PRIMARY CARE MANAGEMENT OF ADHD IN CHILDHOOD

An overview of the literature

A monograph prepared by South Carolina Offering Prescribing Excellence (SCORxE)

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1 Scope and purpose of this summary
This summary of evidence, experience and professional practice guidelines has been created as an adjunct resource for upskilling academic detailers about the attention deficit hyperactivity disorder (ADHD). It is intended as a guide for further reading in this topic. The academic detailing program in question is destined initially for primary care practitioners. The scope of the review is restricted to management of ADHD in children and young adolescents, and does not cover aspects of the ADHD topic concerning adults and older adolescents.

This summary has relied substantially on a number of significant recent publications. Principal amongst these sources are two major recent reviews of the literature. A very deep review of the entire field was published in 2009 by the British Psychological Society and the Royal College of Psychiatrists for the British National Institute for Clinical Excellence (National Collaborating Centre for Mental Health, 2009a). Added to this, in October 2009 a Final Report of a Drug Class Review of the Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder was published by the Drug Effectiveness Review Project (DERP) of the Oregon Evidence-based practice Center of the Oregon Health & Science University. (McDonagh, 2009)

In addition significant direction has been obtained from the 2000 American Academy of Pediatrics Clinical Practice Guidelines on diagnosis and evaluation of the child with Attention-Deficit/Hyperactivity Disorder (American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2000) as well as the 2001 Guideline on treatment of the school-aged child with attention-deficit/hyperactivity disorder. (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001) Additionally, the American Academy of Child and Adolescent Psychiatry have updated their 1997 Practice Parameter, (Dulcan, 1997) taking account of more recent data as at October 2006. (AACAP Workgroup on Quality Issues, 2007)

2 Introduction
ADHD is one of the most extensively studied childhood conditions with more than 18000 articles currently cited in Medline Pubmed, and 139,000 references in Google Scholar using the simple search term ‘ADHD’. In past decades impulsivity, over-activity and distractibility in children have also been known as minimal brain dysfunction, hyperkinetic disorder, attention deficit disorder (ADD) and attention deficit disorder with hyperactivity. Despite this breadth of scholarly effort there are many aspects of the condition which remain uncertain and problematical.

3 ADHD: What is it?
Inattention, hyperactivity and impulsivity are the three characteristics which comprise the Attention-Deficit/Hyperactivity Disorder, a condition now recognized to occur in both children and adults. Importantly in diagnostic terms, symptoms experienced in these domains need to have produced clinically significant impairments of activity and function in at least two settings: home, school or occupational.

The American Psychiatric Association’s revised text version of the fourth edition of the Diagnostic and Statistical Manual (DSM-IV-TR) (American Psychiatric Association, 2000) has
defined the condition as comprising two symptom-groupings. The two groupings are termed respectively inattention, and hyperactivity-impulsivity. Each grouping consists of nine separate symptoms.

Symptoms of inattention include not giving attention to details or making careless mistakes, failure to listen, having difficulty sustaining attention, not following through with things, having difficulty organizing, avoidance or dislike of sustained mental effort, losing things, being easily distracted, and forgetfulness.

Symptoms of hyperactivity include frequent fidgeting or squirming in the seat, leaving a seat when remaining seated is expected, often running about or climbing when such activity is inappropriate, having difficulty playing quietly, persistently being on-the-go, and often talking excessively. The three impulsivity symptoms include having difficulty waiting in-turn, often interrupting or intruding on others, and blurting out answers before questions have been completed.

The DSM-IV-TR divides ADHD into three types depending on whether six or more symptoms are present in either or both of the two groupings: predominantly inattentive, predominantly hyperactive/impulsive, or a combined type. Some of the symptoms need to have been present before the age of seven years, and there needs to be impairment as a result of the symptoms in two or more settings such as school, home or occupational settings. The symptoms should not occur exclusively when another pervasive disorder is being experienced: eg. developmental or psychotic disorders or schizophrenia, nor where a different mental disorder might better account for the symptoms.

3.1 Evolution and current nature of DSM/ICD10 definitions

The earliest medical descriptions of inattention type ADHD are attributed to Scots physician Alexander Crichton in 1798. (Palmer, 2001) Elements of the condition were also described in 1902 by the influential English pediatrician George Still. (Still, 1902) By the 1920s the idea that some behavioral disturbances in children might be attributable to brain damage led to the term ‘minimal brain dysfunction’ and this terminology remained in common usage until the late 1960’s. By 1968 when the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) was published it had become more generally recognized that attention problems and childhood over-activity were rather less likely to routinely have a root cause in neuronal damage. The condition was then termed the ‘hyperkinetic reaction of childhood’ in the DSM-II. Distractibility and problems with attention were included under this definition. (Barkley, 1997)

By 1980 when the first version of the DSM-III was published, the condition’s definition was characterized entirely in behavioral terms without reference to any biological deficit. In this version it was termed ‘ADD (Attention-Deficit Disorder) with or without hyperactivity’. In the 1987 DSM-III revision this was changed to ADHD, un-subdivided between inattentive and hyperactive subtypes. However, with DSM-IV and the current revision (DSM-IV-TR), the two subtypes, (inattention and hyperactivity/impulsivity) and the combined type were differentiated, all being defined exclusively in behavioral terms.

The World Health Organization’s International Classification of Diseases (ICD) has characterized the condition as ‘Hyperkinetic disorder’. In Europe in particular, the ICD
The definition of ‘hyperkinetic disorder’ is more prevalently used than the DSM’s ADHD diagnostic structure. In the ICD10, both inattention as well as hyperactivity/impulsivity need to be present for the hyperkinetic disorder to be correctly diagnosed, i.e. the ‘combined’ form of ADHD described in the DSM-IV-TR.

...Hyperkinetic disorders always arise early in development (usually in the first 5 years of life). Their chief characteristics are lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. These problems usually persist through school years and even into adult life, but many affected individuals show a gradual improvement in activity and attention.

Several other abnormalities may be associated with these disorders. Hyperkinetic children are often reckless and impulsive, prone to accidents, and find themselves in disciplinary trouble because of unthinking (rather than deliberately defiant) breaches of rules. Their relationships with adults are often socially dis-inhibited, with a lack of normal caution and reserve; they are unpopular with other children and may become isolated. Cognitive impairment is common, and specific delays in motor and language development are disproportionately frequent.

From F90: (p206) - Hyperkinetic disorders – ICD10 (World Health Organization, 1992)

Differences between the ICD10 definition and DSM-IV-TR result in a significantly lower proportionate identification of hyperkinetic disorder relative to the diagnostic prevalence of ADHD. (National Collaborating Centre for Mental Health, 2009a)

Both the DSM-IV-TR and ICD10 recognize commonly co-morbid behavior disorders which need to be differentiated from ADHD/Hyperkinetic disorder. DSM-IV-TR defines the Oppositional Defiant Disorder (ODD) as persistent and frequent disobedience and opposition to authority figures (such as parents, teachers or other adults) characterized by negative, hostile or defiant behavior. For diagnosis, these symptoms need to persist for more than six months, being considerably more frequent than normal for a person of the same developmental age. DSM-IV-TR also defines the Conduct Disorder (CD) as consisting of more severe behavioral problems: a persistent pattern of behavior that violates the societal rules and the rights of others. This includes aggression that can take the form of bullying or cruelty to animals, destruction of property, stealing and persistent lying (other than to avoid harm). While ODD and CD can coexist with ADHD they cannot be part of the grounds for making a diagnosis of ADHD. The ICD10 defines the CD with ODD as being one manifestation of CD.

### 3.2 Prevalence and costs

Childhood ADHD is the most prevalently referred condition to children’s and adolescent psychiatric services. (AACAP Workgroup on Quality Issues, 2007) Boys are diagnosed with the condition approximately four times more frequently than girls, and in children of elementary school age the condition is said to occur in one in every twenty children in the United States. (Faraone, 2003) Estimates of prevalence of the condition are strongly influenced both by the changes in definitional characteristics of the condition over the past forty years as discussed above, as well as with poor precision of diagnosis.

