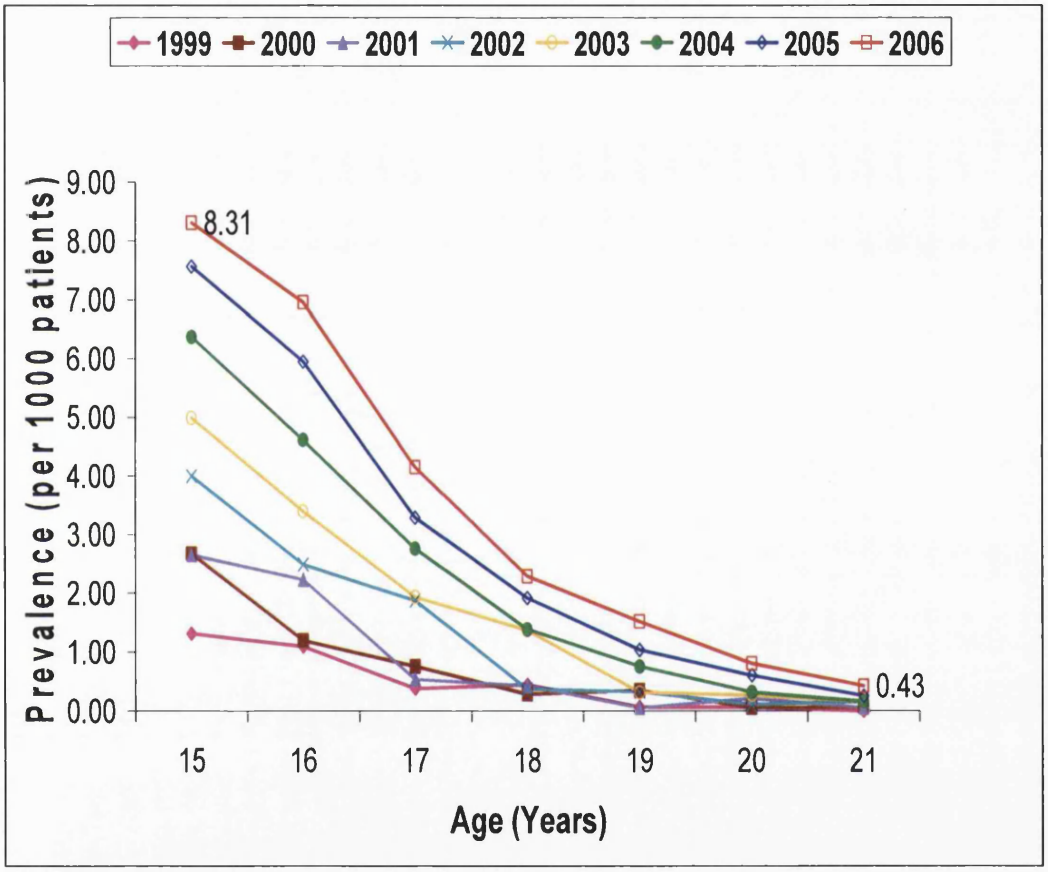
Figure 6.3 illustrates the prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine to males, stratified by age, from 1999 to 2006. This shows a significant increase in prevalence across all ages ($p<0.01$); however, it is noticeable that the biggest increase is in the younger patients, with the rate of increase by year becoming less evident in older patients.

6.4.3. Duration and Cessation of Treatment

Firstly, a cross-sectional analysis was carried out to illustrate the change in prescription rates for males aged 15 to 21 between 1999 and 2006. This is illustrated in Figure 6.4. Along with the data displayed in Figure 6.3, Figure 6.4 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 ($p=0.001$ determined by fitting logistic regression for grouped data) with a marked increase in prevalence for younger 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 olds males (8.31 per 1,000 patients compared to 0.43 per 1,000 patients). The χ^2 test for trend showed a significant linear trend ($\chi_1^2 = 299.14$ $p<0.001$) demonstrating a strong effect of age on decreasing treatment prevalence.

Figure 6-4: Decreasing prevalence of prescribing of methylphenidate, dexamfetamine and atomoxetine in males from age 15 to 21 years from 1999 to 2006



To more directly address the issue of discontinuation, survival analysis was conducted. As previously described, the total treatment duration was determined from the date of the first prescription to the end date of the last prescription. A gap of six 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 6.2

Table 6-2: The 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

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 re-calculated using the definition of 9 months between prescriptions. The results of this, presented in Table 6.3 show that the number of treatment episodes varies little (7.4% change in number of patients with 1 episode). Based on these results and the clinical decision of the team, the initial definition of 6 months was used for all further analysis.

Table 6-3: The number of treatment episodes per patient when a definition of cessation of 9 months between prescriptions was employed

Number of Treatment Episodes	Number of Patients
1	909
2	67
3	7
4	0

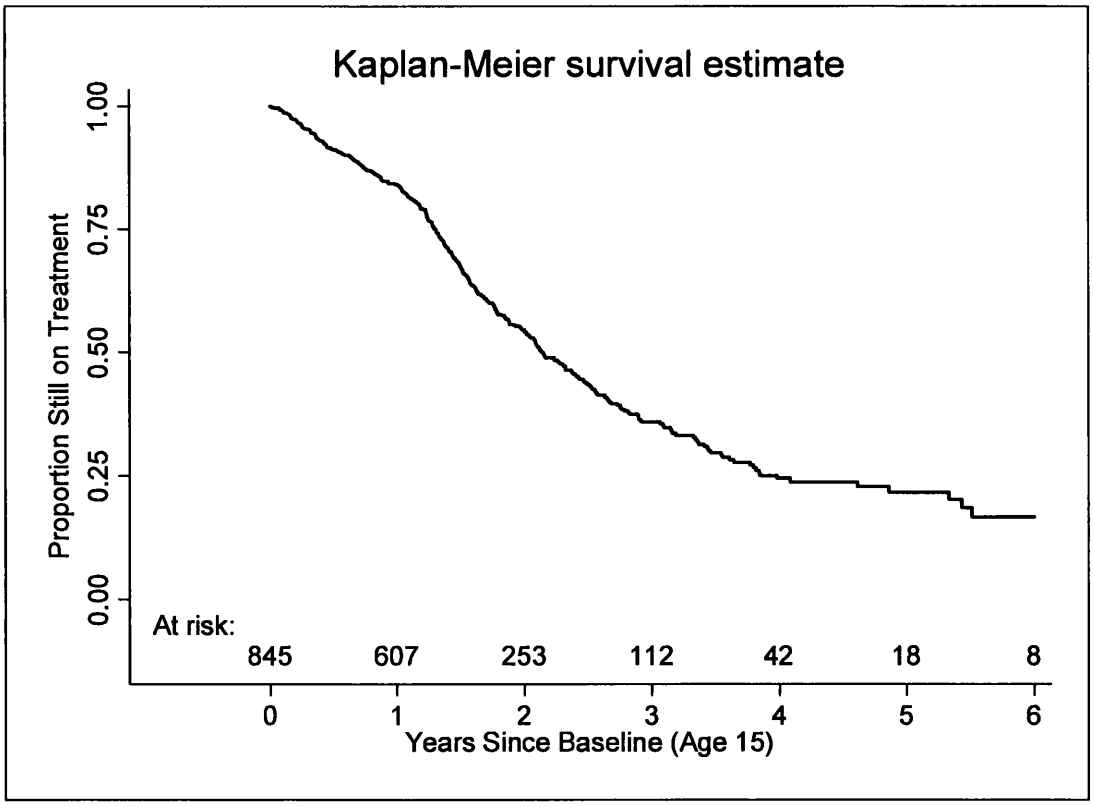
The start point for survival analysis depended on the following:

- For a patient who started a treatment episode before the age of 15, they entered the survival analysis on the date when they turned 15 (e.g. a patient with a date of birth of 01/05/1988 starting treatment in 1998 at age 10, would enter the survival analysis on 01/05/2003).
- 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 6.5 shows the proportion of patients who stopped treatment for each year after turning 15 years.

Figure 6-5: Kaplan Meier plot of duration of treatment after patients turn 15 years of age (n=845)



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.

According to the meta-analysis findings by Faraone et al (2006), 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 to 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 shows that only 17% still receive prescriptions to treat the condition. The number of patients at risk at each time point has also 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 (Weichung, 2002) 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. A stepwise selection procedure was used and the log likelihood ratios were examined in order to select which covariates should be included in the model.
Due to 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 to 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 (measured at baseline)
- Whether a patient had a prescription(s) for other psychotropic medications (measured at baseline)
- Whether a patient had had a referral to specialist (e.g. child and adolescent psychiatrist, measured at baseline)

- 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

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, the year of study entry was grouped into 2 categories (<2004 and ≥2004). 39.4% of patients included started before 2004 and 60.6% started either in 2004 or after. 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.

Table 6-4: The final Cox model using the Breslow method for ties (Breslow and Day, 1987)

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

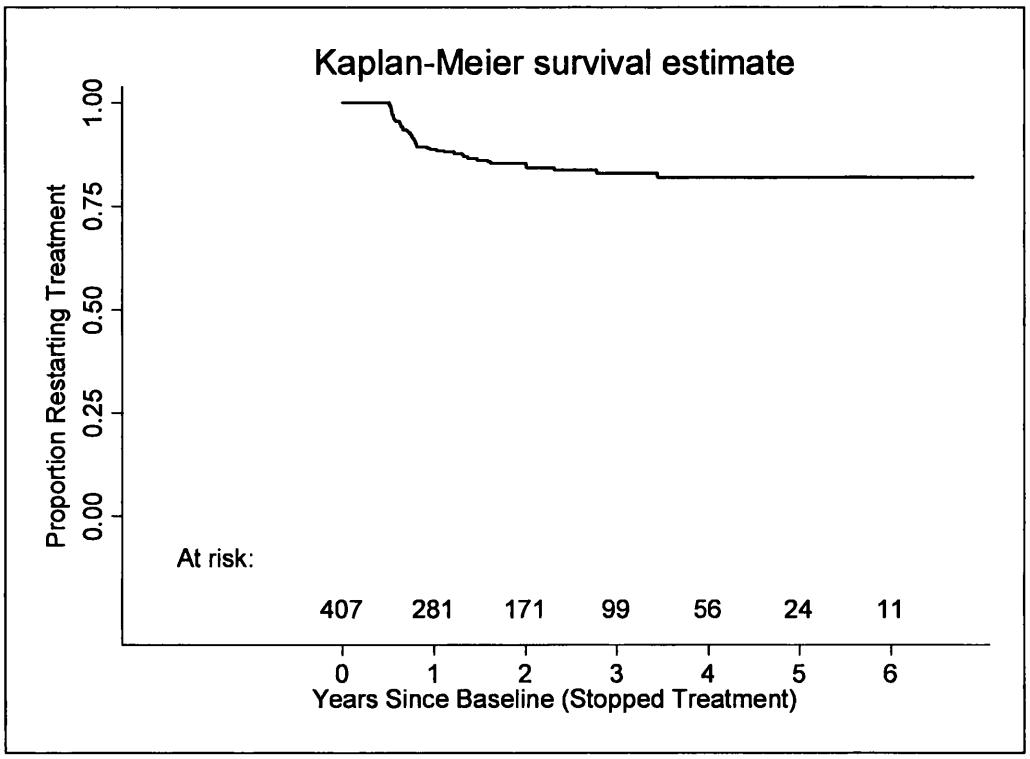
The above model suggests that for gender, there is no difference in the hazards before 6 months, however after this time; the hazard of a female stopping treatment is 63% less than a male.

However, it is worth noting that the number of females in the model was significantly less than males (74 compared to 771). The model also suggests that the patients aged 15 between 2004 and 2006 at inclusion are 40% less likely to stop treatment compared to patients age 15 between 1999 and 2003.

6.4.4. Re-starting Treatment

We then wanted to look at those patients who had stopped treatment, and to see what proportion restarted treatment, and possible factors affecting re-starting. Treatment cessation was defined as having a gap of 6 months or more between prescriptions. Therefore all patients who had stopped treatment, by definition had at least 6 months off treatment. This can be seen in the graph below (Figure 6.6). From the original cohort of 845 patients, 407 stopped treatment. Of these 407 patients, 56 patients restarted treatment. Of the 56 patients who restarted treatment, 40 patients had 1 further treatment episode; 15 had 2 further treatment episodes and 1 patient had 3 further treatment episodes before 31st 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.

Figure 6-6: Kaplan Meier curve showing proportion of patients restarting treatment



The highest rate of treatment restart occurred within the first year following treatment cessation. At 1 year, 11% of patients had re-started treatment. At 2 years, 15% patients had re-started treatment. At 4 and 6 years, only 18% patients had re-started 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 (2004-2006), these patients would not have sufficient follow-up to accurately assess re-starting of treatment and factors affecting this. Due to these reasons, and under the advice of our trial statistician Laura Potts, we believed that a descriptive analysis was most appropriate for the data presented.

6.5. Discussion

6.5.1. 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.

There are four key findings.

- First, 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 eight years studied. By gender, prevalence rose 7.41-fold in males and 21.5-fold in females during the study period.
- Second, 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.

- Third, 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.
- Fourth, a small proportion 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.

6.5.2. 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). However, in contrast, the data indicates that there was no parallel increase in the rates of prescribing in 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. These have been described in detail in Section 1.5.8.2. Faraone et al (2006) 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 to age and gender matched controls. Furthermore, the meta-analytic data by Faraone et al (2006) found a high level of impairment in individuals who no longer met full criteria for ADHD but 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 (Kessler et al, 2006; Fayyad et al, 2007).

Findings from meta-analyses also suggest that the stimulant drugs are equally as effective in reducing ADHD symptoms in adults as they are in children (Faraone et al, 2004). 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 (Faraone et al, 2004) and 0.6 for the non-stimulant atomoxetine (Michelson et al, 2003).

While it is clear that adults with ADHD show response rates to pharmacological treatments for ADHD that are comparable to that seen in children (Nutt et al, 2006; Faraone et al, 2004) there is a lack of trial data providing direct evidence for long term benefits of treatment; however this is also true for childhood ADHD. Although this study focused on the duration of treatment after patients turned 15 years, when duration was calculated from when treatment first started to when it finished, the total duration ranged from over 1 to 10 years, with a median of 2.3 years. In addition, many of the patients started treatment when they were children and therefore, if treatment were not effective in the long-term, we would not have expected patients to remain on treatment until the age of 15. Based on a thorough review of the literature and expert opinion, the British Association of Psychopharmacology 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" (Nutt et al, 2006).

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 National Institute of Health and Clinical Excellence (NICE, 2008) guideline development group.

It must be acknowledged that it was not always the recommendation of NICE that treatment should considered for older adolescents and young adults. In their guidelines issued in 2000, NICE stated that 'treatment should normally be discontinued in adolescence' and therefore the pattern of cessation of treatment may simply reflect adherence by clinicians to national guidelines.

However, as the evidence on the persistence of ADHD grows, it is possible that this is mirrored in the prescribing patterns of clinicians, who in recent years 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 to patients of the same age between 1999 and 2003.

Another factor which 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 sample (Sayal et al, 2006). 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 (1997) revealed that non-referred females with ADHD showed less impairment on inattention, internalizing 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 to males. Girls with ADHD tend to show lower levels of hyperactivity, fewer conduct disorder diagnoses, lower rates of externalizing 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: female ratio in our study compared to 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 theory which has also been suggested by others (Gaub & Carlson, 1997) 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 was 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 (Figure 6.5). 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 to treatment cessation since the school system is known to play a key role in the identification and referral of young people with ADHD (Sayal et al, 2006) and after leaving school, young people may perceive less need for sustained attention, 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 healthcare 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 (Miller and Drotar, 2007). This was identified as one of the factors influencing treatment cessation in the CADDY interview study (Part 2 study).

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 school work and relationships with family at home:

"*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? "* (Wong et al, 2008).

This scenario, whereby the clinician is caught between the diverging wishes of the patient and the family was also identified in the CADDY interview study.

"...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" (Wong et al, 2008).

Thirdly, 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) are available for young people up to the age of sixteen or school-leaving age, however the NSF for Children recommends that CAMHS services should be available up to age 18 (Department of Health, 2004). 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 (Asherson et al, 2007) and clear arrangements for transition are often lacking (NHS Quality Improvement Scotland, 2007). 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.

In the Part 2 CADDY study, the lack of adult services was identified as a reason for treatment cessation. One of the patients interviewed spoke of this problem:

"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". (Wong et al, 2008)

This was also an issue discussed by clinicians:

"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" (Wong et al, 2008)

"A common experience of our patients is that once they reach seventeen, eighteen, 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." (Wong et al, 2008)

As mentioned previously, at present in the UK, neither methylphenidate nor dexamfetamine are 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. This may lead to reluctance by clinicians to prescribe these medications to adults who require treatment for ADHD. A clinician in the Part 2 CADDY study discussed how:

"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" (Wong et al, 2008).

Furthermore, the previous recommendation by NICE in their guidelines in 2000, was that treatment should be stopped during adolescence; although this has been removed from the current guidelines, 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 in chapter five and existing data from Jick et al (2004), 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 hyperkinetic disorders in the UK. Similar to the findings by Green et al (2005), the NHS Quality Improvement Scotland review of ADHD treatment by NHS services across Scotland found that only 0.7% of the children in Scotland are currently being treated for ADHD (NHS Quality Improvement Scotland, 2007).

Kessler et al (2005) conducted a retrospective assessment of childhood ADHD, childhood risk factors and a screen for adult ADHD in a sample of 3197 18 – 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 only patients requiring treatment were included in the study, and therefore this could not be examined. In contrast to the study by Kessler et al (2005), 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. The following factors were identified when clinicians in the Part 2 CADDY study were asked what they believed contributed to successful cessation of treatment; supportive interpersonal relationships, structured home and school life, support from home and school, stable and interesting employment, patient's level of maturity and patient motivation (Wong et al, 2008).

6.5.3. 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 one year of follow-up compared to 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 6.6. However, it can also be noted from Figure 6.6 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 no longer require pharmacological treatment. This was the case in a number of the patients who had stopped treatment in the Part 2 CADDY study. Although they still experienced residual symptoms, they believed that they could cope without having to restart medication:

"When I was on medication I was concentrating a lot better. But I would still rather not take them" (Wong et al, 2008).

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 may have benefited from continued treatment. As the majority of patients who re-started treatment did so within one year of stopping treatment, this would suggest that the impairments of ADHD are noticed by patients quite soon after treatment cessation. 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. Patients from the Part 2 CADDY study found that once discharged from child and adolescent services, it was very difficult to re-engage with services:

"*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"* (Wong et al, 2008)

"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". (Wong et al, 2008)

As the drug treatments for ADHD are unlicensed in adults, it is also possible that clinicians treat patients with other drugs which although not licensed for the treatment of ADHD are licensed for use in adults, such as anti-depressants or anti-psychotics. These patients would not have been identified as re-starting treatment in the current study.

