FACTORS THAT INFLUENCE THE PRESCRIBING AND USE OF METHYLPHENIDATE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PRIMARY SCHOOL CHILDREN IN POLOKWANE

by

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DECLARATION

I, Barbara Corné Coetzee, declare that the dissertation hereby submitted to the University of Limpopo as a partial fulfilment for the degree of Master of Science Medical in Pharmacy, has not previously been submitted by me for a degree at any other university, that it is my own work in design and execution, and that all the material contained therein has been duly acknowledged.

Signature .....

Date .....

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TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF APPENDICES

Page

ABSTRACT

***Background*:** Attention-Deficit/Hyperactivity Disorder (ADHD) is the current diagnostic label for children presenting with significant problems with attention, and typically with impulsiveness and excessive activity as well. It is the most common neurobehavioural disorder of childhood, and therefore critical to clarify the diagnosis. ADHD is a seemingly heterogeneous group of behaviour disorders affecting between 5% - 10% of primary school children. Over-diagnosis of ADHD and overprescribing of stimulants are considered problems in some communities, emphasising the need for careful evaluation and diagnosis. Methylphenidate is currently the first choice of treatment. The main focus of this study was to investigate whether the diagnosis of these children was done by field experts according to the criteria as set in the DSM-IV TR. This influences the decision to prescribe methylphenidate and the monitoring of the child during treatment.

Method: The parents of 50 clinically diagnosed ADHD children, from various primary schools situated in Polokwane, were interviewed and completed a questionnaire.

Results: The findings indicated that 20% of the sample did not meet the DSM-IV TR criteria. 28% of the sample was advised to take methylphenidate by people without appropriate clinical knowledge of ADHD. The final diagnosis and prescribing of methylphenidate is overwhelmingly done by General Practitioners (47%). ADHD symptomatology (hyperactivity-impulsiveness and inattention) was not taken in account when prescribing methylphenidate. There was no definite monitoring of patients before and while on methylphenidate. Positive improvements in ADHD symptoms after methylphenidate therapy, shows that methylphenidate is still prominent and successful in the pharmacotherapy of the ADHD child.

Conclusion: Based on the results of the study there does not appear to be enough evidence that proper protocols or guidelines were followed. Some children were diagnosed as having ADHD with insufficient evaluation and in some cases stimulant medication was prescribed when treatment alternatives might exist. It seems that not all clinicians prescribing methylphenidate have the necessary professional experience and/or qualifications regarding ADHD. This is an indication that there is a need for South African guidelines similar to The American Academy of Pediatrics' Clinical Practice Guidelines and the European Clinical Guidelines for Hyperkinetic Disorder. However, with correct diagnosis and individualised prescribing and usage of methylphenidate, there will be positive improvements in ADHD symptoms after methylphenidate therapy.

Chapter 1

INTRODUCTION

1.1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the current diagnostic label for children presenting with significant problems with attention, and typically with impulsiveness and excessive activity as well (Barkley, 2006). ADHD is a highly prevalent, clinically heterogeneous disorder that exacts an enormous burden on society in terms of financial cost, stress to families, and adverse academic and vocational outcomes (Biederman, Faraone, Monuteaux, Spencer, Wilens, & Bober, 2004). This is a multifactorial disorder with a complex aetiology and strong genetic underpinnings (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren et al., 2005). The areas of impairment associated with childhood ADHD include academic and social dysfunction and skill deficits. The adolescent with ADHD is at risk for academic failure, low self-esteem, poor peer relationships, parental conflict, delinquency, smoking, and substance abuse. Adults with retrospectively defined childhood-onset and persistent ADHD show a pattern of psychological dysfunction, psychosocial disability, psychiatric comorbidity, and school failure that resembles the well known features of childhood ADHD (Barkley, Fischer, Smallish, & Fletcher, 2004).

Additionally, the evolving terminology and definitions assigned to ADHD in the Diagnostic and Statistical Manual of Mental Disorders – connecting DSM-II to DSM-IV (American Psychological Association) have influenced how the characteristics of this disorder are conceptualised (Spencer, Biederman, Wilens, & Faraone, 2002). ADHD is a neuropsychiatric disorder, commonly diagnosed during childhood, characterized by excessive levels of inattentiveness, impulsiveness, and hyperactivity (LeFever, Dawson, & Morrow, 1999; Swanson, Sergeant, Taylor, Sonuga-Barke, Jensen, & Cantwell, 1998b; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Even though reported figures vary considerably depending on diagnosis

criteria, socioeconomic status, geographic source of sample, and gender, it is estimated that up to 15% - 20% of elementary school-age children meet the criteria for diagnosis of ADHD, with a reported population prevalence of up to 12% (Miller & Castellanos, 1998).

1.2 Background of the study

Attention-Deficit/Hyperactive Disorder (ADHD) is a clinically heterogeneous condition. In the past, it has been called hyperkinetic or hyperactive syndrome. It is the most common heritable and behavioural disorder of childhood (Brown et al., 2001). ADHD is a seemingly heterogeneous group of behaviour disorders affecting between 5% - 10% of primary school children (Meyer & Sagvolden, 2006; Swanson et al., 1998b; Taylor, Döpfner, Sergeant, Asherson, Banaschewski, Buitelaar et al., 2004; Volkow, Fowler, Wang, Ding, & Gatley, 2002a). Children with ADHD represent a heterogeneous population who display considerable variation in degree of their symptoms, in the situational pervasiveness of those symptoms, and in the extent to which other disorders occur in association with it (Barkley, 2006). Inattentiveness, overactivity and impulsiveness are presently regarded as the main clinical symptoms. The inattentive component of ADHD is manifested as daydreaming, distractibility, and difficulty focusing on a single task for a prolonged period, whereas the hyperactivity component is expressed as fidgeting, excessive talking, and restlessness. The symptoms of ADHD predispose to accidents, create strain in interpersonal relationships, and disrupt the environment through interruptions and inappropriate behaviour (Biederman, 2005). Although there is a considerable overlap between these symptoms, impulsiveness is increasingly seen as the symptom of greatest significance (Taylor, Sergeant, Doepfner, Gunning, Overmeyer, Möbius et al., 1998).

The disorder usually manifests itself before the child is 7 years old. The disorder is generally more prevalent in males, but more severe among females (Swanson et al., 1998b). Prevalence studies have consistently reported ADHD to be at least 2 times more prevalent among boys than among girls (LeFever et al., 1999). However, there is some evidence that it is

underdiagnosed in females (Nidus, 2006). ADHD represents one of the most common reasons children are referred for behavioural problems to medical and mental health practitioners in the United States and is one of the most prevalent childhood psychiatric disorders (Barkley, 2006; Zito, Safer, dosReis, Madger, Gardner, & Zarin, 1999). The disorder is found to be as prevalent on the African continent as in Western countries (Alarcon, Westermeyer, Foulks, & Ruiz, 1999). ADHD has been identified as the most common child psychiatric disorder in Europe (Swanson et al., 1998b; Taylor et al., 2004), the United States (MTA Cooperative Group, 2004) and South Africa (Meyer, 1998; Meyer, Eilertsen, Sundet, Tshifularo, & Sagvolden, 2004).

ADHD has a pervasive and severe impact on development if left untreated (Barkley, 2006). It has generally been agreed in the empirical literature that only two treatments and their combination have been validated as effective short-term treatment modalities for school-aged children with ADHD: psychosocial treatments, stimulant treatments, and the combination of both (Kutcher, Aman, Brooks, Buitelaar, van Daalen, Fegert et al., 2004). The psychostimulant methylphenidate in various formulations is currently the first choice of treatment (Buitelaar, Montgomery, & van Zwieten-Boot, 2003). Concern has been expressed about the over-diagnosis of ADHD by pointing to the several-fold increase in prescriptions for stimulant medication among children (American Academy of Pediatrics, 2000). Prescriptions for these stimulant medications have increased from less than 2 million in 1991 to over 10 million in 2001, and now it is estimated that approximately 6% of school-aged children are identified and treated with these drugs – about 3 million/year in the United States (National Institute of Mental Health, 2007b; Volkow & Swanson, 2003).

It is critical to clarify the diagnosis of ADHD. Inattention and distractibility can be symptoms of an anxiety disorder, depression, or bipolar disorder. In other cases, these anxiety or mood disorders can coexist with ADHD, just as learning deficiencies and conduct or oppositional disorder are common comorbid disorders. Overdiagnosis of ADHD and overprescribing of stimulants are considered problems in some communities, pointing to the

need for careful documentation that functionally impairing symptoms are indeed attributed to ADHD (Dopheide & Theesan, 2002). Also in South Africa numerous claims have been made that methylphenidate is overused or even abused, especially in school aged children, however a preliminary study done by Truter (2009) indicated that most prescriptions were issued in metropolitan areas and the overuse of methylphenidate could not be established.

Because of the pervasive nature of this disorder and concerns about ''over'' and ''under'' diagnosis of ADHD (National Institute of Mental Health, 2007b), practice guidelines have been developed by organisations such as the American Academy of Child and Adolescent Psychiatry (AACAP), (American Academy of Child and Adolescent Psychiatry, 1997) and the American Academy of Pediatrics (AAP), (American Academy of Pediatrics, 2000). These professional societies recommend an evaluation process based on DSM-IV diagnostic criteria, emphasising physician evaluation of evidence obtained from parents or caregivers, as well as classroom teachers (or other school personnel) regarding ''the core symptoms of AD/HD in various settings, the age of onset, duration of symptoms, and degree of functional impairment'' (American Academy of Pediatrics, 2000, p.1158).

ADHD is now recognised as a universal disorder, with an ever-growing international acceptance of both its existence and its status as a chronic disabling condition, for which combinations of medications and psychosocial treatments and accommodations may offer the most effective approach to management (Barkley, 2006).

1.3 Objective of the study

The objectives of the study were:

(1) to determine all the factors that influence the prescribing and usage of methylphenidate in children with Attention-Deficit/Hyperactivity Disorder in primary schools situated in the Polokwane area in the Limpopo Province of South Africa and to establish

whether the diagnosis was done according to the criteria as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 2000).

(2) to establish if the prescribing and monitoring of methylphenidate was done appropriately. The dose of each individual requires careful titration and medical monitoring to obtain the optimum balance between efficacy and side effect profiles. It is recommended that monitoring should be directed to target outcomes and adverse effects, and that the clinician should periodically provide a systematic follow up for the child with ADHD.

(3) to establish whether there is any improvement in the ADHD symptoms according to the DSM-IV score, after treatment with methylphenidate .

1.4 Purpose and significance of the study

The purpose of the study was to investigate whether the diagnosis of these children was done according to the criteria as set in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). This influences the decision to prescribe methylphenidate, which further will have an effect on the dose and monitoring of the condition and side-effects.

When the specific criteria as set in the DSM-IV are not carefully followed, there is a possibility that children might be diagnosed as ADHD, when other underlying conditions or situations might be the reason for the so-called ADHD symptoms. When diagnosed and methylphenidate is prescribed, it is of extreme importance to monitor the efficacy of the dose, evaluating the improvement of the condition, and presence and severity of side-effects.

1.5 Delineation of study

This study report will comprise of 10 chapters. A brief introduction is provided in Chapter 1. This chapter gives a description of the background of the disorder, the objective of the study, its purpose and significance, and the delineation of the study.

In Chapter 2 the focus is on the historical and general background of the disorder, diagnostic criteria and primary symptoms, prevalence, gender differences, comorbid disorders, aetiology, toxins and environmental factors, assessment tools, and difficulty in identifying ADHD children.

Chapter 3 will concentrate on the neurobiology and neurophysiology of ADHD, the role of dopamine and the neurobiological model on dysfunctioning reinforcement and extinction processes of Sagvolden and colleagues (2005). Chapter 4 focuses on treatment and the role of psycho-stimulants, more specific, methylphenidate.

In Chapter 5 the focus will be on the problem statement, major research questions and hypotheses. Chapter 6 will outline the research methodology, while chapter 7 represents the demographic results as well as results based on the hypotheses and analysis of the study.

In Chapter 8 the critical findings of the study are discussed. Chapter 9 give the limitations and recommendations and Chapter 10 summarises the study and indicate the concluding remarks.

Chapter 2

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

2.1 Historical background

The history of the acknowledgement of and developments in understanding Attention-Deficit/Hyperactivity Disorder (ADHD) has been well-documented (Barkley, 2006). Attention-Deficit/Hyperactivity Disorder (ADHD) is a condition that becomes apparent in some children in the preschool and early school years. It is hard for these children to control their behaviour and/or pay attention. It is estimated that between 5% - 10% of primary school children have ADHD (Swanson et al., 1998b; Taylor et al., 2004), or approximately 2 million children in the United States (National Institute of Mental Health, 2007a).

ADHD was first described by Dr. Heinrich Hoffman in 1845 (Hoffmann, 1845). A physician who wrote books on medicine and psychiatry, Dr. Hoffman was also a poet who became interested in writing for children when he could not find suitable materials to read to his 3-year-old son. The result was a book of poems, complete with illustrations, about children and their characteristics. "The Story of Fidgety Philip" was an accurate description of a little boy who had Attention Deficit/Hyperactivity Disorder. Yet it was not until 1902 that Sir George F. Still published a series of lectures to the Royal College of Physicians in England in which he described a group of impulsive children with significant behavioural problems, caused by a genetic dysfunction and not by poor child rearing-children who today would be easily recognized as having ADHD (Still, 1902). Since then, several thousand scientific papers on the disorder have been published, providing information on its nature, course, causes, impairments, and treatments (National Institute of Mental Health, 2007a).

A child with ADHD faces a difficult but not insurmountable task ahead. In order to achieve his or her full potential, he or she should receive help, guidance, and understanding from parents, guidance counsellors, and the public education system.

Both the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) and the International Classification of Diseases (ICD-10; World Health Organization, 1993) describe a syndrome of childhood onset that is characterized by symptoms of impaired attention and/or hyperactivity/impulsiveness and is associated with significant functional impairment in social, academic and/or occupational settings. Although differences are evident in the specific criteria needed to meet the diagnostic requirements for the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) and the ICD-10 diagnosis of a Hyperkinetic Disorder (HKD), it is clear that a substantial number of individuals throughout the world experience functional problems that are due to impaired attention and lack of behavioural inhibition (Barkley, 2006).

There have been multiple changes in the diagnostic criteria for ADHD over the past two decades. Research in this period has sought to identify more homogeneous subtypes. The emphasis has shifted from an undimensional conceptualisation to a model consisting of two factors: hyperactivity/impulsiveness and inattention (Sagvolden, Johansen, Aase, & Russell, 2005; Taylor et al., 2004). The DSM-IV-TR (American Psychiatric Association, 2000) distinguishes two aspects of ADHD: Inattention and Hyperactivity/Impulsiveness – each of which is assessed with reference to a 9 – item criterion list.

Although one of the first references to a hyperactive or ADHD child (Fidgety Phil) seems to have been in the poems of the German physician Heinrich Hoffmann (1845), recognition is classically awarded to George Still (1902) and Alfred Tredgold (1908) as being the first authors who focused serious scientific attention on the behavioural condition in children that most closely approximates what is today known as ADHD.

2.2 General background of the disorder

A tremendous amount of research has been published on children with Attention Deficit/Hyperactivity Disorder (ADHD) and their primary characteristics and related problems

as well as on the situational variability of these problems, their prevalence, and their aetiologies. Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent, heterogeneous, and debilitating psychological condition with an early onset and a potentially poor prognosis. The disorder consists of a persistent pattern of inattentiveness, impulsiveness, and/or hyperactivity that is inconsistent with the child's developmental level (American Psychiatric Association, 1994). Children with ADHD represent a rather heterogeneous population who display considerable variation in the degree of their symptoms, in the age of onset, in the cross-situational pervasiveness of those symptoms, and in the extent to which other disorders occur in association with ADHD (Barkley, 2006). The disorder represents one of the most common reasons children are referred for behavioural problems to medical and mental health practitioners in the United States and is one of the most prevalent childhood psychiatric disorders (Barkley, 2006; Fone & Nutt, 2005; Swanson et al., 1998b; Taylor, 1998; Taylor et al., 1998). ADHD has a pervasive and severe impact on development if left untreated (Barkley, 2006). The disorder usually manifests itself before the child is 7 years old. The disorder is generally more prevalent in males, but more severe among females (Swanson et al., 1998b). Prevalence studies have consistently reported ADHD to be at least 2 times more prevalent among boys than among girls (LeFever et al., 1999). This is probably because girls are less likely to act out in class (American Academy of Pediatrics, 2000; Biederman, Mick, Faraone, Braaten, Doyle, Spencer et al., 2002). However, there is some evidence that it is underdiagnosed in females (Nidus, 2006).

2.3 Diagnosis, diagnostic criteria and primary symptoms

2.3.1 Diagnosis

The principal sign of hyperactivity should alert clinicians to the possibility of ADHD. A detailed history of a child's early developmental patterns and direct observations usually reveal excessive motor activity. Hyperactivity may occur in some situations (for example, school) but

not in others (for example, one-to-one interviews and television watching), and it may be less obvious in structural than in unstructured situations. Other distinguishing features of ADHD are short attention span and easy distractibility. In school, children with ADHD cannot follow instructions and often demand extra attention from their teachers. At home, they often do not comply with their parents' requests. They act impulsively, show emotional liability, and are explosive and irritable (Kaplan & Sadock, 1998). A child who "can't sit still" or is otherwise disruptive will be noticeable in school, but the inattentive daydreamer may be overlooked. The impulsive child who acts before thinking may be considered just a "discipline problem", while the child who is passive or sluggish may be viewed as merely unmotivated. Yet both may have different types of ADHD. All children are sometimes restless, sometimes act without thinking, or sometimes daydream the time away. When the child's hyperactivity, distractibility, poor concentration, or impulsiveness begin to affect performance in school, social relationships with other children, or behaviour at home, ADHD may be suspected. But because the symptoms vary so much across settings, ADHD is not easy to diagnose. This is especially true when inattentiveness is the primary symptom (National Institute of Mental Health, 2007a).

The importance of early diagnosis and sustained treatment is underscored by research examining the long-term course and adult outcomes in children with ADHD. The diagnosis of ADHD should be established by an experienced clinician and should be based on a comprehensive evaluation in a clinical interview. This evaluation will also be supported by additional information obtained from external informants, for example the parents or other family members, and teachers (Buitelaar et al., 2003).

The American Academy of Pediatrics issued its first guidelines for diagnosing Attention-Deficit Hyperactivity Disorder (ADHD) in children in 2002. They include:

- Children between ages 6 - 12 years should be evaluated for ADHD if they show symptoms of inattention, hyperactivity, impulsiveness, academic underachievement, or

behaviour problems in at least two settings. Such behaviours should be harmful for the child academically or socially for at least 6 months.

- The child should meet the official symptom guidelines.
- A diagnosis requires detailed reports by parents or caregivers. It should be noted that a mother's description of her child's behaviour is a very accurate and reliable guide for diagnosing ADHD. Parents should not be shy about insisting further evaluation if their experience does not match a doctor's single observation of their child.
- Guidelines for primary care doctors emphasise the importance of obtaining direct evidence from the classroom teacher or other school-based professionals about the child's symptoms and their duration, and evidence of functional impairment in the school setting.
- The child should be assessed for accompanying conditions (such as learning difficulties) (Nidus, 2006).

A correct diagnosis often resolves confusion about the reasons for the child's problems that lets parents and their child move forward in their lives with more accurate information on what is wrong and what can be done to help (National Institute of Mental Health, 2007a).

2.3.2 Diagnostic criteria and primary symptoms

Two distinct behavioural dimensions characterise the various behavioural problems seen in ADHD. These two dimensions are represented in the DSM-IV-TR (American Psychiatric Association, 1994) diagnostic guidelines for the disorder that are the standard for diagnosis in the US and increasingly so in other parts of the world. These behavioural dimensions have been identified across various ethnic and cultural groups (Barkley, 2003a; Barkley, 2003b). *Inattention* typically involves failing to finish tasks, not seeming to listen, being easily distracted, having difficulty concentrating on schoolwork, and having difficulty sticking to a play activity. *Impulsiveness* often is manifested as acting before thinking, shifting excessively from one

activity to another, difficulty in organising work, needing much supervision, frequently calling out in class, and difficulty awaiting a turn in games or group situations. *Hyperactivity* generally includes excessive running about or climbing on things, difficulty sitting still or staying seated, and excessive movement during sleep. Symptom presence and severity vary with the situation (Dopheide & Theesan, 2002).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) as well as the International Classification of Diseases (ICD-10; World Health Organization, 1994) describe a syndrome of childhood onset that is characterised by symptoms of impaired attention and/or hyperactivity/impulsiveness and is associated with significant functional impairment in social, academic and/or occupational settings. Although differences are evident in the specific criteria needed to meet the diagnostic requirements for the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) and the ICD-10 diagnosis of a Hyperkinetic Disorder (HKD), it is clear that a substantial number of individuals throughout the world experience functional problems that are due to impaired attention and lack of behavioural inhibition (Barkley, 1998; Bird, 2002). Attention, in the widest sense, refers to the relationship between behaviour and the environment. One is attending to a stimulus, or stimulus property, when variation of that stimulus or stimulus property changes behaviour (Catania, 1998). Attention is modified by a multitude of psychological factors like sensory and motivational processes. In various forms, inattention is found in most psychiatric disorders except mania (Taylor, 1994), and could well be that some non-ADHD disorders masquerade as ADHD (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993).

Practice guidelines have been developed by organisations such as the American Academy of Child and Adolescent Psychiatry (American Academy of Child and Adolescent Psychiatry, 1997), and the American Academy of Pediatrics (American Academy of Pediatrics, 2000). These professional societies recommended an evaluation process based on DSM- IV-TR diagnostic criteria, emphasising physician evaluation of evidence obtained from parents or

caregivers, as well as teachers (Monastra, 2005), regarding the symptoms of ADHD in various settings, the age of onset, durations of symptoms, and degree of functional impairment. These guidelines also stressed the importance of evaluating co-existing conditions.

The DSM-IV-TR diagnostic criteria are some of the most rigorous and most empirically derived criteria ever available in the history of ADHD (Barkley, 2006). According to the DSM-IV-TR ADHD is diagnosed by the following symptoms:

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of inattention should have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Symptoms of inattention:

Six of the following symptoms:

1) Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities.
2) Often has a difficult time sustaining attention in tasks or play activities.
3) Often does not seem to listen when spoken to directly.
4) Often does not follow through on instructions and often fails to finish homework.
5) Often has difficulty organising tasks or activities.
6) Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (schoolwork, homework).
7) Often loses things.
8) Is often easily distracted by extraneous stimuli.
9) Is often forgetful in daily activities.

(2) Six (or more) of the following symptoms of hyperactivity-impulsiveness should have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactive-impulsive symptoms.

Six of the following symptoms:

Hyperactivity:

1) Often fidgets with hands or feet and squirms in seat.
2) Often leaves seat or in other situations in which remaining seated is expected.
3) Often runs about or climbs on objects excessively in inappropriate situations.
4) Often has difficulty in playing quietly during leisure activities.
5) Is often "on the go" or act as if "driven by a motor".
6) Often talks excessively.

Impulsiveness:

1) Often blurts out answers before questions have been completed.
2) Often has difficulty waiting for his/her turn or in lines.
3) Often interrupts or intrudes on others (e.g. butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g. at school/or work and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

Code based on subtype:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months.

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months.

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.

From: DSM-IV-TR (American Psychiatric Association, 2000).

The DSM criteria give little guidance to clinicians on the differential diagnosis of the disorder from other psychiatric disorders with which it may often coexist. ADHD is frequently associated with a variety of cognitive, psychiatric, educational, emotional, and social impairments. Some of these arise directly as a consequence of the disorder while others, such as the comorbid psychiatric disorders and learning disabilities, may be associated conditions or arise from other primary disorders that overlap ADHD at a level greater than expected by chance. Clinicians need to be aware of the primary symptoms associated with these other disorders and their core nature in order to carefully differentiate ADHD from them (Barkley, 2003b).