In a summary of US prevalence studies, it was noted that prevalence percentages are frequently quoted when the symptomatology has only been confirmed in a single setting,
rather than in two separate contexts as required by the DSM-IV-TR. (Faraone, 2003) Further compounding this picture, the additional requirement for functional impairment to be present along with the designated symptomatology has also increased quoted prevalence by about two fold. (Wolraich, 1998; Canino, 2004) This variability in apparent prevalence has been recently studied systematically. Geographic location around the world was considerably less responsible for observed variability in prevalence of the ADHD diagnosis than the actual methods used to estimate overall prevalence in any one country or region. (Polanczyk, 2007)

The prevalence of ADHD in US children between the ages of four and seventeen has been estimated using the 2001 National Health Interview Survey (NHIS). This Survey was undertaken in a representative structured sample of 10,255 US children. The Strengths and Difficulties Questionnaire (SDQ) was administered by trained home interviewers providing weakly accurate estimates of ADHD prevalence in US children. (Cuffe, 2005) In this group, the prevalence of clinically significant SDQ-identified ADHD symptomatology was 4.2% in males and 1.8% in females.

In the full sample of 10,255 children, (without reference to any particular date of diagnosis or proportions receiving treatment), 6.8% of males and 2.5% of females had a parent-reported ADHD diagnosis but were found to be negative for an SDQ-predicted ADHD diagnosis. Likewise, 1.6% of males and 0.8% of females were positive for an SDQ-predicted ADHD diagnosis but were negative for parent-reported ADHD diagnosis.

It can be concluded that in the US there is evidence for both mis-diagnosis as well as under-diagnosis of ADHD, and a modest but probably insignificant variation amongst racial groups.

Male prevalence by race was 5.6% for Blacks, 3.1% for Hispanics and 4.3% for Whites.

Telephone-based interviews of a National Health and Nutrition Examination Survey (NHANES) sample of the US population from roughly the same era as the Cuffe data were analyzed for prevalence of ADHD. (Froehlich, 2007) The sample size in this study was one-third that used in the NHIS analysis but use of the Diagnostic Interview Schedule for Children IV (DISC-IV) may have been a more reliable indicator of ADHD than use of the SDQ. Prevalence by race was 8.7% for ‘African Americans’, 6.0% for ‘Mexican Americans’, 9.8% for ‘White, non-Hispanic’ and 5.2% for ‘Other’.

To date, there appears to be little compelling evidence for systematic differences in the prevalence of ADHD amongst different racial groups. Similarly, persuasive evidence for differential under- or over-diagnosis of ADHD in either girls or boys is also unavailable.

The oppositional defiant disorder has been estimated to be found together with ADHD in more than half of children and adolescents diagnosed with the condition, and a significant number of these patients will then progress on to develop conduct disorder. (Faraone, 1997; Barkley, 2005)

The total excess cost burden of ADHD in the US (relative to comparable control individuals) has been estimated to be $31.6 billion at 2000 prices. (Birnbaum, 2005) This estimate used an ADHD prevalence rate of 8% for boys and 4% for girls aged between seven and eighteen, with adult rates projected to be somewhat less. It was assumed that about two-thirds of children received treatment, and a quarter of adults received treatment. In this model direct
ADHD treatment costs only represented 5% of the total; 38% was associated with other healthcare costs; a further 45% for additional healthcare costs for other family members of ADHD sufferers; 12% of the total was incurred from productivity losses associated with adult sufferers and adult carers of young people with ADHD.

Other workers have demonstrated more recently a similar scale of US costs associated with ADHD ($42.5 billion – range $36-$52.5 billion in 2005 prices). Using an estimated ADHD prevalence rate of 5%, this approach included costs to the education system, as well as costs to society of delinquency. (Pelham, 2007)

These levels of overall excess costs have been noted to be similar to costs associated with asthma in US children. (Chan, 2002)

### 3.3 Challenges to proper diagnosis and management of ADHD

Effective stimulant medications have been available for the management of ADHD for many years. Although the patents on stimulants have expired, the more often prescribed sustained-release dosing forms as well as patch delivery systems continue under US patent protection. Atomoxetine (Strattera®), a non-stimulant medication, will also remain under patent in the US for several more years until 2017. (US Food and Drug Administration, 2010)

As a result, when prescribed, many of these medications come with a substantial price premium.

In some cases, the misuse and overuse of the ADHD diagnosis has led to both public and professional cynicism about the condition and individuals with an ADHD diagnosis. Many parents are reluctant at the thought of needing to continuously medicate children for a condition erroneously believed to be due to poor parenting. (Anonymous, 2010b; Cloud, 2010) To add to this problem, some pharmaceutical companies have also been noted to be blurring the boundaries between ADHD and other psychiatric conditions such as bipolar disorder in an effort to stimulate sales of the atypical antipsychotic drug class. (Berenson, 2008) The fact that the ADHD symptomatology can be readily ameliorated with pharmacotherapies adds to the risks that the symptoms (if not the condition) will become a marketing target for the pharmaceutical industry.

In recent years, school teachers have been identified as a potential resource for early identification of ADHD. (Phillips, 2006) Such triaging of possible ADHD cases by school teachers can potentially lead to effective help for affected children and their caregivers. However, the prevalence of ADHD, the entirely behavioral nature of the ADHD diagnosis, as well as the relative ease with which the symptomatology can be identified (if not the formal ADHD diagnosis), puts individuals at risk of inaccurate diagnosis and of receiving pharmacotherapy to conveniently manage symptoms that may not actually be due to ADHD. Precision in diagnosis can easily be overlooked: correctly diagnosed ADHD features require consistent observations of symptomatology over at least six months; some symptoms need to be observed before the age of seven; the existence of functional impairments as a result of symptoms is a crucial element of correct diagnosis; and the observable symptoms can also at times be better explained by alternative diagnoses.
3.4 Etiology

3.4.1 The social context of ADHD
Over the years in which ADHD has been systematically researched, inadequate parenting has often been suggested as the significant factor in its etiology. Primary care practitioners have been shown in qualitative studies to prevalently hold this view, (Shaw, 2003) and senior UK medical commentators have also recently expressed a similar viewpoint. (Anonymous, 2010b; Walsh, 2010)

Parents of children with the condition inevitably face personal uncertainty over the extent to which their personal child-rearing capabilities have contributed to the behavior patterns of their children. The prevalent observation of greater family dysfunction (DuPaul, 2001) and environmental adversity (McGee, 1991) in families caring for children with ADHD may be more associated with a reaction to the condition, rather than the cause of the condition itself. Supporting this view, studies of pre-schoolers both with and without ADHD/ODD found relatively little difference in the extent of use of coercive or controlling mothering behaviors despite evidence of greater levels of parental depression. (Cunningham, 2002)

Extensive neuropsychological studies have repeatedly shown that ADHD actually results from a complex interplay between genetic and environmental factors.

The psychological concept of ‘executive function’ (EF), or the ability to marshal neurocognitive processes for appropriate problem-solving to achieve future goals, has been used to help understand common features of ADHD. A systematic analysis of 83 studies including more than 6700 subjects (with or without ADHD) has explored this EF-construct for its ability to characterize the nature of psychologically observable ADHD impairments. (Willcutt, 2005) It was concluded that ADHD sufferers consistently exhibited at least moderate impairment on all EF tasks. Deficits were most consistently observed in measures of response inhibition, vigilance, working memory and planning. Notwithstanding these observations it was noted that EF deficits could not by themselves sufficiently characterize all cases of ADHD, but EF was an important component of the complex neuropsychology of the condition.

Important and interesting work is progressing on localization of aspects of EF within the prefrontal cortex areas of the human brain. (Arnsten, 2009) It is hoped that this work will ultimately lead to better understanding of the reasons for effectiveness of drugs successfully used to modulate ADHD symptoms.