This was the case for one of the patients interviewed in the CADDY Part 2 study:

"They put me on antidepressants and they had huge side effects. Being on antidepressants made me more depressed" (Wong et al, 2008).

NICE (2008) concluded that there is no evidence for the use of antidepressants or antipsychotics in the treatment of ADHD and both are associated with a number of potentially serious adverse effects.

6.5.4. Strengths and Weaknesses of the Study

The strengths and weaknesses of the GPRD as a data source have been discussed in Sections 4.3.6 and 5.8.4. However, there are a number of points directly related to this study. The GPRD did not contain information on ADHD severity and level of impairment, factors which may predict persistence of the condition and the continued need for treatment and so these could not be examined in the current study.

Whilst 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 this should be done under specialist supervision. It may also be the case as highlighted in Section 6.5.2 that treatment discontinuation occurred as clinicians followed the NICE (2000) guidelines available at the time, which recommended that ADHD treatment should be stopped in adolescence.

Other therapies which can be used to treat ADHD such as unlicensed drug treatments (e.g. nicotine patches, buproprion, modafinil, antidepressants etc) and behavioural therapies were not studied. The limitation of this exclusion is that potential substitution from a study drug to another alternative treatment would not have been captured and would have been deemed as cessation of treatment leading to a potential overestimation of the problem. It is a limitation of the GPRD that over-the-counter (OTC) drugs such as nicotine patches or non-drug therapies such as behavioural therapy are not reliably recorded thus precluding examination of their use. Other unlicensed medications, which are not often used to treat ADHD, such as antidepressants were not included because the GPRD does not directly link individual prescriptions with an indication and therefore it would not be possible to determine whether the patient was receiving the antipsychotic or antidepressant for ADHD or for another comorbid condition.

From a methodological aspect, a number of weaknesses must be highlighted. The follow-up of some patients who entered the study in the most recent years was limited by the study period and consequently, many patients were censored. Unfortunately there is no escaping that informative censoring is a large problem in this survival analysis and it is not known to what extent it has affected the analysis of the current study. There is no satisfactory way to compare covariates when informative censoring is present. Overall 52% of the data was censored and of that 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 to 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 were censored respectively therefore the years 2004 – 2006 (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. Once gender was split, the model was found 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 or the process of cessation or restarting of treatments, thereby necessitating the qualitative component of the CADDY study.

6.6. 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 age 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 adult.

Furthermore, it is estimated that 18% patients would restart the treatment after cessation, further supporting the view that some patients may stop their treatment prematurely. As there were very few risk factors which 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.

Factors which may also influence cessation include patient, parent and clinician concern over the safety of the medications used to treat ADHD. In recent years in particular, there has been much written in the public and scientific literature on a possible link between the stimulants and atomoxetine and serious cardiovascular events and sudden death. Considering the seriousness of these potential risks, the next step in this study was to investigate the safety of methylphenidate, dexamfetamine and atomoxetine, using evidence from both the literature and the GPRD.

7. Chapter SEVEN: Safety Study Literature Review

7.1. Background

Following a review by the Food and Drug Administration (FDA) in the United States of Adderall XR ® data, as part of a new drug approval process for its use in adults with ADHD, safety concerns were raised leading to a review of Adderall ®, along with other stimulants in its class using the Adverse Event Reporting System (AERS). The AERS is a spontaneous reporting system similar to the Yellow Card System in the UK. The FDA receives adverse drug reaction reports from manufacturers as required by regulation along with reports from healthcare professionals and patients who submit voluntarily through the MedWatch program. This FDA assessment included reports on all stimulant medications used in the treatment of ADHD in the US, including amphetamine, dexamfetamine, methylphenidate, methamphetamine and dexmethylphenidate received by the AERs from January 1st 1999 to December 31st 2003 (FDA, 2004). Only those medications available in the UK will be discussed.

A search of the AERS was performed to retrieve cases in which amphetamines or methylphenidate was considered to have been the suspect drug where the outcome was fatal, or resulted in a serious cardiovascular or cerebrovascular event.

This included cases of cardiac disorders, central nervous system haemorrhage, cerebrovascular accident, accelerated and malignant hypertension, increased blood pressure and hypertension.

Cases were excluded if death was caused by multi-drug intoxication, if drug abuse was reported, if death was more likely to be attributed to another condition or if the report of death was not consistent with the normal therapeutic use of the drug e.g. the intravenous use of amphetamines. Sudden death was defined as instantaneous death or death which occurred within 24 hours of an acute collapse (Roberts, 1986).

Amphetamine-Related Deaths

There were 12 cases of sudden death in paediatrics (aged 1 – 18 years) and 5 cases in adult patients (19+ years) related to the use of amphetamines. 16 of the cases were associated with Adderall ®, a mixed amphetamine salt not available in the UK, whilst the remaining case was linked to the use of Dexedrine ® (dexamfetamine).

Methylphenidate-Related Deaths

Eight cases of sudden death were associated with the use of methylphenidate; 7 in children and adolescents aged 1 – 18 years and 1 in adults aged 19 years and above.

A number of nonfatal serious cardiovascular cases were also reported with the use of dexamfetamine and methylphenidate. These included syncope, loss of consciousness, dyspnoea, arrhythmias, palpitations, cardiac arrest, stroke, QT prolongation, hypertension and chest pain.

Along with reporting the cases of sudden death and serious cardiovascular events, reporting rates were calculated based on the number of cases per million prescriptions dispensed to children (1 – 18 years) and adults (19+ years). IMS data was used to estimate the number of prescriptions for these drugs dispensed in the US during the five years examined. These reporting rates included all the stimulant drugs mentioned above.

Twelve cases of sudden death in paediatric patients receiving amphetamines resulted in a rate of 0.36 per million amphetamine prescriptions dispensed. The rate in adult patients was 0.53 per million amphetamine prescriptions dispensed. The rate of nonfatal serious cardiovascular and cerebrovascular adverse events was 0.53 and 1.79 cases per million amphetamine prescriptions dispensed for paediatric and adult patients respectively.

Seven cases of sudden death in paediatric patients receiving methylphenidate corresponded to a rate of 0.16 per million methylphenidate prescriptions dispensed. For adult patients, the rate was calculated to be 0.07 per million methylphenidate prescriptions dispensed.

The rate of nonfatal serious adverse events was 0.18 and 0.74 cases per million methylphenidate prescriptions dispensed for children and adults respectively.

An updated review was conducted by the Office of Drug Safety (ODS) on the matter in 2006, to include reports from 1992 to 2004 (FDA, 2006). This review uncovered an additional three cases of sudden death with amphetamines (2 paediatric, 1 adult) and 10 cases associated with methylphenidate (7 paediatric, 3 adults). In addition to the stimulants, this review included cases of sudden death associated with the non-stimulant atomoxetine. As atomoxetine was approved for use in the US in 2002, data from then November 2002 to April 2005 was included in the analysis. A total of seven cases of sudden death were reported during this period to the AERS (3 paediatric, 4 adult).

Atomoxetine-Related Deaths

The overall rate of sudden death for atomoxetine was calculated to be 0.74 per million atomoxetine prescriptions dispensed.

Cases from the original review i.e. cases of sudden death from 1999 to 2003 were included as part of a Drug Safety and Risk Management Advisory Committee meeting in February 2006 in order to produce recommendations to the FDA on how best to study the rare occurrences of cardiovascular adverse events associated with medications used in the treatment of ADHD.

Although not part of its original remit, the committee took an independent course and voted by eight members to seven, that the data from the AERS warranted a black-box warning describing these serious adverse events. Information on this decision was published in the New England Journal of Medicine (Nissen, 2006).

A Paediatric Advisory Committee convened a month later in March and decided that the inclusion of a black-box warning, the strongest warning the FDA can impose, was not necessary, however they did recommend that strong warnings regarding the use of stimulants in patients with underlying structural cardiovascular defects or cardiomyopathies were emphasized. For example, in the Summary of Product Characteristics for Concerta ®, the following warning has been included; "Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural cardiac abnormalities" (Concerta ® SPC, 2008).

The product literature also cautions the use of these products in patients with high blood pressure; "Use cautiously in patients with hypertension...caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate" (Concerta ® SPC, 2008).

In addition to the labelling changes, the FDA also recommended the production of Patient Medication Guides; handouts developed with input from professional, private, and public groups, which would be designed to explain to parents and physicians the risks associated with these medications.

Spontaneous reporting systems play a major role in the identification of safety signals once a medicine is marketed; especially identifying those events which occur rarely such as sudden death. However, the accounts of the cases of sudden death reported to the AERS above highlight the many limitations of using and relying on such a method.

Firstly, spontaneous reporting is dependent on clinicians and other health professionals reporting details of suspected adverse reactions in patients. Under-reporting is a serious problem with this method, and it is estimated that in developed countries, less than 5% of reactions are reported (WHO, 2007b).

Secondly, data is often incomplete, whereby information such as duration and dosage of therapy along with essential post-mortem results are often absent.

Thirdly, there can also be a strong bias in reporting, which may have be present in those cases reported by family members, lawyers and journalists.

And finally, reliable rates cannot be calculated using this method and so risks cannot be measured with confidence.

While the method of spontaneous reporting provides important signals to the possibility of serious adverse events associated with the use of these ADHD medications, there are many flaws, confounders and biases present. This prompted us to study these occurrences in further detail.

The first step in determining the possibility of an association between the use of these drugs and the occurrence of sudden death and serious cardiovascular adverse events associated with these drugs was to establish a biological plausibility between the cause and outcome.

The term sudden death denotes a death occurring in a nonviolent or nontraumatic manner which is generally unexpected, is witnessed, and is instantaneous or occurs within a few minutes following an abrupt change in clinical state. (Roberts, 1986). In the US, sudden death accounts for between 5 and 10% of all childhood deaths annually, with an incidence of 0.8 to 6.2 per 100,000 (Berger et al, 2004). A study conducted by Wren et al (2000) in the UK estimated the rate of sudden death in children and young adults aged between 1 and 20 years to be 3.3 per 100,000. Sudden death can be caused by a number of conditions including epilepsy, asthma and cardiovascular complications. The mechanism by which sudden cardiac death occurs is dependent on its cause.

In many cases of sudden death, patients have had previous heart problems such as congenital heart disease, some of which will have undergone surgical repair (Wren, 2002).

Indeed, many patients having undergone surgical repair of Tetralogy of Fallot, transportation of the great arteries or fontan operation, are at risk of sudden death which can occur many years after surgery in young adulthood. Structural or functional cardiac abnormalities such as hypertrophic cardiomyopathy, coronary artery abnormalities and aortic valve stenosis can also lead to sudden death in apparently healthy children.

Those sudden cardiac deaths which remain unexplained after post-mortem are most likely due to primary cardiac arrhythmias, and those which are known to be fatal include polymorphic ventricular tachycardia in congenital long QT syndrome, primary ventricular arrhythmias, atrial fibrillation in Wolff-Parkinson-White syndrome and congenital complete atrioventricular block (Wren, 2002).

Indeed, the most frequent causes of drug-related sudden death are cardiac arrhythmias. The common feature of these arrhythmias such as Torsade de Pointes is delayed repolarisation of the myocardium resulting in a prolonged QT interval and thus leaving the myocardium vulnerable to ventricular tachycardia (Gutgesell et al, 1999).

A description of the proposed modes of action of the drugs used in the treatment of ADHD was given in Section 1.4.2. Although their mechanism of action in humans is not completely understood, it is believed that the stimulants methylphenidate and dexamfetamine exert their effect through their sympathomimetic qualities and their ability to enhance catecholamine (dopaminergic and noradrenergic) transmission both in the central and peripheral nervous system (Biederman et al, 2004b).

Atomoxetine, a non-stimulant, is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter, its presumed mechanism of action, without directly affecting the serotonin or dopamine transporters (Atomoxetine SPC, 2008). Catecholaminergic agents can theoretically affect cardiac rate, conduction, repolarisation and rhythmicity, although in practice, the degree to which this occurs differs amongst the various agents.

The stimulant medications have both chronotropic and ionotropic effects including increasing heart rate and because of their sympathomimetic properties, similar to endogenous catecholamines, these drugs also have an effect on blood pressure (Wilens et al, 2006b).

It has also been proposed that ADHD may be more prevalent in children with cardiac disease. A study conducted into the neurodevelopmental outcome in children with hypoplastic left heart syndrome demonstrated a significant proportion (23/34, 67.6%) had evidence of ADHD by history and physical examination (Mahle et al, 2000). The association between the two conditions is thought to stem from chronic or intermittent hypoxia, which is experienced by many children with heart disease and which in a review by Bass et al (2004) has been demonstrated to have an adverse impact on development, behaviour and academic achievement.

With spontaneous reports of sudden death and serious cardiovascular events, a biological plausibility for an association, and the possibility that a significant proportion of patients with pre-existing cardiac conditions present with the symptoms of ADHD, the next step was to conduct a review of these occurrences in the literature.

7.2. Systematic Literature Review

7.2.1. Introduction

In 1992, Safer published a review in the Journal of Child and Adolescent Psychopharmacology on the relative safety of psychostimulants (Safer, 1992). This review examined all studies conducted from 1936 to 1991 which measured and reported heart rate, blood pressure and electrocardiogram (ECG) findings in patients treated with stimulants. The studies reviewed varied from those where the cardiovascular response to a single dose of stimulant was measured, to studies where children's vital signs were measured following long-term treatment.

When examining the effects of methylphenidate on the heart rate of children, five studies showed that the administration of a single moderate to high test dose to drug-naïve children resulted 1 – 2 hours later in a statistically significant increase in heart rate averaging 8 – 14 beats per minute.

The increase disappeared four hours after administration. Four studies on the effects of methylphenidate on children on long-term treatment showed a mean increase in heart rate of 4 beats per minute. Five studies assessed the heart rate of children who had previously taken long-term methylphenidate and found off-treatment, there was no significant difference when compared with normal controls. A number of studies reported the effect of methylphenidate on blood pressure on patients, with increases in systolic and diastolic pressure ranging from 2 to 7mmHg and -1 to 14mmHg respectively. Although often these were statistically significant, these increases were not thought to be clinically meaningful. Four reports from the review described ECG findings. With the exception of one study which showed a few instances of increased heart rate, no cardiac irregularities were reported in patients taking these medications.

Although small changes in blood pressure and heart rate may not have an effect on children and young adults, these increases may have a more profound consequence on the health of adults taking these medications, in whom hypertension and cardiovascular disease may be more prominent. At the time of the review by Safer, the use of stimulants in adults was not as prevalent as today. A number of studies investigating their use in drug-naive psychiatric adults given high test doses of methylphenidate showed average increases in heart rate of 12 beats per minute and in systolic blood pressure of 5mmHg. In patients tested with low doses of methylphenidate, there were no significant cardiovascular changes. No cardiac arrhythmias associated with the stimulants were reported in the literature at the time.

The conclusion from this review was that there was a lack of evidence to suggest that the stimulants produced adverse cardiovascular effects and while they may be associated with initial rises in heart rate and blood pressure, these increases were not clinically relevant and that tolerance developed to these effects over time.
Although this review was conducted over 15 years ago, it is clear from the recent FDA controversy that concern and doubt remain over the safety of these medications.

7.2.2. Aim

The aim of the literature review was to retrieve and assess relevant published data on the reported safety of methylphenidate, dexamfetamine and atomoxetine in children and adults with ADHD.

7.2.3. Method

A literature search was conducted, using Medline and Embase, to retrieve relevant articles published in English from 1992 to the present day.

Table 7-1: Search terms used in the literature review

Population	Intervention	Outcome
Attention Deficit Hyperactivity Disorder	Stimulant	Cardiovascular
ADHD	Psychostimulant	Cardiac
Hyperkinetic$	Methylphenidate	Hypertension
Hyperactiv$	Dexamfetamine	Blood Pressure
	Dexamphetamine	Pulse
	Atomoxetine	Electrocardiogram
		ECG
		Mortality
		Death

Due to omission of a key search term (arrhythmia), the search was run again, with the same inclusion criteria applying. Data extraction was done in a structured manner through the use of a data extraction form, adapted from the Department of Health Sciences, University of York (2008) (http://www.york.ac.uk/healthsciences/gsp/themes/woundcare/Wounds/Docs/template_data_extraction_sheet.rtf) . The data extraction sheet is included in Appendix 6.

Inclusion Criteria

Only those studies which reported primary data on the occurrence of death, serious cardiovascular adverse events or which reported changes in vital signs due to the use of methylphenidate, dexamfetamine or atomoxetine were included. Those studies which reported cardiovascular events related to the abuse of these drugs were not included. The references of any review articles were hand searched for any additional articles not already identified.

7.2.4. Results

The terms combined retrieved 159 articles. The abstracts were reviewed and 33 relevant studies were included. When the search was re-run to include the search term 'arrhythmia', an additional two studies were identified. Therefore a total of 35 studies were included. The literature was analysed according to two categories, those reporting adverse events in children (aged 18 years and below) and those relevant to use in adults. Twenty seven paediatric studies were identified where cardiovascular monitoring was reported relating to the use of methylphenidate, dexamfetamine and atomoxetine in children. Fourteen of these are presented in Table 7.2. The remaining thirteen studies are discussed separately in Table 7.3. Eight studies relevant to cardiovascular outcomes in adults (19 years and above) were reported in the literature. The results of these are presented in Table 7.4.