2.3.3 Subtypes

Children with ADHD are a heterogeneous group who are believed to have in common the characteristics of developmentally inappropriate levels of inattention, and in most cases hyperactivity-impulsiveness. Despite these apparent commonalities, children so diagnosed are acknowledged to present with a diversity of related psychiatric symptoms/disorders, family

backgrounds, developmental courses, and responses to treatments. Given this diversity, increasing scientific attention has been paid to developing approaches to identifying more homogeneous, clinically meaningful subtypes of ADHD (Barkley, 2006).

ADHD can be usefully subtyped by the presence or absence of hyperactivity-impulsiveness, as in DSM-IV-TR's subtypes of ADHD. The ADHD diagnosis has three subtypes based on two behavioural dimensions. Combined Type (ADHD-C), Predominantly Inattentive type (ADHD-PI), and the Hyperactive/Impulsive type (ADHD-HI) (Barkley, 2006).

Although many individuals presents with symptoms of both inattention and hyperactivity-impulsiveness, there are individuals in whom one or other pattern is predominant. The appropriate subtype (for current diagnosis) should be indicated based on the predominant symptom pattern for the past six months.

In population-based studies, the inattentive subtype comprises about 50% of all ADHD cases but in clinically referred children the DSM-IV-TR combined subtype of ADHD is diagnosed more often than the inattentive or hyperactive/impulsive type (Buitelaar et al., 2003).

2.3.3.1 Attention-Deficit/Hyperactivity Disorder, combined subtype (ADHD-C)

The ADHD Combined (ADHD-C) subtype applies to individuals who have at least six symptoms in both of the categories of inattention and hyperactive-impulsive symptoms. These symptoms must be endorsed as deviant (Barkley, 2006). There must be a history of this disorder. Symptoms begin before 7 years of age. Symptoms are present across settings. If a child is inattentive at school but not so at home or playing with friends, a diagnosis of ADHD is not expected. Symptoms must significantly reduce an individual's ability to work or learn. Most children and adolescents with the disorder have the combined type. ADHD is not diagnosed when a person is depressed, anxious or when the person has another disorder that can explain the ADHD-like behaviours. Symptoms must be present for at least 6 months before a diagnosis can be made (American Psychiatric Association, 2000).

2.3.3.2 Attention-Deficit/Hyperactivity Disorder, predominantly inattentive subtype (ADHD-PI)

The ADHD predominantly inattentive subtype (ADHD-PI) applies to individuals with at least six of the mentioned symptoms of inattention. These symptoms must have persisted for over 6 months. These symptoms must also be maladaptive; that is, they will seem inappropriate for the child's age. This subtype is more typical amongst girls than boys (Taylor et al., 2004). The inattentive subtype may be more socially withdrawn, experience greater academic problems, and develop comorbid anxiety or other mood disorders (Johansen, Aase, Meyer, & Sagvolden, 2002).

2.3.3.3 Attention-Deficit/Hyperactivity Disorder, hyperactive subtype (ADHD-HI)

The ADHD predominantly hyperactive subtype (ADHD-HI) applies to individuals with at least six of the symptoms from the hyperactive-impulsive list (American Psychiatric Association, 2000). Early hyperactive-impulsive behaviour may be associated with externalising problems like aggression, oppositional behaviour, adolescent delinquency, and substance abuse (Barkley, 2006).

2.4 Symptoms

2.4.1 Inattention

Attention is a multidimensional construct and thus complaints of inattention are not useful for differential diagnosis without further clarifying the type of attention that is impaired. ADHD seems to involve an inability to sustain responding to tasks or other activities, to remember and follow through activities on rules and instructions, and to resist distractions while doing so (Barkley, 2003b). Children who have ADHD display difficulties with attention relative to normal children of the same age and gender. ADHD children are usually distracted and made inattentive by an over-stimulating environment (such as a large classroom). They are also inattentive when a situation is low-key or dull. Some experts believe that certain parts of the brain in ADHD children may be underactive, so the children fail to be aroused by non-stimulating activities. In contrast, they may exhibit a kind of "super concentration" to a highly

stimulating activity (such as a video game or a highly specific interest). Such children may even become over-attentive – so absorbed in a project that they cannot modify or change the direction of their attention (Nidus, 2006).

Children who are inattentive have a hard time keeping their minds on any one thing and may get bored with a task after only a few minutes. If they are doing something they really enjoy, they have no trouble paying attention. However, focusing deliberate, conscious attention to organising and completing a task or learning something new is difficult. Homework is particularly hard for these children. They will forget to write down an assignment, or leave it at school. They will forget to bring a book home, or bring the wrong one. The homework is often accompanied by frustration for both parent and child (National Institute of Mental Health, 2007a).

2.4.2 Hyperactivity

Hyperactivity as a clinical condition worthy of attention was first reported at the turn of the twentieth century (Schachar, 1986). Children with ADHD have excessive developmentally inappropriate levels of activity. The term hyperactive however, is often confusing since, for some, it suggests a child racing around non-stop. A boy with ADHD playing a game may have the same level of activity as another child without the syndrome. But when a high demand is placed on the ADHD child's attention, his brain motor activity intensifies beyond the levels of the other children (Nidus, 2006). Hyperactive children always seem to be "on the go" or constantly in motion. They dash around touching or playing with whatever is in sight, or talk incessantly. These movements are often irrelevant to the task or situation and at times seem purposeless. Sitting still at dinner or during a school lesson or story can be a difficult task. They squirm and fidget in their seats or roam around the room. Or they may wiggle their feet, touch everything, or noisily tap their pencil. Hyperactive teenagers may feel internally restless. They often report needing to stay busy and may try to do several things at once (National Institute of Mental Health, 2007a).The excessive level of activity in ADHD is typically seen as restlessness, fidgeting

and generally unnecessary gross body movements. However, there is little correlation between various activities and even movements of the various body parts of ADHD children (Porrino, Rapoport, Behar, Sceery, Ismond, & Bunney, 1983). Although overactivity is seen in some situations like the classroom, it might not be present in others like in play (Taylor et al., 1998). It seems that the ADHD overactivity is absent in novel situations. Motor impulsiveness is a major component of ADHD overactivity (Sagvolden, Aase, Zeiner, & Berger, 1998).

2.4.3 Impulsiveness

In general terms, impulsiveness means acting without reflecting and a failure to plan ahead. In the literature, however, impulsiveness is manifested in planning deficits, premature responding, over-rapid responsiveness, excessive attraction to immediate reward, sensation seeking, recklessness and risk taking, novelty seeking, adventuresomeness, accident-proneness, boredom, unreliability, and impetuous behaviour (Sagvolden et al., 2005). The concept impulsiveness has both a cognitive and motor component. Motor impulsiveness is currently defined as the peculiar ADHD-style of brief, short sequences of activity on tasks and rapid change, and is primarily seen in the premature responding and over-rapid responsiveness. By analysing experimentally various behavioural components in ADHD, it has shown that motor impulsiveness, defined as bursts of responses with short inter-response times. This behaviour has been shown to emerge in children with ADHD (Sagvolden et al., 1998).

Cognitive impulsiveness implies that private events like thoughts and plans are dealt with for short sequences of time with rapid shifts, resulting in problems generating and following plans, problems organising own behaviour, and forgetfulness and inefficient use of time. These behaviour problems have frequently been explained as deficient “executive functions” usually believed to be associated with frontal lobe dysfunction. Cognitive impulsiveness seen in ADHD has also been explained as behavioural inhibition, that is, lack of inhibition (Sagvolden & Sergeant, 1998). Of the three core symptoms (inattention, hyperactivity,

and impulsiveness), impulsiveness is currently seen as the most reliable indicator of ADHD (Johansen et al., 2002; Sagvolden et al., 2005).

Children with ADHD are often associated with deficiency in inhibiting behaviour in response to situational demands. Impulsive children seem unable to curb their immediate reactions or think before they act. They will often blurt out inappropriate comments, display their emotions without restraint, and act without regard for the later consequences of their conduct (National Institute of Mental Health, 2007a). Clinically these children are often noted to respond quickly to situations without waiting for instructions to be completed, which often leads to careless errors. They often fail to consider potentially negative, destructive or even dangerous consequences that may be associated with a particular situation or behaviour. They normally engage in unnecessary risk taking. Their impulsiveness may make it hard for them to wait for things they want or to take their turn in games. They often take short cuts in their work and blurt out answers prematurely. They may grab a toy from another child or hit when they're upset. When they are faced with tasks or situations in which they are encouraged to delay seeking gratification and to work toward a longer term goal and larger reward, they often opt for the immediate smaller reward that require less work to achieve (Barkley, 2006). Even as teenagers, they may impulsively choose to do things that have an immediate but small payoff rather than engage in activities that may take more effort yet provide much greater but delayed rewards (National Institute of Mental Health, 2007a).

2.5 Prevalence of ADHD

ADHD is a worldwide and highly prevalent disorder, estimated to affect 5% - 10% of children (Biederman & Faraone, 2005; Brown, Freeman, Perrin, Stein, Amler, Feldman et al., 2001; Faraone, Sergeant, Gillberg, & Biederman, 2003). Although ADHD is perceived by many to be an American disorder, its prevalence is in the same range in many other countries as the United States (Faraone et al., 2003). Research among different language groups of the Limpopo

Province of South Africa found prevalence rates for ADHD similar to Western rates for both genders and age groups (Meyer, 1998; Meyer et al., 2004). Varying rates in the worldwide prevalence of ADHD in school-aged children might be attributed to methodological differences in criteria used to define this disorder (Faraone et al., 2003).

2.6 Gender differences

ADHD is reported to be more prevalent in boys than in girls. The disorder is most common in first-born boys (Kaplan & Sadock, 1998). According to the DSM-IV-TR (American Psychiatric Association, 2000). ADHD is more frequent in males than in females, with the male-to-female ratios ranging from 2:1 (community sample) to 9:1 (clinic–referred) depending on the type and setting (Biederman, 2005; Swanson et al., 1998b). Affected boys markedly outnumber girls (Taylor et al., 1998). This gender discrepancy suggests that girls with ADHD might be under-identified and under-treated (Biederman, 2005). This gender imbalance may be exaggerated to some extent by referral biases (Kutcher et al., 2004). This may be because girls are less likely to act out in class (Johansen et al., 2002).

Affected girls are more likely to show problems with attention, while affected boys are likely to show more in the way of hyperactivity/impulsiveness (Taylor et al., 1998). In a systematic evaluation of the impact of gender on the clinical features of ADHD, Biederman et al. 2002 reported that girls with ADHD were at less risk for comorbid disruptive behaviour than boys with ADHD.

2.7 Comorbid disorders

Besides their primary problems with inattention, impulsiveness, and overactivity, children with ADHD may have a variety of other difficulties. Such children have a higher likelihood of having other cognitive, developmental (such as speech and language delays), academic (learning disabilities), and even medical or health-related difficulties (American Academy of Pediatrics, 2000; Barkley, 2006). ADHD is associated with a tendency of repeated

accidents, depressive and anxiety disorders, learning disabilities and school failure (American Academy of Pediatrics, 2000). ADHD frequently co-occurs with additional emotional, behavioural, and learning problems in community and primary care settings, with disruptive behaviour disorders being the most common, followed by internalising and learning problems. Interestingly, co-occurring disruptive behaviour problems seem to have more frequent associations with the hyperactive/impulsive dimensions of ADHD, whereas internalising and learning problems are more strongly associated with the inattentive dimension of the disorder (Brown et al., 2001). Throughout the life cycle, a key clinical feature observed in patients with ADHD is comorbidity. In children, psychiatric disorders comorbid with ADHD include oppositional defiant disorder (ODD), conduct disorder (CD), mood disorders (both unipolar and bipolar), anxiety disorders, and learning disorders (Biederman, 2005; Brown et al., 2001).

Studies suggest that girls and boys with ADHD are quite similar in their presenting symptoms, but girls may manifest somewhat lower symptom levels and are considerably less likely to manifest aggressive behaviour. ADHD is frequently comorbidly associated with a number of other conditions including Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD) which sometimes render a differential diagnosis difficult to make. The disorder is also associated with later increased incidence of substance abuse if not treated at an early stage (Biederman, Wilens, Mick, Spencer, & Faraone, 1999). In a comparison of gender differences in observed classroom behaviour of boys and girls, Abikoff, Jensen, Arnold, Hoza, Hechtman, Pollock, et al. (2002) showed that boys with ADHD engage in more rule breaking and externalising impulsive behaviours, Disruptive Behaviour Disorders (DBDs) than did girls with ADHD. Children with ADHD and Disruptive Behaviour Disorders manifested more interference with classroom routine behaviours than children with ADHD and anxiety. Mangus, Bergman, Zieger and Coleman (2004) have found that children with ADHD have at least one comorbid disorder such as learning disorder or abnormal intelligence, while one quarter to one third of these children qualify for the additional diagnosis of CD, ODD, or anxiety disorder. Girls with

ADHD may have a lower risk of ODD, CD, externalising problems more generally, and possibly depression than boys with the disorder, but the girls may have somewhat lower levels of intelligence (Barkley, 2006).

The diagnosis of ADHD is based on information from the child, parents, and/or teachers but the diagnosis of comorbid psychiatric disorder should be made by an experienced trained physician.

2.7.1 Conduct Disorder and Oppositional Defiant Disorder (Externalising disorders)

Children with ADHD and CD present with a complex group of behavioural and emotional disturbances. CD is more prevalent among boys than girls and is typified by a variety of persistent antisocial behaviours including acts of aggression towards people and animals, destruction of property, deceitfulness, lying, or stealing, and general violation of rules (Kutcher et al., 2004; Nidus, 2006). About 20 - 40% of ADHD children may eventually develop conduct disorder (CD), a more serious pattern of antisocial behaviour (Barkley, 2006; National Institute of Mental Health, 2007a). These children are at a real risk of getting into trouble at school or with the police. Youngsters with CD are at high risk of entering the juvenile justice system, having persistent aggressive and antisocial behaviours, and developing substance abuse later on in life (Kutcher et al., 2004). According to Brown et al. (2001), aggressive behaviour is more associated with the hyperactivity/impulsiveness subtype of ADHD. When CD is present in cases of ADHD, it is nearly always associated with ODD as well and has a much earlier onset than when CD develops in the absence of ADHD. The presence of CD signals a more severe form of ADHD (Barkley, 2006).

As many as one-third to one-half of all children with ADHD - mostly boys - have ODD (Barkley, 2006). ODD is characterised by a sustained pattern of argumentative, hostile, resentful, disobedient, and/or defiant behaviours towards adult authority figures. These children are often stubborn, non-compliant, have outbursts of temper, or become belligerent (Kutcher et al., 2004).

2.7.2 Learning Disorders

In the cognitive and academic domains, ADHD is specifically associated with a modest reduction in intelligence, moderate or greater deficiencies in domains of adaptive functioning and academic achievement skills; and a considerably higher risk for Learning Disorders (LD). A LD, however, is not simply failing to do one's work in school; it is typically defined as a significant discrepancy between one's intelligence, or general mental abilities, and academic achievement in some area, such as reading, mathematics, spelling, handwriting, or language (Barkley, 2006). Because individuals with ADHD usually show some academic difficulty and underachievement, clinicians must determine whether the child suffers from ADHD, a learning disability, or coexisting disorders. Many children with ADHD - approximately 20% - 30% - also have a specific learning disability (LD). In preschool years, these disabilities include difficulty in understanding certain sounds or words and/or difficulty in expressing oneself in words. In school age children, reading or spelling disabilities, writing disorders and arithmetic disorders may appear. Although speech and learning disorders are common in children with ADHD, the disorder does not affect intelligence (Nidus, 2006). A type of reading disorder, dyslexia, is quite widespread. Reading disabilities affect up to 8% of elementary school children.

2.7.3 Mood and Anxiety Disorders (Internalising disorders)

Evidence of the co-occurrence of mood disorders (major depression and dysthymia) with ADHD is now fairly substantial. However, clinicians and investigators struggle with whether this combination of symptoms represent severe ADHD or a different diagnostic entity such as comorbid bipolar disorder (BD), or other comorbid conditions (Biederman, Mick, & Faraone, 1998). According to a study conducted by Connor, Edwards, Fletcher, Baird, Barkley, and Steingard (2003), the overlap of anxiety disorders with ADHD was found to range from 10% - 40% in clinic referred children, averaging about 25%.

2.7.3.1 Dysthymia and Depression

The loss of interest and pleasure in normal activities, poor self-esteem and hopelessness are symptoms of depression. Inattentiveness, irritability, and hyperactivity can result from depression especially in children (Faraone & Biederman, 1998a). The coexistence of ADHD and mood disorders (e.g. Major Depressive Disorder and Dysthymia) is ~ 18%. In addition, Wolraich, Hannah, Baumgaertel, and Feurer (1998), suggests that coexisting conditions are more frequent in children with the predominantly inattentive and combined ADHD subtypes.

2.7.3.2 Bipolar Disorder

There are no accurate statistics on how many children with ADHD also have bipolar disorder (BD), but one study suggests that as many as 25% of children diagnosed with ADHD may also have bipolar disorder, commonly called manic depression (Nidus, 2006). In its classic form, bipolar disorder is characterised by mood cycling between periods of intense highs and lows (episodes of depression and mania), with symptoms of irritability, rapid speech, and disconnected thoughts. In children, bipolar disorder often seems to be a rather chronic mood dysregulation with a mixture of elation, depression, and irritability. Furthermore, there are some symptoms that can be present both in ADHD and bipolar disorder, such as a high level of energy and a reduced need for sleep. Differentiating between ADHD and bipolar disorder in childhood can be difficult. Both disorders often cause inattention and distractibility. Children with mania and ADHD may have more aggression, behavioural problems, and emotional disorders than those with ADHD alone. Of the symptoms differentiating children with ADHD from those with bipolar disorder, elated mood and grandiosity of the bipolar child are distinguishing characteristics (National Institute of Mental Health, 2007a).

2.7.3.3 Anxiety

Common symptoms of anxiety disorders, such as restlessness, irritability, impatience, and sleep disturbances are similar to those experienced by ADHD children. Anxiety disorders commonly accompany ADHD. The association between ADHD and anxiety disorders has been

estimated to be about 25% (American Academy of Pediatrics, 2000). Obsessive-Compulsive Disorder is a specific anxiety disorder that shares many characteristics with ADHD, and may share a genetic component. Children with ADHD who experience anxiety or depression are also more likely to suffer from low self-esteem and insecurity as a result of failures at school and interpersonal relationships (Taylor et al., 2004; Nidus, 2006). If the anxiety or depression is recognised and treated, the child will be better able to handle the problems that accompany ADHD. Conversely, effective treatment of ADHD can have a positive impact on anxiety as the child is better able to master academic tasks (National Institute of Mental Health, 2007a). Preliminary studies suggest that coexisting anxiety is more frequent in children with the predominantly inattentive and combined subtypes of ADHD (American Academy of Pediatrics, 2000). Although anxiety disorders may be associated with less severe impulsiveness, they may be associated with more severe inattention and, arguably, a poorer response to stimulant medication (Barkley, 2006).

2.7.4 Tourette Syndrome

A very small proportion of people with ADHD have a neurological disorder called Tourette syndrome. People with Tourette syndrome have various nervous tics and repetitive mannerisms, such as eye blinks, facial twitches, or grimacing. Others may clear their throats frequently, snort, sniff, or bark out words. These behaviours can be controlled with medication. While very few children have this syndrome, many of the cases of Tourette syndrome have associated ADHD (National Institute of Mental Health, 2007a). About 50% of those children with Tourette syndrome also have ADHD (Nidus, 2006). In such cases, both disorders often require treatment that may include medications.

2.8 Aetiology

The exact aetiological pathways of ADHD are unknown. The aetiology of ADHD has not been clearly identified, although evidence supports neurobiological and genetic origins. Family,

twin, adoption, segregation analysis, and molecular genetic studies show that it has a significant genetic component (Faraone & Biederman, 1998b). There seems to be agreement that heritability is an important factor, possibly linked to the dopamine receptors or the dopamine transporter. Structural and functional imaging studies suggest that dysfunction in the fronto-subcortical pathways, as well as imbalances in the dopaminergic- and noradrenergic systems contribute to the pathophysiology of ADHD (Biederman, 2005).

One early theory was that attention disorders were caused by brain injury. Some children who have suffered accidents leading to brain injury may show some signs of behaviour similar to that of ADHD, but only a small percentage of children with ADHD have been found to have suffered a traumatic brain injury (Kaplan & Sadock, 1998).

According to Johansen et al. (2002) and Barkley (2006), the totality of evidence indicates that neurological and genetic factors play a substantial role in the origins and expression of this disorder. Psychophysiological research demonstrated reduced arousal to stimulation (particularly on averaged evoked responses); diminished sensitivity to reinforcement; and increased slow-wave or theta-activity (associated with drowsiness and poor focus of attention) and decreased beta or fast-wave activity (associated with decreased concentration and persistence) on EEG (Barkley, 2006).

2.8.1 Neurological factors

Neurological factors seem to play an important role in the pathophysiology of ADHD. This will be discussed in detail in Chapter 3.

2.8.2 Genetic factors

Genetic factors play the most important role in ADHD. Family, twin, adoption, segregation analysis, and molecular genetic studies show that it has a substantial genetic component (Faraone & Biederman, 1998b). It is therefore suggested that ADHD is highly

hereditary in nature, making heredity one of the best-substantiated aetiologies for ADHD (Barkley, 2006). This will be discussed in detail in Chapter 3.

2.8.3 Toxins and Environmental factors

Several toxins have been associated with risk for ADHD, two of which are maternal smoking and alcohol consumption (Taylor et al., 2004; Barkley, 2006). Chronic intake of dopamine agonists such as cocaine, crack, and amphetamines will produce a down-regulation of dopamine synthesis. The down-regulation and ADHD-like symptoms persist until dopamine function normalises (Sagvolden et al., 2005). Some environmental pollutants may well cause dopamine dysfunction (Holene, Nafstad, Skaare, Bernhoft, Engen, & Sagvolden, 1995). Polychlorinated biphenyls (PCBs) constitute a group of halogenated aromatic hydrocarbons that are lipophilic and, consequently, bioaccumulating (Holene, Nafstad, Skaare, & Sagvolden, 1998). The lipophilic nature of PCBs makes organs like the brain particularly vulnerable. Intake of these pollutants causes developmental abnormalities in human babies including low birth weight, disruptive behaviour, and overactivity (Sagvolden et al., 2005).

Another environmental agent that may be associated with a higher risk of ADHD is high levels of lead in the bodies of young preschool children. Even low levels of lead may manifest symptoms similar to those of ADHD. A child may be easily distractible, disorganised, and have trouble thinking logically. The major cause of lead toxicity is exposure to leaded paint, particularly, in homes that are old and in poor repair. Since lead is no longer allowed in paint and is usually found only in older buildings, exposure to toxic levels is not as prevalent as it once was. Children who live in old buildings in which lead still exists in the plumbing or in lead paint that has been painted over may be at risk (National Institute of Mental Health, 2007a). Therefore, ADHD- like symptoms may be produced not only by genetic factors, but also by other agents altering the dopaminergic functioning.

One study also suggests a potential contribution of streptococcal infection to some cases of ADHD, wherein the infection triggers an immune response of antibodies that destroy cells of

the basal ganglia. It was also found that some of the older anticonvulsant medications e.g. phenobarbital and phenytoin may create or exacerbate symptoms of ADHD (Barkley, 2006).

2.8.4 Psychosocial factors

The evidence for a contribution of psychosocial factors to ADHD is weak. The recent suggestion that television viewing during early childhood may play a contributing role in ADHD was overstated and has not been replicated (Barkley, 2006).

Children in institutions are frequently overactive and have poor attention spans. These signs result from prolonged emotional deprivation, and they disappear when deprivational factors are removed, such as through adoption or placement in a foster home. Stressful psychological events, a disruption of family equilibrium, and other anxiety-inducing factors contribute to the initiation or perpetuation of ADHD. Predisposing factors may include the child's temperament, genetic-familial factors, and the demands of society to adhere to a routinised way of behaving and performing. Socioeconomic status does not seem to be a predisposing factor (Kaplan & Sadock, 1998).