3.4.2 Genetic factors

3.4.2.1 Twin and adoption studies
To explore genetic factors underlying ADHD, both monozygotic and dizygotic twins, as well as adopted and biological children of the same parents have been extensively studied. In summarizing twenty such twin studies from the USA, Australia and the European Union a mean heritability for the condition of 76% has been estimated. (Faraone, 2005b) It was noted that this makes ADHD the most heritable of psychiatric disorders. This strong heritability potential has similarly been confirmed in studies of adoptive and nonadoptive children and their respective biological relatives. (Sprich, 2000)
3.4.2.2 Genetic studies

Despite the high heritability of ADHD demonstrated through observational twin and adoption studies, it has proven difficult to identify specific genes which underlie the condition. A consensus is now emerging that many genes, each with small incrementally additive effects probably contribute to the observable disorder. (Franke, 2009)

In addition to many other neurotransmission genetic sites possibly associated with ADHD, extensive study has been made of specific genes associated with the dopaminergic system. This target for investigation has been selected particularly because stimulant drugs which markedly improve ADHD symptomatology are known to act on the dopaminergic system. However, even in this narrower field of potential gene targets, meta-analysis of multiple studies has only provided evidence for relatively small (but nonetheless significant) increases in the risk of ADHD associated with dopamine D receptor-4 and -5 genes. (Li, 2006)

More recent approaches to understanding the heritability of ADHD have used hypothesis-free studies of genome-wide associations, (Franke, 2009) as well as another strand of research investigating copy-number variants (CNVs). (Williams, 2010) (CNVs are duplicated or deleted regions in one allele resulting in 50% under- or over-dosing of specific genetic effects.)

A review of genome-wide association studies (Franke, 2009) has pointed to potential involvement of potassium channel subunits and associated regulators, as well as basic physiological processes such as cell division and adhesion, neuronal migration, neuronal plasticity and its associated processes. However it was concluded that much larger study groups will be necessary to explore the broader underlying genetic associations with ADHD.

Recently a study has found that relative to normal controls, ADHD patients carry a disproportionate load of large CNVs which are also found in patients suffering autism, schizophrenia, epilepsy and some forms of mental retardation. (Williams, 2010) This new genetic linkage to conditions previously not thought to be associated with ADHD offers important reinforcement of the fundamental part which heritability plays in the etiology of ADHD, defined as it is on an entirely behavioral basis. Implications of these findings place a new focus on the need for more research in this area, as well as throwing light on as-yet largely unexplored genetic issues for parents of ADHD children.

3.4.3 Environmental factors

3.4.3.1 Biological and physical environment factors

Over many years, a range of biological and physical environment factors have been the subject of study for their influence on, and causal contributions to ADHD.

3.4.3.1.1 Maternal lifestyle and factors in pregnancy

On the basis of mainly observational data, a 2003 comprehensive review of studies associated with maternal lifestyle concluded that exposure to tobacco smoke in utero is likely to be associated with ADHD and ADHD symptoms in children. (Linnet, 2003) However evidence of association was believed to be conflicted in relation to other widely suspected factors such as alcohol consumption and psychological stress during pregnancy.
Additional evidence has appeared with regards maternal exposure to alcohol during pregnancy. A single prospective study has related a higher risk of ADHD in children with a dopamine transporter susceptibility gene, to mothers who had been exposed to alcohol during pregnancy. (Brookes, 2006) At present the role of maternal alcohol exposure and its association with ADHD in offspring remains controversial with a number of current commentators affirming that there is significant evidence of association, but without necessarily ascribing clear causality. (Banerjee, 2007; National Collaborating Centre for Mental Health, 2009a)

A review of antenatal maternal stress and its effects on child neurodevelopment noted increasing evidence for an association between pre-natal stress and postnatal developmental outcomes. (Talge, 2007) However whilst citing four post-2003 studies of prenatal stress experiences associated with postnatal ADHD outcomes, they pointed out the inconsistency of these findings with respect the trimester of pregnancy during which the documented stressors had occurred.

A range of additional factors associated with pregnancy have also been linked with ADHD including very low birthweight, fetal hypoxia, brain injury, exposure to toxins such as lead, and deficiency of zinc. (National Collaborating Centre for Mental Health, 2009a)

3.4.3.1.2 Food and diet factors as a contributor

Over the years, dietary factors have attracted much public attention as a potential cause, or at least contributor to ADHD prevalence. As with other environmental factors and their influence on ADHD, a complex picture has emerged.

In the case of sugar and its effect on behavior or cognition in children generally, a meta-analysis of sixteen reports concluded that dietary sugar affects neither behavior or cognition. (Wolraich, 1995) This finding was no different in four of the included reports where the effects of sugar were studied in cohorts of specifically ADHD patients.

In the case of food additives, a 2007 randomized trial (McCann, 2007) studying hyperactive behaviors in three-year old, and eight to nine year old children has provided support for the thirty year-long contention by Feingold (Feingold, 1975) that artificial food colors and other food additives affect the behavior of children. In the 2007 study, it was concluded that artificial colors or a sodium benzoate preservative in the diet resulted in increased hyperactivity in normal children drawn from the general UK population. These results have helped confirm the guarded but significantly positive 2004 meta-analytic finding which positively associated food colorings with childhood hyperactivity. (Schab, 2004) More recently it has been observed that histamine may mediate effects of food additives on ADHD symptoms and that further research is needed to understand this interplay between genes and the dietary environment. (Stevenson, 2010)

Recent family practice commentators have affirmed that dietary interventions “probably” do not improve ADHD symptoms in children, (Ballard, 2010) and other researchers have made the point (Schab and Trinh, 2004) that for the relatively slim margin of symptom-benefit associated with removal of artificial colorings and preservatives, the additional family stresses necessary to explore the required dietary modifications may not be warranted.
It was noted that the extent of behavioral deterioration associated with artificial food colors can be understood as between a third to a half that which might be observed when ADHD children are taken off their stimulant medication. (Schab and Trinh, 2004)

3.4.3.2 Psychosocial environment factors

It has been noted that dysfunctional family structures are more commonly associated with ADHD, (Biederman, 1992) although it is equally possible that such family discordance simply results from the experience of living with a family member suffering from ADHD.

In a study of representative Canadian kindergarten children, (Cunningham and Boyle, 2002) mothers of those gauged as likely to be at risk for ADHD or ODD had a lower sense of competence, and higher depression scores relative to mothers of children adjudged to be without ADHD or ODD symptoms. Interestingly however, when solving child management problems, all mothers of children (both ADHD/ODD and Control) suggested twice as many controlling/negative management strategies as positive/preventive strategies.

The emerging evidence for the extent to which ADHD has a genetic basis raises the possibility of potential adverse effects of unrecognized adult ADHD on their children who have been diagnosed with the condition.

3.4.4 Gene environment interplay

Because of the gathering consensus that ADHD is a result of interplay between many genes and the environment, the challenge which now exists is to better understand the relative significance of environmental and genetic factors acting, (or not acting) together. (Franke, 2009)

While single gene-related issues and their association with environmental factors have been reported in recent years, (Brookes, 2006; Stevenson, 2010) it is expected that in future, genome-wide association studies exploring environmental factors will shed more light onto the interplay between environmental and genetic factors in ADHD. (Sonuga-Barke, 2008; Franke, 2009)

However as concluded in the review of diagnosis of ADHD by the UK National Collaborating Centre for Mental Health: (National Collaborating Centre for Mental Health, 2009b)

“...In most cases it is not known whether specific associated environmental variables represent direct risks for ADHD, or indirect risks acting through correlated environmental or genetic factors, or are passively correlated with the ADHD symptoms themselves...

...The degree to which the observed heterogeneity in the associations with neurobiological and psychological measures represent multiple etiological contributions to a common causal pathway, or independent contributions to multiple causal pathways, is not yet understood. It may also be the case that these associations represent epiphenomena of the ADHD syndrome and play no direct causal role.”
**4 Diagnosis of ADHD**

Establishment of an ADHD diagnosis in childhood with its resulting therapeutic implications has uncommonly significant consequences for children and their families. While most chronic childhood conditions have broad-ranging implications, the entirely non-organic, behavioral criteria necessary for an accurate ADHD diagnosis coupled with the stigma of implied parenting failure demands the utmost care over the final decision to attach to a child the diagnostic label ADHD.

The DSM-IV-TR ADHD criteria when diligently applied to patients requires considerable psychosocial investigation, clinical effort, time and patience.