Table 7-2: Studies Examining Cardiovascular Outcomes in Children Prescribed Medications for Use in ADHD Treatment

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
1	Stowe et al (2002)	17 (17 Male) **Mean (SD)** MPH 9.3 (1.1) **Range** 7 – 11	ABPM [b] comparing on and off therapy	24 hour treatment both on and off therapy	Methylphenidate (n=8) & Adderall (n=9). Results for MPH only displayed	24-hour 1 Awake 3 Asleep -2	- - - 24-hour 1 Awake 2 Asleep -2	- - - - - 24-hour 2 Awake 5 Asleep -2	Not sig at α<0.05 <0.05 <0.05 Not sig at α<0.05 <0.05 <0.05 <0.05 <0.05 <0.05	4 MPH patients were considered hypertensive based on casual BP criteria while on therapy with 1 patient meeting hypertensive criteria both on and off therapy.1 patient was considered hypertensive as defined by ABPM values
2	Samuels et al (2006)	11 (9 Male; 2 Female) **Mean (SD)** 12.5 (1.69) **Range** 5 – 15	Double-blind placebo-controlled 2-phase crossover trial using ABPM [b]	2 x 24 hours (for placebo and active treatment)	Methylphenidate (n=6) Amphetamine (n=4) Dextroamphetamine (n=1)	2.8 - -	- 3.9 -	- - 5.6	0.169 0.021 0.004	Rate pressure product (heart rate x SBP) significantly increased during the active treatment period.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
3	Pataki et al (1993)	16 (16 male) **Mean (SD)** 9.97 (1.6) **Range** 8-12	Randomized, double-blind, placebo controlled crossover design	12-16 weeks	Methylphenidate & Desipramine. MPH results only reported. (n=11)	Max 1.8 Min -0.9	Max -1.4 Min 3.6	6.4	Not sig	PR interval inc.1.0ms, QRS interval inc.3.0ms, QTc interval increased 1.0 ms from baseline. None reached statistical significance. ECG evidence of intraventricular conduction defect (QRS>100) was present in 3 patients on MPH, None were believed to have clinical signs of abnormal cardiac function and did not warrant a change in medication.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
4	Michelson et al (2001)	297 (212 male, 85 female) **Mean (SD)** ATM 0.5mg/kg/day 11.3 (2.5) ATM 1.2mg/kg/day 11.5 (2.4) ATM 1.8mg/kg/day 11.1 (2.1) **Range** 8-18	Multicentre, Randomized, Placebo-controlled, dose-response study	8 weeks	Atomoxetine	0.5mg/kg 3.3 1.2mg/kg 4.3 1.8mg/kg 2.5 - - - -	 - - - 0.5mg/kg 1.5 1.2mg/kg 2.8 1.8mg/kg 1.7 -	 - - - - 0.5mg/kg 5.8 1.2mg/kg 6.3 1.8mg/kg 8.3	 Not sig Not sig Not sig Not sig p<0.05 p<0.05 p<0.05 p<0.05 p<0.05	4 participants (9.1%) in the 0.5mg/kg group experienced dizziness (p<0.05). This AE was reported in 2.4% of 1.2mg/kg group and 4.8% of 1.8mg/kg group, neither were significant.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
5	[c]Michelson et al (2002)	170 (120 Male; 50 Female) **Mean (SD)** ATM 10.1 (2.3) Placebo 10.5 (2.5) **Range** 6 – 16	Multi-centre, Randomized double-blind, placebo-controlled trial	6 weeks	Atomoxetine	2 -	- -	- 6.8	<0.04 <0.001	Differences occurred in the reporting of dizziness between drug and placebo (n=5, n=0 respectively) although it was not significant.
6	[c]Kelsey et al (2004)	197 (139 male; 58 female) **Mean (SD)** ATM 9.5 (1.8) Placebo 9.4 (1.8) **Range** 6 – 12	Randomized, double-blind, placebo-controlled Study	8 weeks	Atomoxetine: Results show difference in increase relative to placebo	- Standing -0.4 Supine 0.4 - -	- - - Standing 1.6 Supine 2.1	5.4 - - - -	0.009 0.753 0.892 0.309 0.155	ECG data showed statistically significant PR interval dec. (ATM -2.6+ 14.3 ms; Placebo 1.9+ 14.3 ms p=0.036). No other significant differences in ECG data were found

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
7	[c]Bangs et al (2007)	142 (104 male, 38 female) **Mean (SD)** ATM 14.6 (1.8) Placebo 14.2 (1.5) **Range** 12-18	Randomized, Double-blind, Placebo controlled acute-treatment phase followed by open-label treatment phase	9 week (acute phase) 6 month (open label)	Atomoxetine	Acute Phase (n=121) 0.1 - - Open-Label (n=118) 1.3 - -	Acute Phase (n=121) - 1.5 - Open-Label (n=118) - 2.5 -	Acute Phase (n=121) - - 6.0 Open-Label (n=118) - - 7.7	0.82 0.93 0.10 0.22 0.005 <0.001	Dizziness occurred in 12.5%-ATM, 2.9%-Placebo. During acute phase, sig dec. in RR (-100.5 ms p<0.001) and PR (-2.5ms p=0.002). intervals in ATM group, not in placebo. Fridericia's or Bazett-corrected QT intervals not significant (-3.0 p=0.83) and (5.3 p=0.053). Sig.dec. in RR interval in open-label phase (-87.5ms p<0.001)

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
8	Findling et al (2001)	137 (105 Male; 32 Female) **Mean (SD)** MPH 10.0 (3.1) **Range** 4 – 17	Placebo-Controlled study of MPH and ADL	4 weeks	Methylphenidate & Adderall at doses of 5, 10 and 15mg. Changes from baseline to 15mg MPH only	3.5 - -	- 4.4 -	- - 2.2	Not sig p<0.05 p<0.05	No clinically significant adverse events occurred during the study.
9	[c]Silva et al (2005)	54 (34 male; 20 female) **Mean (SD)** 9.4 (1.9) **Range** 6 – 12 years	Randomized single-blind, placebo-controlled crossover study	6 weeks	Extended-Release Methylphenidate & OROS Methylphenidate Changes from pre-dose to 12 hour post-dose only are displayed	ER-MPH 20 3.3 ER-MPH 40 1.5 OROS-MPH 18 1.1 OROS-MPH 36 2.4 Placebo -0.1	ER-MPH 20 1.8 ER-MPH 40 2.3 OROS-MPH 18 2.1 OROS-MPH 36 2 Placebo -0.3	ER-MPH 20 10.9 ER-MPH 40 8.1 OROS-MPH 18 9.7 OROS-MPH 36 9.8 Placebo 8.3	Not stated	No cardiac-related adverse events occurred during the study.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
10	Zeiner (1995)	46 (46 male) **Mean (SD)** MPH 9.0 (1.3) Control 9.0 (1.5) **Range** 7 – 12	Prospective, controlled, open-label study	21 months	Methylphenidate	4.6	1.0	-0.1	Not sig	No patient developed hypertension or tachycardia
11	[c]Spencer et al (2001)	432 (gender not specified) **Mean (SD)** Not specified **Range** 6 – 13	Open-Label Study	11 weeks	Atomoxetine	4.4 - -	- 10.9 -	- - 9.0	Not sig <0.001 <0.01	17% patients experienced dizziness. ECGs revealed no evidence of effects on mean conduction, repolarization, or rhythm (PR, QRS and QTc intervals all unchanged).

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
12	[c]Kratochvil et al (2002)	228 (211 male; 17 female) **Mean (SD)** 10.4 (2.1) **Range** 7 – 15	Randomized open-label study	10 weeks	Atomoxetine (ATM) & Methylphenidate (MPH)	ATM 2.68 MPH 3.35	- -	- -	0.001 0.026	Treatment emergent adverse events inc. Tachycardia 6%-ATM, 5%-MPH; Palpitation 1.6%-ATM, 5%-MPH. ECG results showed no statistically or clinically significant changes in corrected QT interval.
						-	ATM 2.58 MPH	-	<0.001	
						-	2.95	-	0.040	
						-	-	ATM 6.14	<0.001	
						-	-	MPH 5.65	0.009	

Study	Author	No. of Participants (Gender) / Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg)		Heart Rate (bpm [a])	p-value	Other points
						Systolic	Diastolic			
13	[c]Wilens et al (2004b)	432 (gender not specified) **Mean (SD)** 9.2 (1.8) **Range** 6 – 13	Open-Label Follow-up Study	12 months	OROS® Methylphenidate	3.3 -	1.5 -	- 3.9	<0.001 <0.0001	1 patient developed elevated BP during the study.
14	[c]Wilens et al (2005a)	407 (83% male, 17% female) **Mean (SD)** 9.2 (1.8) **Range** 6-9 yrs (54%) 10-13 yrs (46%)	Open-Label Study	24 months	OROS Methylphenidate	3.4	-	-	p<0.0001	1 patient discontinued the study at month 4 due to elevated blood pressure. No other patients experienced clinically significant changes in vital signs.

[a] – bpm, beats per minute [b] – ABPM, Ambulatory Blood Pressure Monitoring [c] – Studies which acknowledge Drug company funding

Table 7-3: Additional Studies Examining Cardiovascular Outcomes in Children Prescribed ADHD drug treatment

Study	Description
15	Rajesh et al (2006) reported a case of an 11 year old boy who developed unusual cardiac repolarisation changes associated with palpitations on treatment with atomoxetine. The patient had initially showed a good response to methylphenidate, however he developed severe tics leading to discontinuation of the drug at which stage he was initiated on atomoxetine. Ten months later, he developed palpitations associated with pallor, without signs of dizziness, nausea or vomiting. The symptoms were also not associated with exertion or any other triggers. The frequency of these episodes, each lasting approximately 10 minutes, increased to around three times a week. An echocardiogram showed normal ventricular function, with no cardiomyopathy or valvular abnormalities. ECG showed sinus rhythm, but unusual repolarisation changes after the T wave. QTc interval on atomoxetine treatment was 0.32 s compared with 0.31 off treatment. Both his symptoms and ECG abnormalities disappeared on discontinuation of atomoxetine.
16	This study by [c]Greenhill et al (2002), was a 3-week, multicentre, randomized, double-blind, placebo-controlled study of modified-release methylphenidate. The 314 participants (155 MPH, 159 Placebo) were aged between 6 – 16 years. There were no significant differences reported between treatment group (at any dose level) and placebo in mean and median systolic or diastolic blood pressure or pulse rate.

17	This study by [9]Wolraich et al (2001), was another multicentre, randomized, double-blind, placebo-controlled study of OROS methylphenidate in children aged 6 – 12 years. This study involving 282 children lasted 4 weeks and again demonstrated no clinically significant changes in vital signs between any of the treatment groups and placebo.
18	This study by Wigal et al (2006) reported the safety of methylphenidate in children aged 3 – 5 years during one year of treatment. This study incorporated a number of treatment phases, starting with a 1-week open-label lead-in trial which involved 183 patients, a 5-week placebo-controlled, double-blind crossover phase (n=165), a 5-week double-blind, parallel phase (n=114) followed by 10 months of open-label maintenance therapy (n=140 of which 95 completed). Pulse, blood pressure and any treatment emergent adverse events were recorded at the end of each phase. BP and pulse measurements increased over the study period; however no significant differences were detected between treatment and placebo groups. Mean pulse increased 11bpm from baseline to the end of the parallel phase ($p<0.0001$) however the increase in the MPH group was 4bpm less than the placebo group (94.3 bpm and 98.3 bpm respectively). Mean blood pressure readings during the parallel phase did not differ significantly between the active and placebo groups (101.6/61.8 and 99.4/61 respectively). These readings also did not differ significantly from those taken during the end of the last month of maintenance therapy (103.6/61). There were no cardiovascular adverse events reported.

19	This study by [c]McGough et al (2006) was an 8-week, open-label extension of a double-blind study examining the safety of once-daily OROS ® Methylphenidate in 171 adolescents aged 13 – 18 years. No significant differences in mean change for diastolic blood pressure or heart rate from baseline to the end of the open-label phase were observed (at $p<0.05$ level) . The mean change for systolic blood pressure approached statistical significance ($p=0.06$) however the authors note that there were no consistent treatment effects as both increases and decreases in SBP were observed. 156 of the 171 patients had ECG recordings at both baseline and end of the study. ECGs were classified as normal or abnormal by a cardiologist. 19 participants (12%) were considered to have abnormal ECGs, of whom 7 had abnormal readings prior to initiation of the study medication. The remaining 12 participants (8%) had normal readings at the beginning of the study. None of the ECG changes observed for these 12 participants were considered by the cardiologist to be clinically significant. 11 participants (7%) had abnormal ECGs at baseline, however at the end of the study period, were considered to have normal readings. Treatment emergent cardiovascular adverse events or discontinuation due to cardiac events were not specified in the study report.
20	This study by [c]Michelson et al (2004) was the first phase of a multi-centre, maintenance atomoxetine treatment study in 416 children (373 male) aged 6 – 15 years. Subjects had completed a 12-week, open-label atomoxetine treatment phase, and were entered into a 9-month, double-blinded, randomized, placebo-controlled relapse prevention study. No clinically meaningful differences in cardiac QT intervals (corrected for heart rate) were observed between the groups. Any effects on blood pressure were not stated

21	This study by [c]Buitelaar et al (2007) was the second phase of the multi-centre, maintenance atomoxetine treatment study. This study was designed to assess the efficacy of continuing atomoxetine for six additional months in those subjects who had completed one year of treatment. The study randomly assigned the 163 children and adolescents (146 male) aged 6 – 15 years, in a double-blinded fashion to continued atomoxetine or placebo for six months. Again, there were no clinically meaningful differences in blood pressure or cardiac QT intervals (corrected for heart rate) observed between the atomoxetine and placebo groups.
22	This study investigated the cardiovascular responses to methylphenidate in a group of children with ADHD compared to a group of children with ADHD and anxiety. This study by Urman et al (1995) utilised a randomized, double-blind, placebo-controlled crossover design in a group of 63 children (34 nonanxious, 29 anxious) aged between 6 and 12 years. This 4-day trial obtained blood pressure and pulse measurements at baseline, immediately before administration of MPH or placebo, and 2 readings post-administration (1 and 2 hours). The results presented below showed a significant effect for drug was found for diastolic and systolic blood pressure and pulse ($p<0.0001$) in both anxious and nonanxious children. Compared with placebo, the changes in vital signs of nonanxious and anxious ADHD children who received the highest MPH dose (Urman et al, 1995)

	Non-Anxious ADHD children	Anxious ADHD children
Diastolic Blood Pressure (mmHg) pre-dose	0.9	-0.2
Diastolic Blood Pressure (mmHg) 1-hour post dose	2.1	6.7
Diastolic Blood Pressure (mmHg) 2-hours post dose	6.4	9.4
Systolic Blood Pressure (mmHg) pre-dose	-2.2	-0.6
Systolic Blood Pressure (mmHg) 1-hour post dose	3.6	4.5
Systolic Blood Pressure (mmHg) 2-hour post dose	9.1	6.5
Pulse (beats per minute) pre-dose	0	1.8
Pulse (beats per minute) 1-hour post dose	7.1	11.7
Pulse (beats per minute) 2-hour post dose	11.8	14.9

Compared with nonanxious children, those with ADHD and anxiety showed a significantly greater increases in diastolic blood pressure ($p<0.0001$), systolic blood pressure ($p<0.005$) and pulse ($p<0.023$).

23	This study by [9]Weiss et al (2005), was a 7-week, multi-site, randomized, placebo-controlled study of atomoxetine in 153 children (123 male) aged 8 – 12 years. No serious safety concerns were observed in the study. Atomoxetine was associated with an increase in heart rate. Mean change [SD] in heart rate was 3.3 beats per minutes [11.33] for atomoxetine and -0.1 beats per minute [9.82] for placebo; however this did not reach statistical significance p=0.067. There were no treatment group differences in change in mean diastolic or systolic blood pressure.
24	A study by [c]Gau et al (2007) was a 6-week, randomized, double-blind, placebo-controlled study of atomoxetine in 106 Taiwanese children and adolescents (94 male) aged 6 – 16 years. Atomoxetine was well tolerated, although one patient discontinued the drug due to dizziness. The results of the study showed no statistically or clinically significant differences in vital signs between the two treatment groups.
25	This study by Gadow et al (1999) looked at long-term methylphenidate therapy in 34 children (31 male) aged 6 – 12 years with ADHD and comorbid chronic multiple tic disorder. Initially, for the first 2 weeks of the trial, subjects received placebo, followed by 3 increasing doses of methylphenidate. A minimal effective dose of methylphenidate was determined. Subjects were then followed up every 6 months for two years (at 12, 18 and 24 months). Examination of group means indicated increasing values over time for systolic blood pressure and heart rate, both of which were statistically significant (p=0.02 and p=0.01 respectively). Diastolic blood pressure was not significantly different p=0.41.

26	Hammerness et al (2008) present a case of an 8-year old boy with ADHD and symptoms of anxiety. The patient had been stable on OROS-methylphenidate for 2 years with significant symptomatic and functional improvement. The patient reported symptoms including shortness of breath and dizziness. Ambulatory cardiac event monitoring revealed an episode of sustained tachycardia, consistent with a supraventricular tachycardia. The patient underwent radiofrequency catheter ablation which was curative and did not result in any complications. Treatment discontinuation was not warranted in this case.
27	The final study was an epidemiological study which used a retrospective cohort design to determine the cardiac risks associated with the stimulants. The study by Winterstein et al (2007) used 10 years of data from the Florida Medicaid program and included patients aged between 3 and 20 years. (This study includes patients defined as adults in the methods section, however as it is mainly concerned with younger patients, it will be discussed here). For inclusion into the study, all patients had to have a diagnosis of ADHD. The follow-up of patients from the time of the diagnosis was then classified according to their drug use. The follow-up time for those patients who had a diagnosis of ADHD and never received a stimulant was categorised as non-use. For those patients who did receive stimulant treatment, the time period between diagnosis of ADHD and receipt of first prescription was determined as non-use. The time period when patients were receiving prescriptions for a stimulant was determined as current-use and any time after stimulant treatment was categorised as former use. Cardiac death, hospital admission for a cardiac related-event or visits to the emergency department for a cardiac event was determined according to drug use as described above. Current use of stimulants contributed 42,612 patient years of data, former use contributed 35,671 patient years and non-use contributed 46,649 patient years of data. No cardiac death occurred during current use of stimulants. The rate of hospital admissions for cardiac events (including current, former and non-use) was 21.6 per 100,000 patient years. The rate of emergency department visits

	for cardiac causes (for all groups) was 8.7 per 1,000 patient years. Current stimulant use was associated with a 20% increased in the hazard (adjusted HR: 1.20; 95% CI 1.04 – 1.38) of emergency department visits compared with non-use of stimulants. A number of risk factors which were significant with an increased hazard included age greater than 15, congenital anomalies, history of circulatory disease, disability, use of antidepressants, antipsychotics and bronchodilators.

[c] – Studies which acknowledge Drug company funding

Table 7-4: Studies Examining Cardiovascular Outcomes in Adults Prescribed Medications for Use in ADHD Treatment

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
1	Wilens et al (2005b)	125 (56 male, 69 female) **Mean (SD)** 39 (9) **Range** 19 – 55	5 Randomized, Placebo-Controlled Studies, (3 crossover, 2 parallel design)	6 – 10 weeks	*Amphetamine compounds, (n=51) *Methylphenidate (n=35) *only results reported	5.3 - - 2.4 - -	- 4.0 - - -0.2 -	- - 7.3 - - 4.5	0.02 0.5 0.05 0.9 0.7 0.4	New-onset hypertension (bp>140/90mmHg) was noted in 10% active-medication treated and in 8% of placebo patients
2	[c]Michelson et al (2003)	280 (178 male, 102 female) **Mean (SD)** 40.3 (11.6) (Placebo) 40.2 (11.7) (ATM)	Randomized, double-blind, placebo-controlled studies	10 weeks	Atomoxetine	- 2.3 -	2.3 - -	- - 6.7	0.063 0.015 <0.001	No serious safety concerns were observed.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
3	[c]Michelson et al (2003)	256 (170 male, 86 female) **Mean (SD)** 41.2 (11.2) (Placebo) 43.0 (10.3) (ATM)	Randomized, double-blind, placebo-controlled studies	10 weeks	Atomoxetine	- 3.5 -	1.2 - -	- - 3.8	0.556 0.059 0.002	No serious safety concerns were observed.
4	[c]Biederman et al (2006)	141 (73 male, 68 female) **Mean (SD)** 32.7 (18.5) (MPH) 37.6 (8.4) (Placebo) **Range** 19-60	Double-blind, randomized, placebo-controlled, parallel-design	6 weeks	OROS Methylphenidate	3.5 - -	- 4.0 -	- - 4.5	0.02 <0.001 <0.001	Dizziness reported in 7% (MPH) 0% (Placebo). 9% MPH had CV complaints vs.1% Placebo. Patients discontinued study: increased pulse (n=2), elevated bp (n=1). 8% MPH patients had SBP > 140mmHg and 9% had pulse > 100bpm. Change in QT interval: MPH (-16.5ms) vs. placebo (6.5ms) p=0.001. No other parameters were significant.