2.9 Assessment of ADHD

Assessment of ADHD must be done to a child who presents with inattention, hyperactivity, impulsiveness, and underachievement or behavioural problems. According to Brown et al. (2001), there is no compelling evidence to support the use of medical and laboratory tests in the identification and diagnosis of ADHD, which often makes the diagnosis of ADHD subjective. The following methods are usually used when making an ADHD diagnosis (Taylor et al., 2004):

Firstly, the parents are interviewed in order to get the presenting problems, developmental history, and family history.

Secondly, the child is also interviewed with regard to home, school, and social functioning if the age of the child allows it.

Thirdly, rating scales describing home and school functioning are completed.

Fourthly, data is obtained from school, which includes academic results, achievement test scores, current placement, and other pertinent information.

The assessment of ADHD requires evidence directly obtained from classroom, teacher and parents regarding the core symptoms of ADHD in various settings, the age of onset, duration of symptoms, and degree of functional impairments. This is to rule out any other conditions that can solely account for the problems observed, and to evaluate the pervasiveness of the problems (Meyer & Aase, 2003).

2.10 Difficulty in identifying ADHD children

There is currently no laboratory- or imaging tests to reliably diagnose ADHD. A diagnosis relies only on behavioural symtoms and ruling out other disorders. Many experts believe that the disorder is both over- and underdiagnosed. Diagnosis is difficult for some of the following reasons:

Arguments that ADHD is overdiagnosed in some children.

- The popularity of methylphenidate (Ritalin®) has encouraged some parents and teachers to pressure doctors into prescribing this standard ADHD drug for children who are aggressive or who have poor academic performances. In one study of fifth graders in two different cities in the USA, 18% and 20% of Caucasian boys were treated with medications. In one centre, after careful testing, ADHD was the actual diagnosis in only 11% of children referred for ADHD, and 18% had no disability. Others were simply poorer learners or had no problems at all (Nidus, 2006).
- According to the Nidus Information Services Report (2006), children more likely to receive medication were young for their grade, indicating that they may have been socially and intellectually immature, rather than behaviourally impaired.

- Being poor and growing up in a single parent household contribute to emotional and behavioural problems. The significant increase in this problems has also paralleled an increase in the diagnosis of ADHD children, who may be simply responding to social and economic problems (Nidus, 2006).

Arguments that ADHD is underdiagnosed in some children.

- Some evidence suggests that many girls with ADHD may go underdiagnosed. Research indicates that girls with ADHD are often inattentive but not hyperactive or impulsive. In fact, older girls with ADHD tend to have social problems due to withdrawal and internalized emotions, showing symptoms of anxiety and depression (Faraone & Biederman, 1998a).

- Doctors may fail to diagnose children with ADHD because they often behave normally in the quiet doctor's office where there are no distractions to trigger symptoms (Nidus, 2006).

2.11 Treatment

A combination of a psychostimulant, most commonly methylphenidate (Ritalin®), and cognitive-behavioural therapy is providing to be the best option for treatment of children with ADHD. Medication with dopaminergic and noradrenergic activity seem to reduce ADHD symptoms by blocking dopamine and noradrenaline reuptake. Such alterations in dopaminergic and noradrenergic function are apparently necessary for the clinical efficacy of pharmacological treatments of ADHD (Biederman, 2005).

ADHD is a serious and common disorder where appropriate treatment is able to improve the condition and reduce suffering (Buitelaar et al., 2003). Treatment with psychostimulants such as methylphenidate (Ritalin®) will be discussed in detail in Chapter 4.

2.12 Prognosis

ADHD is associated with a tendency for repeated accidents, depressive and anxiety disorders, learning disabilities, and school failure (American Academy of Pediatrics, 2000). The course of ADHD is highly variable. Symptoms may persist into adolescence or adult life; they may remit at puberty; or the hyperactivity may disappear, but the decreased attention span and impulse-control problems may persist. Children with the disorder whose symptoms persist into adolescence are at high risk for developing Conduct Disorder. Approximately 50% of children with conduct disorder develop antisocial personality disorder in adulthood. Children with both ADHD and Conduct Disorder are also at risk for developing a substance-related disorder. The development of substance abuse disorders during adolescence appears to be related to the presence of Conduct Disorder rather than the ADHD alone (Kaplan & Sadock, 1998).

Follow-up studies in the USA have confirmed a poor prognosis for children with ADHD (Mannuzza et al., 1993). Also, a 10-year follow-up study of 6 and 7 year-old boys in London community survey found that hyperactive behaviour was a strong risk for later psychiatric diagnosis, antisocial behaviour, and social and peer problems, even after allowing for a coexistent conduct disorder. This study provides a strong argument for the recognition and treatment of ADHD in childhood (Swanson et al., 1998b).

A correct diagnosis is essential so that the child and family can begin to receive whatever combination of educational, medical, and emotional help they need. This may include providing recommendations to school staff, seeking out a more appropriate classroom setting, selecting the right medication, and helping parents to manage their child's behaviour (National Institute of Mental Health, 2007a).

Chapter 3

THE NEUROBIOLOGY OF ADHD

3.1 Introduction

ADHD is a seemingly heterogeneous group of behavioural disorders. Various aetiologies have been proposed as a chief cause of ADHD symptoms. It is argued that there is no brain damage involved but that genetic factors, mainly those giving rise to dopamine hypofunction, are responsible for the behavioural symptoms. Family, twin, adoption, segregation analysis, and molecular genetic studies show that it has a substantial genetic component (Faraone & Biederman, 1998b). Other neurochemical imbalances may also be involved.

Research into the neuropsychology of ADHD has increased substantially in the past decade; it supports the view of ADHD (primarily the Combined Type) as not only an inhibitory disorder, but one associated with deficits in executive functions (Barkley, 2006). Neuropsychological researchers found substantial evidence for deficits in behavioural inhibition, sustained attention (task persistence), resistance to distraction, and executive functioning (the internalisation of speech, verbal working memory, temporal sequential working memory, motor co-ordination and the timing of fine motor movements, emotional and motivational self-regulation, verbal fluency, and planning). The executive functions are known to be mediated by the prefrontal cortex and its networks with the basal ganglia and cerebellum suggesting that these regions may play a prime role in ADHD (Barkley, 2006). Notably, these pathways are rich in catecholamines (Faraone & Biederman, 1998b).

Although there are inconsistencies among studies, it is notable that the pattern of deficits that has emerged in neurobiological, neuroimaging and neuropsychological studies of ADHD across the life cycle support the hypothesis that deficits in frontal lobe function and the connections between the frontal lobe and key subcortical regions underlie this disorder. Evidence continues to mount that ADHD is associated, at least in part, with structural and/or

functional differences from normal in the frontal lobes, basal ganglia, and cerebellum, and possibly the anterior cingulate (Barkley, 2006).

Psychophysiological research demonstrates reduced arousal to stimulation (particularly on averaged evoked responses); diminished sensitivity to reinforcement; increased slow-wave or theta activity (associated with drowsiness and poor focus of attention) and decreased beta or fast wave activity (associated with decreased concentration and persistence) on EEG (Barkley, 2006).

Abnormal dopamine function has been the focus of attention of recent research in the search for the neurobiological basis of ADHD because of the assumed dopamine agonistic action of the stimulant drugs (Johansen et al., 2002; Volkow, Wang, Fowler, Gatley, Logan, Ding et al., 1998) that for several decades have provided the primary pharmacological treatment for ADHD (Solanto, Arnsten, & Castellanos, 2001a).

The following underpinnings of ADHD will be discussed in this chapter:

Neuroanatomy

Neurochemistry, role of dopamine, reinforcement and extinction and the Model of Sagvolden, Johansen, Aase, and Russel (2005)

Genetics

Neuropharmacology

3.2 Neuroanatomy

It is generally agreed that the pattern of symptoms of ADHD is likely to be mediated by some abnormalities in the brain functioning. ADHD seems mainly but not exclusively to be associated with reduced metabolism and volume of the right frontal cortex and right sub-cortical structures, smaller total cerebral volume and smaller cerebellum as well as reduced corpus callosum (Castellanos & Swanson, 2002). Studies of cerebral blood flow indicate

reduced flow to the frontal lobes, striatum and cerebellum, consistent with underactivity in these regions (Barkley, 2006).

Figure 3.1 Dopamine pathways of the human brain (Purves et al., 2001)

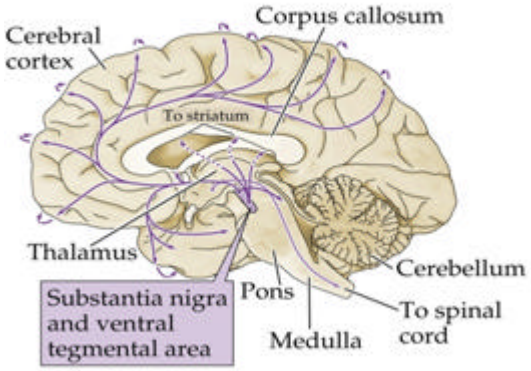

Figure 3.1 Diagram of the human brain showing the different Dopamine pathways, and particularly the location of the cerebral cortex, corpus callosum, cerebellum and substantia nigra.

Some knowledge of the structure of the brain is helpful in understanding what the research scientists are doing in searching for a physical basis for Attention-Deficit/ Hyperactivity Disorder. One part of the brain that scientists have focused on in their search is the frontal lobes of the cerebrum. The frontal lobes allow us to solve problems, plan ahead, understand the behaviour of others, and restrain our impulses. The two frontal lobes, the right and the left, communicate with each other through the corpus callosum, (nerve fibres that connect the right and left frontal lobes).

The basal ganglia (striatum) are the interconnected grey masses deep in the cerebral hemisphere that serve as the connection between the cerebrum and the cerebellum and, with the cerebellum, are responsible for motor coordination. The cerebellum is divided into three parts. The middle part is called the vermis.

All of these parts of the brain have been studied through the use of various methods for seeing into or imaging the brain. These methods include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). The main or central psychological deficits in those with ADHD have been linked through these studies. By 2002 the researchers in the NIMH Child Psychiatry Branch had studied 152 boys and girls with ADHD, matched with 139 age- and gender-matched controls without ADHD. The children were scanned at least twice, some as many as four times over a decade. As a group, the ADHD children showed 3 - 4% smaller brain volumes in all regions - the frontal lobes, temporal grey matter, caudate nucleus, and cerebellum. Studies using fMRI indicate differences from typical brain activity in the frontal region, basal ganglia, and cerebellum (Barkley, 2006; National Institute of Mental Health, 2007a).

This study also showed that the ADHD children who were on medication had a white matter volume that did not differ from that of controls. Those never-medicated patients had an abnormally small volume of white matter. The white matter consists of fibres that establish long-distance connections between brain regions. It normally thickens as a child grows older and the brain matures (Castellanos, Lee, Sharp, Jeffries, Greenstein, Clasen et al., 2002).

Although this long-term study used MRI to scan the children's brains, the NIMH researchers stressed that MRI remains a research tool and cannot be used to diagnose ADHD in any given child. This is true for other neurological methods of evaluating the brain, such as PET and SPECT (National Institute of Mental Health, 2007a).

3.3 Neurochemistry

Many neurotransmitters have been associated with ADHD symptoms. Deficits in specific neurotransmitters have not been definitively established, but a clear role for dopamine (DA) and noradrenaline (NA) is suggested by the positive response of those with ADHD to stimulants (dopamine reuptake inhibitors and agonists) and atomoxetine (noradrenaline reuptake

inhibitors), and by the distribution of these two neurotransmitters in the brain regions implicated in ADHD (Barkley, 2006).

Castellanos (1997) proposed that different abnormalities might exist in two dopamine regions: underactivity in a cortical region (i.e. anterior cingulate), which results in cognitive deficits, and overactivity in a subcortical region (i.e. caudate nucleus), which results in motor excesses. Arnsten, Steere and Hunt (1996) however, suggested that different abnormalities may also exist in two noradrenergic regions: underactivity in a cortical region (i.e. dorsolateral prefrontal), which results in primary memory deficits and overactivity in a subcortical region (i.e. locus coeruleus), which results in overarousal. The dopamine systems are linked to the noradrenergic neuromodulator system originating in the locus coeruleus. In an article published by Johansen et al. (2002), ADHD is explained as the outcome of hypofunctioning dopamine systems influencing both learning, behavioural planning, and motor coordination.

Plasma noradrenaline concentrations may be significantly increased in ADHD children with reading disorder and other cognitive disabilities compared to ADHD children without learning disabilities (Halperin, Newcorn, Koda, Pick, McKay, & Knott, 1997). The dopamine systems are also closely linked anatomically to the serotonergic (5HT) neuromodulator systems. Reduced central serotonergic activity has been implicated in poor impulse regulation and aggressive behaviour (Sagvolden et al., 2005). Up and above that, Qian et al. (2003) have found that catechol-O-methyltransferase (COMT), a catecholamine metabolising enzyme, may be involved in ADHD gender differences in Han Chinese.

3.3.1 Role of Dopamine

Dopamine effects on prefrontal functioning are complex. Although their results are still tentative, molecular genetic studies done by Faraone and Biederman (1998), suggest that three genes may increase the susceptibility to ADHD: the D4 dopamine receptor gene, the dopamine transporter gene (DAT1), and the D2 dopamine receptor gene. Dopamine exerts a strong regulatory effect on prefrontal cortical neuronal activity. The dopamine actions may best be

described as gating of inputs and modulation of states of neuronal elements, rather than in terms of inhibition or excitation (Grace, 2002). Dopamine is the predominant cathecholamine neuromodulator in the mammalian brain. There are at least five distinct G protein-coupled dopamine receptor subtypes (see Fig 3.2) (Missale, Nash, Robinson, Jaber, & Caron, 1998).

Figure 3.2 Dopamine synaptic transmission (Waters, 1995)

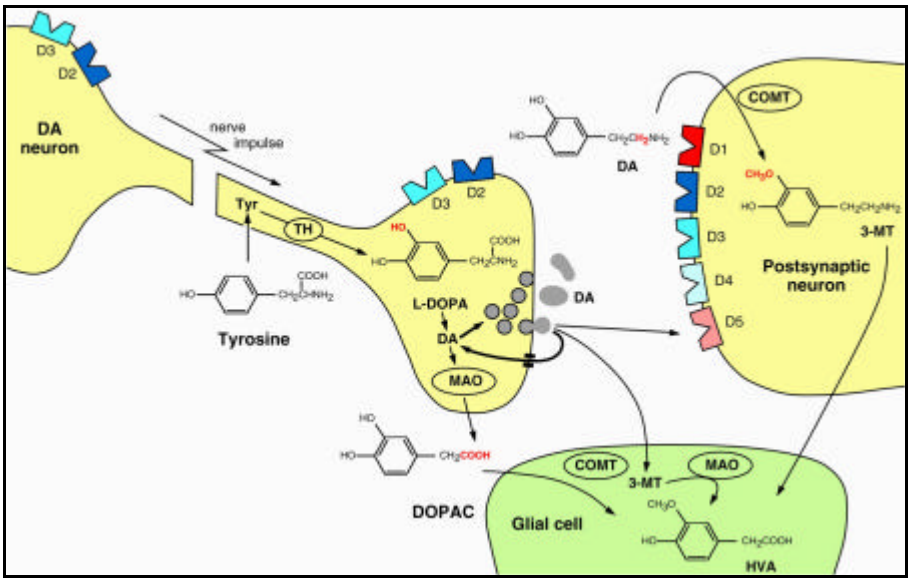

Fig 3.2. Neurons and glial cell showing dopamine synthesis, metabolism, and typical positions of dopamine receptors. Note that D1/5 and D2/3/4 receptors are not generally colocalized on the same neuron as they have opposite effects. Abbreviations: 3MT =3-methoxytyramine, COMT = catechol-O-methyl transferase, D1–D5 = dopamine receptors 1 through 5, DA = dopamine, DDC = DOPA decarboxylase, HVA = homovanillic acid, MAO = monoamine oxidase, TH = tyrosine hydroxylase, Tyr =tyrosine. (Modified after Waters 1995.)

Dopamine plays a critical role in the neurobiology of ADHD. ADHD-like symptoms may be produced not only by genetic factors but also by agents altering the dopamine functioning. Chronic intake of dopamine agonists like cocaine, crack and amphetamines will produce a down-regulation of dopamine synthesis (Johansen et al., 2002). It is hypothesised that a dysfunctioning dopamine system may be linked to altered reinforcement and extinction processes, which determine the behavioural characteristics of ADHD (Johansen et al., 2002; Sagvolden et al., 2005). Reinforcement is associated with dopamine release in the nucleus

accumbens shell. Dopamine release is seen when reinforcers start controlling behaviour and is associated with reinforcer unpredictability (Schultz, 1998).

3.3.2 Dysfunctioning, reinforcement and extinction processes

The main behavioural selection mechanisms, reinforcement and extinction, are associated with dopamine neuron activity. A stimulus is a positive reinforcer if its presentation increases the probability of future occurrence on the response that produced it. The reinforcement possibilities are the conditions under which a response produces a reinforcer (Catania, 1998). Hence, reinforcers act on responses that already took place by increasing the probability of future responding (Catania, Sagvolden, & Keller, 1988). The reinforcing effect is the largest when the reinforcer is delivered immediately after the occurrence of the response and wanes as a function of delay in the delivery of the reinforcer. This relation between the effect of the reinforcer and the time interval between response and reinforcer is generally known as the 'delay-of reinforcement gradient' or simply as the 'delay gradient' (Catania, 1998; Sagvolden et al., 1998). In addition, a reinforcer acts not only on the response that produced it, but also on responses emanated earlier. Reinforcers are required both in attainment and in maintenance of behaviour (Johansen et al., 2002). It has been argued by Sagvolden and colleagues (1998) that the key features of ADHD, deficient attention, overactivity, and impulsiveness, may all be due to altered reinforcement mechanisms and a shorter and steeper delay-of-reinforcement gradient.

When the reinforcer is powerful and frequent, however, the differences in behaviour between children with ADHD and controls are expected to be minimal. Therefore, halting of reinforcers starts an extinction process. Neurobiological, reinforcement and extinction may be separate processes associated with different facets of dopamine activity. Dopamine dysfunction may lead to a reduced tonic dopamine activity in ADHD. Extinction is normally signalled by a depression in tonic dopamine activity. Extracellular dopamine levels are characterised by low, tonic background activity and short-lasting phasic activity. Abnormal low tonic activity may

thus cause a failing extinction signal (Schultz, 1998). This view is consistent with studies done by Sagvolden and colleagues (1998), finding excessive responding during extinction in children with ADHD. It is therefore suggested an extinction deficit as an alternative explanation of behaviour previously attributed to behavioural disinhibition in ADHD (Johansen et al., 2002).

3.3.3 The Dopamine Dysfunctioning Model

Johansen et al. (2002); Sagvolden et al. (1998); and Sagvolden et al. (2005) argued that the main symptoms of ADHD are caused by a deficit in the reinforcement process, due to dysfunctioning dopamine branches, impairing non-dopaminergic signal transmission. Their dynamic developmental theory is based on the hypothesis that altered dopaminergic functions play a pivotal role by failing to modulate nondopaminergic (primarily glutamate and GABA) signal transmission appropriately. There are three primary dopamine projection branches: the meso-cortical, meso-limbic, and nigrostriatal (Fig 3.3).

1. **Meso-limbic branch**

   A hypofunctioning meso-limbic dopamine branch produces altered reinforcement of behaviour and deficit extinction of previously reinforced behaviour. This gives rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioural variability, and failure to “inhibit” responses (“disinhibition”) (Sagvolden et al., 2005).

2. **Meso-cortical branch**

   A hypofunctioning meso-cortical dopamine branch will cause attention response deficiencies (deficient orienting responses, impaired saccadic eye movements, and poorer attention responses toward a target) and poor behavioural planning (poor executive functions) (Sagvolden et al., 2005). The frontal lobes are responsible for the so-called executive functions. This is an umbrella term for a variety of cognitive

functions and includes cognitive flexibility, problem solving and distractibility (Shue & Douglas, 1992).

3. **Nigrostriatal pathway**

The nigrostriatal pathway projects from the substantial nigra to the basal ganglia, and is thought to control movement. A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficient nondeclarative habit learning and memory (Johansen et al., 2002; Sagvolden et al., 2005).

Sagvolden et al. (2005) reasoned that these impairments will lead to marked developmental delay, clumsiness, neurological "soft signs", and a 'failure to inhibit" responses when quick responses are required. They argued that the time available for associating behaviour with its consequences will be shorter in ADHD than in normal children if dopamine systems are hypofunctioning. In addition, they suggested that hypofunctioning dopamine systems lead to a deficient behavioural extinction process. This will cause excessive behaviour, usually labelled as hyperactivity, and increased behavioural variability, frequently interpreted as failure to inhibit responses. They argued that response disinhibition is at best misleading and usually a misinterpretation. Their dynamic developmental theory disentangles aspects of various deficient executive functions in ADHD into impulsiveness caused by inefficient reinforcement, deficient extinction of previously obtained behaviour, and impaired motor control. The concept of impulsiveness has both a motor and a cognitive component.

The developmental behavioural theory of Sagvolden and colleagues (2005) is based on the idea that ascending dopamine pathways are dysfunctional and perhaps hypofunctional. The ability to associate an event with reinforcement is constrained by a necessarily relative short time interval. If neuronal systems are functioning poorly in ADHD, then the time-window available for making appropriate associations is predicted to be even shorter (Sagvolden et al., 2005). The hypofunctioning dopamine branches are well illustrated in the Dopamine

Dysfunctioning Model of Sagvolden and colleagues (Johansen et al., 2002; Sagvolden et al., 2005). According to this model, ADHD is caused by altered dopamine functioning. (see Figure 3.3).

Figure 3.3 A model of Dopamine Dysfunction in ADHD (Sagvolden et al., 2005)

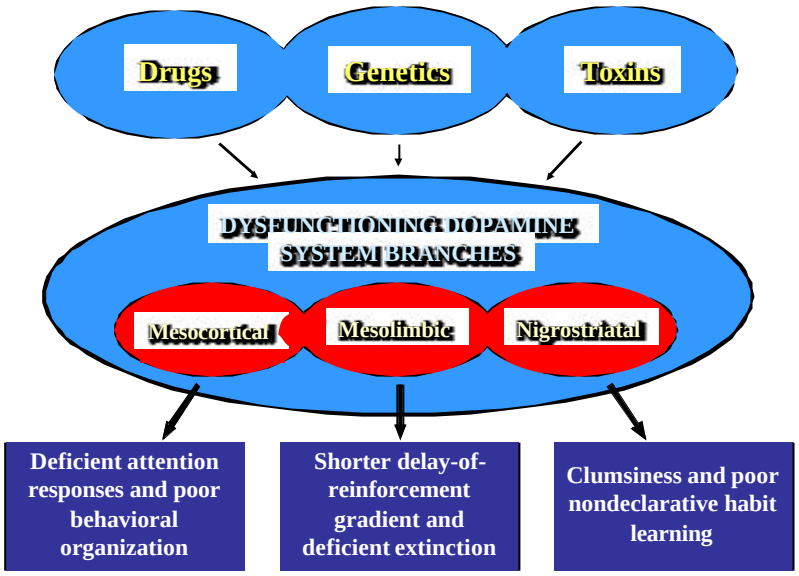

Figure 3.3 Dysfunction of dopaminergic systems resulting from drug abuse, genetic transmission, or environmental pollutants may cause ADHD symptoms by interacting with frontostriatal circuits (not shown)

3.4 Genetic factors

Genetic factors play the most important role in ADHD. Attention disorders often run in families, so there are likely to be genetic influences. Evidence for a genetic basis for ADHD includes the greater concordance in monozygotic than in dizygotic twins, also siblings of hyperactive children have about twice the risk of having the disorder as does the general population. One sibling may predominantly have hyperactivity symptoms, and others may have predominantly inattentive symptoms. Biological parents of children with the disorder have a higher risk for ADHD than adoptive parents (Kaplan & Sadock, 1998). Family studies showed a markedly elevated risk of ADHD among the biological relatives of children with ADHD (10% -

35%) rising to a risk of 55% to at least one parent in families with two affected children. Parental ADHD conveys a risk to offspring of up to 57%. Adoptive studies indicate no increased risk of ADHD among adoptive children with ADHD, further supporting a genetic contribution to ADHD (Barkley, 2006).