Table 1 contains the DSM-IV-TR criteria for an ADHD diagnosis: - see page 51

In 2000 the American Academy of Pediatrics published an extensive clinical practice guideline for diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. (American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2000) This document from the Academy’s Committee on Quality Improvement, Sub-Committee on Attention-Deficit/Hyperactivity Disorder provided sound recommendations for diagnosis of the condition in children six to twelve years of age. It should be noted that the Academy routinely withdraws policy documents after five years, and this Guideline is therefore no longer technically in force. However it remains a substantially useful summary articulating sound principles for diagnosis and evaluation.

Six recommendations are laid out in this clinical Guideline, and the strength of each recommendation, and the strength of evidence underlying all recommendations was classed uniformly as ‘strong’. Table 2 contains a summary of these recommendations together with selected key explanatory quotations from the Guideline text: - see page 52

The Guideline includes a descriptive algorithm for diagnosis and evaluation of a child with ADHD which is reproduced in Figure 1 – see page 58

The authors stress that for any child being evaluated for a possible ADHD diagnosis, clinicians will generally need more than one visit, “...often indeed two to three visits”.

Importantly, the Guideline was not intended to be used in children with mental retardation, pervasive developmental disorder, moderate to severe sensory deficits such as visual or hearing impairment, nor chronic disorders associated with medications that could affect behavior, or patients who have experienced child abuse or sexual abuse.

Most recently in 2009, summary recommendations for diagnosis and immediate post-diagnostic advice were published by the UK National Collaborating Centre for Mental Health (National Collaborating Centre for Mental Health, 2009a). These summary recommendations are found in Table 3: see page 53. In addition, general principles for the diagnostic process were summarized, and common key questions about implementation of diagnostic criteria were elaborated and a summary position statement was provided for each question. These principles and key questions are reproduced in Figure 2 at page 59.
4.1 Clinical issues in diagnosis and ongoing care

4.1.1 The clinical interview
Key to the establishment of an ADHD diagnosis is the quality and nature of communication at clinic visits when problems are being evaluated with parents and child. Structured interview processes have been devised, (Costello, 1984) but these are rarely used in clinical practice because of their length and inflexibility.

A primary goal of the clinic visits needs to be gaining an understanding of the full range of problems and their history, in particular the child’s developmental history. In addition, family, general health, social, educational and demographic information needs to be documented. Understanding the way that families have coped and managed the problems that they have faced is critical. To achieve this understanding, generally separate interviews with different family members are necessary. The opportunity to see the child and parent individually is generally valuable. During this interview process, groundwork can be laid for gaining the necessary triangulating input from the young person’s school, or other separate social context.

In addition, full medical assessment is necessary to uncover any other undiagnosed problems.

4.1.2 Standardized rating scales
As noted in the AAP Clinical Guideline on Diagnosis of ADHD (American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2000), broad-based rating scales are generally not sufficiently sensitive and specific for diagnosing ADHD.

However, a ten-year review of narrow-range rating scales assessing ADHD in children and adolescents summarized (Collett, 2003) and confirmed that most of the available specific ADHD rating scales have adequate reliability, and in most cases, good face validity:

- ACTeRS-Second Edition – Ullman:
- ADHD rating Scale-IV – DuPaul:
- ADHD Symptoms Rating Scale – ADHD-SRS:
- Attention Deficit Disorder Evaluation Scale-Second Edition – ADDES-2:
- Brown Attention-Deficit Disorder Scales for Children and Adolescents – BADDS:
- Conners Rating Scales-Revised– CRS-R:
- IOWA Conners Teacher Rating Scale:
- Swanson, Nolan and Pelham-IV questionnaire – SNAP-IV:
- SKAMP Rating scale:
- Strengths and Weaknesses of ADHD Symptoms and Normal Behavior – SWAN:
- Vanderbilt ADHD Teacher Rating Scale and Vanderbilt ADHD Parent Rating Scale VADTRS and VADPRS:

In diagnosis, the value of these rating scales has generally been agreed to be the provision of greater depth to the clinical interview assessment as well as provision of adjunct input complementing the evaluation of the ADHD symptomatology and functional impairment crucial to the diagnosis. (Collett, 2003; Pelham, 2005; National Collaborating Centre for
Mental Health, 2009a) Some of the above rating scales such as certain older versions of the CRS contain large numbers of items which make them less attractive options for contemporary primary care practice. It is worth noting that validation of parent scales has been almost entirely performed by mothers rather than fathers, and that there is generally poor inter-rater reliability between teachers and parents in these rating scales. (Collett, 2003)

Each of these rating scales has individual features which may make one or other of them more suitable in individual circumstances. For example the now-prevalently used VADTRS contains subscales which provide assessment of Oppositional Defiant Disorder/Conduct Disorder, as well as anxiety/depression in addition to inattention and hyperactivity/impulsivity. The VADPRS provides the two sub-scales of inattention and hyperactivity/impulsivity, delivering a DSM-IV symptom count score with symptoms being rated as occurring ‘occasionally’, ‘often’ or ‘very often’. As with the VADTRS, the VADPRS also assesses ODD/CD and provides a screening for anxiety/depression. Recent evaluation of the VADTRS and VADPRS school performance items has demonstrated that these instruments assist in helping rule out learning difficulties in reading and spelling, (but not mathematics.) (Langberg, 2010)

For ongoing management of ADHD, a more recent summary of assessment in children and adolescents (Pelham, 2005) has emphasized the need to move away from targeting specifically the eighteen possible DSM-IV-TR ADHD symptoms. Clinical treatment goals are advocated, characterized in terms of the functional behavioral impairments identified during the diagnostic process. The ubiquitous use of rating scales (sometimes providing little or no parallel indications of functional behavioral impairments) was considered to be inhibiting busy clinicians from moving their focus away from symptoms, and onto the core functional problems being experienced by the child and their family.

In treatment planning, the preceding circumstances, the consequences and the settings of symptoms and their impact on functioning should be collected and documented. In this way the focus will be shifted to the contexts of the sufferers’ problems so that socially valid target behaviors rather than the DSM-IV-TR symptoms of ADHD can more appropriately become the goals of treatment.

While functional behavioral impairment in children has for nearly thirty years been itself subject to rater-scaling with instruments such as the Children’s Global Assessment Scale (C-GAS) (Shaffer, 1983) or more recently, the Impairment Rating Scale (IRS), (Fabiano, 2006) they are still not widely used for evaluating treatment outcomes. In practical primary clinical care, use of such scales to create goals for treatment is difficult, and certainly less likely to gain parent or carer support than targeting individually identified functional difficulties (or even symptoms) faced by the child and their family or carers.

4.1.3 Educator input
An essential step for diagnosis of ADHD in children of school age will be obtaining input from their teachers or other relevant adult school/educator staff. This goal of evaluation in this particular context is to gain information on social and academic functioning. The quantification of symptom counts for the DSM-IV-TR ADHD inattention or
hyperactivity/impulsivity signs can be done in simple direct fashion, or else through use of one of the validated teacher rating scales such as the VADTRS.

The requirement for this communication with schools has been identified as one of the barriers identified by primary care physicians in their management of ADHD. (Power, 2008)

4.2 What are ADHD’s common co-morbidities?

In 1999 after analyzing ADHD studies from the preceding two decades, (Green, 1999) an AHRQ report affirmed that almost one-third of children with ADHD also experienced more than one co-morbid condition (range between 16 and 50 percent). – (See Table 4 at page 54)

An important additional point beyond the need to identify and manage such co-morbidities in children with ADHD, is the need to ensure that depressive and anxiety states prevalently found in parents and carers of children with ADHD are similarly identified and effectively managed. (National Collaborating Centre for Mental Health, 2009a)

4.2.1 ODD & CD – Learning disorders

There is some controversy over whether ODD and its more severe manifestation of CD are components of ADHD, or whether they constitute distinct diagnoses in themselves. (Lahey, 2008) ODD is defined (American Psychiatric Association, 2000) as “a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior directed at authority figures that persists for at least six months” and CD is defined as “a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated”

The 1999 AHRQ report (Green, 1999) in summarizing results of three earlier studies estimated that one third of children diagnosed with ADHD also qualified for a diagnosis of ODD. In four studies, a quarter of ADHD children had been diagnosed with the more serious conduct disorder. These studies summarized largely general populations of ADHD sufferers drawn from both referred populations as well as primary care practices. In young children, the AACAP has affirmed that ODD and CD are nearly always present concurrently. (AACAP Workgroup on Quality Issues, 2007) A number of the commonly used rating scales such as the VADTRS provide indications of whether ODD and CD are present comorbidly with ADHD.