Study	Author	No. of Participants (Gender) Age (years)	Study Design	Duration of Study	Drug under Study	Change in Blood Pressure (mmHg) Systolic	 Diastolic	Heart Rate (bpm [a])	p-value	Other points
5	[c]Fallu et al (2006)	32 (18 male, 14 female) **Mean (SD)** 36.8 (10.4) **Range** 18-65	Pilot, uncontrolled, open-label study	38 days	OROS Methylphenidate	-2.9 - -	- -1.4 -	- - 5.9	0.16 0.27 0.003	25% patients palpitations, 6% dizziness, 6% tachycardia. AEs not deemed serious. No drug discontinued due to AEs. No clinically sig changes in ECG.
6	Paterson et al (1999)	45 (27 male, 18 female) **Mean** 35.5 **Range** 19-57	Randomized, double-blind placebo controlled trial	6 weeks	Dexamfetamine	-4 -	- -4	- -	Not sig	No severe adverse events occurred during the study.
7	[c]Spencer et al (2005)	146 (85 male, 61 female) **Mean (SD)** 35.6 (9.7) – MPH 40.3 (10.0) – Placebo **Range** 19-60	Randomized, double-blind, placebo-controlled parallel design	6 weeks	Methylphenidate	2 - -	- 2 -	- - 7	Not sig at $\alpha<0.01$ Not sig at $\alpha<0.01$ $p<0.001$	No serious CV AEs. 5% MPH & placebo groups discontinued due to high BP. QTc interval inc from 0.413 to 0.42ms $p<0.01$. No statistically sig changes in other conduction parameters.

8	[c]Adler et al (2006)	**218 (152 male, 66 female)** **Mean (SD)** **37.0 (8.17)**	Randomised, double-blind, multicentre study	6 weeks	Atomoxetine (Comparing 40mg and 80mg dosing)	No sig difference from baseline in either group or sig differences between groups	No sig difference from baseline in either group or sig differences between groups	Increase of 6.32 bpm from baseline (40mg group) Increase of 7.16bpm from baseline (80mg group)		No statistically significant treatment group differences for mean change in ECG values from baseline to endpoint. No clinically significant changes in ECG.

[a] – bp, blood pressure [b] – bpm, beats per minute [c] – Studies which acknowledge Drug company funding

In addition to the studies retrieved from the literature search, a number of long-term follow-up studies of children with ADHD were examined for any evidence of mortality. These studies can be divided into three categories, the first of which included two different long-term multimodal trials including the MTA with reports at 14, 24 and 36 months (MTA Cooperative Group, 1999; MTA Cooperative Group, 2004; Jensen et al, 2007) and a 2-year multimodal study by Abikoff et al (2004).

The second category of studies examined long-term use of medication, mainly the use of stimulants in patients with ADHD (Charach et al, 2004; Sleator et al, 1974; Charles and Schain, 1981; Bussing et al, 2005, Gillberg et al, 1997; Barbaresi et al, 2006).

The third category consists of follow-up studies of children with ADHD into adolescence and adulthood, although not all subjects continue to receive treatment. These studies (Mannuzza et al, 1998; Mannuzza et al, 1997; Barkley et al, 2004; Fischer et al, 2002; Weiss et al, 1985) have examined amongst other things, the development of conduct disorder, psychiatric conditions and substance abuse and the educational and occupational outcome of these childhood in later life. None of the studies in the first two categories reported any cases of death. In the third category, the study by Weiss et al (1985), which followed 63 hyperactive children and 41 controls for 15 years, reported 3 deaths (5%) in the hyperactive cohort, two in accidents and one from suicide; however the majority of ADHD patients were not receiving medication treatment.

Barkley et al (2004) and Fischer et al (2002) reported on over 13 years of follow-up of 147 children and 71 controls and reported one case of suicide in the hyperactive cohort and two deaths in the control group, one from a car accident and one from sudden cardiac death. 1% of the control group and 8% of the hyperactive group were taking medications, primarily stimulants or antidepressants, however the medication status of the deceased patients were not stated. The final studies by Mannuzza et al (1997 & 1998) followed between 61 and 104 children with ADHD and between 41 and 78 controls for between 15 and 21 years. One death was reported in the ADHD cohort, the cause of which was not stated. Additionally, it was not reported whether this patient was taking medication to treat ADHD at the time of death.

7.2.5. Discussion

As the aim of the study was to gather as much data from the literature on the safety of methylphenidate, dexamfetamine and atomoxetine, few restrictions were imposed for inclusion into the study. However, this strategy resulted in the retrieval of studies utilising very different methods and reporting very different result. These differences are summarized in Table 7.5.

Table 7-5: Summary of differences in studies retrieved from the literature review

Participants	Gender: The percentage of males in the study populations varied from 63%-100% in studies involving children however the proportion was more even in those studies involving adults, ranging from 45-66%. Age: The age range of children studied varied from 3-18 years and in adults varied from 18-65 years. Ethnicity: 11/26 of paediatric studies and 1/7 adult studies made reference to the ethnicity of the study participants. Co-morbidities: Although all patients had a diagnosis of ADHD, various co-morbidities were included and excluded depending on the study. Some studies had no formal inclusion or exclusion criteria; some did not

	exclude patients with concurrent psychiatric illnesses and allowed conditions such as depression and anxiety while others excluded patients with histories of psychotic illnesses, motor tics, Tourette's syndrome and substance abuse. Some studies did not specifically mention exclusion based on pre-existing cardiovascular conditions, whilst others excluded patients with a history of hypertension, cardiac arrhythmias, abnormal baseline laboratory values, or abnormal baseline ECGs. Concurrent Medications: Some studies did not make any reference to the exclusion of specific concurrent medications, whereas others excluded patients who were taking any other medications that were known to affect blood pressure

	and heart rate such as tricyclic antidepressants, specific serotonin reuptake inhibitors, venlafaxine and pseudoephedrine. Some patients were drug-naïve prior to study entry; some studies required patients to have a minimum duration of treatment on the drug before study initiation and other studies were extension studies and so included patients who had previously taken and responded to the study medication.
Intervention	Studies retrieved included data on methylphenidate, dexamfetamine and atomoxetine. Within each drug group, studies varied on the doses used, frequency of administration and the release mechanism of the drug used i.e. immediate compared to modified-release

Comparisons	15/26 paediatric trials and 6/7 adult trials compared the active drug with placebo. 1 paediatric study compared methylphenidate and atomoxetine
Outcomes	For some of the studies, the assessment of cardiac safety was not the primary outcome. Many aimed to assess the efficacy of the treatment and were powered to detect differences in this outcome. For many studies, tolerability and safety were secondary outcome measures. Many of the studies did not specify how measurements were obtained. Some studies measured blood pressure using ambulatory blood pressure monitoring; others were obtained using a sphygmomanometer cuff whilst others used digital blood pressure monitors.

	Many of the studies did not state the time interval from drug administration to vital sign measurements.
Other Study Design Points	Study designs varied from a single-case report, crossover and parallel designs to a large database epidemiological study. 10/26 paediatric trials and 5/7 adult trials were double-blinded. 1/26 paediatric trials was single-blinded. Study duration varied from 48 hours – 24 months for paediatric trials and 6 – 10 weeks for adult trials. 15/26 paediatric trials and 5/7 adult trials specifically acknowledged funding for the trial from drug companies.

It was felt that extent of the clinical and methodological heterogeneity precluded the meta-analysis of the data, and so the results obtained will be summarized and discussed.

7.2.6. Mortality

None of the studies, neither paediatric nor adult, reported any cases of death of any cause due to the use of methylphenidate, dexamfetamine or atomoxetine. The study by Winterstein et al (2007) did not report any cardiac deaths in over 42,000 patient-years of stimulant use.

Even including the long-term follow-up studies of children into adolescence and adulthood, the number of deaths reported was very low, and the only sudden cardiac death reported occurred in a control patient. Loss to follow-up in these long-term studies may be interpreted in a number of ways. It has been suggested that pathology is linked to attrition, whereby those non-participants tend to have more behavioural problems, higher rates of conduct disorder and greater marital discord than subjects (Cox et al, 1977). Therefore, it cannot be excluded that patients lost to follow-up may have died. Conversely, others have found that those lost to follow-up represented a healthier group of patients, doing well who do not wish to participate as it is a reminder of the past (Weiss et al, 1985). Whichever is the case, the studies retrieved from this review suggest that the rate of death and certainly sudden cardiac death is very low.

7.2.7. Adverse Cardiovascular Events

7.2.7.1. ECG Changes

Nine of the paediatric studies and three of the adult studies reported ECG findings. Of the paediatric studies, changes have been reported both in terms of statistical and clinical significance. Studies have also reported QT interval and corrected QT (QTc) interval. The QTc interval adjusts for heart rate (which the QT interval is dependent on) and therefore aids in the interpretation of results. Kratochvil et al (2002) reported no statistically or clinically significant changes, Spencer et al (2001) revealed PR, QRS and QTc intervals were unchanged, Michelson et al (2002) reported no clinically meaningful differences in QTc intervals as did Buitelaar et al (2007).

Kelsey et al (2004) showed a statistically significant decrease in PR interval, while no other ECG changes were found. Bangs et al (2007) reported statistically significant decreases in RR and PR intervals, although QTc interval was not statistically changed. Pataki et al (1993) found increases in PR, QRS and QTc intervals, although none of these reached statistical significance. The case report by Rajesh et al (2006) found a change in repolarisation after the T wave. McGough et al (2006) reported abnormal ECG readings in patients after drug treatment, some of whom had abnormal readings before treatment and others who did not.

Conversely, a number of patients had abnormal ECG readings prior to drug treatment, which were normal afterwards. The nature of these abnormalities was not specified nor were any considered to be clinically significant.

Of the three adult studies, Fallu et al (2006) reported no clinically significant changes in ECG readings, Biederman et al (2006) reported a change in QT interval which was statistically significant, however QTc interval was not significant and no other parameters were affected and Spencer et al (2005) reported a statistically significant increase in QTc interval although again, no other conduction parameters were changed.

As stated previously, the most common method by which drug-related sudden cardiac death occurs is through delayed repolarisation of the myocardium resulting in a prolonged QT interval, thus leaving the myocardium vulnerable to ventricular tachycardia.

From the literature above, only two adult studies reported statistically significant prolongation, Biederman et al (2006) who found a significant increase in QT but not in QTc interval and Spencer et al (2005) who found an increased QTc interval. Some reports have described ventricular arrhythmias associated with the stimulants, however these have mainly been related to their abuse (Massello, 1999; Stratton et al, 2001). In the main, these studies have reported little effect on conduction parameters with the use of the stimulants and atomoxetine.

7.2.7.2. Heart Rate

Of those paediatric studies reporting significant changes in heart rate (n=11), increases ranged from 2 – 11.8 beats per minute. Urman et al (1995) reported an increase of 14.9 beats per minute 2 hours post methylphenidate dose in children with ADHD and comorbid anxiety. Many of the studies reported no statistically significant changes in heart rate, and even those where the increase was statistically different, the change was not considered to be of clinical significance. Those adult studies reporting changes in heart rate (n=6) similarly showed increases of between 3.8 and 7.3 beats per minute.

7.2.7.3. Blood Pressure

The majority of paediatric studies showed non significant changes in systolic blood pressure (both statistically and clinically). Of those which demonstrated a statistically significant increase, this ranged from 2 – 3.4 mmHg.

One study by Urman et al (1995) showed a much higher increase in systolic blood pressure in patients given a 0.9mg/kg dose of methylphenidate (increase of 9.1mmHg two hours post-ingestion).

More diastolic blood pressure changes were reported as statistically significant, however many were not considered to be of clinical significance. Many of the increases were in the range 1.5 – 4.4 mmHg, however two of the studies reported increases of 10.9 and 9.4 mmHg.

Two of the studies reported ABPM findings, a method that performs frequent measurement and recording of blood pressure in order to compute a mean blood pressure during the day, the night and over the 24-hour period. The study by Samuels et al (2006) reported a non-significant increase in systolic blood pressure and a significant increase in diastolic blood pressure of 3.9 mmHg. The study by Stowe et al (2002) showed a significant increase in systolic blood pressure of 3mmHg during the day but not over the 24-hour period and a significant increase of 2 mmHg in the daytime diastolic blood pressure but again a non-significant increase over the 24-hour period.

The Fourth Report of the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents from the United States (National High Blood Pressure Education Working Group on High Blood Pressure in Children and Adolescents, 2004) define hypertension as an average systolic blood pressure and/or diastolic blood pressure that is $\geq 95^{th}$ percentile for gender, age and height on ≥ 3 occasions.

In the study by Stowe et al (2002), 4 patients were considered hypertensive based on casual BP criteria while on therapy, with 1 patient also being hypertensive whilst off treatment. One patient was considered hypertensive as defined by ABPM criteria. One patient discontinued the study by Wilens et al (2004) due to elevated blood pressure. Apart from these patients, no other subjects discontinued due to high blood pressure.

Many of the adult studies did not report statistically significant changes in systolic or diastolic blood pressure. Significant systolic changes ranged from 2.3 – 5.3 mmHg while only one diastolic change was noted of 4mmHg. In the study by Wilens et al (2005), 9 patients in the medication group (10%) developed new-onset hypertension, defined as a blood pressure ≥ 140/90 mmHg, compared with 7 in the control group (8%). Those patients who had higher blood pressure measurements at the beginning of the study had higher corresponding blood pressure levels at the endpoint, however they did not automatically manifest the largest change. An inverse relationship was found between baseline blood pressure and change in indices whereby adults with lower blood pressure at the beginning of the study were found to produce the most change in blood pressure at the end of the study.

7.2.7.4. Treatment Emergent Adverse Events

Syncope is a frequent problem and is thought to occur in up to 15% of the normal population at some time during childhood. Syncope in children can often be postural or as a consequence of a trigger such as surprise, frustration or pain (Wren, 2002). In this review, although syncope was not reported as an adverse event, a number of studies reported on patients experiencing dizziness. In the study by Spencer et al (2005), 17% of children taking atomoxetine reported dizziness. Other adverse events reported included palpitations, which in the study by Fallu et al (2006) occurred in 25% of adults taking OROS methylphenidate, and tachycardia.

7.2.8. Conclusion

We have seen in Chapter 5 that the use of these drugs is increasing in children, although the level of persistence with treatment into adulthood is lower than the rate expected, as seen in Chapter 6. However, as the evidence on the persistence of the condition increases, it is likely that in the future, there will be many patients continuing these medications for longer periods. The concern surrounding these medications is that patients will develop high blood pressure and heart rate, predisposing them to future serious cardiac events. The literature retrieved from this review highlighted that the stimulants and atomoxetine can increase blood pressure and heart rate, in both children and adults and although these increases reached statistical significance in some studies, for many, the changes were not considered to be of clinical significance. Of those studies which reported ECG data, the findings suggest that the drugs used to treat ADHD have little effect on conduction parameters, in particular the QTc interval.

There was little data in any of these studies on the most important adverse event, namely death, which prompted us to use the GPRD to investigate the occurrence of mortality and specifically sudden death in patients taking methylphenidate, dexamfetamine and atomoxetine.

8. Chapter EIGHT: Mortality Study

8.1. Introduction

Following a review of the FDA's AERS, reports of sudden death associated with the use of stimulants raised much concern over the safety of these drugs used in the treatment of ADHD. These cases caused so much concern that they led Health Canada (the government department concerned with health) to temporarily suspend marketing of the mixed amphetamine salt Adderall XR ® from the Canadian market (FDA, 2007a).

The controversy and uncertainty over the safety of the stimulants also prompted the FDA and the Agency for Healthcare Research and Quality (AHRQ) to collaborate in a study to examine the potential for increased risk of heart attack, stroke and other cardiovascular problems associated with medications used to treat ADHD. This study, the largest of its kind, will examine the clinical data of approximately 500,000 children and adults from a seven year period, ending in 2005 (FDA, 2007b). However the analysis is still ongoing and in the interim, concern still surrounds the issue of sudden death associated with ADHD medications.

8.2. Aim

The aim of this study was to determine any association between methylphenidate, dexamfetamine and atomoxetine and sudden death in children and young adults.

8.3. Objectives

To achieve the above aim, the following objectives were followed:

- To identify cases and causes of death in a cohort of patients taking methylphenidate, dexamfetamine and atomoxetine in the GPRD.
- To assess the likelihood of an association with any of the study drugs
- To calculate mortality ratios in the study cohort compared to the general population
- To determine the number of reports of death submitted to the Yellow Card System suspected to be caused by any of the study drugs.

8.4. Method

8.4.1. Data Source

The data for this study was obtained from the GPRD and the Yellow Card System. These data sources have been described previously.

8.4.2. Study Period

The study period was 1st January 1993 to the 30th June 2006. Compared to other studies of utilisation and cessation, the end of the study period in this study was reduced by a period of six months. This was done, as suggested by the GPRD, as it can sometimes take up to six months after death for a death code or a Transferred Out date to be recorded in the database. Therefore, to ensure all deaths would be captured, only patient records from before 30th June 2006 were included so as to enable a 6-month follow-up period until the end of 2006.
The study frame from which Yellow Card data was obtained was 1st January 1992 until 31st December 2006.

8.4.3. Eligibility Criteria

Patients who had received at least one prescription for methylphenidate, dexamfetamine or atomoxetine during the study period and were aged between 2 and 21 years at the time when the prescription was issued were eligible for inclusion into the study. Patients were required to be registered to an up-to-standard practice and were not permitted to have temporary registration status with a practice. So as not to exclude patients who may have had an event soon after joining the database, or soon after starting treatment, patients were neither required to have a minimum amount of up-to-standard data on the database nor a minimum duration of treatment with the study drug.

8.4.4. Patient Identification and Follow-Up

The cohort of patients was identified previously. The index date for patients was the date of their first prescription for a study drug. The follow-up time from the first prescription was calculated in two ways.

The first method involved following patients from the index date until the earliest occurrence of the date of death, transferred out date, age greater than 21 years old, or end of the study period. Participants were censored if they transferred out of a practice or if a practice ceased to contribute data to the database.