Researchers continue to study the genetic contribution to ADHD and to identify the genes that cause a person to be susceptible to ADHD. Since its inception in 1999, the Attention-Deficit Hyperactivity Disorder Molecular Genetics Network has served as a way for researchers to share findings regarding possible genetic influences on ADHD (National Institute of Mental Health, 2007a).

3.4.1 Molecular genetics

The genetic basis of ADHD seems to be rather complicated in the sense that no single gene stands out as an obvious candidate. This pointed towards a polygenetic and multi-determinant aetiology of ADHD (Sagvolden et al., 2005). Dopamine genes have been the initial candidates for investigation (Solanto, Arnsten, & Castellanos, 2001b). Dopaminergic neurons are complicated structures with complex interactions with other neurons and glial cells (see Fig. 3.2). Even the simplest of behavioural reflexes is controlled by many neurons involving several neuronal signal substances and a multitude of receptors. The different neuromodulators that have been implicated in ADHD are very tightly linked neuroanatomically (Sagvolden et al., 2005).

Research has focused much attention on dopamine - regulating genes, given the positive response of ADHD cases to dopamine agonists and reuptake inhibitors, as well as the large role of dopamine in the frontal cortex and striatum. Five different dopamine receptors (D1- D5) have been identified, each produced by a different gene. D1 and D5 are believed to generate stimulatory signals, while D2-D4 receptors are believed to transmit inhibitory signals. The sensitivity of the receptors to dopamine appears to be determined in part by the particular

sequence (substitutions, deletions, or more often number of repeats) of the gene, known as a "polymorphism" (Barkley, 2006). Specific alleles of these dopamine genes may alter dopamine transmission in the neural networks implicated in ADHD (Faraone, Doyle, Mick, & Biederman, 2001). Two approaches are used to evaluate the genetic aetiology of ADHD: 1) the genome scan, which examines all chromosomal locations without prior guessing as to which genes underlie ADHD; and 2) the candidate gene approach, which examines one or more genes based on theory and empirical evidence (Faraone et al., 2005).

A great deal of scientific interest has focused on the human DRD4 gene (gene for the D4 receptor) mapped to chromosome 11p15.5. DRD4 is highly expressed in the frontal- subcortical networks (Faraone & Biederman, 1998b). It has been demonstrated that D4 receptors play a vital role in cognitive an emotional functions, as opposed to motor activity and have also been linked to exploratory behaviour, excitability and impulsiveness. The human DRD4 gene display extensive polymorphic variations within the coding sequence (Missale et al., 1998). The DRD4 gene, particularly in its 48-bp form has 7 or more repeats. A study done by LaHoste, Swanson, Wigal, Glabe, Wigal, King et al. (1996), found that the 7-repeat version of this polymorphism was initially overrepresented in children with ADHD.

The dopamine transporter gene (DAT1) has also been implicated in a number of studies of ADHD children. (Cook, Stein, Krasowski, Cox, Olkon, Kieffer et al., 1995) observed an association between ADHD and the 48-bp allele (or genotype) in the dopamine transporter gene (DAT1). The plasma membrane transporter (DAT1) provides major regulation of synaptic and extrasynaptic levels of dopamine and is the principle target of psychostimulant drugs (Grace, 2002; Missale et al., 1998; Volkow et al., 1998). The DAT1 gene has 15 exons, several introns, and several polymorphisms. The 10- repeat allele of the DAT1 gene may be associated with increased reuptake of dopamine (Sunohara, Roberts, Malone, Schachar, Tannock, Basile et al., 2000; Swanson, Flodman, Kennedy, Spence, Moyzis, Schuck et al., 2000). The dopamine

transporter was found to be elevated by approximately 70% in adults with ADHD, according to single photon emission computed tomography (Dougherty, Bonab, Spencer, Rauch, Madras, & Fischman, 1999).

Although the presence of the DRD4 7-repeat allele may be associated with an increased risk for ADHD, it is not a necessary condition as about half of the ADHD children do not have a 7-repeat allele (Swanson, Oosterlaan, Murias, Schuck, Flodman, Spence et al., 2000). However, throughout all the studies, the gene most strongly implicated in ADHD, is the 7-repeat allele of the D4 gene (DRD4), confirming a strong dopamine component in the pathogenesis of ADHD (Faraone & Doyle, 2001).

3.5 Neuropharmacology

The regions of neuroanatomical abnormalities associated with ADHD and the modulation of neural networks by neurotransmitter systems provide the theoretical basis of neuropharmalogical treatment of this disorder (Swanson, Castellanos, Murias, LaHoste, & Kennedy, 1998a). The fronto-subcortical systems pathways associated with ADHD are rich in catecholamines, which are involved in the mechanism of action of stimulant medications used to treat this disorder (Elia, Borcherding, Potter, Mefford, Rapoport, & Keysor, 1990). The primary treatment of ADHD is with stimulant medication (e.g. methylphenidate and amphetamine), which has stood the test of time and the scrutiny of controlled research (Wilens & Biederman, 1992). Stimulants, such as methylphenidate, seem to reduce core ADHD symptoms (i.e. inattention, hyperactivity, impulsivity) by inhibiting the dopamine transporter and blocking dopamine and noradrenaline reuptake into the presynaptic neuron, thereby increasing the release of these monoamines into the extraneuronal space (Elia et al., 1990). New evidence also suggests that the catecholaminergic nonstimulant, atomoxetine , is also effective in improving ADHD symptoms (Biederman & Spencer, 2008; Pliszka, 2005). Treatment changes in the dopaminergic and noradrenergic function seem to be necessary for the clinical efficacy of pharmacologic treatments of ADHD (Biederman, 2005; Levy, 2008).

3.6 Conclusion

As clearly seen in this chapter, it is likely that dopamine dysfunction plays an integral role in the neurobiology of ADHD. Genetic, neurochemical, pharmacological and neuropsychological studies have tried to give explanation about the development of the distinctive symptoms which are seen to be associated with ADHD. As a result, ADHD needs a multimodal approach in order to insure a positive outcome. Pharmacotherapy, more specific treatment with methylphenidate, will be discussed, in detail, in the next chapter.

Chapter 4

PHARMACOLOGICAL TREATMENT OF ADHD

4.1 Introduction

Treatment can include the use of medications, special educational programmes to help the child keep up academically, and psychotherapy. Between 70% and 80% of children with ADHD respond to medications, which allow them a chance to improve their attention span, perform tasks better, and control impulsive behaviour. As a result, children get along better with their teachers, classmates, and parents, which, in turn, improve their self-esteem (Barkley, 2006; Meyer & Aase, 2003).

4.2 Pharmacotherapy

Pharmacotherapy is an important component of the multimodal management of ADHD. Changes in the dopaminergic and noradrenergic function seem to be necessary for the clinical efficacy of pharmacologic treatments of ADHD. A plausible model for the effects of medications in ADHD suggest that, through dopaminergic and/or noradrenergic pathways, these agents increase the inhibitory influences of frontal cortical activity on subcortical structures (Zametkin & Rapoport, 1987). After a dramatic increase in the prescription of stimulant medication over several years in the USA, it was estimated in 1998 that about 6% of boys and 2% of girls in the USA received this type of pharmacological treatment (Swanson et al., 1998a). Management to date has been dominated by the use of the psychostimulants methylphenidate and dexamphetamine, for which there is a substantial evidence base describing their efficacy (Swanson, Kraemer, Hinshaw, Arnold, Conners, Abikoff et al., 2001). These drugs release and inhibit the reuptake of cathecholamines, mainly dopamine, in the central nervous system (Swanson et al., 1998b).

Table 4.1 South African increase in the ADHD market, stimulant and non- stimulant usage

	2005	2006	2007	2008
Increase in ADHD market	40%	33%	23%	13%
Increase in stimulant usage	27%	18%	25%	16%
Increase in non-stimulant usage	*	*	15%	2%

*Non-stimululant drug, atomoxetine, only recently available on the South African market
From : (IMS Data, 2008)

According to Truter and Kotze (2005), the pharmacotherapy of ADHD is under-researched in South-Africa. Although there are sales figures available for different drugs, no comprehensive South-African database exists from which methylphenidate prescribing patterns can be investigated. They also stipulated the need for further studies which include the quality of life of patients before and after receiving methylphenidate, and the quantification of the impact of methylphenidate on the academic performance of young patients.

Although the range of formulations of psychostimulants has increased over the years to include long acting and continuous release formulations, their use is limited by their duration of action, problematic adverse effects, abuse potential, and reluctance on the part of some children and families to take controlled drugs. Atomoxetine is the first non-stimulant to be approved for the treatment of ADHD (Barton, 2005). A range of other drugs including, tricyclic antidepressants, venlafaxine, guanfacine, and clonidine are also used in the management of ADHD; however, the evidence base for their effectiveness is less extensive than that for the psychostimulants and none are licensed for this use (Spencer, Biederman, Wilens, Harding, O'Donnell, & Griffin, 1996)(see Table 4.2.)

Table 4.2 Drug treatment for ADHD

Stimulants	**MOA inhibitors**
Methylphenidate	Phenelzine
Amphetamine	Selegiline
Pemoline	
Tricyclic antidepressants	**a_2 agonists**
Amitriptyline	Clonidine
Desimipramine	Guanfacine
Imipramine	
Clomipramine	
Nortriptyline	**Others**
	Atomoxetine
SSRI's	Modafinil
Venlafaxine	Bupropion

From: (Biederman & Faraone, 2005)

Tricyclic antidepressants are considered as second-choice drugs for ADHD but are less effective than psychostimulants and less frequently used because of potential cardiotoxicity. The antihypertensive, a_2-adrenoceptor agonist, clonidine, is used, particularly in ADHD with co-morbid conditions, but is associated with more severe side effects, such as sedation. Some work suggests that clonidine could be useful as an adjunct to stimulant treatment. Buproprion, an antidepressant drug, has few side effects but is mainly prescribed for comorbid ADHD and depression (Elia, Ambrosini, & Rapoport, 1999; Wilens, Biederman, & Spencer, 2002; Kutcher et al., 2004).

4.3 Non-stimulant drug: Atomoxetine

Atomoxetine is a methylphenoxy-benzenepropanamine derivate with antidepesssant activity and is thought to enhance noradrenergic function via selective inhibition of the presynaptic noradrenergic transporter. It is a non-stimulant agent approved by the U.S. Food and Drug administration for the treatment of ADHD in 2002 (Newcorn, Spencer, Biederman, Milton, & Michelson, 2005). Studies done by Bymaster et al. (2002) suggested that atomoxetine administration increases dopamine and noradrenaline in the prefrontal cortex, similarly to methylphenidate, but, unlike methylphenidate, atomoxetine does not increase dopamine in the

striatum or the nucleus accumbens (Newcorn et al., 2005). Atomoxetine is rapidly absorbed from the gastrointestinal tract, reaching peak levels in 1.83 hours in paediatric patients and 1-1.5 hours in adults. Clinical trial data indicate that atomoxetine is safe and well tolerated for the treatment of ADHD; however safety data about long-term use (greater than one year) are unavailable. Adverse events reported in clinical trials were mainly mild to moderate and transient in nature. This compound does not have anticholinergic side-effects and has a safe cardiovascular profile (Biederman & Faraone, 2005). Recommended dosing of atomoxetine is weight based, and dosages should be adjusted to a target dose of 1.2mg/kg/day in children. While current guidelines from the American Academy of Pediatrics recommend stimulants and behaviour modification as first-line therapy for the management of ADHD, atomoxetine offers those patients who have not responded to or cannot tolerate one or more stimulants an alternative treatment option (Corman, Fedutes, & Culley, 2004). There is also some evidence that it may reduce anxiety so that it may be more effective for children with those co-morbidities (Wolraich, 2006).

Combinations of psychotropic medications are used regularly, especially in comorbid situations, and there some are prescribed for very young children. The safety and efficacy of several of the agents prescribed have not been adequately researched in children. There is an urgent need for paediatric psychopharmacology research to inform current prescribing practice (Efron, Hiscock, Sewell, Cranswick, Vance, Tyl et al., 2003).

4.4 Psychostimulant drugs

Central Nervous System (CNS) stimulant medications are the most commonly used psychotropic drugs to treat the symptoms of individuals with ADHD. Psychostimulants have been the drug treatment of choice for children with ADHD since a report was made, 60 years ago, of immediate and often dramatic improvement in the conduct and academic performance of children with behavioural disturbances when they were treated with racemic amphetamine

(Bradley, 1937). Prescriptions for these stimulant medications have increased from less than 2 million in 1991 to over 10 million in 2001, and now it is estimated that approximately 6% of school-aged children are identified and treated with these drugs – about 3 million/year in the United States (National Institute of Mental Health, 2007b; Volkow & Swanson, 2003). Stimulants are structurally similar to the monoaminergic CNS neurotransmitters (Barkley, 2006). The primary mode of action of stimulants is to enhance catecholamine activity in the CNS, probably by increasing the availability of noradrenalin and dopamine in the synaptic cleft (Solanto, 1998). These agents are so named because of their ability to increase the level of activity or arousal of the brain. Even though the psychostimulants are the most widely researched, clinically effective, and commonly prescribed treatments for ADHD, their use in children has become a major controversy.

A 1998 Consensus Development Conference sponsored by the National Institute of Health on ADHD conclude that stimulants were effective in reducing the defining symptoms of ADHD in children in the short term, but indicated the controversy about their use demand serious consideration. They also noted the lack of evidence for their long-term benefit and safety; the considerable risk of treatment; wide variation in prescribing practises among practitioners; and the absence of evidence "regarding the appropriate ADHD diagnostic threshold above the benefits of psychostimulant therapy outweigh the risks" (Greenhill, 2001, p.32). The same year a report by the Council on Scientific Affairs of the American Medical Association was published, in which they concluded that the risk-benefit ratio of stimulant treatment in ADHD must be evaluated and monitoring on an on-going basis in each case (Goldman, Genel, Bezman, & Slanetz, 1998).

Stimulants improve disruptive ADHD behaviours cross-situationally (classroom, lunchroom, playground, and home) when repeatedly administered throughout the day. According to Taylor et al. (2004), stimulants markedly and rapidly reduce the overt clinical

manifestations of restlessness, inattentiveness and impulsiveness; they improve the quality of social interactions, decrease aggression and improve compliance. Psychostimulants also produce significant responses in ADHD children when compared with placebo using tasks that test attention and reaction time. These responses are task and dose dependent. Higher doses of psychostimulants may interfere with cognitive functions (i.e. complex memory tasks). It was also reported that stimulants reduce excessive motor behaviour (Greenhill, 2001).

Table: 4.3 List of stimulants, their trade names, and generic names.

Trade Name	Generic Name	Approved Age (years)
Adderall®	Mix salts: amphetamine, dextroamphetamine	3 and older
Concerta®	methylphenidate (long acting)	6 and older
Cylert®	pemoline	6 and older
Dexedrine®	dextroamphetamine	3 and older
Dexedrine Spansule®	dextroamphetamine	3 and older
Dextrostat®	dextroamphetamine	3 and older
Focalin®	dexmethylphenidate	6 and older
Focalin XR®	dexmethylphenidate (extended release)	6 and older
Metadate ER®	methylphenidate (extended release)	6 and older
Metadate CD®	methylphenidate (extended release)	6 and older
Ritalin®	methylphenidate	6 and older
Ritalin SR®	methylphenidate (extended release)	6 and older
Ritalin LA®	methylphenidate (long acting)	6 and older

From (National Institute of Mental Health, 2007a)

Stimulant medications currently available include short-, intermediate-, and long-acting methylphenidate, and short-, intermediate-, and long-acting dextroamphetamine. Pemoline, a

long-acting stimulant, is rarely used now because of its rare but potentially fatal hepatotoxicity (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). Stimulants do not cure ADHD. Rather, they are an intervention that must be used in conjunction with other psychoeducational interventions as part of an overall treatment plan. Stimulants do not cause increased risk of substance abuse; rather, the risk of substance abuse is conferred by ADHD. Appropriate treatment of ADHD, including the use of stimulants, may actually decrease the future risk of substance use disorders (Barkley, 2006).

Established indications for stimulants include ADHD symptoms in children 6 years of age and older, adolescents, and adults. All three subtypes of ADHD (the Combined, Predominantly Hyperactive-Impulsive, Predominantly Inattentive Types) respond to stimulant therapy (Barkley, 2006). A study done by Zito et al. (1999), found that primary care physicians conducted the majority of ADHD visits involving stimulants alone. The co-prescription of nonstimulant psychotherapeutic drugs was likely to be written by psychiatrists. In summary, there are major differences in physician prescribing practises for the treatment of ADHD when comparing the practise of primary physicians with that of psychiatrists. Psychiatrists prescribe stimulants alone less often, prescribe stimulants in conjunction with other psychotherapeutic agents more often, and prescribe nonstimulant psychotherapeutic agents alone more often to treat youths with ADHD (Zito et al., 1999).

The amphetamines are prohibited in South Africa, therefore, methylphenidate and more recently, atomoxetine are first line treatment of non-comorbid ADHD (South African Medicines Formulary, 2003). At the moment methylphenidate still remains the mainstay for the pharmacological management of ADHD in South Africa (Truter & Kotze, 2005) (see Table 4.1).

4.4.1 Methylphenidate

Methylphenidate (α-Phenyl-2-piperidineacetic acid methyl ester hydrochloride) is a piperadine derivative that is structurally related to amphetamine (Hoffman & Lefkowitz,1996).

It is well known under the trade name Ritalin® and was first introduced in 1956 by the pharmaceutical company Ciba- Geigy, now known as Novartis.

Figure 4.1 Chemical structure of methylphenidate

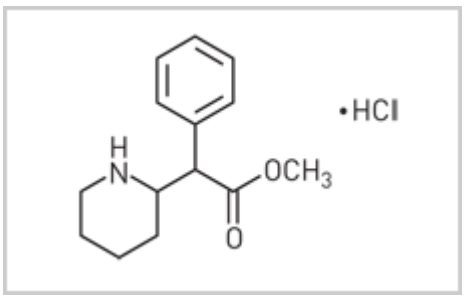

Fig. 4.1 shows the molecular structure of methylphenidate

Methylphenidate is a mild Central Nervous System (CNS) stimulant with more potent effects on mental than on motor activities (Hoffman & Lefkowitz, 1996). Furthermore, it is a potent DAT inhibitor and is first-line medication for non-comorbid ADHD (Fone & Nutt, 2005). It is assumed that methylphenidate ameliorate both hyperactivity and impulsiveness, the two main problems in ADHD (Overtoom, Verbaten, Kemner, Kenemans, van Engeland, Buitelaar et al., 2003). Methylphenidate is the drug that is most widely prescribed, because it has been studied more often and has been promoted more extensively in the drug industry (Barkley, 2006; Elia et al., 1999; Volkow et al., 2002a). A study done by LeFever, Dawson and Morrow (1999) to determine the extent of medication use for ADHD in south-eastern Virginia, illustrated that 90% of the children were using methylphenidate as treatment.

It is the drug of choice and very effective for the treatment of ADHD; it is estimated that 60%-70% of ADHD subjects have favourable responses (Swanson, Cantwell, Lerner, McBurnett, & Hanna, 1991). The methylphenidate preparations include immediate release methylphenidate (Ritalin®), lasting 4 hours on average, long acting methylphenidate (Ritalin LA®, Metadate CD®), lasting 8 hours on average, OROS (Osmotic-release oral system)methylphenidate (Concerta®), lasting 12 hours on average. Dextromethylphenidate

include the immediate release Focalin®, lasting 4 hours on average and Focalin XR®, lasting 8 hours on average (see Table 4.3). A dermal patch formulation of methylphenidate (Daytrana®) has been approved in the USA. This formulation is recommended to last up to10 hours, but its duration of action is dependent on how long the patch is left in place (Wolraich, 2006). Currently only Ritalin® and Concerta® are available in South Africa.

4.4.1.1 Mechanism of action

Cathecholamines, such as dopamine (DA) and nordrenaline (NA), are released from synaptic terminals primarily by a spike-dependant process, achieved via action potential discharge in DA and NA cell bodies. This action potential then propagates to the action terminal to trigger calcium-dependent release of transmitter into the synaptic cleft. The release of neurotransmitter at high concentrations into the synapse then triggers postsynaptic receptors to elicit a response. This process is terminated via a high-capacity reuptake system that rapidly removes the transmitter from the synaptic cleft by taking it back up into the terminal that released the catecholamine. Once taken back into the terminal, the transmitter can then undergo metabolism by exposure to the enzyme monoamine oxidase, or can be repackaged into vesicles for subsequent storage and release (Grace, 2001).

The psychostimulant, methylphenidate (MPH), is the classic treatment for ADHD, yet the mechanisms underlying its therapeutic actions remain unclear (Arnsten & Dudley, 2005). Many researchers assumed that MPH acts by blocking dopamine (DA) transporters (Solanto, 2002), thereby interfering with the uptake process. PET imaging studies of DA transporter occupancy in striatum, done by Volkow et al. (2002a), have shown that MPH acts at this site. However, the striatum contains very few noradrenergic (NA) transporters. Imaging studies are still unable to reliably visualise the low levels of NA and DA actions in the cortex (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998).

The primary mechanism of action of stimulants like MPH, is to enhance the cathecholamine activity in the CNS, probably by increasing the availability of noradrenaline and dopamine in the synaptic cleft (Solanto, 1998). Preclinical studies have shown that methylphenidate blocks the reuptake of dopamine and noradrenaline into the presynaptic neuron (Faraone & Biederman, 1998b). Methylphenidate largely exerts its action by reversibly binding to the presynaptic transporter protein with resultant inhibition of catecholamine reuptake into the presynaptic neuron, increasing concentrations of catecholamines in the extraneuronal space (Volkow, Wang, Fowler, Logan, Franceschi, Maynard et al., 2002b).

Furthermore, Seeman and Madras (1998) suggested that MPH blocks the dopamine transporter (DAT), resulting in increased extracellular DA, activating autoreceptors and leading to a reduction of DA release in response to phasic DA firing. On the other hand, a second hypothesis by Volkow et al. (2005) suggested that the blocked DAT overcomes the inhibitory effects for activation of the autoreceptors, leading to a net effect of DA accumulation in the synapse, with augmentation of DA signals resulting from tonic as well as phasic DA.

Grace (1991) has pointed out that by interfering with DA re-uptake; stimulants allow DA to escape the synaptic cleft thereby depressing subsequent spike-dependent phasic DA release by increasing the tonic stimulation of the autoreceptor. Thus, subcortical down-regulation depends on presnaptic auto-inhibition through autoreceptors (Grace, 1991). This mechanism is similar to that proposed by Seeman and Madras (2002), who pointed out that, stimulants like MPH, raise extracellular levels of DA several-fold, but reduce the extent to which DA is released with nerve impulses, compared with the impulse-associated release in the absence of the drug.

Although there seem to be different hypotheses on the exact mechanism of action of MPH, it all boils down to the fact that MPH exerts its effect via interference with the uptake process of the neurotransmitters, DA and NA.

4.4.1.2 Clinical effects of methylphenidate

Methylphenidate is a mild CNS stimulant; it has a calming effect on humans who have ADHD, reducing impulsive behaviour, and facilitates concentration on work and other tasks. Adults who have ADHD often claim that MPH increases their ability to focus on tasks and organise their lives.

4.4.1.2.1 Effects on behaviour

Stimulants, like methylphenidate have strong effects on various age-inappropriate behaviours that commonly cause impairment on a daily basis for individuals with ADHD. These behaviours often include impulsiveness, disruptiveness, noncompliance, talking out of turn, out-of-seat behaviours, restlessness, and impulsive displays of aggression (Rapport, Stoner, DuPaul, Kelly, Tucker, & Schoeler, 1988; Whalen, Henker, & Granger, 1990). Stimulant dose effects are generally linear and positive on core behavioural problems in ADHD, so that higher doses may be more effective than lower doses (Rapport et al., 1988). However, dose must be individualised for each patient. A meta-analysis of stimulant effects on aggressive behaviour in ADHD, separate from effects on the core symptoms of inattention, impulsiveness, and hyperactivity, found large effect sizes for stimulant treatment on symptoms of both overt and covert aggression (Connor, Glatt, Lopez, Jackson, & Melloni, 2002). This suggests that ADHD may amplify or increase conduct problem behaviours in some children, and that treatment of ADHD symptoms with methylphenidate may reduce vulnerability to antisocial and aggressive behaviours (Connor, Barkley, & Davis, 2000).