Academic difficulties are relatively commonly experience by children with ADHD. Higher rates of both specific and generalized learning disabilities and poor reading skills have been reported. (McGee, 1992) Compared with children who do not have ADHD, both grade retention (Hinshaw, 2002; Molina, 2009b) and lower probability of completing school (Mannuzza, 1993) have been observed.

The prevalence of ODD, CD, anxiety/depression, learning difficulties and language impairment in 698 children with ADHD from a representative sample 4323 children at school in a single county in Tennessee (Wolraich, 1998) are described in Table 5 at page 54.

A recent review of ODD and CD symptoms in relation to ADHD (Connor, 2010b) has pointed out that more research is required to establish an optimal approach to management of ADHD when it is complicated by oppositional symptoms. They suggest that management of such ODD-complicated ADHD warrants both behavioral treatments as well as pharmacotherapy,
adding that higher doses of ADHD medications such as stimulants or atomoxetine may be warranted, although further research is needed to confirm this point. Conversely it was acknowledged that the positive symptomatology response to both behavioral and pharmacotherapies in multiple studies was not notably different irrespective of whether oppositional symptoms complicated the ADHD picture.

5 Management of ADHD

Management of ADHD always needs to be tailored to individual circumstances and preferences of families living with the condition.

It has increasingly been recognized that ADHD is a chronic condition (Richters, 1995; National Collaborating Centre for Mental Health, 2009a) and with its relatively high prevalence in the community, pediatric and other primary care practitioners need to be prepared to regularly become engaged in its diagnosis and ongoing management. (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001)

In broad terms, there is evidence supporting behavioral, pharmacological and dietary interventions.

5.1 Primary Care issues

The American Academy of Pediatrics (AAP) published a Guideline for treatment of school-aged children with ADHD in 2001. (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001) (This Guideline is no longer formally endorsed by the Academy because more than five years have passed since its initial publication. However the recommended details and processes suggested by the Guideline are still largely supported by more recent evidence.)

Table 6 at page 55 summarizes the recommendations in this Guideline, and provides a digest of the principal reasons cited for each recommendation. Figure 3 at page 60 is an algorithm drawn from the Guideline which outlines a process which can be followed in treatment of school-aged children with ADHD.

Since 2001 there has been considerable discussion about the extent of use of the AAP guidelines in customary primary care. (Rushton, 2004; Polaha, 2005; Epstein, 2008; Epstein, 2010) Most researchers have found low levels of adherence to these guidelines in primary care practices. Nonetheless a primary care before/after intervention study (Epstein, 2008; Epstein, 2010) targeting greater use of the Guidelines in primary care practice has demonstrated that improvements in care and patient symptomatology are certainly possible. An intensive education and an individual practitioner support approach was used as the intervention in these studies. After the intervention, results of care became comparable to those observed in university-based randomized controlled clinical trials targeting improved practice: ADHD symptoms were notably reduced but no change was observed in the measured functional impairments of patients.

There has been recent systematic study of barriers to primary care implementation of the Guidelines. (Power, 2008) Problem areas identified were in three main domains: assessing ADHD, (eg. getting and maintaining communication with schools); the practicalities of providing mental health care in the ADHD context (eg. delivering effective behavioral support
and training for parents); as well as recommending and managing ADHD medications, for example using parent and teacher rating scales.

Studies of primary care attitudes to management of ADHD in other countries have revealed low levels of confidence about necessary knowledge, as well as gaps in essential child psychiatry training. (Thapar, 2002; Shaw, 2003; Ghanizadeh, 2010) Skepticism about the condition and its treatment also led to reticence about extensive engagement in managing ADHD. While these attitudes are not necessarily generalizable to US primary care practitioners, possible parallel attitudes deserve consideration.

5.2 The NIMH Multisite Multimodal Treatment study (MTA)

Reviewers of the literature on ADHD have repeatedly noted (King, 2006; McDonagh, 2009) that despite the very large number of studies which have been performed assessing management of the condition, good quality evidence on the use of drugs and psychosocial treatments is lacking. The evidence about comparative efficacy and adverse events of drugs for treating ADHD has been acknowledged as being severely limited by small sample sizes, generally very short durations of interventions, and the lack of studies measuring functional and long-term outcomes.

Twenty years ago, an Institute of Medicine Report (Institute of Medicine, 1990) highlighted the need for a multi-site treatment study of children with ADHD. After further reports and discussion the National Institute of Mental Health (NIMH) commissioned a consortium of six leading ADHD research groups to develop a combined protocol for a single large study. This key research, known as the MTA study (Richters, 1995) has resulted in an extensive stream of publications: a total of 71 were cited in a 2008 publication from the consortium. (Swanson, 2008)

The original aim of the MTA study was to provide answers to key questions: What are the additive or synergistic benefits of combined pharmacologic and psychosocial treatments compared to either form of treatment delivered alone? – What is the relative effectiveness of systematic, well-delivered treatments (ie. medication alone, psychosocial treatment alone, and their combination) compared to standard treatments delivered in the community? – Additionally, it was agreed that the mediation and moderation of treatment benefits would be studied. It was thereby hoped that predictions might be able to be made about individual family characteristics and social contexts where the intervention strategies might differentially produce benefits. (Hinshaw, 1997)

Subjects between the ages of 7 and 9.9 years at study-commencement were drawn from demographically diverse populations surrounding the six geographically dispersed study sites. Referral sources for the study included mental health settings, pediatricians, advertisements and school notices. (Hinshaw, 1997) Around one-third of patients entering the study had been receiving ADHD medications before enrolment. Care was taken to ensure that all patients at enrolment were accurately diagnosed both formally and consistently with combined-type ADHD. Random assignment then occurred to one of four groups for parallel observation across a fourteen month period of intensive interventions. Power calculations taking account of the multiple sites in the analysis required a total of 576 subjects to be enrolled, 96 from each site.
The three active intervention groups were studied over the fourteen month period with an additional ten month followup after the intensive interventions had finished. During the ten month followup, participants returned to community care and were free to choose their own management and treatments. (Arnold, 1997a; Arnold, 1997b) One group received stimulant therapy alone, the second group received intensive psychosocial behavioral therapies, and the third group, both the stimulant therapy as well as intensive psychosocial behavioral therapies. In the fourth randomized group which served as a comparator, parents were free to choose whatever care they thought best for their children in their local community. The researchers subjected this comparator group to identical batteries of testing and review at baseline, 3 months, 9 months, and 14 months, as well as at the 24 month follow-up, but no other intervention.

The two intervention groups that were allocated to stimulant therapy (ie. with and without behavioral therapy) received methylphenidate or, if it was found not to be tolerated or effective, another medication in a non-sustained release form which was to be administered three times daily. Methylphenidate was titrated up to a ‘best-dose’ during a run-in phase over a one-month period during which time dosing conditions were switched with placebo in a random fashion. (Greenhill, 1996) The ‘best dose’ was arrived at by balancing symptoms, functional impairments and adverse effects, with the parent/child/teacher and clinicians being blind to the switching and actual dose adjustments. Further un-blinded dose adjustments throughout the following thirteen month study period were controlled using an algorithmic protocol. These dosing adjustments were made by a trained pharmacotherapist who had half-hour, monthly medication maintenance visits where support, encouragement and practical advice was provided. In addition if the methylphenidate therapy was found in the titration phase or afterwards to be ineffective, alternative pharmacotherapies were titrated and used during the fourteen month intervention period.