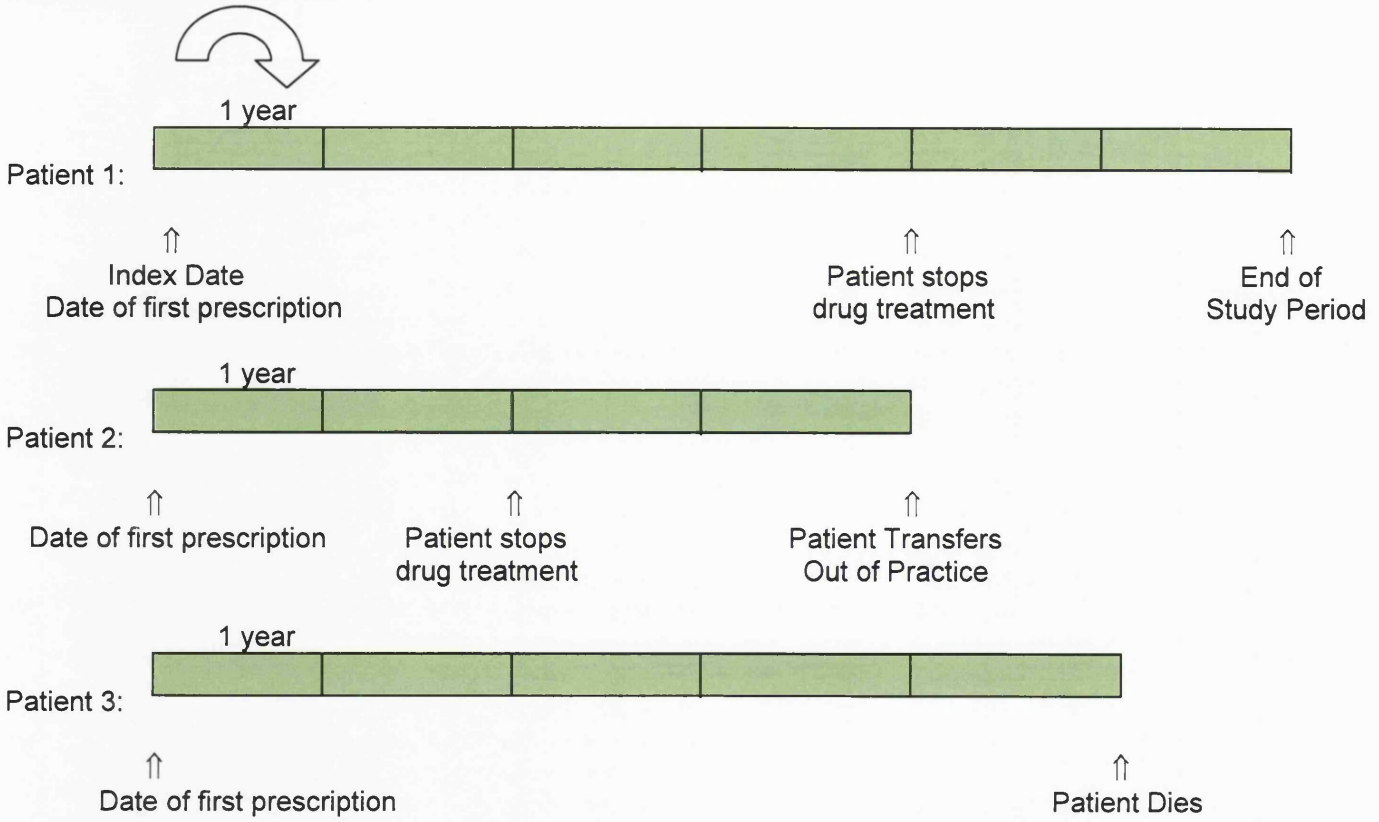
This method assumed patients to be at risk at any time after the first prescription, whether or not they were currently exposed to the drug at the time of the event. This method used person-years at risk as the denominator for subsequent calculations.

The second method again followed patients from the time of the first prescription to the first occurring study endpoint, however, only periods when the patient was exposed to the drug were included as periods at risk.

This method used person-years exposed as the denominator for calculations. These two methods have been demonstrated schematically in Figure 8.1 and 8.2.

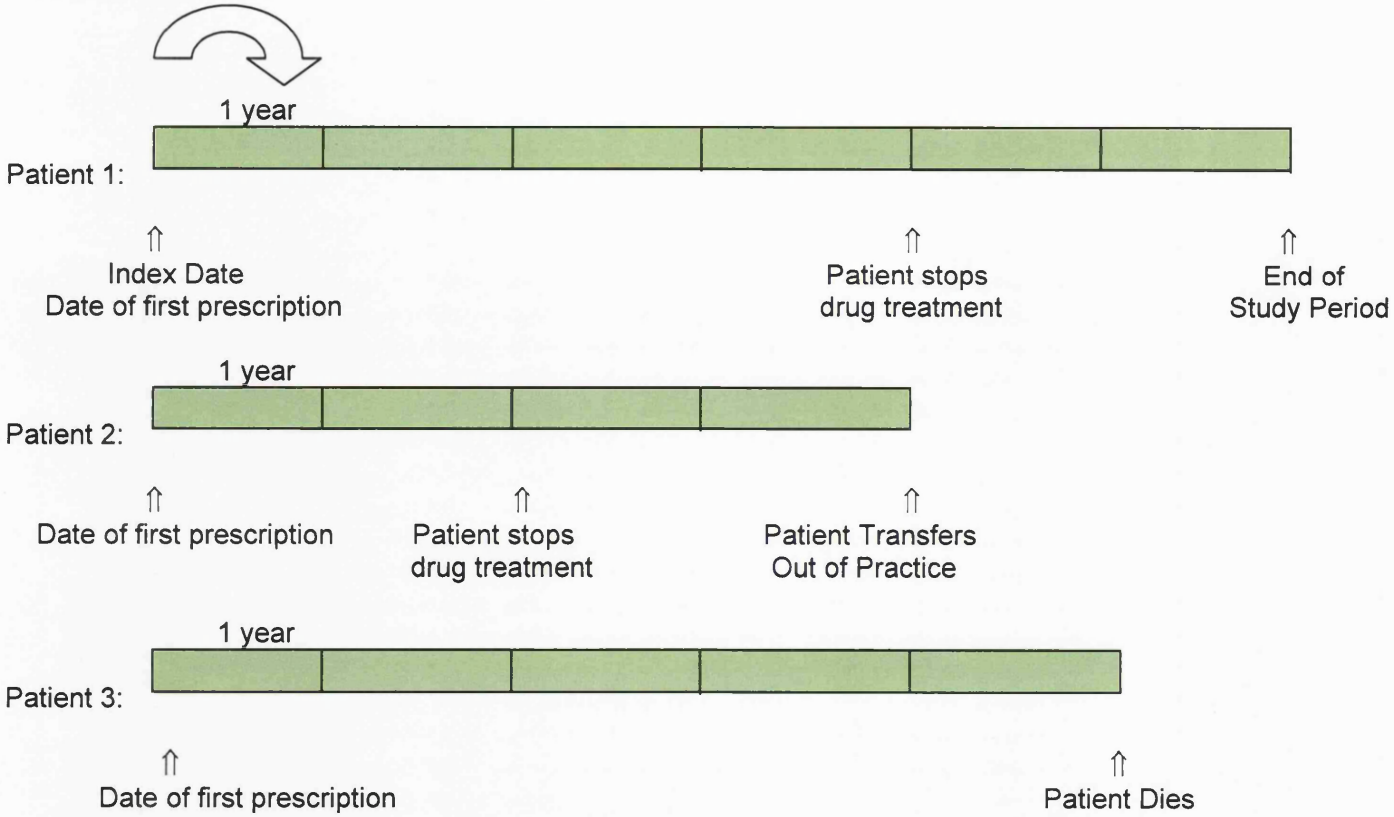
The period of treatment exposure was calculated using a method previously described (Section 6.3.4). To summarise, the duration of prescriptions was calculated by dividing the total quantity by the daily dose. The duration of treatment was calculated from the start date of the first prescription to the end date of the last prescription. Gaps of six months or more between prescriptions denoted treatment breaks.

Figure 8-1: Method 1: Person-Years at Risk



Person-Years at Risk: Patient (1) 6 years, Patient (2) 4 years, Patient (3) 5 years.

Figure 8-2: Method 2: Patient Years Exposed



Person-Years Exposed: Patient (1) 4 years, Patient (2) 2 years, Patient (3) 5 years.

8.4.5. Case Identification

There are a number of ways in which GPs can enter death in a patient's medical record using the Vision management system.

Once a GP has been given notice of a patient death, they can enter a Read/OXMIS code known as the Statement of Death code (SoD) in the patient's medical record. A list of Read/OXMIS codes for death is given in Appendix 3. GPs also have the option of using a structured data area to enter specific information on death administration or cause of death, while the third way of recording death in the GPRD is through recording the transferred out reason from a practice as death. Cases of death were identified by screening patients' medical records using the above three methods. The recording guidelines for GPs state that terms denoting death should never appear in a patient's medical record unless the patient has died. However, the GPRD acknowledge that GPs may enter death codes incorrectly, such as a code of suicide which may only refer to an attempted suicide or a code of death which refers to a death of a family member and not the patient themselves. For this reason, all cases of death retrieved using the above algorithm were screened for any indicators that the code had been incorrectly entered. If a patient continued to have 6 months or more of prescription records after the code of death, and the death code was suicide, or the patient did not have a transferred out date or reason, it was assumed that the patient had not died.

If there was any doubt as to whether the patient had died, they were included in the next step of case validation.

8.4.6. Case Validation

Although death recording in primary care is considered accurate, it is considered necessary to further validate cases of death, and this was done through the use of questionnaires. A benefit of using the GPRD for a study such as the current one is their provision of a verification service. As the GPRD is an anonymised database, it is necessary for the GPRD to unanonymise the patient data to enable them to send the questionnaire to the patient's GP. On return of the questionnaire, the patient details are anonymised and sent back to the researcher.

The questionnaire was developed by the study team which consisted of a pharmacist (Suzanne McCarthy), a pharmacoepidemiologist (Professor Ian Wong), a clinical pharmacologist (Professor Noel Cranswick) and a consultant child and adolescent psychiatrist (Professor Eric Taylor).

A copy of the invitation letter and questionnaire sent to the GP is given in Appendix 7 and 8 respectively. GPs were asked to confirm that the patient had died, to give the patient's date of death (as it is often difficult to ascertain this accurately from the database), to detail the cause of death and any post-mortem information if applicable, to list any co-morbid conditions or suicidal tendencies, to give prescription information on the study drug and any other drugs the patient was taking concurrently, and to record whether the patient had in the past or was taking clonidine at the time of the event.

This was done as the stimulants and clonidine are often co-prescribed, the later used to counter-act tics which can occur due to stimulant treatment. There have been reports, although the evidence is weak, of an association between the combination of methylphenidate and clonidine and sudden death (Popper, 1995).

8.4.7. Data Analysis

8.4.8. Case Classification

Once cases had been identified and validated, the study group assessed each case to determine, firstly whether it was a case of sudden death and secondly, whether there was an association between the death and the use of the ADHD drug treatment.

The definition of sudden death used in this study was the WHO definition which includes instantaneous death and all deaths occurring within 24 hours of an acute collapse (Roberts, 1986). Sudden death does not include cases such as suicide, murder or other causes of unnatural death such as drowning or poisoning.

The cause of death given by the GP as stated in the questionnaire was accepted as the true cause of death.

The deaths of patients were then classified using a method described by Wren et al (2000), in which death was classified into one of five categories:

- Death (not sudden) from known medical conditions
- Unnatural deaths (including homicide, suicide, drowning, poisoning, and all other violent deaths)
- Sudden deaths attributed to known pre-existing conditions
- Unexpected sudden deaths attributed to a natural cause discovered at autopsy
- Unexpected sudden deaths which remained unexplained after autopsy.

8.4.9. Mortality Rates

Crude mortality rate (CMR) and standardised mortality ratios (SMR) were calculated on all cases of death. Crude mortality rate is defined as the rate of death in the study population, without taking into consideration the age distribution of the population (Bland, 1993). This was calculated as:

$$\frac{\text{Deaths occurring over a given period}}{\text{Number in population over length of period}}$$

The calculation of SMRs is an epidemiological technique that aims to make comparisons of mortality between populations, often comparing a subset of a large population with the population as a whole, while accounting for possible confounding factors such as gender and age (Armitage and Berry, 1994).

The SMR was calculated using the indirect method of standardisation, which is used when there are few deaths in the observed population (Bland, 1993). Initially, the age and gender specific mortality rates in the general population were calculated using population and mortality data obtained from the Office for National Statistics (ONS) using data for the mid-year of the study (1998). Using these rates, the expected number of deaths in the drug cohort was calculated, assuming it had the same rate as the general population. The SMR was defined as:

$$\frac{\text{Number of deaths observed in the study group}}{\text{Number of deaths expected in the study group}}$$

The SMR was standardised by age and gender.

8.4.10. Sudden Death Calculation

The rate of sudden death was not available from population figures and so for comparison purposes, a rate of sudden death from the literature was used. Although the reported incidence of sudden death varies from 0.8 to 6.2 cases/100,000 population per year (Berger et al, 2004), for comparison purposes, we chose a rate of sudden death obtained from a study which was similar to the present study in terms of demographics of the population and the country in which the study was conducted. This study by Wren et al (2000) involved reviewing all deaths at age 1-20 years in the North of England between 1985 and 1994. They obtained death certificates from the ONS and further information if necessary from coroners, paediatricians, physicians and pathologists.

They used a definition of sudden death which was more strict than the WHO definition and only included deaths that occurred suddenly out of hospital, or on arrival at hospital, or in the accident and emergency department. They excluded any deaths that occurred after admission to hospital, even when they occurred within 24 hours from the initial collapse. The rate of sudden death estimated by Wren et al was 3.3/100,000 per year.

The incident rate of sudden death in the GPRD study was calculated and incident rate ratio calculations were performed using Poisson exact methods to handle small event numbers.

8.4.11. Yellow Card Data

Due to the lack of data on the overall use of these drugs in the population, calculations on the incidence of mortality cannot be made. Therefore, data will only be analysed descriptively.

8.4.12. Ethical Approval

Ethical approval for the project was granted by ISAC – Protocol Number 06_035 (See Appendix 9). Ethical approval was not necessary for the Yellow Card Data.

8.5. Results

The sample size for the defined cohort was 5,351 patients. From this, we identified seven patients who had died. Questionnaires were sent to the respective GPs with a response rate of 100%. Though the GPRD is an anonymised database, the ethics committee requested that additional steps were taken to protect the anonymity of the small numbers of cases identified. Therefore certain patient characteristics, including age, gender, and date of death have not been reported. As a result, patients' age was categorised into the following groups: age 2-7, 8-15, and 16-21 years. Each of the cases is presented in turn below:

Case #1: This patient was aged between 2 – 7 years at the time of death. The patient had been prescribed dexamfetamine 10mg on alternate days for less than one month before death. The patient had an active prescription for dexamfetamine at the time of death. Nine months prior to death, the patient had a record of convulsion, three months prior had a record of vomiting, and two months prior was diagnosed with a brain tumour, the listed cause of death. Other medications the patient was prescribed by the GP at the time of death included nystatin, co-trimoxazole, phenytoin, carbamazepine and paracetamol. According to the death classifications given above, this patient's death was classified as death (not sudden) from a known medical condition.

Case #2: Patient was aged between 8 – 15 years at the time of death. At the time of death, the patient had been prescribed dexamfetamine at a dose of 2.5mg three times a day. The duration of treatment with therapy was over two and a half years. The patient had an active prescription for dexamfetamine at the time of death. The patient also suffered from severe epilepsy and was receiving triple therapy for its management: sodium valproate, lamotrigine and ethosuximide. A month before death, the patient was started on acetazolamide, however this was stopped two weeks later (2 weeks before death) as the patient became withdrawn. The cause of death given was pancreatitis. According to the classifications given above, this patient's death was classified as death (not sudden) from a known medical condition.

Case #3: Patient was aged between 8 – 15 years at the time of death. At the time of death, the patient had an active prescription for methylphenidate modified-release at a dose of 36mg daily. The patient had been receiving treatment for over one and a half years prior to death. In addition to ADHD, the patient had an aggressive personality, but no other co-morbid medical or psychiatric conditions noted. The cause of death was suicide. The GP recorded that the patient did not have any suicidal tendencies prior to death. This case was classified as an unnatural death.

Case #4: This patient was also aged between 8 – 15 years at the time of death. This patient had an active prescription for methylphenidate (Ritalin®) at the time of death, prescribed at a dose of 20mg twice a day. This patient had been receiving treatment for over 8 months prior to death. The patient did not have any other recorded co-morbid conditions or concurrently prescribed medications. The cause of death was suicide by hanging. Again, the GP recorded that the patient did not have any suicidal tendencies prior to death. This case was also classified as a case of unnatural death.

Case #5: This patient was aged between 16 – 21 years at the time of death. This patient did not have an active prescription for a study drug at the time of death. The patient had received treatment with methylphenidate for a period of six months, but had not received any prescriptions from the GP in over three years prior to death.

The GP was not aware of any other co-morbid conditions or co-prescribed medications at the time of death. The cause of death was stab wounds and so this was classified as a case of unnatural death.

Case #6: This patient was aged between 16 – 21 years at the time of death. This patient did not have an active prescription at the time of death. The patient had received methylphenidate for over one and a half years, at a dose of 10mg three times a day, however the patient had stopped receiving prescriptions from the GP over two and a half years before death. Other co-morbidities the patient had included anxiety and insomnia, and the patient was taking fluoxetine 20mg daily at the time of death. The cause of death was an overdose; however the intent of the patient was unknown. This death was classified as an unnatural death.

Case #7: This final patient was also aged between 16 – 21 years at the time of death. The patient had received only one prescription for methylphenidate, approximately five months prior to death, the duration of which was 14 days. The patient did not have an active prescription for methylphenidate at the time of death. As well as ADHD, the patient had a history of depression. The patient did not have any other recorded medical conditions or medications prescribed. This patient did not have a reason of death in the GPRD medical records and it was not known by the GP.

A number of attempts were made to obtain the death certificate for this patient to ascertain cause of death, however due to a number of issues with the patient's GP practice; it was not possible to do so. Therefore, it was not possible to determine the cause of death and whether this was a case of sudden death.

8.5.1. Mortality Rates

8.5.2. Method 1: Person-Years at Risk

8.5.2.1. CMR and SMR

The 5,351 patients in the cohort provided 18,637 person-years at risk from the time of the first prescription of a study drug to the first occurring study end-point.

The CMR was calculated based on all cases of death (n=7) and was 3.76 per 10,000 person-years.

The SMR was stratified by age and gender, however only total figures are reported due to the ethical restrictions discussed above. The SMR was 1.44 (95% CI: 0.58 to 2.96) indicating no difference was detected in mortality rates between the general population and study cohort when applying a 5% two sided significance level.