4.4.1.2.2 Effects on cognition, learning and academic performance

Numerous studies have found that MPH enhance performance on measures of vigilance, impulse control, fine motor coordination, and reaction time (Barkley, 1998; Rapport, Quinn, DuPaul, Quinn, & Kelly, 1989). Pharmacotherapy with MPH improves cognitive function (i.e. attention and working memory). Positive drug effects have been obtained on measures of short-term memory and learning of paired verbal or nonverbal material. It also improved

school-based academic productivity and accuracy in treated children with ADHD (Barkley, DuPaul, & Connor, 1999; Gillberg, Melander, von Knorring, Janols, Thernlund, Hagglof et al., 1997; Schachar & Tannock, 1993). Solanto (1998) found that at low doses of MPH used in the treatment of ADHD, the drug is without any locomotor–activating effects, and instead reduce movement and impulsiveness and increase cognitive function including sustained attention and working memory.

The administration of low, oral doses of methylphenidate to rats have effects on prefrontal cortex cognitive function similar to those seen in human patients with ADHD (Arnsten & Li, 2005).

4.4.1.2.3 Effects on interpersonal and social relationships

Treatment with MPH has been found to improve the quality of social interactions between children with ADHD and their parents, teachers, and peers (Danforth, Barkley, & Stokes, 1991). In young children MPH increase compliance with parental commands, decrease hostile and negative responses, and enhance responsiveness to the interactions of others (Barkley, 1981; Barkley, 1988; Barkley, 1989).

4.4.1.3 Pharmacokinetics

Methylphenidate is a racemic mixture composed of d-threo and l-threo enantiomers, and it is believed that the d-enantiomer is responsible for the therapeutic effects of MPH (Volkow et al., 2002a). Routes of administration affect the pharmacokinetic properties, which in turn affect the reinforcing effects of stimulant drugs. Two primary pharmacokinetic properties are relevant for relating serum concentration of methylphenidate to its therapeutic use: 1) the time to reach maximum (peak) concentration (Tmax), which is related to the absorption and distribution of the drug, and 2) the time required for the concentration to drop by 50% from the peak level ($T_{½}$), which is related to the metabolism and excretion of the drug. Tmax (rise time) differs dramatically for intravenous and oral dosing, but $T_{½}$, (fall time) is the same for these two routes (Volkow & Swanson, 2003).

MPH readily absorbed after oral administration, has a rapid onset of action (20-60 minutes), and reaches peak concentrations (Tmax) in plasma in about 2 hours. Its bioavailability is low and variable due to extensive first-pass metabolism (Mycek, Harvey, & Champe, 2000; Rang, Dale, Ritter, & Moore, 2003). Volume of distribution (Vd) is 13.1 L/kg and protein binding is 10% - 33%. Its half-life in plasma ($T_{½}$) is 1-3 hours, but concentrations in the brain exceed those in plasma (South African Medicines Formulary, 2003; Barkley, 2006; Parasrampuria, Schoedel, Schuller, Gu, Ciccone, Silber et al., 2007). The main urinary metabolite is a de-esterified product, ritalinic acid, which accounts for 80% of the dose (Hoffman & Lefkowitz, 1996). It is metabolised in the liver and excreted in the urine.

4.4.1.4 Dose

Dosage should be individualised according to the needs and response of the patient (Elia et al., 1999). Low doses of MPH are highly effective and widely prescribed for the treatment of ADHD (Greenhill, 2001). Importantly, the majority of the documented cognitive-enhancing and behavioural-calming actions of low-dose MPH are not paradoxical or unique to ADHD. Instead these actions are apparent in both human and animal subjects. Neurochemically, higher doses of psychostimulants increase the catecholamine efflux widely throughout the brain. In contrast, low, clinically relevant doses of MPH preferentially increase the catecholamine efflux in the prefrontal cortex, with little effect on these neurotransmitters outside this region (Berridge, Devilbiss, Andrzejewski, Arnsten, Kelly, Schmeichel et al., 2006). The administration of low, oral doses of methylphenidate to rats have effects on prefrontal cortex cognitive function similar to those seen in human patients with ADHD (Arnsten & Dudley, 2005; Berridge et al., 2006).

A Dose-Response Study done by Stein et al. (2003) showed consistent results with the report of Barkley, DuPaul and McMurry (1991), that the ADHD subtype moderated the dose-response relationship. ADHD-PI (without hyperactivity), are more likely to do well on lower MPH dosages, whereas children with ADHD-C (subtype with inattention and hyperactive-impulsiveness) and ADHD-HI (subtype with hyperactivity), are likely to require higher dosages

for clinical management. The findings of both Stein et al. (2003) and Barkley et al. (1991) suggest improvement in inattentive symptoms at lower doses relative to doses effective for treating children with both hyperactivity and impulsiveness symptoms.

The effective doses of MPH are narrow and cannot be predicted by the patient's age, body mass, level of hyperactivity, or measurements of plasma drug concentrations (Barkley et al., 1991), however there are guidelines available. Therefore, dose must be adjusted in each patient to obtain the maximal benefit, and in a given patient the efficacy of a particular dose in treating different types of behaviour, varies. For example, academic performance may improve at a lower dose, but higher doses may be needed to improve motor restlessness and attention (Barkley et al., 1991; Rapport, Denney, DuPaul, & Gardner, 1994). The initial dose of standard MPH is 2.5-5 mg once daily. The dose may be increased every three to five days whilst adverse effects, behaviour, and academic function are assessed. Once the lowest effective dose is determined, the duration of behavioural efficacy can be determined and used to assess the need for and timing of additional doses. Additional daily doses of MPH should be similar to the first dose (Elia et al., 1999). The average clinically effective dose range in children is 0.3-1.0mg/kg/day (Greenhill, Abikoff, Arnold, Cantwell, Conners, Elliott et al., 1996; Solanto, 1998). The immediate-release MPH preparations require up to 3 doses per day, whereas the intermediate-release preparations (Ritalin LA®) require one to two doses per day, and the newer once daily formulation (Concerta®) duration is 10-14 hours (Barkley, 2006).

It is clear that MPH require careful titration and medical monitoring to obtain the optimum balance between efficacy and side effect profiles (Kutcher et al., 2004).

4.4.1.5 Side Effects

Stimulants are generally considered safe medications, with few contraindications to their use. Most adverse effects of methylphenidate are minor and are usually related to the dose of the medication being taken. The most common side effects are insomnia, decreased appetite,

headache, abdominal pain, anxiety, and irritability or proneness to crying. With the exception of decreased appetite, the other side effects have not been demonstrated within the mild to moderate dose ranges (i.e. 0.3-0.5mg/kg) (Barkley, 2006; Kaplan & Sadock, 1998; Stein et al., 2003; Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). Decreased appetite is reported in approximately 80% of children, but is often mild and limited to daytime eating, and intake increased in the evening (Elia et al., 1999). A Dose-Response Study done by Stein at al. 2003 demonstrated that, younger children and those who weighed less seemed more prone to side effects. Consequently, clinicians should be alert to greater risk of stimulant side effects in younger children with lower body mass. In children with a history of motor tics, some caution must be used; in some cases MPH may cause an exacerbation of the tic disorder (Biederman & Faraone, 2005; Kaplan & Sadock, 1998).

Small negative effects on height and weight gain have been documented during the initial 1-2 years of medication use, but it remains unclear whether these continue beyond adolescence (Barkley, 2006; Kaplan & Sadock, 1998; Klein, Landa, Mattes, & Klein, 1988; Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001).

Cardiovascular effects, limited to variable increases in heart rate (HR) and blood pressure (BP), are most evident at rest and diminish with exertion (Klein & Bessler, 1992). Negrao and colleagues (2009) confirms previous findings that MPH causes an increase in HR as well as increases in both systolic and diastolic BP, but found no change in cardiac depolarisation and repolarisation duration and homogeneity. Recent concern has been raised about the use of stimulants, especially amphetamines, in children with underlying and often silent cardiac anomalies. A total of 12 cases of sudden death (in the period 1999-2003), in children and adolescents receiving amphetamine stimulants, are known to the US Food and Drug Administration (FDA). Of the 12 cases, five occurred in patient with underlying structural heart defects, including abnormal arteries, abnormal cardiac valves, hypertrophic sub-aortic stenosis,

and anomalous origin of the cardiac arteries. These are all conditions that increase risk for sudden death regardless of stimulant use. The Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration (FDA) voted in February 2006 to recommend a black box warning describing the cardiovascular risk of stimulant drugs to treat ADHD (Barkley, 2006; Winterstein, Gerhard, Shuster, Johnson, Zito, & Saidi, 2007).

The existing data do suggest that patients with underlying heart defects (often clinically silent) might be at increased risk for sudden death. Clinicians should therefore, take a careful cardiac history in patients and exclude those children with ADHD and known heart defects from stimulant treatment (Barkley, 2006).

Children who receive too high a dose or who are overly sensitive may become overfocused on the medication or appear dull or overly restricted. Many times this side-effect can be addressed by lowering the dose. The best dose of medication for a given child is the one that leads to optimal effects with minimal side effects (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001).

4.4.1.6 Prescriber information

In the treatment of ADHD, it is important for the prescribing clinician to be aware of the high comorbidity rate between ADHD and depression, anxiety, learning disabilities, tic disorders, and CD/ODD. The possibility of comorbid conditions needs to be considered in treatment planning for an individual with ADHD (Barkley, 2006).

The clinician should periodically provide a systematic follow up for the child with ADHD. It is recommended that monitoring should be directed to target outcomes and adverse effects, with information gathered from parents, teachers, and the child (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). Furthermore, should clinicians continue to monitor growth in children treated with stimulants (Biederman & Faraone, 2005). It is especially recommended to monitor growth in children

(both height and weight) where doses of methylphenidate exceed 30mg/day for prolonged periods (South African Medicines Formulary, 2003).

Monitoring should include recording blood pressure and pulse (at each adjustment of the dose, then every six months), height, weight, and appetite (6 monthly) with a maintenance of a growth chart; tics, depression, irritability, lack of spontaneity, withdrawal, and excessive perseveration (at every visit) (Taylor et al., 1998).

Despite their efficacy, the short duration of action of methylphenidate requires multiple daily doses or a longer acting preparation for most of the children, to ensure adequate coverage during and after the school day. Also, the last dose must be administered at a time when it will not adversely affect sleep. The complexity of dosing schedules can cause problems with compliance, especially in school children with the disorder (Swanson, 2003).

Research has shown that the positive effects of MPH cease down as soon as the medication is stopped (Abikoff, Hechtman, Klein, Weiss, Fleiss, Etcovich et al., 2004). When psychostimulant medication like methylphenidate, is stopped abruptly, withdrawal reactions may occur. Then, 4-12 hours after the last dose, 'rebound' symptoms of ADHD including increased activity, excitability, irritability and insomnia may occur. In the longer term depression and extreme fatigue may be seen. It is therefore advisable not to do the so-called 'drug holidays', where the medication is stopped over weekends and during school holidays. If the medication needs to be discontinued, doses should be reduced gradually, approximately 25% weekly. Treatment breaks, 'drug holidays' , may be considered if there is an identifiable need (e.g. significant adverse effects on the youngsters' rate of growth in height and/or weight) but these should be carefully timed (e.g. to avoid disruption at important times during the child's schooling); otherwise they are not generally recommended (Kutcher et al., 2004). In the South African Medicine Formulary (2003) medication-free periods (e.g. over weekends or during school holidays) are recommended to determine the need for continued therapy.

Spencer and the rest of the Concerta Study Group (2006) came to the conclusion that the effects of prolonged OROS MPH therapy on growth were clinically insignificant and limited to slight decreases in weight during the first months of therapy. Furthermore, the 'drug holidays' did not reduce any impact on growth and are thus of questionable utility for limiting potential effects of treatment on growth (Spencer, Faraone, Biederman, Lerner, Cooper, & Zimmerman, 2006). However, in a study done in Porto Alegre, Brazil, Martins and colleagues (2004) found that weekend holidays during MPH administration reduce the side effects of insomnia and appetite suppression without a significant increase in symptoms, either on weekends or in the first school day after them (Martins, Tramontina, Polanczyk, Eizirik, Swanson, & Rohde, 2004).

Stimulants are contraindicated in several circumstances, most of them uncommon in childhood: schizophrenia, severe depression, hyperthyroidism, cardiac arrhythmias, moderate to severe hypertension, angina pectoris, glaucoma, previous hypersensitivity, or concomitant use of monoamine oxidase (MAO) inhibitors. Caution is advised in patients with motor tics, patients with known drug dependence or history of drug dependence or alcoholism, pregnancy and breastfeeding, anorexia nervosa, or a history of suicidal tendency. People with pre-existing cardiac abnormalities may be at special risk. Clinicians should also be alert to the greater risk of side effects in younger children with/and lower body mass. Strategies in dealing with side effects include monitoring, dose adjustment and titration of the stimulant, switching medication, and adjunctive pharmacotherapy to treat the side effects (Taylor et al., 2004).

Treatment is likely to be necessary for several years. The younger the child, the longer the treatment is likely to be required. Some individuals will benefit from treatment into adulthood (Kutcher et al., 2004). When the selected management of a child with ADHD has not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan and presence of co-existing conditions (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001).

4.4.1.7 Results and outcomes of methylphenidate therapy in ADHD

According to Whalen and Henker (1991), Elia et al. (1999) and Kutcher et al. (2004) methylphenidate is successfully used in ADHD, and effectively reduces hyperactivity, impulsiveness, and inattention in 60% - 90% of children diagnosed with ADHD. These studies also documented that the stimulant medication improved the children's ability to follow rules and decreases emotional overreactivity, thereby leading to improved relationships with peers and parents (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). Improved social skills and school performance have also been documented by (Swanson, McBurnett, Christian, & Wigal, 1995). However, the optimal dosages have not yet been established and clinical anecdotal descriptions report some children as becoming overfocused, cognitively constricted, introverted, and "zombie-like" on higher doses (Swanson et al., 1991). A study done by Tannock and Schachar (1992) has shown opposing effects of a high dose level at different test sessions with children making more perseverative errors in the first session and fewer in the second, while another study by this same group reported that despite clinical observations of overfocusing, measured attention performance was not affected by a high dose (Tannock, Schachar, Carr, & Logan, 1989).

In the MTA follow-up, exploratory naturalistic analyses suggest that consistent use of stimulant medication was associated with maintenance of effectiveness although there was continued mild growth suppression. At the first (24 month) follow-up, the absolute ratings of symptom severity reveal that all four groups still had lower ratings of ADHD symptoms than at baseline, providing evidence of some persistence of the effects of the treatments (MTA Cooperative Group, 2004).

4.5 Conclusion

ADHD is a chronic disorder, and the affected children are a heterogeneous group, with a range of behavioural, cognitive, and social deficits. In some of these children, drug therapy is

insufficient because of persistent symptoms or coexisting conditions. Integrated treatment (combinations of drug therapy and psychosocial interventions) is being advocated. Strategies (both psychosocial and pharmacotherapeutic) need to be developed to prevent conduct disorder and delinquency in young children with ADHD (Elia et al., 1999). Optimal outcomes may be promoted by ameliorating children's social functioning, diminishing aggression, and improving family situations as early as possible (Kaplan & Sadock, 1998). Results of a study done by Zachor, Roberts, Hodgens, Isaacs, and Merrick (2006) emphasise that the benefits of stimulant medications outweigh the growth-related side effects over time. Close growth monitoring of individuals is still required, but growth changes are not shown to be clinically significant for a diverse group of children treated for ADHD over 3 years.

There is considerable variation between European countries in the place and acceptance of stimulant medication in the treatment of ADHD - this may be due to concerns about the potential for abuse with psychostimulants and their perceived overprescription (Buitelaar et al., 2003). The psychostimulant methylphenidate in its various formulations is currently the first choice of treatment. The evidence for their efficacy in the treatment of ADHD in children between 5 and 15 years is based on the many controlled trials showing clinically meaningful benefit in about 80% of the patients. Although it has been shown that efficacy persists if treatment is maintained for 1 year or longer (Gillberg et al., 1997), reliable data on eventual outcome from very long-term follow-up are lacking.

Stimulants do not cure ADHD; they are an intervention that must be used in conjunction with other psychoeducational interventions as part of an overall treatment plan. They do not cause increased risk of substance abuse; rather, the risk of substance abuse is conferred by the ADHD. Correct diagnosis and appropriate treatment of ADHD, including the use of stimulants, may actually decrease the risk of future substance disorders (Barkley, 2006).

Chapter 5

PROBLEM STATEMENT AND HYPOTHESES

5.1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioural disorder of childhood. The core symptoms of ADHD include inattention, hyperactivity, and impulsiveness. ADHD affects an estimated 4%-12% of school-aged children in the United States (American Academy of Pediatrics, 2000), and is also prevalent on the African continent (Kashala, Tylleskar, Elgen, Kayembe, & Sommerfelt, 2005; Meyer et al., 2004; Ofovwe, Ofovwe, & Meyer, 2006). ADHD is diagnosed by the presence, in two or more settings, of at least 6 of 8 characteristics indicating hyperactivity, impulsiveness, and inattention according to the DSM IV-TR (American Psychiatric Association, 2000).

Symptoms of inattention include poor attention to details, limited attention span during tasks or distractibility and failure to finish assigned activities. Symptoms of hyperactivity/impulsiveness include fidgeting, extreme restlessness, excessive motor activity, difficulty awaiting turns and tendency to blurt out answers or interrupt others. In order to meet diagnostic criteria, the symptoms of ADHD must cause clinically significant impairment in school and at home (American Psychiatric Association, 2000). When children posses the above attributes to a degree that is highly deviant for their developmental level and sufficient to create impairments in major life activities, they may be diagnosed as having ADHD. Their problematic behaviour is thought to arise early in childhood, often in preschool years, and to persist over development in most cases. While clinical description has focused on inattentive, impulsive, and overactive behaviour, theoretical work gives increasing weight to problems with responses in inhibition, self-regulation, and the related domain of executive functioning (Barkley, 2003a).

Central nervous system (CNS) stimulant medications are the most frequently psychotropic drugs to treat the symptoms of individuals with Attention-Deficit/Hyperactivity

Disorder (ADHD). Stimulants have demonstrated effectiveness across a wide range of patients, including preschoolers, school-age children, adolescents, and adults with ADHD. Despite the success of medication management of ADHD in school settings, important roles for psycho-educational interventions remain (Barkley, 2006).

5.2 Aim of the study

The main focus of this research project was to look into all the factors that influenced the diagnosis, prescribing and usage of methylphenidate for ADHD. All the participants were primary school children in the Polokwane area of the Limpopo Province.

5.3 Research Hypotheses

5.3.1 Research hypothesis 1

The diagnosis of ADHD in children is not done by fully qualified experts in the field, according to the criteria as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV).

Specific hypothesis derived from Research Hypothesis 1

1.1 Not all children referred for methylphenidate medication do meet the criteria for ADHD.

1.2 Not all involved role players suggesting that methylphenidate should be prescribed, have the necessary professional qualifications/expertise.

1.3 Not all clinicians prescribing methylphenidate are specialists in neuropaediatrics and/or neuropsychiatry.

5.3.2 Research hypothesis 2

In most cases, the correct procedure of prescribing, monitoring and usage of methylphenidate is not adhered to. No follow-up examinations are made.

Specific hypothesis derived from Research Hypothesis 2

2.1 Body mass was not taken in account when methylphenidate was prescribed.

2.2 The age of the patient was not considered in most cases.

2.3 The ADHD symptomatology (hyperactivity-impulsiveness and inattention) was not taken in account when prescribing methylphenidate.

2.4 There was no definite monitoring of patients before and while on methylphenidate.

5.3.3 Research hypothesis 3

There will be a decrease in the severity in symptoms of ADHD, both inattention and hyperactivity/impulsiveness, after medication with methylphenidate, according to the DSM-IV criteria.

A description of the methods employed to accept or reject the hypothesis formulated, will be supplied in the next chapter.

Chapter 6

RESEARCH METHODOLOGY

6.1 Introduction

In recent years, ADHD has been a subject of great public attention and concern. Children with ADHD – one of the most common of the psychiatric disorders that appear in childhood - cannot stay focused on a task, cannot sit still, act without thinking, and rarely finish anything. If untreated, the disorder can have long-term effects on a child's ability to make friends or to do well at school. Effective treatment depends on appropriate diagnosis of ADHD. A comprehensive medical evaluation of the child must be conducted to establish a correct diagnosis of ADHD and to rule out other potential causes of the symptoms. ADHD can be reliably diagnosed, and treated, when appropriate guidelines are used (National Institute of Mental Health, 2001).

The purpose of this study was to determine all the factors that influenced the prescribing and use of methylphenidate for ADHD in primary school children in Polokwane.
The most important objectives of this study were:

- To determine the evaluations performed before methylphenidate therapy was initiated.
- To record the steps taken to confirm the diagnosis and classification of ADHD.
- To determine gender differences in the subtypes.
- To determine the profession of the initial recommender of methylphenidate therapy.
- To determine the medical qualification of the prescriber of methylphenidate.
- To determine if the correct procedures were followed before prescribing methylphenidate.
- To determine prescribing patterns in different age groups and subtypes i.e. dosages.
- To determine if the patients were monitored while on methylphenidate therapy.
- To determine the prevalence and detail of drug holidays in patients on methylphenidate.

6.2 Method

6.2.1 Research design and setting

This is a quantitative study. The research design included descriptive studies, comparison studies (quasi-experimental design) and correlations to determine all the factors involved.

The study was conducted at various primary schools. All the schools were situated in Polokwane in the Limpopo Province of South Africa. The parents of the subjects were interviewed and completed a questionnaire. The questionnaire was compiled by the researcher.

6.2.2 Sample

The sample was drawn from various primary schools situated in Polokwane in the Limpopo Province. Written permission was obtained from the Department of Education, Limpopo Province, as well as the principals of various schools. Possible candidates were obtained by inviting parents with ADHD children to participate in the study. The invitation to participate was "advertised" in the various schools' weekly newsletters. Sampling was done this way as it was easy accessible and the costs involved was fairly low. The only criterion for this study was that the children needed to be already clinically diagnosed with ADHD and/or on methylphenidate therapy. A sample of 50 (N=50) clinically diagnosed children was obtained from the community.

The research topic was also introduced to delegates attending the mini ADHD conference, held in Polokwane, 6-7 September 2004. The speaker was Dr. John F. Taylor, an expert on ADHD and related conditions. This mini-conference was organised by ADHASA (Attention-Deficit/Hyperactivity Disorder Association of South-Africa). Most delegates were parents of children with ADHD, and had enthusiastically volunteered to be part of a study like this.

Table 6.1 Sample characteristics

Gender	Age group (years)	N	MPH	Stratt	Non
Boys	5 - 9	18	13	1	4
	10 - 13	17	13	2	2
Girls	4 - 9	7	4		3
	10 - 13	8	8		

6.3 Data collection methods and procedure

A sample of 50 children, clinically diagnosed with ADHD of both genders was used for this study. The provincial Department of Education granted written permission to conduct the research among the primary school children. The Research, Ethics and Publication Committee, Faculty of Medicine of the University of Limpopo - Medunsa Campus, approved the study. A letter was obtained from the Research, Ethics and Publication Committee, outlining the aim of the study which was presented to the respective school principals. Parents or guardians and school principals were given a letter describing the study and parents/guardians were asked to complete a consent form. The purpose of the study was explained verbally and in writing to the participants. Parents/guardians were ensured that the researcher will respect their privacy and that their names will not be revealed in the research reports emanating from the study.