The two intervention groups allocated to intensive behavioral intervention (ie. with and without pharmacotherapy) comprised 27 group and 8 individual sessions for each family during the fourteen month intensive intervention period, first weekly and then less frequently. It began after randomization, in concert with biweekly teacher consultation on behavior management. The same therapists conducted both parent and teacher training sessions. An eight-week-long child-directed summer treatment program used integrated behavioral and cognitive-behavioral interventions to teach social, academic and sports skills. School-based treatment included twelve weeks of a half-time behaviorally trained paraprofessional aide in the classroom immediately after the eight-week-long summer program. The same aide was involved in the summer treatment program as in the classroom, and after the twelve week period in the classroom, parents were coached to maintain teacher contact while the paraprofessional’s involvement with the teacher faded to periodic telephone calls. A daily ‘report-card’ system was used to link the parent, the teacher and the summer treatment program. Target behaviors were scored in a way so that parents could initiate reward processes for their child when they achieved target behaviors.
After use of well-established psychosocial measures, six major outcome domains were reported:

1. ADHD symptoms of inattention and hyperactivity/impulsivity from both parent and teacher perspectives
2. Oppositional/aggressive symptoms from both parent and teacher evaluations
3. Social skills estimated from parent and teacher evaluations
4. Anxiety and depression from both parent and teacher evaluations
5. Parent-child relationships
6. Academic achievement in reading, spelling and mathematics

The study proper extended from 1994 until 1998 with staggering of study commencement across the six different sites. Primary results were reported in 1999. (MTA Cooperative Group, 1999a; MTA Cooperative Group, 1999b) A strict intention-to-treat approach was used for analysis although principal findings were no different when tested without dropouts and crossovers.

Over the fourteen month intervention period, symptoms of patients in all four groups were sizably reduced.

In terms of reducing ADHD symptoms, the medication management and the combination treatment groups were both significantly superior to either the behavioral or the community care groups.

With respect other outcomes, (anxiety/depression, academic performance, parent-child relations and social skills), combination treatment was superior to community care, but medication management and behavioral treatment alone were not significantly different to community care.

During the ten month observation period after the intensive interventions had stopped (ie. in the period 14-24 months after study commencement) the beneficial effects of medication management on symptoms diminished. However symptom improvements in the medication management group were still significantly better than those observed in the behavioral and community care groups at the 24 month time point. (MTA Cooperative Group, 2004a; MTA Cooperative Group, 2004b) During this period, study subjects chose the nature of their care at will, essentially in the same way the community comparison group had done throughout the fourteen month intervention period. It was noted that during the ten month observation period, considerable switching of medications and dosages occurred between the three intervention groups. At the end of the initial fourteen month intervention period, the average daily dose of stimulant (in equivalent methylphenidate doses) for the medication management group (37.7mg) was higher than for the combination treatment group (31.2mg). (MTA Cooperative Group, 1999a) However at the 24 month time point, mean equivalent methylphenidate dosages were 37.5mg, 30.4mg, 25.7mg, and 24mg for the medication management, combined, behavioral and community care groups respectively. (MTA Cooperative Group, 2004a)

A further follow-up of enrollees occurred thirty-six months after the study commenced. At this time, the earlier advantage of medication management reducing symptoms had disappeared, and none of the original randomized groups were different from each other.
However, the numbers of children taking medication had changed significantly between the groups when comparing the 14 and 36 month time points. 45% of those in the behavioral group were now taking stimulants as compared to 14% at the conclusion of the fourteen month intervention period, while in the combination and medication management groups this percentage fell from 91% to 71% across the same time period. (Jensen, 2007)

A follow-up of enrolled patients six, and eight years after enrolment was published in 2008. (Molina, 2009b) The age of subjects at the eight year follow-up was between 13 and 18 years, and 406 of the original 579 children were still available for evaluation. The type or intensity of their fourteen months of treatment in childhood was shown not to have influenced their functioning six to eight years later.

Early symptom patterns appeared to be more prognostic for outcomes at the eight year follow-up. It was concluded that children with behavioral or socio-demographic advantage who had had the best response to any of the treatments had the best prognosis. At 8 years, 32% were medicated (mostly with stimulants) for more than 50% of the days in the preceding year. Notably, at the 8 year follow-up, only 30% still fulfilled the DSM-IV criteria for ADHD.

At the 24 month time point, an additional comparator group (N=289) had been assembled without respect to ADHD or any other mental health state. This group was randomly selected from local populations from which the MTA sample had been drawn (ie. from the same schools and grades, and in the same gender proportions and matched ages as with the MTA children.) This additional comparator group was followed up to the eight-year time point. By that time, the MTA group were functioning significantly less well than the additional comparator group. Delinquency, clinically significant antisocial behavior and academic performance were noted to be significantly worse in the MTA group.

Problems with generalizations from the MTA study which have drawn comment (Banaschewski, 2009) or criticism include the highly intensive and practically difficult-to-reproduce interventions which were tested, as well as the comparison of intensive interventions against a ‘usual care in the community’ group rather than a ‘no-treatment’ group.

The repercussions of the MTA study continue to significantly inform opinion and practice in the care of patients with ADHD.

5.3 ADHD clinical management principles

5.3.1 Selection of therapies

In interpretation of the overall MTA findings it has been suggested that there is no case for advising parents that medication should only be short term, nor that behavior therapy is not worth the effort, nor that intensive and expensive therapy should be continued indefinitely. Rather, “...final decisions on therapeutic plans should depend on the analysis of the individual child, the strengths and weaknesses of their school and classroom environments, the severity of disturbance of peer relationships and the preferences of their families.” (Banaschewski, 2009) Twelve months ago, these particular comments drew agreement from the architects and executors of the MTA study. (Molina, 2009a)
However an alternative approach has been suggested by the American Academy of Child and Adolescent Psychiatry (AACAP) in their Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. (AACAP Workgroup on Quality Issues, 2007) Whilst suggesting that ‘psycho-education’‡ of parents should be an essential precursor to establishment of pharmacotherapy, the findings of the MTA study were cited as a reason for commencing ADHD patients on pharmacotherapy at the outset.

Nonetheless AACAP has acknowledged that behavior therapy alone can produce improvement in ADHD symptoms relative to baseline symptoms or to wait-list controls. In cases where a patient has less than an optimal response to medication, they suggest that psychosocial treatment in conjunction with medication treatment is “often beneficial”. In support of this position they cited MTA findings that where the child’s parent had co-morbid anxiety symptoms, (AACAP Workgroup on Quality Issues, 2007) particularly in the presence of the child having ODD or CD symptoms, (Jensen, 2001) a better outcome from behavior therapy could be predicted. It was also noted that children receiving public assistance and ethnic minorities also demonstrated improved outcomes on combined treatment. (MTA Cooperative Group, 1999b; Arnold, 2003)

5.3.2 Followup frequency and monitoring of therapy

AAP ADHD Management Guidelines (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001) highlight the importance of periodic follow-up so that responses to treatment plans can be evaluated and documented. Impact of either behavior therapies or medications on the selected target behaviors, educational outputs and medication side effects ideally needs to be recorded in a flow sheet or within the child’s medical records.

Maintenance and further development of communication with the child’s school teacher or other school personnel before follow-up visits is suggested. The purpose of this ongoing communication being to consider normal developmental changes in behavior over time, educational expectations and the ongoing changes in the family and school environments.

The frequency of monitoring is said to depend on the degree of dysfunction, complications and apparent adherence to care plans. Once the child’s condition is found to be stable, it is suggested that office visits every three to six months allows for assessment of learning and behavior.

In the case of poor response to treatment (either psychosocial, or pharmacological) it has been recommended (National Collaborating Centre for Mental Health, 2009a) that there should be a further clinical review of:

- The diagnosis
- Coexisting conditions

‡ Psycho-education was distinguished by the AACAP from Psychosocial interventions such as behavior therapy. Psycho-education was said to generally be performed by the physician in the context of medication management and involves educating the parent and child about ADHD, helping parents anticipate developmental challenges that are difficult for ADHD children, and providing general advice to the parent and child to help improve the child’s academic and behavioral functioning.
- Response to drug treatment, and the occurrence of side effects and importantly, treatment adherence
- Uptake and use of psychological interventions for the child, their parents or carers
- Effects of stigma on treatment acceptability from the family’s perspective
- Concerns related to school and/or family
- Motivation of the child or young person and the parents or carers
- The child or young person’s diet

Following review of treatment, AAP Guidelines suggest (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001) that when one stimulant medication has been found to be ineffective despite appropriate titration, a second stimulant (or alternative pharmacotherapy) should be tried. Continued lack of response was said to possibly reflect unrealistic target symptoms, lack of information about the child’s behavior, an incorrect diagnosis, a coexisting condition affecting the ADHD treatment, or lack of adherence to the treatment regimen.