8.5.2.2. Incident Rate Ratios

For those patients with a confirmed cause of death (n=6), none were considered to be cases of sudden death. The incident rate ratio calculations were performed to both include and exclude the one case of death of unknown cause.

The best case scenario would be that none of the cases (0/7) were cases of sudden death. Comparing this rate from the GPRD to the rate of sudden death in the literature (Wren et al, 2000), this gave an incident rate ratio of 0 (95% CI: 0 to 6.35). The worst case scenario was that the one unconfirmed case was a case of sudden death (1/7). This gave an incident rate ratio of 1.63 (95% CI: 0.04 to 9.71).

8.5.3. Method 2: Person-Years Exposed

8.5.3.1. CMR and SMR

The 5,351 patients in the cohort provided 11,016 person-years exposed to treatment. Four of the seven patients were taking treatment at the time of death and so the CMR was calculated to be 3.63 per 10,000 person-years exposed. The SMR was calculated, stratifying for age and gender and was 1.74 (95% CI: 0.47 to 4.45), again indicating no difference in mortality rates between the general population and study cohort exposed to treatment when applying a 5% two sided significance level.

8.5.3.2. Incident Rate Ratio

The incident rate ratio was calculated by comparing the incident rate of sudden death in the treatment group exposed to the rate of sudden death in the literature. However, as the one case of unknown cause was not exposed to medication at the time of death, the incident rate ratio was 0 (95% CI: 0 to 10.74).

8.5.4. Suicide

Following reports of suicides from the questionnaires, we examined the rate of suicide in the study cohort and compared it to rates of suicide in the general population, again using data from the ONS. The ONS defines suicide differently for children and adults; in adults and young people over 15, the suicide figures include those deaths from intentional self-harm, and those from 'injury or poisoning of undetermined intent' whereas in children under 15 years, deaths from injury or poisoning of undetermined intent are not included when examining suicide (intentional self-harm) due to the possibility that these deaths were caused by unverifiable abuse, neglect or accidents. Therefore, the cases of suicide in the drug cohort have been classified into two age categories, under 15 and over 15 years. As there were no events in either the study population or the general population in children aged less than 11 years, the age categories were further refined to include children aged 11-14 and adolescents and young adults aged 15-21 years.

Again, suicide rates have been calculated based on both person-years at risk and person-years exposed.

8.5.4.1. Method 1: Person-Years at Risk

In the 11 – 14 age category, there were two recorded suicides. Table 8.1 displays the cases of suicide compared to those in the general population.

Table 8-1: Cases of suicide in young people aged 11 - 14 years from 1993 to 2006 in the study cohort and the general population (using ONS data)

	Study Cohort	General Population
Number of suicide cases	2	56
Population (patient years)	7,543	37,234,000

The incident rate of suicide in the general population was 0.015 per 10,000 patient years. The incident rate of suicide in the study cohort was 2.65 per 10,000 patient years. The standardised mortality ratio for suicide for ages 11-14 adjusting for gender was 161.91 (95% CI: 19·61 to 584·88).

In the 15 – 21 age category, there was one case where the GP recorded a case of possible suicide. This is compared to the rate in the general population in Table 8.2.

Table 8-2: Cases of suicide in young people aged 15 - 21 years from 1993 to 2006 in the study cohort and the general population (using ONS data)

	Study Cohort	General Population
Number of suicide cases	1	4,142
Population (patient years)	5,824	63,130,526

The incident rate of suicide in the general population was 0.66 per 10,000 patient years. In the study cohort, the incident rate of suicide was 1.72 per 10,000 patient years. For ages 15-21, the standardised mortality rate for suicide, adjusting for gender was 1.84 (95% CI: 0·05 to 10·25).

8.5.4.2. Method 2: Person-Years Exposed

In the 11 – 14 age category, there were two recorded suicides. Table 8.3 displays the cases of suicide compared to those in the general population.

Table 8-3: Cases of suicide in young people aged 11 - 14 years from 1993 to 2006 in the study cohort and the general population (using ONS data)

	Study Cohort	General Population
Number of suicide cases	2	56
Population (patient years)	5,001	37,234,000

The incident rate of suicide in the general population was 0.015 per 10,000 patient years. The incident rate of suicide in the study cohort was 4.00 per 10,000 patient years. The standardised mortality ratio for suicide for ages 11-14 adjusting for gender was 243.56 (95% CI: 29·50 to 879.82).

In the 15 – 21 age category, the one case of possible suicide was not exposed to treatment at the time of death.

Table 8-4: Cases if suicide in young people aged 15 - 21 years from 1993 to 2006 in the study cohort and the general population (using ONS data)

	Study Cohort	General Population
Number of suicide cases	0	4,142
Population (patient years)	1,610	63,130,526

The incident rate of suicide in the general population was 0.66 per 10,000 patient years. In the study cohort, the incident rate of suicide was 0 per 10,000 patient years. For ages 15-21, the standardised mortality rate for suicide, adjusting for gender was 0 (95% CI: 0·00 to 19·51).

8.5.5. Yellow Card Data

During the 15 year period studied, there were two reports of death, one accidental and one sudden death in patients prescribed methylphenidate. However, due to small number of reports, restrictions imposed under the Data Protection Act, prevented us obtaining any further information on these cases.

8.6. Discussion

The FDA concluded in their report on sudden death, that due to limitations in the information available on the cases and the methods used to obtain the data, it was not possible to make a direct comparison between the reported rates of sudden death during stimulant therapy with background rates of sudden death in the general population. It also acknowledged that using a spontaneous reporting system, under-reporting was likely to underestimate the incidence of these events. This study was unable to obtain any usable data from the Yellow Card System due to regulations on data protection. This highlights some of the difficulties incurred using spontaneous reporting systems. However, the evidence from the Yellow-Card data reported above suggests that death associated with the use of methylphenidate, dexamfetamine and atomoxetine either occurs very rarely, is reported very rarely or both.

In the GPRD study, it was possible to accurately identify and validate cases of death from a defined cohort of patients receiving ADHD drug therapy. In total, seven cases of death were identified from a cohort of 5,351 patients.

When examining cases of death of all causes, standardised mortality ratios were calculated based on both person-years at risk and person-years exposed, resulting in ratios of 1.44 and 1.74 respectively.

Patients could be between 3 and 4 times more likely to die compared to the general population, as indicated by the upper 95% confidence intervals, however, as both intervals included 1, this study failed to demonstrate an increased risk in mortality in the study group at a 5% two sided significance level.

Cases of sudden death were then examined in the ADHD cohort. As it was not possible to confirm the cause of death of one patient, calculations, performed to both include and exclude this case as one of sudden death, were compared to the rate of sudden death in the literature. The worst case scenario was that the one case of unknown cause was a case of sudden death. This gave an incident rate ratio of 1.62, however again, this was not statistically significant. In addition, the patient did not have an active prescription for a study drug at the time of death.

Although medications used in the treatment of ADHD could theoretically set in motion a cascade of biological events which may result in sudden death, as the confidence interval contained 1, this study failed to demonstrate an increased risk of sudden death in the study cohort taking methylphenidate, dexamfetamine and atomoxetine when compared to the rate of sudden death described in the literature.

The evidence from this study and others reviewed in Chapter 7 suggests that the risk of sudden death from the use of the stimulants and atomoxetine does not appear to be higher than the general population risk.

However, rare events occur rarely, and so clinicians should be aware of the necessary precautions to take to potentially avoid an event as tragic as sudden death in patients requiring treatment for ADHD.

The American Heart Association (Vetter et al, 2008) published a scientific statement on the cardiovascular monitoring of children and adolescents with heart disease receiving medications for ADHD and recommended the following:

Once a patient has been diagnosed with ADHD and a decision has been made that drug treatment is warranted, the clinician should undertake a thorough examination of the patient. This involves taking a complete history to determine whether the patient currently has or has had episodes of fainting or dizziness, seizures, chest pain or shortness of breath on exertion, palpitations or high blood pressure. A complete family history should be obtained to determine whether there have been any sudden or unexplained deaths, any heart attacks in family members less than 35 years of age, a history of any cardiac arrhythmias including long QT syndrome, or a history of cardiomyopathy. In addition to this, the clinician should elicit all prescribed medication, over-the-counter medication and health food supplements taken.

Though not mentioned in the AHA statement, it may also be appropriate in some circumstances for the clinician to enquire about the use of illicit drug substances.

Following this, the clinician should undertake a physical examination of the patient, taking baseline blood pressure and pulse measurements.

This assessment should check for the presence of an abnormal heart murmur, irregular cardiac rhythm and hypertension. They suggest that it is reasonable for a clinician to consider performing an ECG before a patient begins drug treatment. However, it is not mandatory and therapy should not be withheld if one has not been done. It is up to the clinician's judgement to determine whether an ECG should be obtained or not. This recommendation was classified as a Class IIa, level C of evidence; however this has recently been disputed by the American Academy of Pediatrics (Perrin et al, 2008). Perrin et al claim that due to the lack of any clinical evidence or scientific studies suggesting that ADHD drugs are implicated in causing sudden death, the recommendation to obtain an ECG before initiating therapy is not warranted.

Regardless of the above debate over ECG monitoring, once a patient has been initiated on drug treatment, they should have regular follow-up assessments to perform blood pressure and pulse measurements and to determine the emergence of any possible cardiac symptoms or the initiation of any new medications.

As mentioned previously, patients with a history of cardiac disease have been identified as having a greater propensity for developing behavioural conditions such as ADHD and so the clinician may be faced with a situation whereby a patient with heart disease requires treatment with a stimulant.

The AHA recommends that "it is reasonable to consider the use of stimulant medication in patients with congenital heart disease that is not repaired or repaired but without current haemodynamic or arrhythmic concerns or congenital heart disease that is considered to be stable by the patient's paediatric cardiologist unless the patient's paediatric cardiologist has specific concerns" (Vetter et al, 2008).

They also recommend that if other non-drug therapies are insufficient in treating ADHD, it is reasonable to use stimulants, albeit with caution, in:

- Patients with heart conditions such as LQTS, short-QT syndrome, HCM, WPW, Marfan syndrome and Brugada syndrome
- Patients with a history of arrhythmias which in the past have required cardiopulmonary resuscitation
- Patients with previously aborted sudden cardiac death
- Patients with QTc intervals of more than 0.46 seconds
- Patients with blood pressure or heart rates which are more than two standard deviations above the means for age
- Patients with clinically significant arrhythmia which is not treated or controlled.

Careful initiation of drug treatment is recommended in these patients.

Should any of these conditions arise during drug treatment, clinicians should consider discontinuing medication until tests can be conducted on the patient. If the condition can be controlled, the patient may be restarted on ADHD drug treatment, following approval from a paediatric cardiologist.

Although not an original outcome measure of the study, in light of the results obtained, further analysis was conducted into the rate of suicide amongst the cohort. The SMR for suicide among younger children (aged ≤14 years) showed that the ADHD cohort was 162 times more likely to commit suicide in comparison to the general population at 5% two-sided significance level. When calculated by patient-years exposed, the ADHD cohort was 244 times more likely to commit suicide.

The SMR for suicide in older children and young adults was 1.8 for person-years at risk and 0 for person-years exposed, although 95% confidence intervals for both indicated that there was no difference in suicide rates between the ADHD cohort and the general population.

Suicide is rare in young children, however the incidence increases as children enter adolescence and reaches a peak in early to mid-twenties. Studies have been conducted to determine the factors which predict suicide in adolescence and young adulthood. In a long-term follow-up study of children with major depressive disorder (MDD) and children with MDD and co-morbid conduct disorder (CD-MDD), it was found that the incidence of completed suicides and suicide attempts was higher in the CD-MDD group than in those with MDD.

A study by Shaffer et al (1996) examined the psychiatric risk factors associated with child and adolescent suicide and found a relationship between suicide and the presence of previous suicide attempts, mood disorders alone or in combination with conduct disorder and/or substance abuse. A study by Renaud et al (1999) examined the psychiatric risk factors for suicide in adolescents with ADD and/or CD, and found that conduct disorder was more common in the group that completed suicide, as was current alcohol and drug abuse. Those who had completed suicide were also more likely to have had suicidal ideation, had previous suicide attempts, had a history of physical abuse and a family history of mood disorders and substance abuse.

The evidence of an association between suicide and ADHD was reviewed by James et al (2004). This study reviewed the literature from epidemiological suicide studies, psychological post-mortem studies of teenage and young adult suicides and also studies of long-term follow-up of children with ADHD in adulthood. The results of this review suggested an association between ADHD and completed suicides, a link that was found especially in younger males. It is believed that this increased risk is mediated via the increased risk of co-morbidities with which patients with ADHD frequently present including depression, anxiety, oppositional defiant disorder, conduct disorder and substance abuse.

Our study revealed a much greater risk of suicide when compared to the general population. An FDA review of ADHD medications revealed a slight increased risk (~1 in 1000) in drug-related psychiatric adverse events such as hearing voices, becoming suspicious for no reason, and in some cases, becoming manic (FDA, 2007c), however, no other research known to us has reported on the incidence of suicide association with ADHD medication. Therefore, although we cannot exclude that the medications may contribute to the increased risk, there are other factors such as depression, conduct disorder and substance, which frequently co-exist with ADHD, can also predispose to teenage suicide (James et al, 2004).

In addition to this, it must be borne in mind that untreated ADHD increases the risk of substance abuse (tobacco, alcohol and drugs) which increases the risk of morbidity and mortality and being involved in motor vehicle accidents (Cox et al, 2004; Barkley et al, 2002; Wilens et al, 1997; Wilens et al, 2003; Biederman et al, 2007) which has been identified as the leading cause of death worldwide in young people aged 10 to 24 years. (WHO, 2007c)

8.7. Limitations

There are a number of limitations with this study which must be acknowledged. A sample size calculation was performed to determine the number of patients required in the study to detect an odds ratio of 2, assuming the risk of sudden death to be 3.3 per 100,000. With a 2-sided significance level of 95%, and a power of 80%, a total cohort of 1,427,142 patients would be required (Kelsey et al, 1996). Using one of the largest databases in the world, it was not possible to achieve this sample size in the current study. Even with a large cohort of 18,637 patient years, the extreme rarity of sudden death in children has resulted in poor precision surrounding the SMR and incident rate ratio calculations. Although the SMR for mortality and the incident rate ratio for sudden death were not statistically significant, the wide confidence intervals mean that one cannot exclude a 2-fold and 9-fold increased risk respectively. However, the absolute risk of these events occurring still remains very low.

Secondly, as has been a limitation in the other studies presented, the database only records prescriptions issued by the GP and does not record whether these prescriptions were ever dispensed or whether the patient was compliant with the prescription instructions.

It is also possible that patients were prescribed a study drug or other drugs from specialists in secondary or tertiary care, again which may not be recorded on the database or indeed known by the GP. As previously mentioned, the issue of hand-written prescriptions for controlled drugs may have impacted on the results obtained. It is possible that if a patient's GP had never entered a prescription for a study drug on the database, this patient would not have been captured in this study. It would not have been possible to detect how often this situation arose, however, in this study, inclusion of a patient relied only on the fact that they had ever received a prescription for a study drug and not how many prescriptions they received and so while we cannot discount the fact that this is a real limitation of the database, we believe that a GP, in line with the recording guidelines, would have entered at least one record of a study drug in the patient's therapy file.

Thirdly, we have compared our rate of sudden death with a rate published in the literature of 3.3/100,000 per year (Wren et al, 2000). Comparisons with population based reports are very difficult as the methods used to gather data, the time when the study is conducted and the demographics of the populations can vary between reports. Although the comparator study was conducted in the same country as the present study, it was examined data from a decade previous to the current study and it did not report exact ages of deceased patients which may have resulted in confounding by age and time.

This study employed a standard epidemiologic method involving the comparison of sudden death in the GPRD ADHD drug cohort with the population rate of sudden death. Alternative approaches which could have been chosen include case-control and a matched cohort design. These were not conducted for the following reasons. A case-control design would have involved obtaining and verifying the causes of death of all patients in the GPRD, in order to determine the rate of sudden death in the GPRD population. The current study cost almost £500 and took over one and a half years to collect data on the seven cases of death. To obtain and verify each case and cause of death in the GPRD would not have been feasible within the current study. In addition, the current study was unable to detect any case of sudden death in patients taking ADHD medication and therefore a case-control study would not have been possible. A matched cohort study, whereby children with ADHD taking stimulants would have be matched with controls could have been undertaken to answer the research question, however, as children with ADHD already have an increased risk of morbidity and mortality finding appropriate matches would have been very difficult. Therefore, although the methodological approach chosen for the current study has its limitations, it was felt to be the most appropriate choice considering the database used and the nature of the research question.

8.8. Conclusions

In concordance with the current literature and epidemiological data, this study was unable to demonstrate an increase in the risk of sudden death associated with methylphenidate, dexamfetamine or atomoxetine using the GPRD cohort. This study was limited by the sample size of the cohort and the rarity of the outcome of interest and it is therefore possible, as stated in the limitations that this study was unable to detect an increase in sudden death simply due to insufficient power. The lack of data in the literature on the occurrence of death with the stimulants and atomoxetine has led to confusion and anxiety amongst clinicians, patients and their families. Therefore, while the results of this study should be interpreted with caution it is important to utilise those resources available to provide information on the risks involved. From a cohort of 18,637 person-years at risk, our study did not identify any case of sudden death.

However, clinicians should undertake thorough evaluations of patients in order to identify patients with increased cardiovascular risks and identify those patients at increased risk of suicide, particularly males with comorbid conditions, and to monitor them appropriately.

Whilst it is imperative that clinicians, patients and parents are aware of the risks, benefits and side-effects of methylphenidate, dexamfetamine and atomoxetine, it is important that patients are not deterred for using these highly effective and well-studied medications.

9. Chapter NINE: Overall Discussion

In 1994, a 9 year old boy named Michael was diagnosed with ADHD. According to his mother, "he was always full of energy, talked constantly, and asked questions nonstop. He had trouble focusing in school, and his teachers couldn't get him to interact during learning time. He was always pushing, nudging, shoving, and fidgeting. It was hard for him to listen unless it was something that really captivated his attention". Michael was prescribed stimulant medication which helped him to concentrate at school. It also helped him to focus more on his sports, swimming in particular which he used as an outlet for excess energy (Hahn, 2008).

Fourteen years later, this young man, Michael Phelps went on to become the greatest Olympian ever, winning eight gold medals in swimming at the Beijing Olympics (fourteen Olympic gold medals in total) and holding seven world records.

This story highlights the fact that children and adults with ADHD can lead normal lives, and like Michael Phelps can go on to achieve great things. However, to do so, a diagnosis of ADHD needs to be taken seriously and not be viewed as a label attached to difficult children. Many patients require some form of treatment to help overcome the symptoms and impairments associated with the condition and while not all patients will require medications, for some it is deemed necessary.