The researcher obtained all information by means of semi-structured interviews with the parents/guardians of the respondents. The interviews included pre-determined questions that were in the form of a questionnaire. It was presented to all the interviewees systematically and constantly. The questions were formulated according to Barkley's semi-structured interview (Barkley & Murphy, 1998). The questionnaire comprised of 4 sections.

- Section A requested biographical and medical data from the respondents (Barkley & Murphy, 1998).
- Section B focused on the DSM-IV-TR criteria for diagnosis of ADHD - DBD questionnaire, (Meyer et al., 2004).
- Section C was on management, monitoring and treatment of this condition.
- Section D was a repetition of section B, but after methylphenidate therapy was initiated - DBD questionnaire, (Meyer et al., 2004).

The Disruptive Behavior Rating Scale (DBD) (Meyer et al., 2004) formed part of the researcher's questionnaire. The Disruptive Behavior Disorders rating scale (DBD) (Pelham, Jr., Gnagy, Greenslade, & Milich, 1992; Pillow, Pelham, Jr., Hoza, Molina, & Stultz, 1998), based on the DSM-IV (American Psychiatric Association, 2000), had been translated, standardised and norms been established for all the language groups in the Limpopo Province and adjacent areas, by Meyer et al. (2004).

The Cronbach's alpha reliability test was performed on the questionnaire. An a coefficient of 0.7 is the cut-off value for being acceptable (Bland & Altman, 1997; Santos, 1999). A value of 0.933 (Section B) and 0.959 (Section D) was obtained, with the conclusion that this questionnaire was highly reliable.

The researcher conducted all the questionnaire interviews. The researcher is registered with the South African Pharmacy Council.

6.4 Method of data analysis

Data were analysed by means of the Statistica 8 for Windows programme (StatSoft, 2008).

Statistical analysis of Hypothesis 1: Descriptive statistics were used to show the distribution of ADHD subtypes after re-evaluation of the sample, the profession of the

recommender of methylphenidate therapy, and the medical qualification of the initial prescriber of methylphenidate.

Statistical analysis of Hypothesis 2: A correlation study was carried out to show the relationship between age, body mass, ADHD symptoms and the methylphenidate dose. Analysis of Variance (ANOVA) was employed to investigate possible differences in the methylphenidate dose between the different ADHD subtypes. Descriptive statistics were applied to demonstrate the presence of treatment breaks, 'drug holidays', the monitoring of body mass and height and heart by clinicians.

Statistical analysis of Hypothesis 3: Descriptive statistics were used to illustrate the distribution of subtypes after methylphenidate therapy was initiated. *t*-Tests were employed to show before and after symptoms of ADHD, and therefore to establish possible improvements in ADHD symptoms after initiating methylphenidate therapy.

Chapter 7

RESEARCH RESULTS

7.1 Introduction

The aim of the study was to determine all the factors that influenced the prescribing and usage of methylphenidate in children with Attention-Deficit/Hyperactivity Disorder in primary schools situated in the Polokwane area in the Limpopo Province of South Africa.

7.2 Results of the Study

A: Demographic results

B: Testing of Hypotheses

The results for the analyses of the questionnaires are presented as follows:

- Descriptive statistics (in table and graph form)
- Inferential statistics; ANOVA, *t*-tests, and correlations (Pearson's moment correlation coefficient *r*) to show between-group differences and relationships.

A: Demographic results

Table 7.1 Age, Inattention- and Hyperactive-impulsive scores of the sample

Gender	N	Age (years)	Inatt (DBD scores)	H/I (DBD scores)
Boys	35	9.371 ± 2.250	20.77 ± 5.610	17.143 ± 6.486
Girls	15	9.133 ± 2.167	18.933 ± 4.667	16.266 ± 7.620

There were no significant statistical difference between the ages and ADHD symptoms for both genders - as determined after re-evaluation by the researcher with the standardised DBD questionnaire.

Figure 7.1 Gender Distribution of the sample

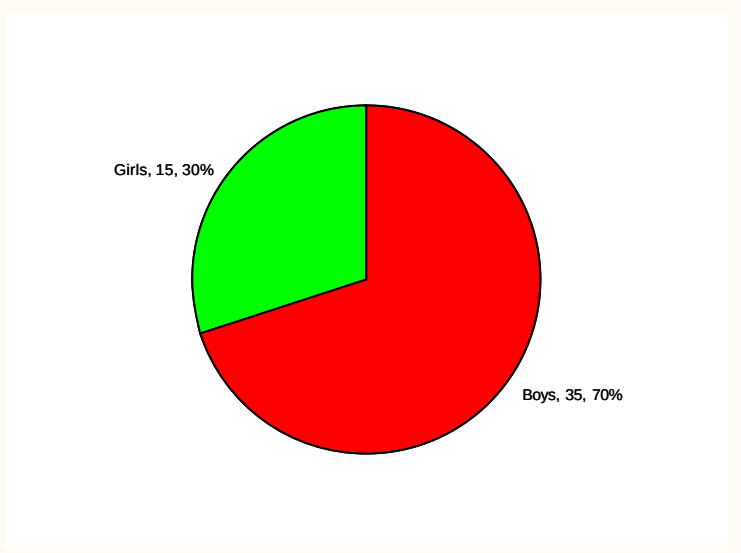

Figure 7.1 shows that the gender distribution of the sample corresponds with the literature. Boys are two to three times more likely to have behaviours consistent with ADHD, than girls. (LeFever et al., 1999; American Academy of Pediatrics, 2000; Barkley, 2006)

Figure 7.2 The age distribution of the sample

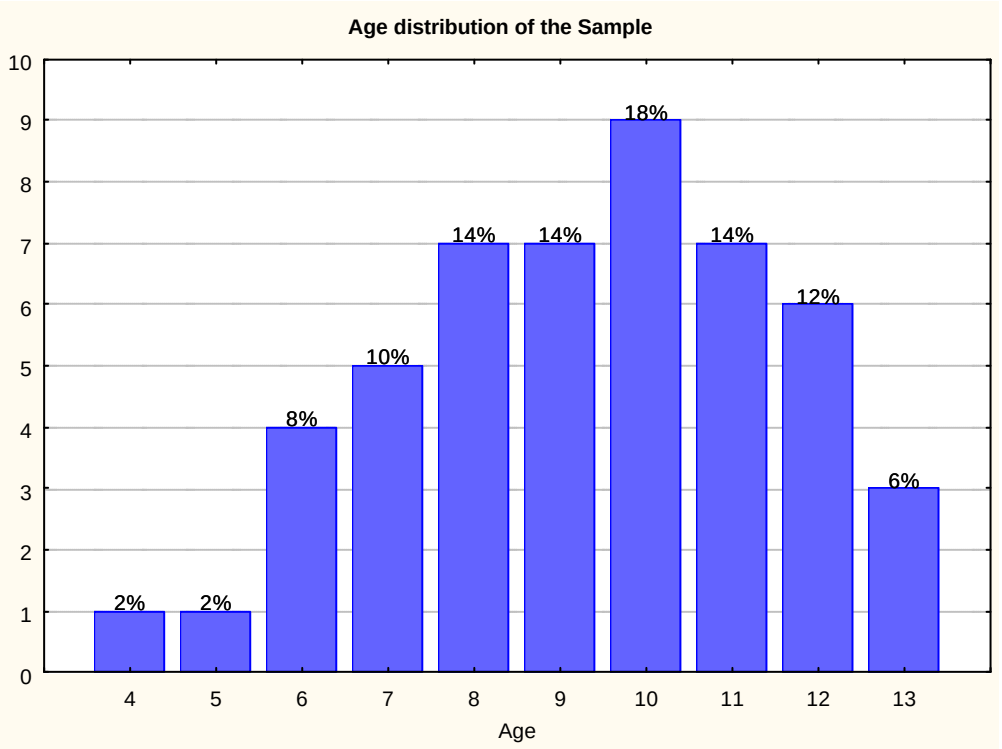

Figure 7.2 shows the distribution of age in the sample. The highest prevalence of ADHD in this sample is amongst the age group 8-12 years.

Tables 7.2 and 7.3 show that there were no effects of age and gender on the inattention and hyperactivity/impulsive scores of the sample before medication with methylphenidate.

Table 7.2 ANOVA of the results of the Inattention scores before medication

	DF	F	*p*
Age Group	1, 46	0.0061	0.938
Gender	1, 46	0.5629	0.457
Age Group x Gender	1, 46	0.5062	0.480

Table 7.3 ANOVA of the results of the Hyperactive/Impulsive scores before medication

	DF	F	*p*
Age Group	1, 46	0.1266	0.724
Gender	1, 46	0.0419	0.839
Age Group x Gender	1, 46	0.1266	0.724

There was no effect of age and gender, neither main nor interacting on the inattention and hyperactive/impulsive scores of the sample before medication.

Figure 7.3 Distribution of the medication used by the sample

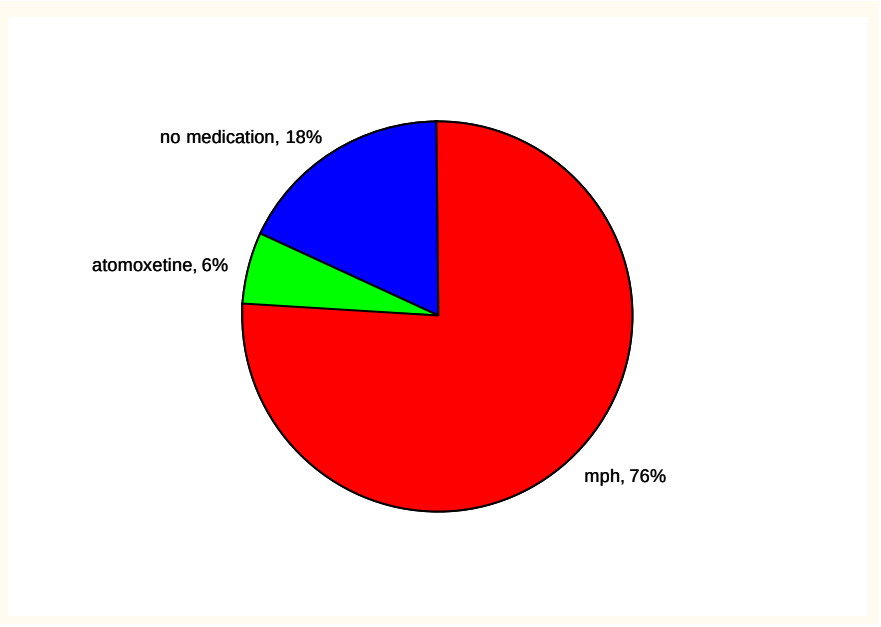

Figure 7.3 shows that 76% of the clinically diagnosed sample was on methylphenidate (mph) therapy, 6% on atomoxetine therapy and 18% did not use any medication for ADHD symptoms. (N=50)

B: Testing of Hypotheses

7.2.1 Hypothesis 1

The diagnosis of ADHD in children is not done by fully qualified experts in the field, according to the criteria as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV).

After re-evaluating the sample, it transpired that not all the children did comply with the DSM-IV criteria for ADHD symptoms (see Figure 7.4)

Figure 7.4 Distribution of ADHD subtypes before medication

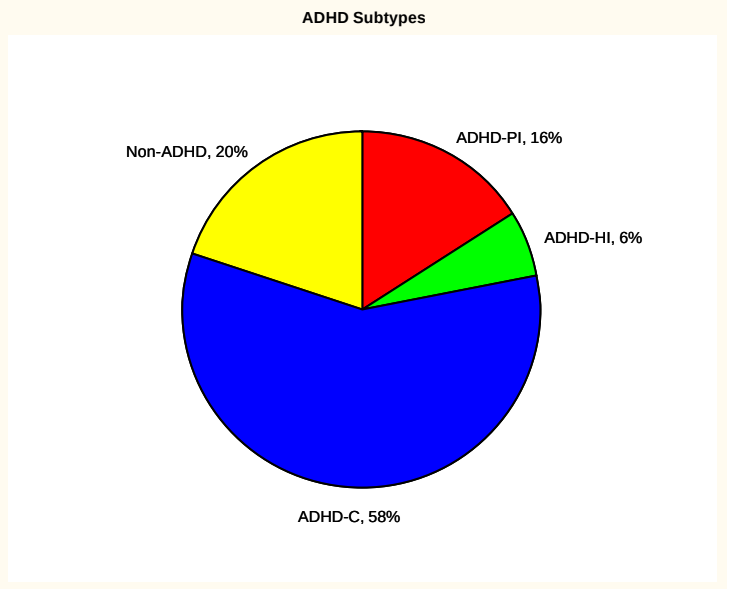

Figure 7.4 shows that 20% of the clinically diagnosed by the clinicians ADHD children did not meet the DSM-IV-TR criteria, after re-evaluation (as determined by the DBD questionnaire) therefore they were not ADHD – misdiagnosed.

Figure 7.5 Sources of recommenders for prescribing methylphenidate to the clinically diagnosed ADHD children in the sample

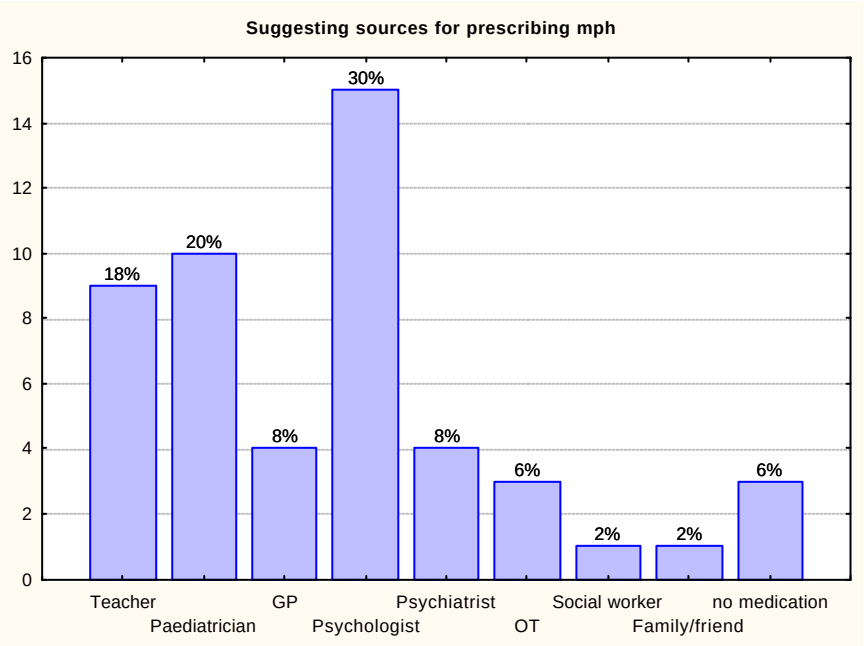

Figure 7.5 shows that too many people without the necessary appropriate knowledge of ADHD (e.g. teacher, occupational therapist (OT), social worker), suggested that the candidates should use methylphenidate. No proper protocol or guidelines were followed.

Figure 7.6 Medical qualification of the prescriber of methylphenidate

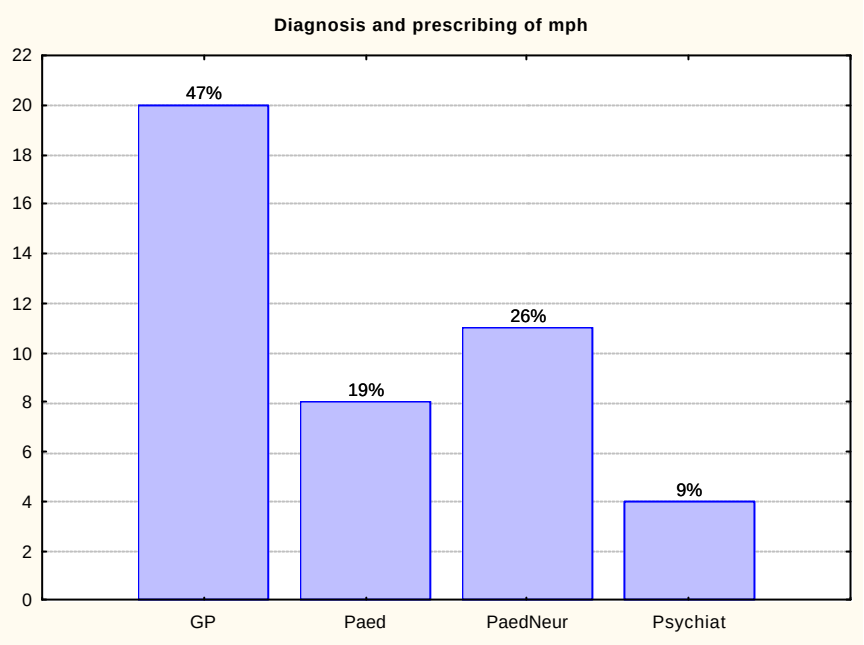

Figure 7.6 shows that the final diagnosis and prescribing of methylphenidate was overwhelmingly done by General Practitioners (GP) (47%). The fact that 20% of the clinically diagnosed participants were Non-ADHD (see Fig. 7.4), can probably account for the lack of specialised knowledge of the main prescriber about the disorder.

7.2.2 Hypothesis 2

The correct procedure of prescribing, monitoring and usage of methylphenidate is not adhered to. No follow-up examinations are made.

Table 7.4 Correlations: (r-value) between MPH dose, age, body mass, inattentive and hyperactive-impulsive scores

	MPH dose	***p***
Age (yrs)	*r* = 0.248	n/s
Body mass (kg)	*r* = 0.311	n/s
Inatt scores	*r* = 0.178	n/s
H/I scores	*r* = 0.223	n/s

There was no correlation between MPH dose and age, body mass, inattentive and hyperactive-impulsive scores.

Figure 7.7 Relationship between body mass and the methylphenidate dose

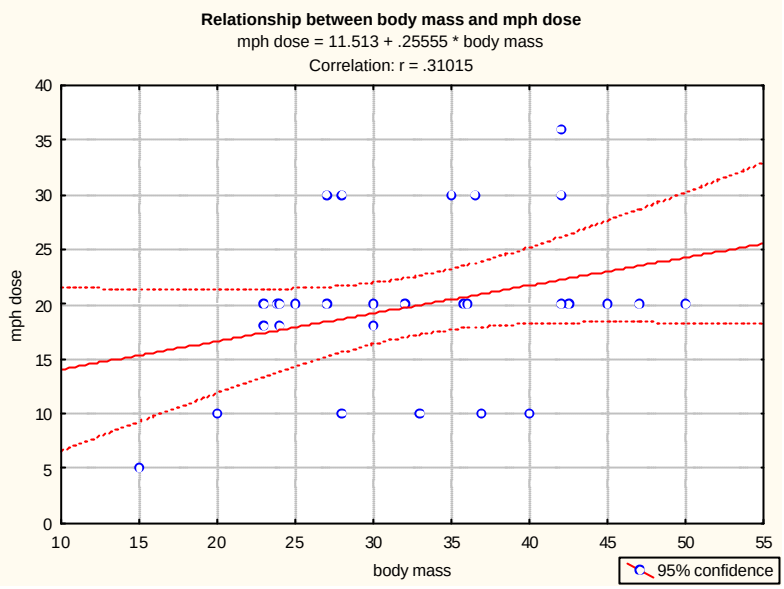

Figure 7.7 demonstrates that there was no significant relationship (p=0.102) between the body mass and the methylphenidate dose prescribed. A child with body mass of 50kg received the same dosage of methylphenidate as a child with the body mass of 23kg, i.e. 20mg/day. Another child with body mass of 40kg used 10mg/day, far less than a child with body mass of 26kg, i.e. 30mg/day. Body mass was not taken in account when methylphenidate was prescribed. (N=38)

Table 7.5 Weight of ADHD subtypes

Subtype	N	Means
ADHD-PI	7	35.21 ± 9.49
ADHD-HI	2	30.50 ± 6.36
ADHD-C	20	32.14 ± 13.72
Non-ADHD	8	36.16 ± 7.26
All Groups	37	33.50 ± 11.38

There were no significant differences between the body mass of the ADHD subtypes (p = 0.81). N = 37 because not all candidates' weights were known.

Table 7.6 Comparison between clinically effective dose range and actual dosages received per certain body mass

Body mass (kg)	Clinically effective dose range 0.3 - 0.5mg/kg/day	Maximum dose 1mg/kg/day	Actual prescribed dose range for body weight (mg)
15	4.5 - 7.5	15	5
20	6 - 10	20	10
26	7.8 - 13	26	10 - 30
30	10 - 15	30	18 - 20
36	10.8 - 18	36	10 - 30
40	12 - 20	40	10
43	12.9 - 21.5	43	20 - 36
45	13.5 - 22.5	45	20
50	15 - 25	50	20

For a dose of e.g. 20mg the body mass varied from 26-50 kg, which give the indication that body mass was not taken in account when MPH was prescribed.

Figure 7.8 Relationship between age and the methylphenidate dose

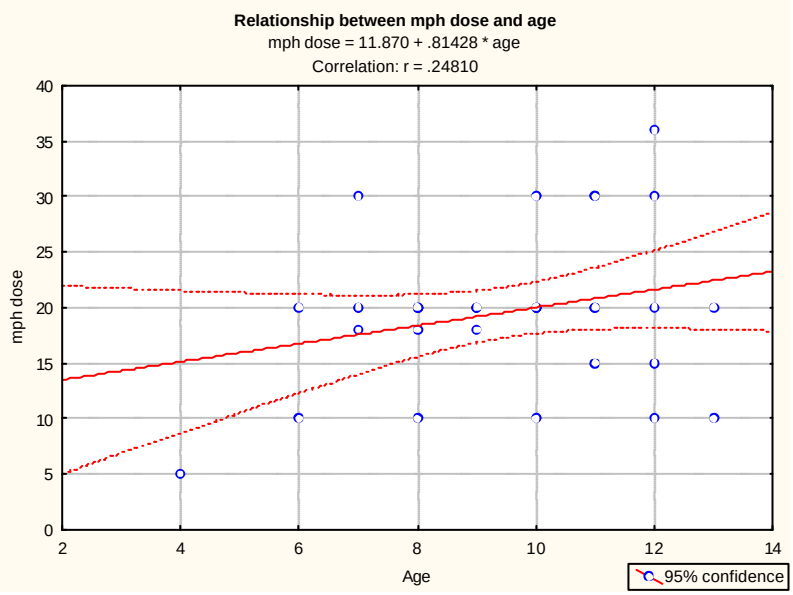

Figure 7.8 shows that there was no significant relationship (p=0.139) between the age of the child and the methylphenidate dose. Doses of methylphenidate for 12 year old children varied from 10-36mg/day. For a dose of 20mg the children's ages varied from 6-13 years. In most cases, the age of the patient was not considered when prescribing methylphenidate. (N=38)

Table 7.7 Range of daily doses for different ages of ADHD children

Age in years	5	6	7	8	9	10	11	12	13
Average daily dose (mg)	5	10 - 20	18 - 30	10 - 20	18 - 20	10 - 30	15 - 30	10 - 36	10 - 20

Table 7.7 shows that children with ages 6, 8 and 13 were prescribed the same range of daily methylphenidate dose.