### 5.4 Non-Pharmacological treatments

#### 5.4.1 Behavioral treatments

In customary clinical practice, and in much of the available research, behavioral treatments are an amalgam of different techniques which to a greater or lesser degree are differentiated in strands of psychological theory and practice. To complicate matters further, these techniques and their application differ with respect the age of the young person with ADHD, as well as in their application in the home for the parent/carer, or for the school and its professional staff. (APA Working Group on Psychoactive Medications for Children and Adolescents, 2006) Some broad definitions of these techniques follow:

##### 5.4.1.1 Behavioral parent training (BPT)

BPT combines behavior therapy with parent training in such a way that parents become able to use behavioral techniques with their child. Increases in the sense of parental confidence and competence in raising children is a key target of the training. Behavior therapy involves use of rewards and other re-enforcers which encourage a child to implement changes in targeted motor, impulse or attentional control. (Chronis, 2004) Judiciously chosen rewards of value to the individual child are selected and provided when desired changes are achieved. Rewards may be in the form of praise or tokens of appreciation. Negative consequences can sometimes be of value, for example where impulsive behavior needs to be stopped immediately. Response cost techniques can also sometimes be useful where withdrawal of rewards already earned are a consequence of undesirable behaviors. A ‘time-out’ approach can also be useful when it is felt that overactive, inappropriate behaviors are being compounded by social interactions with others.

##### 5.4.1.2 Cognitive interventions (CI)

Cognitive therapy involves self-instructional training using techniques such as cognitive modeling, self-evaluation, and self-enforcement and response costs. Using these techniques, the young person is taught how to adopt a more reflective, systematic and goal oriented way of approaching tasks and problems. (National Collaborating Centre for Mental Health, 2009a) In a review of effective behavioral treatments in 1998, cognitive interventions were said to
be ineffective, (Pelham, 1998) although more recently self-instructional training was said to be probably the most commonly used cognitive therapeutic approach in the psychological treatment of ADHD. (National Collaborating Centre for Mental Health, 2009a)

5.4.1.3 Social skills training
Poor social skills and compromised peer and family relationships are often a feature of ADHD. Social-skills training aims to teach social interaction skills such as eye contact, smiling and body posture. Additionally assisting the child to better manage stresses, and to initiate, delay, and to generally modulate the amount or intensity of thoughts, emotions, behavior and psychological responses. (National Collaborating Centre for Mental Health, 2009a) It is customarily taught in groups drawing on both behavioral and cognitive approaches, with the overall objective of assisting in the development and maintenance of positive social relationships.

5.4.1.4 Family therapy
Family therapy generally aims to produce changes in the way that families function. A number of models of family have been described: (National Collaborating Centre for Mental Health, 2009a) – Structural family therapy assumes that all well-functioning families have an intergenerational hierarchy with demarcated roles and boundaries. A therapist working with this model challenges existing family structures with the aim of enabling disorganization to be resolved. – Strategic family therapy is based on the assumption of fundamental dysfunctionality in communications within families, aiming for a resolution of such communication failure. – Brief solution-focused therapy uses circumstances where families have managed problems successfully to examine what is different about these interactions, thereby demonstrating that the family can indeed find within their experiences the methods which are needed to handle problematic events characterizing the experience of living with ADHD.

5.4.2 Evaluating behavioral treatments
Assessing evidence for the effectiveness of ADHD behavioral treatments is complicated by many factors. These factors include: the reproducibility of interventions in actual practice (or in confirmatory research); intervention intensity and follow-up duration; the nature and age of patients studied; as well as the extent and nature of impact of the intervention on different aspects of the child’s symptomatology and/or functional impairments. Additionally by far the majority of published reports evaluating behavioral treatments cover studies with low numbers of participants, often using before/after methodologies without parallel control groups. There are many published single subject studies.

Reviewers have repeatedly (Jadad, 1999; National Collaborating Centre for Mental Health, 2009a) confirmed that more and larger randomized controlled trials of approaches to support parents and carers of children with ADHD would be valuable. It has been stressed that particularly where these interventions have been applied to parents/carers, it is important to ensure that assessments of effects include outcomes for the child.

There have been many attempts at summarizing the literature on behavioral treatments for ADHD. (DuPaul, 1997; (Pelham, 1998; (Chronis, 2004; Bjornstad, 2005; Lundahl, 2006; Fabiano, 2009; National Collaborating Centre for Mental Health, 2009a)
5.4.2.1 Child/parent interventions

One of the most recent meta-analyses of behavioral treatments for ADHD covered literature published from 1976 until December 2006 and was published in 2009. (Fabiano, 2009) This review included separate assessment of four classes of studies: ‘Between group’ designs which included both randomized controlled trials aggregated together with non-RCTs containing an active treatment group and a control group; ‘pre-post designs’ as well as ‘within subject’ designs and ‘single subject reports’ were also evaluated in this particular review. Effect sizes were estimated for each of these four designs after data aggregation.

When the between-group studies were evaluated, there were 20 studies available where effect sizes could be calculated. (A small proportion of these studies included school-interventions either as well, or instead of child/parent interventions.) A total of only 523 patients received behavior therapy across all these group studies. A weighted random effects average effect size was calculated to be 0.74 with a 95% confidence interval of 0.52-0.95. For these group studies aggregating both RCTs and non-randomized studies, a significant negative correlation was noted between the size of effect and the year of publication: ie. as the date of the study approaches the present day, the effect size has become smaller. One interpretation of this finding might suggest that the approach of mixing RCTs with less rigorous study designs deserves further consideration. The before/after, within subject designs and single subject studies were found to have considerably larger apparent effect sizes.

Another systematic review also published in 2009 (National Collaborating Centre for Mental Health, 2009a) took a more conservative approach to this difficult literature. Using studies published up until December 2007, they identified ten evaluable randomized controlled trials of behavioral treatments applied to either or both the child and their parent/carer. These studies covered in aggregate, data from a total of 549 participants. (Studies were excluded from analysis where outcomes were only reported in terms of the parents themselves rather than the child.) Control conditions for these studies included assignment to waiting list, treatment as usual and benign interventions with comparable contact times but without active therapeutic components of the experimental condition. The interventions were all broadly based on cognitive behavioral principles with parent training for participants in studies where the child’s age was less than eight years. Only three out of these ten RCTs were carried out in the absence of ADHD medication, and the children’s age range in these studies was between three and thirteen years. There were no studies available which tested family therapy interventions.

It was concluded that compared with controls, parents rated as ‘moderately beneficial’ the effects of these strategies on ADHD symptoms and conduct problems at the end of treatment. From the parent’s perspective 3-6 months after the end of treatments, beneficial effects were still perceived to be present. However it was also noted that positive effects of psychological interventions on the child with ADHD did not appear to transfer to the classroom environment. None of the teacher-rated outcome differences at the end of the intervention, or 3-6 months later reached a level of statistical or practical significance.

Problems exist for evaluation of all studies where the group in whom the intervention was applied cannot be ‘blind’ to the fact of their engagement in the intervention: this may contribute to confounding of results of the meta-analysis, particularly as there were no
positive effects found to exist in the separate educational context where the intervention did not take place.

5.4.2.2 Teacher/School interventions

A review of teacher/school interventions was completed in 1997, including a total of 63 studies, more than half of which were single subject studies both published and unpublished between 1971 and 1995. (DuPaul and Eckert, 1997) Only two of their included studies had more than forty subjects. When comparing the eight ‘between-group’ studies included, a mean effect size of 0.45 was calculated and from this it was concluded that school-based interventions “are significantly effective in enhancing the classroom behavior of elementary school-aged students with ADHD.” Almost all of these studies were carried out at the elementary school level and it was generally not possible to confirm the diagnoses of ADHD in the children who were the subjects of these studies.