Decades of research into the use of stimulants (and more recently atomoxetine) have established that they are both clinically and cost-effective for the treatment of ADHD. The review of the literature in Chapter 1 identified a number of gaps in the knowledge base, gaps which this study sought to address.

The first research question proposed was: How are ADHD drugs utilised in the UK and how has this changed in the last decade?

The drug utilisation studies conducted using the GPRD and IMS-DA provided data on the patterns of methylphenidate, dexamfetamine and atomoxetine use in the UK over the last decade. The results of the IMS-DA correlated strongly with those obtained from the GPRD. In terms of prescribing patterns, methylphenidate remains the most frequently prescribed drug for the treatment of ADHD. This falls in line with the current recommendations by NICE (2008). The use of modified-release preparations, since their introduction to the market, has increased significantly indicating their popularity over the immediate-release preparations. The benefits of the long-acting medications likely to contribute to this increase include reduced frequency of dosing, avoidance of drug administration during school and less fluctuations in behaviour. The prevalence of drug prescribing has increased 8-fold over the decade 1996 to 2006. This does not necessarily signify that the prevalence of the condition has increased, as it is likely that the condition is now more recognised, diagnosed and treated.

The majority of drug use occurs in male school-aged children; however, the prevalence of use in females and in younger adolescents continues to grow. A similar increase in prescribing was not observed in the very young children. Drug treatment is not first-line for pre-school ADHD children, and the data from the drug utilisation studies illustrate a decrease in their prescribing over the last decade.
The data presented here from the GPRD and the IMS database suggests that both the prevalence and incidence of prescribing of methylphenidate, dexamfetamine and atomoxetine to school-aged children and young adults have increased over the last decade in the UK. Although the rates are well below the reported prevalence of the condition in the UK and are also lower than the prescribing rates reported in the Netherlands and the US, further work is required to determine whether levels of prescribing are appropriate to the level of the condition.

The second research question proposed was: What are the patterns of drug use when children transition to older adolescence and adulthood?

ADHD was once considered a condition of childhood only, one in which children would grow out of once they reached adolescence and adulthood. Prospective follow-up studies have identified that this is not necessarily the case and while the symptoms and impairments will remit in some children, the majority will continue to suffer some impairment from the condition into later years.

Some patients can adapt their lives around these impairments and may not require any treatment, however for others, drug treatment is necessary for daily functioning. It is widely recognised in the area of mental health that children can fall into the gap between child and adult services. This often results in children failing to get access to services and treatment they desperately require. This is especially the case with ADHD, an area in which adult services are currently poorly developed, where adult clinicians have very little training, and for which drug treatment is mainly unlicensed. The CADDY study was commissioned to determine the current situation of drug use in adolescence and young adults and to examine the reasons and processes behind drug cessation. Data on drug use from the GPRD highlighted that while overall the use of the ADHD drugs has increased over the last decade, this increase has not been observed in older adolescents and young adults.

The study demonstrated a significant decline in prescribing between the ages of 15 and 21; a decrease which greatly exceeded the expected rate of decline of the condition. A number of possible reasons contributing to treatment cessation were postulated. These included patients leaving school and thus no longer perceiving a need for medication, less input from key adult figures such as teachers, a growing sense of autonomy and decision-making by the patient, the unlicensed use of ADHD medications in patients beyond the age of 18, and the inability to access services.

These factors could not be examined using data from the GPRD; however information from patients and clinicians obtained from the CADDY interview study conducted confirmed many of these hypotheses. In patients where treatment cessation was not successful, many accounts were given of their difficulties trying to re-engage with mental health services in order to get access to treatment for the condition. The results from the CADDY 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.

The third research question was: What is the evidence in the literature concerning the serious adverse effects of the ADHD drugs?

Despite the decades of research into ADHD and its treatment, it continues to be surrounded by controversy. This has been especially the case in the last few years, with reports of sudden death and serious cardiovascular events associated with the drugs used to treat the condition. In many of these cases, death was either not considered to be directly linked to the use of stimulant drugs or patients already had pre-existing underlying cardiac defects. The FDA calculated the rate of sudden death from these reports and found that it to be no higher than the rate in the general public.

However, this did not prevent an FDA committee from proposing a black-box warning or the Canadian health authority from temporarily suspending Adderall ® from the market. In order to investigate the cardiovascular safety of the ADHD medications, a review of the literature was undertaken. The results of 33 studies, contributing thousands of patients' data revealed that if death is associated with the use of methylphenidate, dexamfetamine and atomoxetine, then it is a very rare event. None of the studies, neither paediatric nor adult revealed any cases of death. Cardiovascular events including increased heart rate, blood pressure and ECG changes were also examined. The literature retrieved from this review highlighted that the stimulants and atomoxetine can increase blood pressure and heart rate, in both children and adults. Due to the mode of action of these drugs, it is not unexpected that would be the case. While these increases reached statistical significance in some studies, in many, the changes were not considered to be of clinical significance. In addition, findings from the literature review suggest that ADHD drugs have little effect on conduction parameters, in particular the QTc interval. This information is reassuring, however with the increasing numbers of patients taking these drugs, some for many years, and the rising number of adult patients who are more prone to cardiovascular problems; the data needs to be interpreted with some caution. Firstly, it is not known what effects these increases in blood pressure and heart rate could have on patients following chronic use, especially in adult patients and secondly, many of these controlled studies excluded patients with high blood pressure or a history of cardiovascular dysfunction.

As mentioned previously, the FDA and AHRQ are currently investigating the potential for increased risk of heart attack, stroke and other cardiovascular problems associated with medications used to treat ADHD in both children and adults, and hopefully this study, the largest of its kind, will provide the necessary data to confirm the safety of these medications. Unfortunately, the available data from the GPRD would not be sensitive enough to facilitate a study examining changes in blood pressure, heart rate and conduction parameters associated with the ADHD drugs. However, the database is ideal in its ability to study the most important adverse event of all, death.

The final research question proposed was: Are methylphenidate, dexamfetamine and atomoxetine associated with an increased risk of mortality in patients treated for ADHD?

The use of the GPRD database enabled us to study a large cohort of patients exposed to methylphenidate, dexamfetamine and atomoxetine, and to follow them over a period of years. The total sample size of the cohort was over 18,000 patient years. From this sample of patients, we identified seven patients who had died, for six of whom we obtained causes of death. None of these were cases of sudden death. Calculating the incidence of mortality and sudden death to both include and exclude the one unconfirmed death as a case of sudden death, the rates were no higher than those cited for the general population.

An unexpected finding from this study revealed the incidence of suicide in the drug cohort to be much greater than that in the general population. Two of the patients were actively receiving drug treatment (methylphenidate) at the time they committed suicide. There is limited evidence in the literature on an association between ADHD and completed suicides. It is believed that the increased risk of suicide (particularly in younger male patients) is mediated via the increased risk of co-morbidities with which patients with ADHD frequently present including depression, anxiety, oppositional defiant disorder, conduct disorder and substance abuse.

Therefore, while an association between the stimulants and suicide cannot be excluded, the presence of comorbid conditions, which can increase the risk of suicide, must be considered. The recommendation from this study is that clinicians should not be deterred from using these effective drugs in patients who require drug treatment for ADHD. However, it is essential that both before initiating drug treatment and during maintenance treatment, clinicians undertake complete and thorough physical and psychological evaluations of the patient to identify those with increased cardiovascular risks and identify those patients at increased risk of suicide, particularly males with comorbid conditions, and monitor them appropriately.

10. Overall Conclusion

ADHD is a condition which left untreated can cause significant impairments in the lives of patients and their families. It also has wider implications for society as patients with untreated ADHD are more likely to be involved in motor vehicle accidents, substance abuse and crime. Drug treatment is not necessary for all patients with ADHD and should only be reserved for patients with moderate ADHD symptoms and impairments.

This study examined the use and safety of the stimulants and atomoxetine in the UK by utilising large population databases. Chapters 5 to 8 presented the individual studies with in-depth discussions of the results and limitations. Below is a summary of the key findings and suggestions for future work:

i) Prescribing of methylphenidate, dexamfetamine and atomoxetine by GPs to treat ADHD has increased significantly over the last decade.

ii) This increase in use has occurred mainly in children aged 5 to 15 years.

Iii) Similar increases in prescribing were not observed in pre-school children or older adolescents and young adults.

iv) The results from the CADDY study raises the possibility that treatment may be prematurely discontinued by or for some adolescents and young adults with ADHD, potentially increasing their risk of numerous adverse adult outcomes.

v) A review of the literature has identified that while the stimulants and atomoxetine can cause a rise in blood pressure and heart rate, these increases are not usually of clinical significance and serious cardiovascular events rarely occur.

vi) A study to investigate the association of ADHD drugs and mortality demonstrated no increase risk of death or sudden death, however an increased risk of suicide was observed. It is therefore essential that clinicians monitor patients regularly, in particular those at an increased risk of cardiac events or suicide.

10.1. Areas for Future Research

The first area of further research identified from the drug utilisation study would be to validate the diagnosis of ADHD used in the GPRD. Once this was done, it would then be possible to identify those patients with ADHD who do and do not receive any drug treatment and to further examine possible factors associated with prescribing. In addition, the presence of co-morbid conditions and concurrent medications should be examined.

The second main area of future research will follow on from data obtained from the CADDY study. It is planned that a randomised placebo-controlled withdrawal trial will be conducted on patients receiving long-term drug treatment for ADHD.

This study will examine the effectiveness and efficacy of stimulant treatment compared to placebo in adolescents who have received treatment for more than 18 months in order to determine the benefits or disadvantages associated with long-term use of medication compared to discontinuation and to determine the extent to which long-term medication use affects quality of life, ADHD and associated symptoms.

The final area identified for further research surrounds the safety of the stimulants and atomoxetine. The GPRD was used in the present study however as adverse events such as sudden death occur so rarely, the next step would be to increase sample size and power by combining data from other databases in the UK such as those discussed in Chapter 4 and possibly Europe in order to increase sample size and power. In addition to sudden cardiac death, further research should be conducted into the association between the ADHD drugs and the occurrence of suicide to determine factors which may predispose patients to take their own lives.

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12. Appendices

Appendix 1: GPRD Product Codes for methylphenidate, dexamfetamine and atomoxetine

GPRD Product Code	GPRD Product Name	Strength	Unit
M13066001	DEXAMFETAMINE oral liquid 1mg/ml	NULL	NULL
4013832	DEXAMPHETAMINE 10 MG CAP	10	MG
4013833	DEXAMPHETAMINE 15 MG SPA	15	MG
4063247	DEXEDRINE tablets 5mg	5	MG
M03577001	DEXAMFETAMINE tablets 5mg	5	MG
4086659	EQUASYM tablets 10mg	10	MG
4089329	EQUASYM tablets 5mg	5	MG
4089330	EQUASYM tablets 20mg	20	MG
4090953	TRANQUILYN tablets 10mg	10	MG
4092593	EQUASYM XL capsules 20mg	20	MG
4092635	TRANQUILYN tablets 5mg	5	MG
4093143	TRANQUILYN tablets 20mg	20	MG
4096580	CONCERTA XL tablets 18mg	18	MG
4096581	CONCERTA XL tablets 36mg	36	MG

4111897	EQUASYM XL capsules 10mg	9.98	MG
4111898	EQUASYM XL capsules 20mg	20	MG
4111899	EQUASYM XL capsules 30mg	29.94	MG
4111897	EQUASYM XL capsules 10mg	9.98	MG
4080748	RITALIN tablets 10mg	10	MG
M08155001	METHYLPHENIDATE modified release capsule 20mg	20	MG
M08551001	METHYLPHENIDATE tablets 10mg	10	MG
M08551002	METHYLPHENIDATE tablets 5mg	5	MG
M08551003	METHYLPHENIDATE tablets 20mg	20	MG
M10450001	METHYLPHENIDATE modified release tablet 18mg	18	MG
M13050001	METHYLPHENIDATE modified release capsule 10mg	9.98	MG
M13051001	METHYLPHENIDATE modified release capsule 30mg	29.94	MG
M12516001	ATOMOXETINE capsules 10mg	11.43	MG
M12517001	ATOMOXETINE capsules 18mg	20.57	MG
M12518001	ATOMOXETINE capsules 25mg	28.57	MG
M12519001	ATOMOXETINE capsules 40mg	45.71	MG
M12520001	ATOMOXETINE capsules 60mg	68.56	MG
4110981	STRATTERA capsules 10mg	11.43	MG
4110982	STRATTERA capsules 18mg	20.57	MG

4110983	STRATTERA capsules 25mg	28.57	MG
4110984	STRATTERA capsules 40mg	45.71	MG
4110985	STRATTERA capsules 60mg	68.56	MG

Appendix 2: GPRD Medical Codes for ADHD/HKD

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

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

Appendix 3 GPRD medical codes for death

GPRD Medical Code	Read / OXMIS Code	Read / OXMIS Term
202781	9681D	DEATH ANAESTHETIC
203428	22J..14	Patient died
203432	2329	O/E - death rattle
205709	9411	Death cert. Med A due
205710	9413	Med A given to family
205711	9454	Ask for hosp death disch lett.
205712	9484	Crem. form part C completed
208562	R2...12	[D]Mortality, cause unsure
208563	R210.00	[D]Sudden infant death syndrome
208564	R213100	[D]Found dead
209256	T053200	Killed by rolling stock - pedestrian
209258	T0y0y00	Found dead on railway unspecified - other spec person
209722	TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic
209722	TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic
209723	TK55.00	Suicide and selfinflicted injury by explosives

209724	TK5z.00	Suicide and selfinflicted injury by firearms/explosives NOS
209725	TKx0z00	Suicide + selfinflicted inj-jump/lie before moving obj NOS
209726	TKx5.00	Suicide and selfinflicted injury by crashing motor vehicle
209727	TKx6.00	Suicide and selfinflicted injury by crashing of aircraft
209728	TKx7.00	Suicide and selfinflicted injury caustic subst, excl poison
210633	T4002	SUDDEN DEATH
211371	661 DH	DELIVERY SUDDEN DEATH (MOTHER)
212395	22J..13	Died
214702	941..00	Death certificate form Med A
214703	943Z.00	Report for Coroner NOS
214704	944Z.00	Coroner's PM report NOS
214705	9451	Death notif. from hospital
214706	947..00	Cause of death clarif. SD17/18
214707	9483	Crem. form part C arranged
214708	948Z.00	Cremation certification NOS
214709	949..00	Patient died - to record place
214710	949..14	Place of death
214711	94C0.00	Post mortem report received

217383	Q016.11	Fetus affected by maternal death
217544	R212000	[D]Death, not instantaneous cause unknown
217555	RyuC.00	[X]Ill-defined and unknown causes of mortality
217556	RyuC000	[X]Sudden infant death syndrome
218674	TGyz400	Accidentally killed NOS
218753	TK01200	Suicide and self inflicted injury by Butabarbitone
218754	TK2z.00	Suicide + selfinflicted poisoning by gases and vapours NOS
218755	TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate
218756	TK5..00	Suicide and selfinflicted injury by firearms and explosives
219023	U2...13	[X]Suicide
219554	L0010GP	CORONER REFERRED TO
221486	22JZ.00	O/E - dead NOS
223678	8HG..11	Death in hospital
223731	944..00	Coroner's post-mortem report
223732	945Z.00	Hospital death disch. NOS
223733	948..00	Cremation certification
223734	9498	Dead on arrival at hospital
223735	949A.00	Patient died in hospice
226667	R211.00	[D]Instantaneous death

227366	T053y00	Killed by rolling stock - other specified person
227822	TK08.00	Suicide + selfinflicted poisoning by arsenic + its compounds
227823	TK70.00	Suicide+selfinflicted injury-jump from residential premises
227824	TK7z.00	Suicide+selfinflicted injury-jump from high place NOS
227825	TKx3.00	Suicide and selfinflicted injury by extremes of cold
227826	TKxz.00	Suicide and selfinflicted injury by other means NOS
229519	662 N	DELIVERY DEATH DUE ANAESTHETIC
230556	22J..12	Death
232864	945..00	Hospital death discharge notif
232865	947Z.00	SD17/18 cause of death NOS
232866	9497	Patient died in publ.place NOS
232867	94Z..00	Death administration NOS
235748	R210200	[D]Nonspecific sudden infant death
235749	R212100	[D]Died, with no sign of disease
235750	R213.00	[D]Unattended death
236409	T053300	Killed by rolling stock - pedal cyclist
236843	TK01z00	Suicide and self inflicted injury by barbiturates
236844	TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS

236844	TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS
236845	TK1..00	Suicide + selfinflicted poisoning by gases in domestic use
236846	TK52.00	Suicide and selfinflicted injury by hunting rifle
236847	TK72.00	Suicide+selfinflicted injury-jump from natural sites
237692	T140 F	DEATH
239551	22J2.00	O/E - dead - expected
241918	9412	Death cert. Med A signed
241919	9473	SD17/18-no details, returned
241920	9481	Patient for cremation
241921	94B..00	Cause of death
244660	Q4z..13	Newborn death
244769	R212z00	[D]Death less than 24 hours from onset of illness NOS
244770	R21z.00	[D]Sudden death, cause unknown NOS
245500	T053.00	Killed by rolling stock
245503	T0y0100	Found dead on railway unspecified - passenger
245968	TK2y.00	Suicide + selfinflicted poisoning by other gases and vapours
245970	TKx0000	Suicide + selfinflicted injury-jumping before moving object

246910	T4001	VIOLENT DEATH
248767	22J..00	O/E - dead
248768	22J3.00	O/E - dead - unattended death
248769	22J4.00	O/E - dead - sudden death
248776	236..12	O/E - respiratory death
251103	9234	FP22-death
251109	943..00	Report for Coroner
251110	9441	Coroner's PM report awaited
251111	9442	Coroner's PM report requested
251112	946..00	Death notif.- non.hosp source
251113	947..11	SD17 - cause of death clarif
251114	9471	SD17/18 received-death clarif.
251115	9472	SD17/18 completed
251116	9492	Patient died in part 3 accom.
251117	9494	Patient died in resid.inst.NOS
251118	9499	Found dead at accident site
253053	L39A.00	Death obst cse occur more 42 day less than one yr aft deliv
253054	L39B.00	Death from sequelae of direct obstetric causes
253055	L39X.00	Obstetric death of unspecified cause
253102	Lyu7500	[X]Obstetric death of unspecified cause
253824	Q016.00	Fetus or neonate affected by maternal death
254742	T0y0.00	Found dead on railway right-of-way unspecified

255198	TK...14	Suicide and self harm
255198	TK...14	Suicide and self harm
255199	TK01400	Suicide and self inflicted injury by Phenobarbitone
255200	TK53.00	Suicide and selfinflicted injury by military firearms
255202	TK7..00	Suicide and selfinflicted injury by jumping from high place
255203	TKx1.00	Suicide and selfinflicted injury by burns or fire
255203	TKx1.00	Suicide and selfinflicted injury by burns or fire
255204	TKx2.00	Suicide and selfinflicted injury by scald
255205	TKxy.00	Suicide and selfinflicted injury by other specified means
256003	L0010GN	REFERRED TO CORONER
256083	T140 FH	DEATH AT HOME
257956	22J5.00	O/E - dead - cot death
260290	9431	Coroner report - requested
260291	9433	Coroner report - paid for
260292	9453	Receiv hosp death disch letter
260293	947..12	SD18 - cause of death clarif
260294	949..12	Deceased - place patient died
260295	949..13	Died - place patient died
260296	9493	Patient died in nursing home