Figure 7.9 Relationship between inattention symptoms before medication and the methylphenidate dose

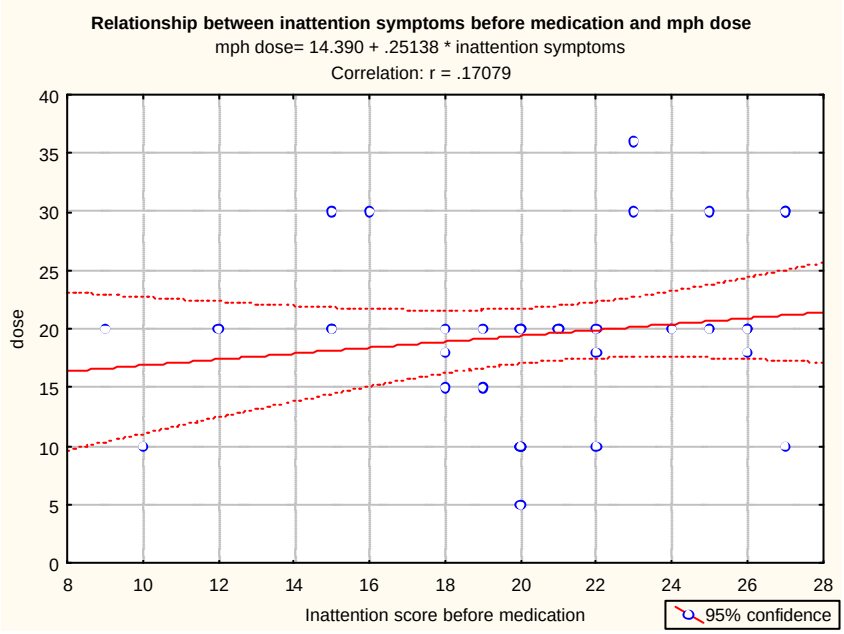

Figure 7.9 indicates that there was no significant correlation (p=0.312) between the inattention symptoms before medication and the daily dosage of methylphenidate. A child with a score of 9 received the same dose as a child with a score of 26, i.e. 20mg/day. With a score of 20, children's dosages varied from 5-20mg/day. (N=38)

Figure 7.10 Relationship between hyperactive-impulsive symptoms before medication and the methylphenidate dose

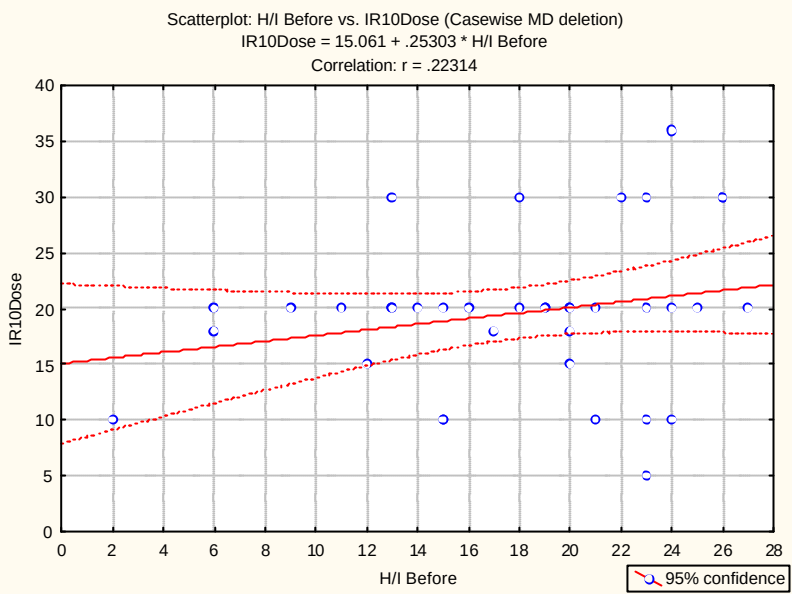

Figure 7.10 points out that there was no significant correlation (p=0.184) between the hyperactive-impulsive symptoms before medication and the daily dosage of methylphenidate. A child with a score of 2 received the same dose as a child with a score of 24, i.e. 10mg/day. With a score of 23, children's dosages varied from 5-30mg/day. (N=38)

Figure 7.11 Differences between the ADHD subtypes and the daily methylphenidate dose

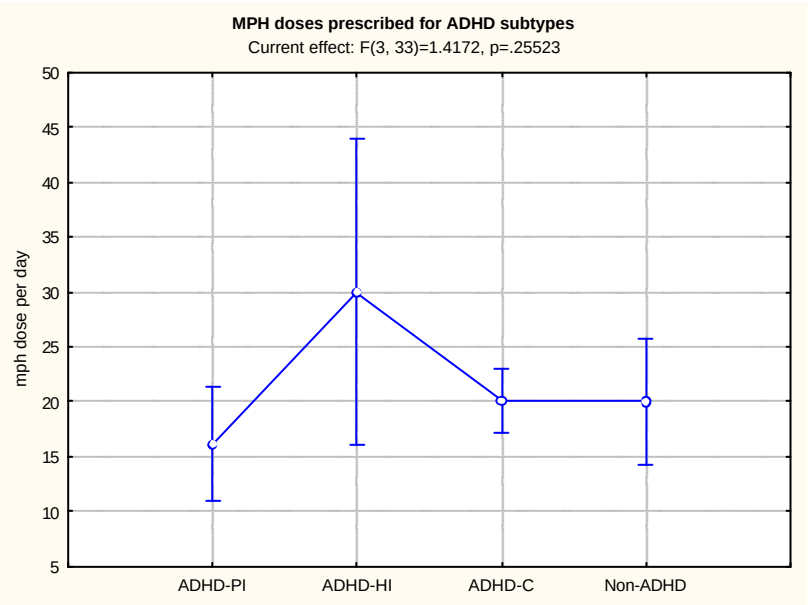

Figure 7.11 illustrates that the subtype of the ADHD child did not influence the prescriber when deciding the candidate's dose. The Non-ADHD children (children who do not qualify to be classified as ADHD according to DSM IV score), received the same daily dosage as the ADHD-Combined subtype. (N=38)

Figures 7.9, 7.10, and 7.11 show clearly, that the ADHD symptomatology (hyperactivity-impulsiveness and inattention) was not taken in account when prescribing methylphenidate.

Table 7.8 Relationship between ADHD subtypes, ADHD subtypes average body mass and ADHD subtypes average mph dosage

ADHD Subtypes	Average weight (kg)	Average mph daily dose (mg)
ADHD-PI	35,2	16
ADHD-HI	30,5	30
ADHD-C	32,14	20
Non-ADHD	36,16	20

There was no significant difference between the body mass of the different ADHD subtypes. (p = 0.81). See Table 7.5. It is clear that the subtype of the ADHD child did not influence the prescriber when deciding the candidate's dose. The Non-ADHD children received the same daily dosage as the ADHD-Combined subtype.

Figure 7.12 Presence of treatment breaks, 'drug holidays'

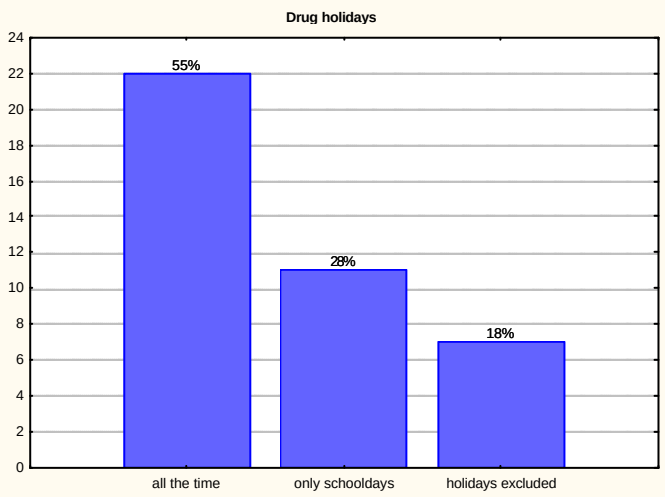

Figure 7.12 shows that only 55% of the sample adhered to the medication all the time. (Only schooldays = Mon – Fri)

Figure 7.13 Monitoring of body mass and height by clinicians

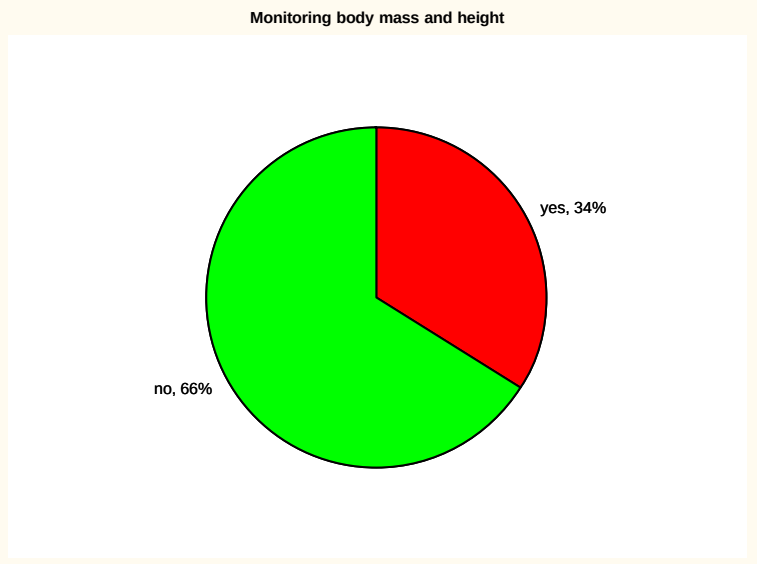

Figure 7.13 indicates that only 34% of the patients' growth (body mass and height) were monitored.

Figure 7.14 Heart monitoring of the patients

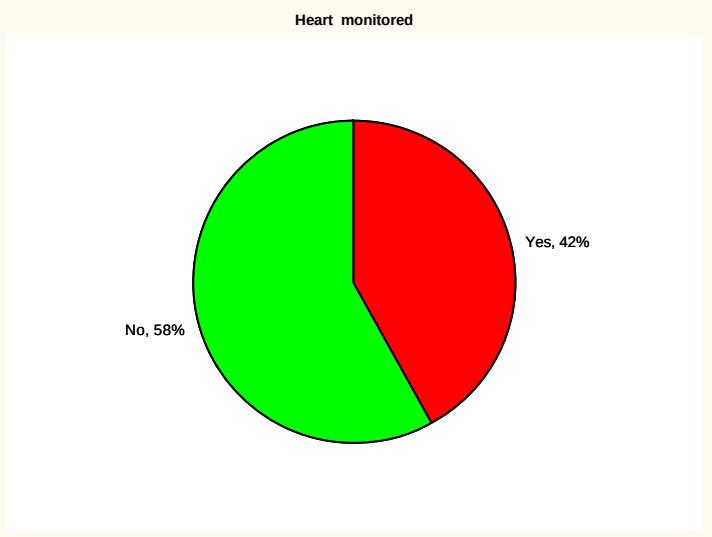

Figure 7.14 shows that 58% of the sample's heart rate and blood pressure was not monitored while on methylphenidate therapy.

7.2.3 Hypothesis 3

There will be a decrease in the severity of the symptoms of ADHD, both inattention and hyperactivity/impulsiveness, after medication with methylphenidate.

Figure 7.15 Distribution of subtypes after methylphenidate therapy was initiated

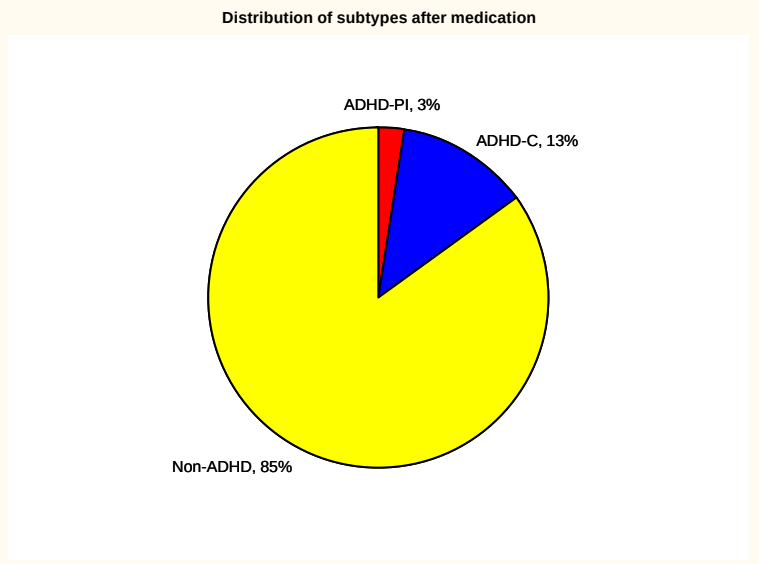

Figure 7.15 illustrates that 85% of the sample presented as Non-ADHD (no ADHD symptoms) after medication.

Figure 7.16 Difference in distribution of ADHD subtypes before and after methylphenidate therapy

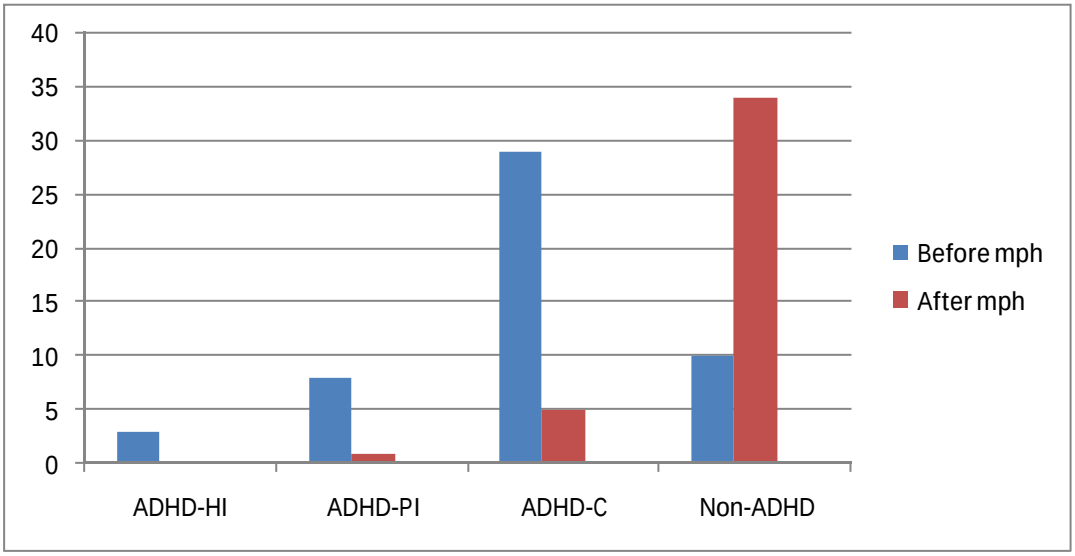

Figure 7.16 shows that there was a marked improvement in the representation of ADHD subtypes, before and after methylphenidate therapy.

Table 7.9 represents the results for the hyperactive-impulsive symptoms in boys and girls before and after methylphenidate.

Table 7.9 Boys and Girls: Hyperactive-impulsive symptoms before and after methylphenidate

Gender	N before	N after	H/I score before	H/I score after	*t*-value	df	*p*
Boys	35	26	17.143 ± 6.486	8.714 ± 6.335	5.178	61	0.000**
Girls	15	12	16.267 ± 7.620	9.667 ± 6.746	2.351	25	0.027*

***p* < 0.001

**p* < 0.05

Sample size (N) decreased from 50 to 38:

a) Some parents decided not to give their child methylphenidate.

b) Some parents stopped the medication after a short time of usage.

c) Some patients were on atomoxetine.

Figure 7.17 Hyperactive-impulsive symptoms in boys before and after methylphenidate

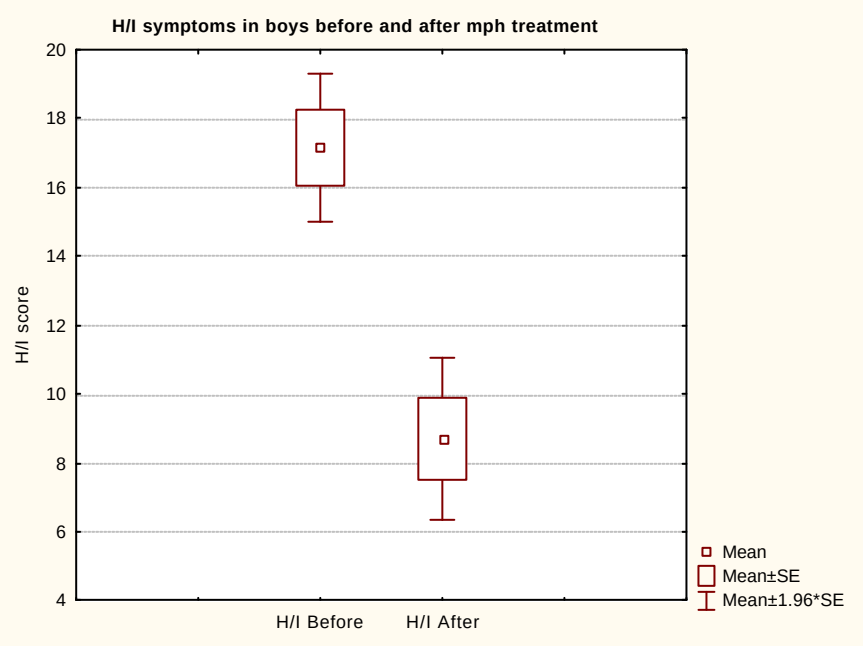

Figure 7.17 shows a vast improvement in hyperactive-impulsiveness symptoms in boys after medication was initiated. The mean score has improved from 17 to 9.

Figure 7.18 Hyperactive-impulsive symptoms in girls before and after methylphenidate

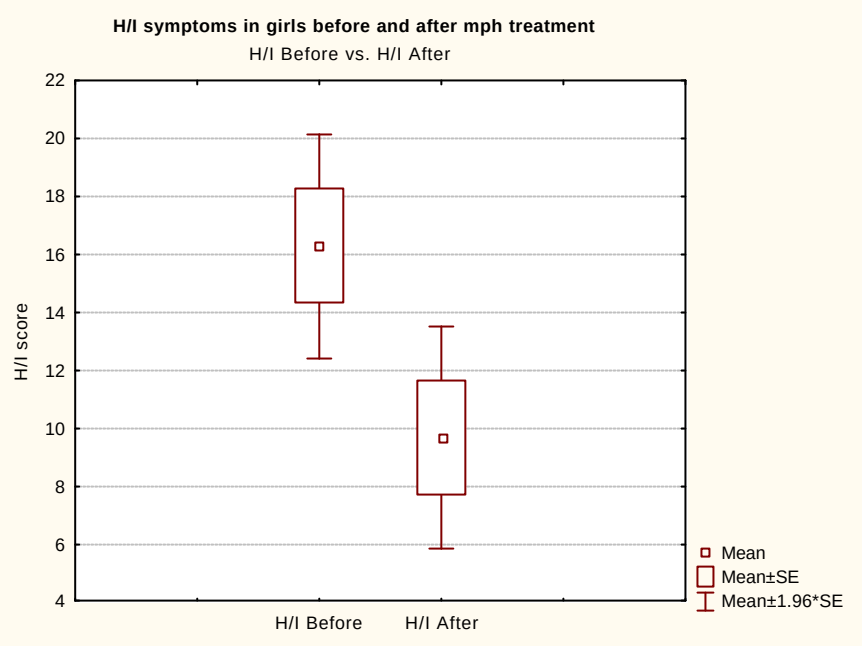

Figure 7.18 shows a substantial improvement in hyperactive-impulsiveness symptoms in girls after medication was initiated. The mean score has improved from 16 to 10.

Table 7.9, Figure 7.17 and Figure 7.18 show that there were definite improvements in the hyperactive-impulsive symptoms seen in both boys and girls, after treatment with methylphenidate.

Table 7.10 represents the results for the inattentive symptoms in boys and girls before and after methylphenidate.

Table 7.10 Boys and Girls: Inattentive symptoms before and after methylphenidate

Gender	N before	N after	Inatt score before	Inatt score after	*t*-value	df	*p*
Boys	35	26	20.771 ± 5.610	10.214 ± 5.846	7.285	61	0.000**
Girls	15	12	18.933 ± 4.667	12.250 ± 5.529	3.407	25	0.002*

**$p < 0.001$

*$p < 0.05$

Figure 7.19 Inattentive symptoms in boys before and after methylphenidate

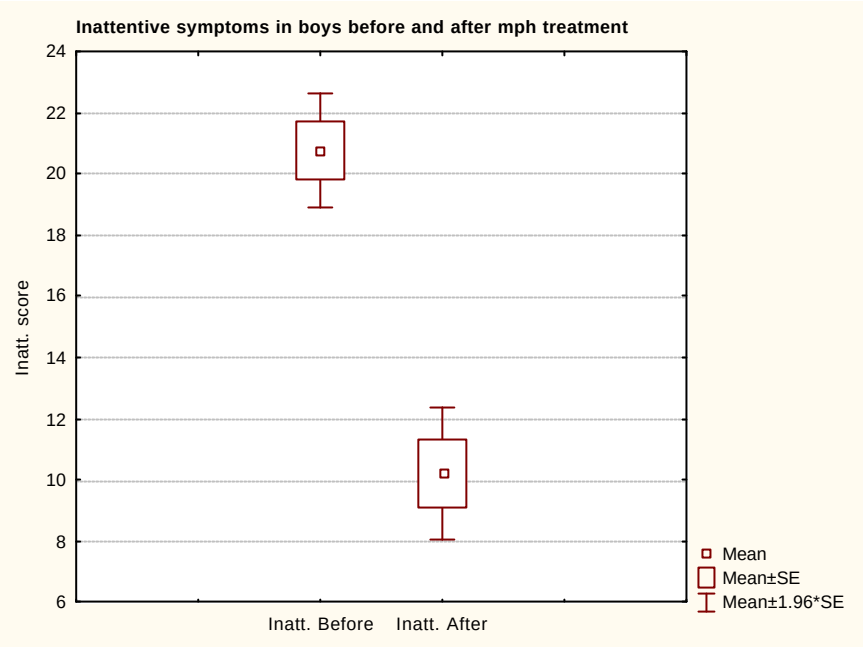

Figure 7.19 shows a vast improvement in inattentive symptoms in boys after medication was initiated. The mean score has improved from 21 to 10.

Figure 7.20 Inattentive symptoms in girls before and after methylphenidate

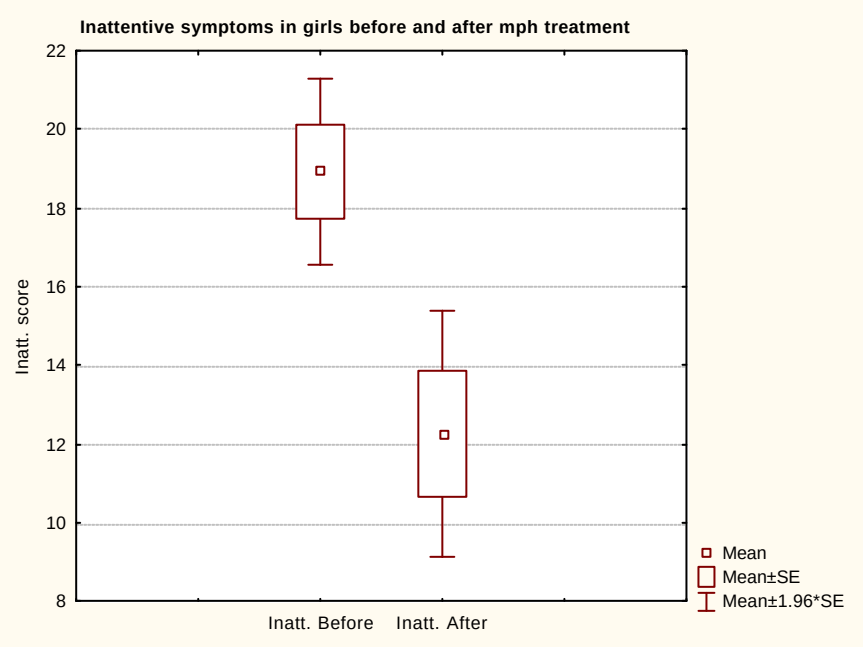

Figure 7.20 shows a definite improvement in inattentive symptoms in girls after medication was initiated. The mean score has improved from 19 to 12.

Table 7.10, Figure 7.19 and Figure 7.20 show that there were marked improvements in the inattentive symptoms seen in both boys and girls, after treatment with methylphenidate.

7.3 Hypotheses testing

Based on the presented results, the following conclusions about the research hypotheses can be made:

7.3.1 Research hypothesis 1

Hypothesis 1 can be accepted as there was clear evidence that the diagnoses of the children did not follow proper guidelines according to the DSM-IV criteria.

1.1 There were clear indications that not all the children referred for methylphenidate medication did meet the criteria for ADHD symptomatology, according to the DSM-IV-TR. 20% of the clinically diagnosed ADHD children did not meet the DSM-IV-TR criteria; therefore they were incorrectly diagnosed as suffering from the disorder.