260297	94A..00	Unexpected death-Coroner told
260298	94B..11	Condition fatal-cause of death
260299	94C..00	Post mortem report
263052	Q4z..14	Perinatal death
263156	R210z00	[D]Sudden infant death syndrome NOS
263157	R213z00	[D]Unattended death NOS
264370	TK01.00	Suicide + selfinflicted poisoning by barbiturates
264370	TK01.00	Suicide + selfinflicted poisoning by barbiturates
264371	TK07.00	Suicide + selfinflicted poisoning by corrosive/caustic subst
264372	TK1z.00	Suicide + selfinflicted poisoning by domestic gases NOS
264373	TK30.00	Suicide and selfinflicted injury by hanging
264373	TK30.00	Suicide and selfinflicted injury by hanging
264374	TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
264374	TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
264375	TK3z.00	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
264376	TK54.00	Suicide and selfinflicted injury by other firearm
264377	TK6..00	Suicide and selfinflicted injury by cutting and stabbing

264377	TK6..00	Suicide and selfinflicted injury by cutting and stabbing
264378	TKx0.00	Suicide + selfinflicted injury-jump/lie before moving object
265290	T1400SI	SUDDEN INFANT DEATH
266336	7789ND	NEONATAL DEATH
266439	795 C	COT DEATH
266987	13M2.00	Death of infant
267185	22J1.00	O/E - dead - unexpected
269465	8HG..00	Died in hospital
269509	9482	Crem. form part B completed
269510	9495	Patient died in hospital
272392	R210000	[D]Cot death
272402	RyuC200	[X]Other ill-defined and unspecified causes of death
273081	T0y0z00	Found dead on railway unspecified - unspecified person
273554	TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances
273554	TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances
273555	TK01100	Suicide and self inflicted injury by Barbitone
273556	TK01300	Suicide and self inflicted injury by Pentabarbitone

273557	TK20.00	Suicide + selfinflicted poisoning by motor veh exhaust gas
273558	TK31.00	Suicide + selfinflicted injury by suffocation by plastic bag
273559	TK51.00	Suicide and selfinflicted injury by shotgun
273559	TK51.00	Suicide and selfinflicted injury by shotgun
273560	TK6z.00	Suicide and selfinflicted injury by cutting and stabbing NOS
273561	TKx4.00	Suicide and selfinflicted injury by electrocution
273562	TKz..00	Suicide and selfinflicted injury NOS
273562	TKz..00	Suicide and selfinflicted injury NOS
275218	661 DN	SUDDEN DEATH CHILDBIRTH CAUSE UNKNOWN
275223	6770AD	SUDDEN DEATH PUERPERIUM CAUSE UNKNOWN
278563	94...11	Administration after pat. died
278564	941Z.00	Death cert. Med A NOS
278565	9432	Coroner report - sent off
278566	9443	Coroner's PM report received
278567	9452	Await hosp death disch letter
278568	9496	Patient died in street
281331	Q4z..12	Neonatal death
281406	R21..00	[D]Sudden death, cause unknown

282113	T053100	Killed by rolling stock - passenger
282595	TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic
282595	TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic
282596	TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines
282596	TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines
282597	TK4..00	Suicide and selfinflicted injury by drowning
282598	TK50.00	Suicide and selfinflicted injury by handgun
283173	ZV68011	[V]Issue of death certificate
283395	L 917WD	REPORT RECEIVED FROM CORONER
283503	T140 FP	DEATH IN HOSPITAL
284701	795 DR	DROPPED DEAD
285439	22J6.00	O/E - dead - suspicious death
287729	9414	Med A not signed-coroner case
287730	949..11	Dead - place patient died
287731	9491	Patient died at home
289080	G575100	Sudden cardiac death, so described
290473	Q4z..11	Infant death
290566	R213000	[D]Found after death, unknown cause of death
290575	RyuC100	[X]Other sudden death, cause unknown

291278	T053z00	Killed by rolling stock - unspecified person
291285	T0y0200	Found dead on railway unspecified - pedestrian
291735	TK...00	Suicide and selfinflicted injury
291735	TK...00	Suicide and selfinflicted injury
291736	TK06.00	Suicide + selfinflicted poisoning by agricultural chemical
291737	TK2..00	Suicide + selfinflicted poisoning by other gases and vapours
291738	TK60.00	Suicide and selfinflicted injury by cutting
291738	TK60.00	Suicide and selfinflicted injury by cutting
291739	TK71.00	Suicide+selfinflicted injury-jump from oth manmade structure
292688	T400	PATIENT DIED
294371	13M3.00	Sudden infant death
294585	22J..11	O/E - dead - condition fatal
296484	7L1M000	Preoperative anaesthetic death
296898	94...00	Death administration
296899	948..11	Stat B,C and F cremation certs
296900	949Z.00	Patient died in place NOS
296901	94A..11	Referral to coroner
299832	R210100	[D]Crib death
299833	R212.00	[D]Death less than 24 hours from onset of illness

300566	T053000	Killed by rolling stock - railway employee
301065	TK01000	Suicide and self inflicted injury by Amylobarbitone
301066	TK01500	Suicide and self inflicted injury by Quinalbarbitone
301067	TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
301067	TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
301068	TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS
301069	TK10.00	Suicide + selfinflicted poisoning by gas via pipeline
301070	TK11.00	Suicide + selfinflicted poisoning by liquified petrol gas
301071	TK1y.00	Suicide and selfinflicted poisoning by other utility gas
301072	TK21.00	Suicide and selfinflicted poisoning by other carbon monoxide
301073	TK61.00	Suicide and selfinflicted injury by stabbing
301073	TK61.00	Suicide and selfinflicted injury by stabbing
301074	TKx..00	Suicide and selfinflicted injury by other means
301075	TKx0100	Suicide + selfinflicted injury-lying before moving object

301899	L 917PM	POST MORTEM REPORT RECEIVED
302004	T1400M	DIED
303412	3009D	SUICIDE
305432	795 N	SUDDEN DEATH NONVIOLENT
305437	7962	FOUND DEAD
305438	7963	UNKNOWN CAUSE DEATH
307376	795 B	SUDDEN DEATH INFANT SYNDROME
307873	941..11	Certificate - death
340888	94D..00	Hospital notified of death
342243	949B.00	Patient died in community hospital
342841	94E..00	Date of death
344547	949C.00	Patient died in GP surgery

Appendix 4: Ethical approval for GPRD Drug Utilisation Study

GPRD
Excellence in Public Health Research

RESTRICTED-COMMERCIAL

Scientific & Ethical Advisory Group

SEAG EVALUATION OF PROTOCOLS

FEED-BACK TO APPLICANTS

CONFIDENTIAL *by e-mail*

PROTOCOL NO: 779

PROTOCOL TITLE: Cessation of attention deficit hyperactivity disorder drugs in young (CADDY)

APPLICANT: Prof Ian Wong, The Centre for Paediatric Research, The School of Pharmacy, University of London

APPROVED ☐	APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required) ☒	REVISION/ RESUBMISSION REQUESTED ☐	REJECTED ☐

COMMENTS

Protocol 779 is approved but the investigators are requested to amend the protocol in line with the following comments by members of SEAG. Resubmission is not required.

The investigators should note that the drugs for ADHD are sometimes prescribed in secondary care and some cases will therefore be missed, affecting the results for purpose 1. Most of these cases will have a recorded diagnosis but not a therapy record. There may be free text records of secondary care prescriptions attached to codes for terms such as "treatment started" or to the ADHD diagnosis code.

It is not clear why the study will be limited to those treated for a full year. Indeed, one would get a better picture of drug treatment in this population if all patients with a diagnosis and a prescription were included. A sub-group analysis could be conducted of those treated for a year or more. The investigators should perhaps consider including all patients in their age range with a diagnosis of ADHD and looking at drug use in that population.

DATE: 17 January 2006

C:\program files\quakcommfeedcrs\attach\779_feedback.doc

Appendix 5: Ethical Approval for IMS study

ims

10 October 2008

Professor Ian Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London,
First Floor , BMA House,
Tavistock Square,
London,
WC1H 9JP

Dear Ian,

I am writing to confirm that the Centre for Paediatric Pharmacy Research has submitted a protocol to the Independent Scientific and Ethics Committee established to review uses of the IMS Disease Analyzer database. The Committee approved the use of the database for drug utilisation studies in children as described in that protocol.

Yours sincerely

Peter Stephens
VP Public Health Affairs Europe, Middle East & Africa,
IMS Co-ordinator for ISEAC
IMS Health®
7 Harewood Avenue
London, NW1 6JB, UK
Tel: +44 207 393 5323 Mobile: +44 (0)7711 148653
email: pstephens@uk.imshealth.com
www.imshealth.com

IMS HEALTH
7 Harewood Avenue
London NW1 6JB
United Kingdom

Tel +44(0)20 7393 5300
Fax +44(0)20 7393 5900
www.imshealth.com

Appendix 6: Data Extraction Sheet

Study No	
Author	
Title	
Source	
Date of Study	
Study Location	
Inclusion / Exclusion Criteria	
Inclusion	
Exclusion	
Sample Size	
Number in each arm	
Patient Characteristics	
Age range	
Gender	
Other	
Design Details	
Single centre / multicentre trial	

Study Type	
Randomised controlled trial / matched control / unmatched	
Allocation	
Was it random?	
Method of randomisation	
Was it concealed?	
Intervention Details	
Treatment group(s)	
Control(s)	
Duration of intervention	
Who delivered intervention?	
Blinding?	
Outcome Measures	
What were they?	
Methods of assessing outcome measures	
Blind assessment?	
When were they measured?	
Costs	
Funding / Sponsorship obtained	
Analysis	
Description of analysis employed	

Statistical methods	
Comparisons made	
Intention to treat analysis	
Subgroups considered	
Results	
Length of follow-up	
Results of analyses	
Withdrawals	
Reasons for withdrawal	
Loss to follow-up	
Conclusions	
Other comments	

Appendix 7: GP invitation letter for participation in mortality study

Dear GP

Here at The Centre for Paediatric Pharmacy Research, Great Ormond Street for Children, we are investigating the occurrence of death in patients taking stimulant drugs (methylphenidate and dexamfetamine) and atomoxetine using the General Practice Research Database (GPRD).

As you may be aware, in February 2006, the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) in the United States voted to recommend a "black-box" warning describing the cardiovascular risks of stimulant drugs used to treat Attention deficit/hyperactivity disorder (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, which include Adderall (mixed amphetamine salts) and Ritalin (methylphenidate).

We have identified a cohort of patients from the GPRD who were prescribed methylphenidate, dexamfetamine or atomoxetine (between 1992 and 2006), and from this list of patients we have further identified patients who also had a clinical code of death in their records. Such a patient has been identified from your practice and we would be very grateful if you would complete the attached questionnaire to aid us in this important research. The questionnaire will ask you to

confirm that the patient died (as patients may not have died but have a clinical code of death in their records that relates to a family member for example), along with a number of questions regarding medications and other illnesses.

All data received will be treated with the utmost confidence and no individual cases will be reported.

Many Thanks in advance

Appendix 8: Mortality associated with ADHD drug treatment Questionnaire.

Please tick the relevant box where appropriate

1. Is the patient dead? Yes □ No □

2. Date of death (dd/mm/yyyy)

_____/_____/_____

3. Where did the patient die?

Home □ Hospital □ Other (please specify) _____

4a. If a death certificate is available, what was the cause of death as recorded on the certificate

_____

OR

4b. If no death certificate is available, what was the likely cause of death?

_____

5. Was a post-mortem performed?

Yes □ No □ Unknown □ If Yes, please indicate results

_____

6. Were you (GP) directly involved in the recording of death?

Yes □ No □

7. At the time of death, did the patient have any illnesses which may have contributed to death?

Yes □ No □ If Yes, please specify

_____

8. If suicide was the cause of death, did the patient show any suicidal tendencies prior to death?

Yes □ No □ Not applicable □

9. Did the patient have an active prescription for methylphenidate, dexamfetamine or atomoxetine at the time of death?

Yes □ No □ If yes, please specify which drug(s)

_____

10. When was the last prescription issued? (dd/mm/yyyy)

_____/_____/_____

11. What dose was the patient taking?

Dose_____ Frequency (eg once daily)_____

12. What was the maximum dose the patient had ever been prescribed?

Dose_____Date(dd/mm/yyyy)

_____

13. Had the patient ever been prescribed clonidine?

Yes □ No □ If yes, what date was the last prescription? _____

14. Was the patient prescribed any other medications at the time of death?

Yes □ No □

If Yes, please give details on drug, dose and date of last prescription

Drug _____ Dose_____ Date of last prescription _____

Drug _____ Dose_____ Date of last prescription _____

Drug _____ Dose_____ Date of last prescription _____

Drug _____ Dose_____ Date of last prescription _____

Drug _____ Dose_____ Date of last prescription _____

Drug _____ Dose_____ Date of last prescription _____

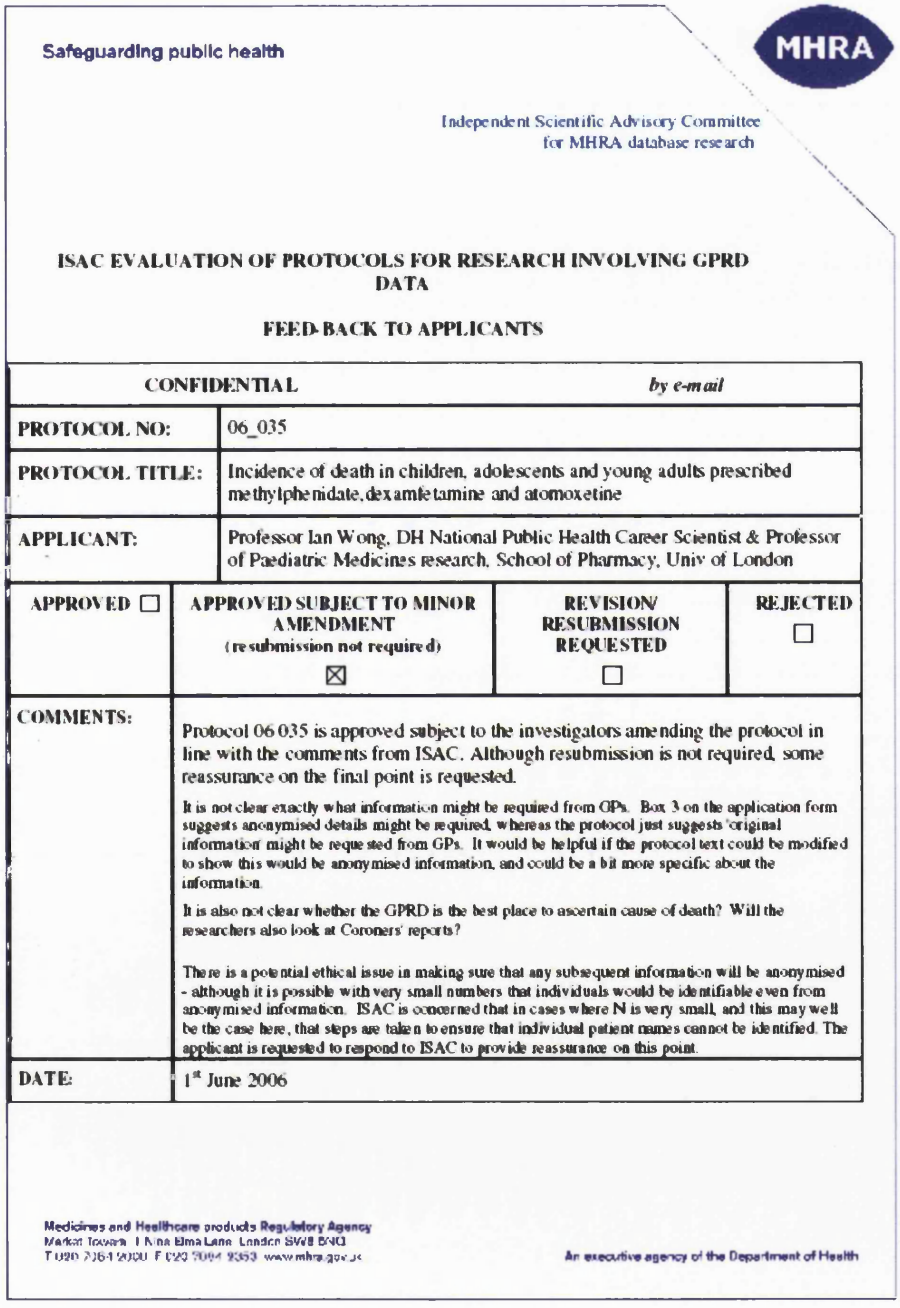
Any other information you may feel is relevant

_____

_____

Many Thanks for your time in completing this questionnaire

Appendix 9: Ethical approval for GPRD Mortality Study



Safeguarding public health

MHRA

Independent Scientific Advisory Committee
for MHRA database research

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING GPRD DATA

FEED-BACK TO APPLICANTS

CONFIDENTIAL			*by e-mail*
PROTOCOL NO:	06_035		
PROTOCOL TITLE:	Incidence of death in children, adolescents and young adults prescribed methylphenidate, dexamfetamine and atomoxetine		
APPLICANT:	Professor Ian Wong, DH National Public Health Career Scientist & Professor of Paediatric Medicines research, School of Pharmacy, Univ of London		
APPROVED ☐	**APPROVED SUBJECT TO MINOR AMENDMENT** (resubmission not required) ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
COMMENTS:	Protocol 06 035 is approved subject to the investigators amending the protocol in line with the comments from ISAC. Although resubmission is not required, some reassurance on the final point is requested. It is not clear exactly what information might be required from GPs. Box 3 on the application form suggests anonymised details might be required, whereas the protocol just suggests 'original information' might be requested from GPs. It would be helpful if the protocol text could be modified to show this would be anonymised information, and could be a bit more specific about the information. It is also not clear whether the GPRD is the best place to ascertain cause of death? Will the researchers also look at Coroners' reports? There is a potential ethical issue in making sure that any subsequent information will be anonymised - although it is possible with very small numbers that individuals would be identifiable even from anonymised information. ISAC is concerned that in cases where N is very small, and this may well be the case here, that steps are taken to ensure that individual patient names cannot be identified. The applicant is requested to respond to ISAC to provide reassurance on this point.		
DATE:	1st June 2006		

Medicines and Healthcare products Regulatory Agency
Market Towers, 1 Nine Elms Lane, London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

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