1.2 From the results it was evident that too many people without appropriate knowledge of ADHD suggested that the candidates should use methylphenidate. No proper protocol or guidelines were followed.

1.3 The results indicated that the final diagnosis and prescribing of methylphenidate was overwhelmingly done by General Practitioners. The fact that 20% of the clinically diagnosed participants were Non-ADHD, can account for the lack of specialised expertise of the main prescriber.

7.3.2 Research hypothesis 2

Hypothesis 2 can be accepted, as the results show that the correct procedure of prescribing, monitoring and usage of methylphenidate was not always adhered to.

2.1 There was no significant relationship between body mass and the prescribed methylphenidate dose.

2.2 There was no significant relationship between the age of the child and the methylphenidate dose.

2.3 There was no significant relationship between the ADHD symptomatology (hyperactivity-impulsiveness and inattention) and the methylphenidate dose.

2.4 There was no definite monitoring of patients before and while on methylphenidate.

7.3.3 Research hypothesis 3

Hypothesis 3 can be fully accepted, as there are statistically significant results that there were marked improvements in hyperactive-impulsive and inattentive symptoms, seen in both genders, after treatment with methylphenidate.

A discussion of the obtained results will follow in the next chapter.

Chapter 8

DISCUSSION OF RESULTS

8.1 Introduction

The aim of the study was to:

1. Ascertain whether the diagnosis of ADHD children is done by field experts according to the criteria as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV-TR).
2. Establish the procedure of prescribing, monitoring and usage of methylphenidate.
3. Verify that with the correct prescribing and usage of methylphenidate, there will be a significant improvement in the symptoms of ADHD, according to the DSM-IV scores.

This chapter will report on the results obtained when the collected data were analysed for testing the postulated hypotheses.

8.2 Results of Research Hypothesis 1

8.2.1 Diagnosis, role players in the 'recognising' of ADHD, and prescribing of methylphenidate

When analysing the data on ADHD symptoms of the sample, 20% of the clinically diagnosed children did not meet the DSM IV-TR criteria (Fig 7.4). This renders the fact that some of the children could have been initially misdiagnosed. The fact that too many people without appropriate knowledge of ADHD, suggested that the candidates should use methylphenidate may contribute to this matter. On the other hand, GPs (primary care physicians) were the prescribers of methylphenidate in 47% (N=38) of the sample (Table 8.1). The finding of the study alluded to that no proper protocol or guidelines were followed to ensure correct diagnosis and treatment. The use of methylphenidate was also suggested by 58% of non-prescribers of the agent.

Table 8.1 Summary of role players in suggesting methylphenidate therapy and actual prescribers of methylphenidate.

Recommender/ prescriber	MPH therapy suggested by	Prescriber of MPH therapy
Teacher	18%	
General practitioner	8%	47%
Paediatrician	20%	19%
Psychologist	30%	
Psychiatrist	8%	9%
Paediatric neurologist		26%
Occupational therapist	6%	
Social worker	2%	
Family friend	2%	

According to a study done in the greater Washington DC area, teachers and other school personnel are often the first to suggest the diagnosis of ADHD in children (Sax & Kautz, 2003). Regional variations in the prescribing of medication for ADHD may be caused at least in part by variations in the likelihood of a teacher suggesting the diagnosis of ADHD. Nolan and colleagues (2001) found in their study that teachers collectively identified 23% of boys in their classrooms as having ADHD. In their discussion about this unexpectedly high prevalence, they speculated that teachers may have confused ADHD behaviours with other problems, e.g. low IQ, anxiety and/or psychosocial stressors. Sax and Kautz (2003) also hypothesised that the shift from a play-based pre-school curriculum to a more academically orientated curriculum in the past 10 to 20 years may be partly responsible for the increased propensity of teachers to suggest the diagnosis of ADHD. A child who is fidgety and inattentive in such a classroom might well be labelled "ADHD" by the teacher, when in fact that child may have no underlying

psychopathology but merely needs a more developmentally appropriate curriculum (Sax & Kautz, 2003).

Studies done on the knowledge, attitudes and perceptions of teachers reported limited knowledge about ADHD, and the how and why medication works. There was also a correlation between teachers' knowledge about ADHD and their attitude towards those children (Ghanizadeh, Bahredar, & Moeini, 2006; Lien, Carlson, Hunter-Oehmke, & Knapp, 2007). The main sources of knowledge about ADHD were: television and radio, friends and relatives, periodicals, newspapers and magazines. ADHD is however among other, a disorder of educational performance, and so the teachers have a critical role in advocating for the illness and the treatment. The attitudes, expectations, and behaviours of teachers toward children with ADHD may have a lasting impact on the academic self-efficacy and success of these children.

The present study's results regarding the diagnosis of ADHD and prescribing of methylphenidate correspond with a study done by Zito et al. (1999) which showed that primary care physicians conducted the majority of ADHD visits involving stimulant prescribing. Furthermore, there were major differences in primary care physician prescribing practices for the treatment of ADHD when comparing the practice of primary care physicians with that of psychiatrists. Psychiatrists prescribe stimulants alone less often (Zito et al., 1999). Evink and colleagues (2000) found that paediatricians used more special tests and assessment scales than family physicians. Paediatricians also reported to use DSM-IV criteria in their practises when making diagnoses more often than family physicians.

There is a considerable debate among psychiatrists as to whether many cases of ADHD go untreated. In a study done in North-Carolina, one-quarter of those confirmed to have ADHD according to the DSM-III (American Psychiatric Association, 1972) criteria were not receiving drug therapy and more than half receiving stimulants failed to meet the diagnostic criteria (Angold, Erkanli, Egger, & Costello, 2000), suggesting a considerable mismatch between

symptoms and medication. Possible over-diagnosis and overtreatment of ADHD in the United States was recognised in 1998 by the National Institutes of Health as an important public health problem (National Institutes of Health, 1998). Similar claims were made in South Africa (Truter, 2009). In addition, practice surveys among primary care paediatricians and family physicians revealed wide variations in practice patterns about diagnostic criteria and methods (Wolraich, Lindgren, Stromquist, Milich, Davis, & Watson, 1990). The revised criteria for ADHD and hyperkinetic disorder in DSM-IV and ICD-10 classification systems, respectively, require a pervasive impairment in psychological development (occurring in two or more life settings) which may improve diagnostic consistency.

Establishing a diagnosis of ADHD requires a strategy that minimises over-identification and under-identification. Paediatricians and other primary care health professionals should apply DSM-IV criteria in the context of their clinical assessment of the child. The use of specific criteria will help to ensure a more accurate diagnosis and decrease variation in how the diagnosis is made (American Academy of Pediatrics, 2000). Children who meet the diagnostic criteria for the behavioural symptoms of ADHD but who demonstrate no functional impairment do not meet the diagnostic criteria for ADHD (American Psychiatric Association, 1994).

Clinicians also need to be aware of the possibility of other psychiatric disorders with which ADHD often may coexist. The coexistence of other disorders does not preclude the diagnosis of ADHD but there should be caution in proceeding with diagnosis, mindful of the fact that other conditions can effectively mimic the ADHD phenotype but may need different management strategies (Davis & Sabir, 2008).

Based on the results of the present study there does not appear to be enough evidence that proper protocols or guidelines were followed in the diagnosis of children with ADHD and prescribing of methylphenidate for appropriate candidates. Some children were diagnosed as having ADHD with insufficient evaluation and in some cases stimulant medication was

prescribed when treatment alternatives might exist. According to the findings of this study the conclusion may be drawn that not all clinicians prescribing methylphenidate have the necessary professional experience and exposure to this condition to diagnose and treat ADHD.

8.3 Results of Research Hypothesis 2

8.3.1 Correlations between body mass, age and the methylphenidate dose

There was no relationship between the body mass, age, and the methylphenidate dose. A child with body mass of 50kg received the same dosage of methylphenidate as a child with a body mass of 23kg, i.e. 20mg/day. Another child with body mass of 40kg used 10mg/day, far less than a child with body mass of 26kg, i.e. 30mg/day. Body mass and the clinically effective dose range were in most cases not taken into account when methylphenidate was prescribed (see Table 7.4, 7.6 and Figure 7.7). From the interviews there was also no significant evidence that individuals' doses were titrated until optimal effects were reached.

Doses of methylphenidate for 12 year old children varied from 10-36mg/day. For a dose of 20mg the children's ages varied from 6-13 years. In most cases, the age of the patient was not considered when prescribing methylphenidate (see Tables 7.4, 7.7 and Figure 7.8). Although the effective doses of methylphenidate are narrow and cannot be predicted by the patient's age, body mass, level of hyperactivity, or measurements of plasma drug concentrations (Barkley et al., 1991), the average clinically effective dose range in children with mild to moderate cases is 0.3-0.5mg/kg/day (Barkley, 2006; Kaplan & Sadock, 1998; Stein et al., 2003). In some cases daily dose can be increased up to 1mg/kg/day (Greenhill et al., 1996; Solanto, 1998), however, higher doses will also be more associated with side effects. In a Dose-Response Study done by Stein et al. (2003) it was demonstrated that, younger children and those who weighed less seemed more prone to side effects. Consequently, clinicians should be alert to greater risk of stimulant side effects in younger children with lower body mass.

Clinicians should begin with a low dose of medication and titrate upwards because of the marked individual variability in the dose-response relationship (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). It is clear that methylphenidate requires careful titration and medical monitoring to obtain the optimum balance between efficacy and side effect profiles (Kutcher et al., 2004).

8.3.2 Correlations between ADHD symptomatology, and the methylphenidate dose

There was no correlation between the inattention symptoms before medication and the daily dosage of methylphenidate. A child with a score of 9 received the same dose as a child with a score of 26, i.e. 20mg/day. With a score of 20, children's dosages varied from 5-20mg/day. The same was found for the hyperactive-impulsive symptoms before medication and the daily dosage of methylphenidate. A child with a score of 2 received the same dose as a child with a score of 24, i.e. 10mg/day. With a score of 23, children's dosages varied from 5-30mg/day (see Table 7.4, 7.8, Figures 7.9, 7.10 and 7.11).

From these results it appears that the ADHD symptomatology (hyperactivity-impulsiveness and inattention) as indicated by DSM-IV scores, was not necessarily considered when methylphenidate was prescribed. The non-ADHD children (children who do not qualify to be classified as ADHD according to DSM-IV score), received the same daily dosage as the ADHD-Combined subtype.

A Dose-Response Study done by Stein et al. (2003) indicated consistent results with the report of Barkley et al. (1991), that the ADHD subtype moderated the dose-response relationship. ADHD-PI (without hyperactivity), are more likely to do well on lower methylphenidate dosages, whereas children with ADHD-C (subtype with inattention and hyperactive-impulsiveness) and ADHD-HI (subtype with hyperactivity), are likely to require higher dosages for clinical management. The findings of both Stein et al. (2003) and Barkley et

al. (1991) suggest improvement in inattentive symptoms at lower doses relative to doses effective for treating children with both hyperactivity and impulsiveness symptoms.

It is indisputable that the initiation of treatment requires the accurate establishment of a diagnosis of ADHD (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001).

8.3.3 Presence of monitoring and managing by clinicians

Only 34% of the patients' growth (body mass and height) was occasionally monitored, whereas, 58% of the children's heart rates, blood pressure etc., were not monitored while on methylphenidate therapy. Patients were advised by clinicians to take 'drug holidays'. Only 55% of the sample adhered to the medication all the time (see Figures 7.12, 7.13, 7.14).

ADHD is a chronic condition that requires ongoing management and monitoring (Brown, Amler, Freeman, Perrin, Stein, Feldman et al., 2005). The clinician should periodically provide a systematic follow-up for the child with ADHD. Monitoring should be directed to target outcomes and adverse effects, with information gathered from parents, teachers, and the child (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001). Monitoring should include recording blood pressure and pulse (at each adjustment of the dose, then every six months), height, weight, and appetite (6 monthly) with a maintenance of a growth chart; tics, depression, irritability, lack of spontaneity, withdrawal, and excessive perseveration (at every visit)(Taylor et al., 1998).

Research has shown that the positive effects of MPH cease down as soon as the medication is stopped (Abikoff et al., 2004). When psychostimulant medication like methylphenidate, is stopped abruptly, withdrawal reactions may occur. Then, 4-12 hours after the last dose, 'rebound' symptoms of ADHD including increased activity, excitability, irritability and insomnia may occur. In the longer term depression and extreme fatigue may be seen. It is therefore advisable not to do the so-called 'drug holidays', where the medication is stopped over

weekends and during school holidays. If the medication needs to be discontinued, doses should be reduced gradually, approximately 25% weekly. Treatment breaks, 'drug holidays' , may be considered if there is a specific need (e.g. significant adverse effects on the youngsters' rate of growth in height and/or weight) but these should be carefully timed (e.g. to avoid disruption at important times during the child's schooling); otherwise they are not generally recommended (Kutcher et al., 2004).

8.4 Results of Research Hypothesis 3

The study investigated the efficacy of methylphenidate in reducing the ADHD symptoms, both hyperactivity/impulsiveness and inattention, in both genders. Results of the *t*-tests done to compare the ADHD symptoms in the different genders before, and after methylphenidate therapy can be summarised as follows (see Tables 7.9 and 7.10). The results of the *t*-tests showed that there was a significant improvement in the hyperactivity/impulsive and inattention symptoms in boys ($p<0.001$). For girls the improvement was also significant for both hyperactivity/impulsive and inattention symptoms ($p<0.05$). An interesting finding is that the improvement was much stronger in boys than in girls.

The distribution of the subtypes in the sample after medication (see Fig. 7.15) indicates that 85% of the sample presented as non-ADHD (no ADHD symptoms) after medication. With regards to the ADHD symptoms, statistically significant results were obtained in both hyperactive-impulsiveness and inattention after methylphenidate therapy (see Tables 7.9, 7.10 and Figures 7.17. 7.18, 7.19, 7.20). The results of this study emphasise the benefits of methylphenidate therapy when comparing the ADHD symptoms before and after medication was initiated (see Figure 7.16). There was a definite improvement of the severity in symptoms of ADHD, both inattention and hyperactivity/impulsiveness, after medication with methylphenidate. The findings confirm previous studies (Whalen & Henker, 1991; Zito et al., 1999) concerning the benefit of methylphenidate therapy in ADHD children.

Methylphenidate is very effective for the treatment of ADHD. It effectively reduces hyperactivity, impulsiveness, and inattention in 60% - 90% of children diagnosed with ADHD (Whalen & Henker, 1991). Many other studies have documented the efficacy in reducing the core symptoms of ADHD (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001; Whalen & Henker, 1991; Van der Oord et al.,2008; Zachor et al., 2006). In many cases, stimulant medication also improves the child's ability to follow rules and decrease emotional overreactivity, thereby leading to improved relationships with peers and parents (Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001).

8.5 Summary of Results

The results of the present study can therefore be summarised as follows:

1. There is strong evidence that the criteria for diagnosing ADHD, as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV) were not appropriately followed. No proper guidelines were followed to ensure correct diagnosis.
    a. Not all children referred for methylphenidate medication do meet the criteria for ADHD.
    b. Not all involved role players suggesting that methylphenidate should be prescribed, had the necessary professional qualifications and/or knowledge.
    c. Not all of the clinicians involved in the diagnosis of ADHD and the prescribing of methylphenidate had the necessary professional experience and/or exposure to diagnose and treat ADHD.
2. The correct procedure of prescribing, monitoring and usage of methylphenidate was not adhered to.
    a. No proper guidelines were followed to ensure the correct treatment and dose for each individual.

b. ADHD symptomatology (hyperactivity-impulsiveness and inattention) was not taken in account when prescribing methylphenidate.

c. There was no definite monitoring of patients before and while on methylphenidate.

3. In spite of some inaccurate diagnoses, it is clear that there was an improvement of the severity in symptoms of ADHD, both inattention and hyperactivity/impulsiveness, after medication with methylphenidate.

The findings of this study have shown that not all clinically diagnosed ADHD children meet the criteria as set in the DSM-IV. There also seem to be too many 'inexperienced' role players involved in the suggesting and prescribing of MPH. This can be clearly explained by the results obtained. There is a definite lack in monitoring the patients when on methylphenidate therapy. Proper advice in the usage of methylphenidate, were not given to parents, with reference to the appearance of drug holidays. Positive improvements in ADHD symptoms after methylphenidate therapy, shows that methylphenidate is still prominent and successful in the pharmacotherapy of the ADHD child.

8.6 Clinical Implications

The findings of the study show that children are diagnosed with ADHD and referred for methylphenidate medication while not meeting the criteria for ADHD, according to the DSM-IV. Assessment and diagnosis of ADHD should be done by a mental health professional, preferably one who is trained in children's mental health, and always adhered to the criteria as set in the DSM-IV. Diagnosis of the condition requires both medical and psychosocial expertise and is usually made by multi-/inter-disciplinary team. It is suggested that the Health and/or Educational Ministry should provide a special course on ADHD for teachers. Providing these educational programmes on television and radio may be highly effective for all involved with an ADHD child as they are the most common source of information.

Furthermore, it was observed from this study that methylphenidate was prescribed without taking into account the ADHD symptomatology (hyperactivity-impulsiveness and inattention). There was no relationship between the ADHD symptomatology and the methylphenidate dose. There was also no evidence of dose-titration, and the findings indicate no definite monitoring of patients before and while on methylphenidate.

The use of proper guidelines when diagnosing and prescribing, cautious monitoring of patient and outcomes are essential and recommended.

With the positive results seen in the improvement of the severity of ADHD symptoms after methylphenidate therapy was initiated, it is clear that also in South Africa, methylphenidate is first-line treatment and very effective for the treatment of ADHD.

8.7 Concluding Remarks

The study confirms that there is a possibility that not all clinicians involved in the diagnosis of ADHD, and prescribing of methylphenidate, have the necessary professional experience and/or awareness regarding ADHD. Optimal outcomes for the ADHD child request thorough assessment and diagnosis. The study also revealed that systematic monitoring and follow up procedures was not in place for most of the children in the sample.

The findings of this study confirm the research findings from the USA and Europe, especially when it comes to the improvement of ADHD symptoms after methylphenidate therapy (Brown et al., 2005). With correct individualised prescribing and usage of methylphenidate, there will be a significant improvement in the symptoms of ADHD, according to the DSM-IV scores.

It is however, regrettable that some of the information in the public domain about ADHD is very misleading and misinformed. In some quarters there is considerable hostility towards the diagnosis, either total denial of the existence of ADHD as a discreet clinical entity or a focus on attributing blame. The best counter to this is to be as objective as possible about the

impairment suffered by the child and the impact this is having on their social, educational and family life. Thorough assessment and careful diagnosis by experts are essential. It must be emphasised that ADHD is an inherent neurodevelopmental disability (Davis & Sabir, 2008) and that without treatment the prognosis for many children is poor. It is hoped that in time specialist child and adolescent mental health services (CAMHS), can be established in South Africa.

This study emphasise that pharmacotherapy plays a primary role in the management of ADHD, despite the availability of effective behavioural interventions. Psychostimulants are the most commonly prescribed form of pharmacotherapy for patients with ADHD. The use of these agents, however, requires careful consideration and management by health plan stakeholders for optimal effectiveness. Initiatives promoting medication adherence, such as patient/parent education, provider follow-up, and adverse effect management, are crucial for ensuring treatment success (Dopheide, 2009).

Irrespective of the fact that, the diagnoses in all cases were not correct, no proper guidelines were adhered to, and no known monitoring and follow up procedures were applied, methylphenidate therapy is, when the correct dose is prescribed to an appropriate patient by an expert in the field, still very successful and adequate treatment for the ADHD child.

Chapter 9

LIMITATIONS AND RECOMMENDATIONS

9.1 Limitations

- The sample was too homogeneous, as mostly Afrikaans speaking children participated in this study. This may not represent the populations of South Africa and therefore generalisation of the results may be affected.

- Only parent ratings were used, as interviews with teachers did not form part of the research design, therefore children could only be assessed in one setting only, which may bias the reporting (Meyer & Aase, 2003). However, parents' ratings and reporting were appropriate, since the questionnaire included personal, family information, and only parents could report on the presence of treatment breaks.

- The patients/candidates were not evaluated by the researcher before and after initiation of methylphenidate therapy.

9.2 Recommendations

- The study could be replicated using a more heterogeneous and diverse sample. Future research could be extended to a larger sample of many different cultural groups.

- Children beyond school age and adolescents could be included in the investigation.

- Diagnosis of the condition requires both medical and psychosocial expertise by a multi-/inter-disciplinary team.

- The use of proper guidelines when diagnosing and prescribing, cautious monitoring of patient and outcomes are essential.

- Further research in paediatric psychopharmacology is needed, as pharmacotherapy of ADHD is under-researched in South Africa.
- Establishment of a Pharmacist Monitoring Service for children with ADHD is recommended.
- The Health and/or Educational Ministry should provide a special course on ADHD for teachers.

Chapter 10

SUMMARY AND CONCLUSION

10.1 Summary

- There is strong evidence that the criteria for diagnosing ADHD, as set in the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV - TR) were not appropriately followed, as 20% of the sample did not meet the DSM-IV TR criteria.
- The study confirms that there is a possibility that not all clinicians involved in the diagnosis of ADHD, and prescribing of methylphenidate, have the necessary professional experience and/or awareness regarding ADHD.
- No proper guidelines were followed to ensure correct diagnosis.
- Too many people/role players without appropriate clinical knowledge of ADHD, advised the patients to take methylphenidate.
- The final diagnosis and prescribing of methylphenidate is overwhelmingly done by general practitioners (47%) followed by paediatric neurologists (26%).
- No proper guidelines were followed to ensure the correct treatment and dose for each individual.
- ADHD symptomatology (hyperactivity-impulsiveness and inattention) was not taken in account when prescribing methylphenidate.
- The study also reveals that systematic monitoring and follow up procedures was not in place for most of the children in the sample.

- In spite of some inaccurate diagnoses, it is clear that there was an improvement of the severity in symptoms of ADHD, both inattention and hyperactivity/impulsiveness, after medication with methylphenidate.
- With correct diagnosis and individualised prescribing and usage of methylphenidate, there will be positive improvements in ADHD symptoms after methylphenidate therapy.
- Methylphenidate is still prominent and successful in the pharmacotherapy of the ADHD child.
- This study emphasise that pharmacotherapy plays a primary role in the management of ADHD.
- Research in paediatric psychopharmacology and ADHD pharmacotherapy is needed.

10.2 Conclusion

Based on the results of the study there does not appear to be enough evidence that proper protocols or guidelines were followed in the diagnosis and treatment of children with ADHD. Some children were diagnosed as having ADHD with insufficient evaluation and in some cases stimulant medication was prescribed when treatment alternatives might exist. It seems that not all clinicians prescribing methylphenidate have the necessary professional experience and/or qualifications regarding ADHD.

Thorough assessment and careful diagnosis by experts are essential. It must be emphasised that ADHD is an inherent neurodevelopmental disability and that without treatment the prognosis for many children is poor. The best counter to this is to be as objective as possible about the impairment suffered by the child and the impact this is having on their social, educational and family life.

Psychostimulants are the most commonly prescribed form of pharmacotherapy for patients with ADHD. The use of these agents, however, requires careful consideration and management by health plan stakeholders for optimal effectiveness. Initiatives promoting medication adherence, such as patient/parent education, provider follow-up, and adverse effect management, are crucial for ensuring treatment success. It is hoped that in time specialist child and adolescent mental health services (CAMHS), can be established in South Africa.

Regardless of the fact that, the diagnoses in all cases were not appropriate, no proper guidelines were adhered to, and no definite monitoring and follow up procedures were applied, methylphenidate therapy is, when the correct dose is prescribed to an appropriate patient by an expert in the field, still very successful and adequate treatment for the ADHD child. The results could be even more impressive and positive when proper protocols would be followed as a routine.

In general, the finding of this study makes a strong case for the need for South African guidelines similar to The American Academy of Pediatrics' Clinical Practise Guidelines (American Psychiatric Association, 2000) and the European Clinical Guidelines for Hyperkinetic disorder (Taylor et al., 2004 World Health Organization, 1993) .

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