In reviewing studies of teacher and school interventions in 2009, the NICE report (National Collaborating Centre for Mental Health, 2009a) concluded that teacher-led interventions for children with ADHD, such as giving effective commands have large beneficial effects on conduct problems, but that the beneficial effects of teacher training on children with ADHD remained inconclusive.

5.4.2.3 Practice implications

It was concluded from these studies that in school-age children, the clinical evidence supports interventions using mixed behavioral and cognitive training and social skills training group sessions for children along with parallel group sessions for parents. In general between eight and twelve sessions lasting one to two hours following a pre-specified curriculum have produced positive results. (National Collaborating Centre for Mental Health, 2009a)

For the pre-school age group it was concluded that good evidence exists for individual parent training being helpful for core ADHD symptoms and conduct problems. The generic Triple P program§ of individual parent training has been shown to be suitable in this regard for parents of pre-school children. (Bor, 2002) (This particular program has also been evaluated more generally in South Carolina, and found to be effective in the prevention of child maltreatment. (Prinz, 2009))

It has been noted that parental anxiety, depression and substance abuse may be contributors to family dysfunction, complicating effective management of the child with ADHD. (Chronis, 2004) The AACAP Guidelines point out that such issues of parental health need to be probed and where necessary, addressed. (AACAP Workgroup on Quality Issues, 2007)

5.4.3 Dietary interventions

As discussed at section 3.4.3.1.2, despite the emergence in 2007 of more convincing information supporting the long-standing contention that food colorings and additives exacerbate hyperactivity in children, (McCann, 2007) there is little support in current Guidelines for dietary interventions as a means of management of ADHD. The 1997 AACAP Guidelines suggested that dietary treatments should not be recommended except possibly with pre-school children. (AACAP Workgroup on Quality Issues, 1997) At that time they noted

§ [http://www.tpinfo.sc.edu](http://www.tpinfo.sc.edu) [Accessed July 2011]
that there was some evidence from the 1980’s that there was a greater likelihood of response to dietary interventions in children under six years of age. (Kavale, 1983; Mattes, 1983; Wender, 1986) However, such dietary interventions were felt primarily to be acceptable only to avoid disrupting the physician’s therapeutic alliance with families who may insist on trying such diets. In the 2007 AACAP Guideline it was repeated that no evidence for dietary interventions existed to justify their use. (AACAP Workgroup on Quality Issues, 2007)

The more recent NICE Guideline concluded that the quality of evidence for dietary interventions is generally poor, and that the evidence that elimination or supplementation diets, when compared with placebo may reduce ADHD symptoms is inconclusive. (National Collaborating Centre for Mental Health, 2009a) However, they recommended that clinical assessment should include asking about foods or drugs that appear to influence a child’s hyperactive behavior. If a clear link is found, healthcare professionals should advise parents to keep a diary of food and drinks taken and ADHD behavior. Then, if the diary supports a relationship between specific foods and drinks and behavior, strategies such as specific dietary eliminations should be tried under professional supervision.

### 5.5 Pharmacological treatments

Repeated high quality systematic reviews (Jadad, 1999; Schachter, 2001; King, 2006; McDonagh, 2009) have failed to find evidence of notable differences between either efficacy, or adverse effects associated with various pharmacotherapies currently used to manage ADHD.

However, these reviews have consistently noted that much of the efficacy data has been gathered from trials performed decades ago and in the intervening time, definitions of ADHD have changed. In almost all cases, studies have been of short duration using small sample sizes lacking power to confidently detect differences. Additionally, a significant proportion of studies have been of poor quality from the perspective of issues of randomization, blinding, outcome definitions, and adverse event assessment and reporting. Notwithstanding these major difficulties, it has generally been concluded that differences between the drug groups in terms of adverse events are relatively minor.

There are very few long-term studies of pharmacotherapy for ADHD, and the MTA study (MTA Cooperative Group, 1999a) provides the most significant contribution to understanding possible benefits and harms flowing from long-term use of pharmacotherapies in school-age children. However, the naturalistic nature of MTA makes even these data difficult to interpret. At the end of the fourteen month intervention period, 23% and 55% of those enrolled in the Behavioral and Community treatment arms respectively were receiving medications, as were only 87% and 93% of those in the Combined, and Medication management arms respectively. (MTA Cooperative Group, 2004a)

The conclusions from the eight-year follow-up of patients from this study (Molina, 2009b) discussed at page 22 are important. The efficacy of ADHD medications to notably alter later trajectories of children’s lives seems limited, irrespective of whether pharmacotherapies are combined with behavioral interventions, even after application of the MTA’s highly sophisticated interventions delivered from specialized pediatric mental health units.
The review of pharmacotherapy approaches which follows should be considered in light of these findings.

5.5.1 Approaches to pharmacotherapies

A listing of commonly used ADHD pharmacotherapies, their dosing forms, durations of action as well as indications of their relative costliness is found at Table 7: see page 56.

5.5.1.1 Pre-school children

There is a concerning lack of evidence for efficacy or effectiveness of pharmacotherapy for ADHD in children, five years of age and younger. (McDonagh, 2009). Additionally, the FDA labels for stimulant pharmacotherapies specify that safety and efficacy of these products have not been proven in children younger than six years of age.

The DERP review identified six placebo controlled studies of immediate release MPH for children in this age group, but only two of these studies were felt to be of sufficient quality to warrant analysis. (Musten, 1997; Firestone, 1998; Greenhill, 2006; Kollins, 2006)

In the first of these studies (Musten, 1997; Firestone, 1998) both high dose MPH (0.5mg/kg twice daily) and low dose (0.3mg/kg twice daily) at the end of seven to ten days of treatment apparently produced small improvements of uncertain significance in learning skills relative to placebo. However, using parental report, the MPH regimen did not result in better task-compliance than placebo. Higher rates of adverse effects were noted in the children when they were treated with increasing doses of MPH relative to placebo treatment. A total of 31 children participated in this study.

The second of these studies (Greenhill, 2006; Kollins, 2006) was a multi-center, multi-phase research initiative known as the Pre-School ADHD Treatment Study. (PATS) This study was supported by the NIMH, and was carried out in six large academic centers. Children from three to five years of age were recruited from clinics, primary care, paid and public service newspaper and radio advertisements, nursery schools, daycare centers and kindergartens. Careful assessment of the children ensured that they had valid ADHD diagnoses which in aggregate were classed as ‘severe’. A total of 261 completed a ten-week ‘parent training’ program which resulted in 37 (14%) either showing significant improvement or the parents being satisfied with their child’s improvement such that they did not proceed onto the next phases of the study to test the efficacy of pharmacotherapy.

Ultimately, a total of 165 were randomized to receive pharmacotherapy: 53% of these children had ODD, 22% also had communication disorder, 16% anxiety disorder, and 8% an elimination disorder. Each child was randomized to receive week-long doses of immediate release MPH three times a day: 1.25mg, 2.5mg, 5.0mg and 7.5mg in a double-blind fashion. Assessments were made using conventional rating scales. A composite standardized outcome on these scales from both parents and teachers was used to gauge the child’s ‘best dose’ which balanced the minimization of ADHD symptoms with acceptable medication side effects. This process paralleled the dose-finding approach used in the MTA study. At the end of this dose-finding phase, children were entered into a double blind placebo controlled parallel-design efficacy trial using their ‘best dose’ or placebo over a further four week period. The primary outcome specified for this phase of the study was to be classified as an ‘excellent’ responder using the SNAP ratings scale. (Swanson, 2001)
22% (13/61) of subjects randomized to best-dose MPH met the criteria for an ‘excellent response’, and 13% (7/53) had the same ‘excellent response’ to placebo. There was no significant difference between MPH and placebo on an intent-to-treat basis with the categorical ‘excellent response’ outcome.

Post hoc non-pre-planned analysis using a continuous outcome variable of symptom score, and an intent-to-treat, last observation carried forward approach, resulted in a significant difference in mean symptom-score favoring MPH. However, 9 of 14 children who withdrew through the crossover-titration and parallel treatment phases left because of irritability and emotionality. Side effects of appetite loss, trouble sleeping, stomachaches, social withdrawal and lethargy were more common on the MPH higher doses than placebo and lower dose MPH groups. Weight inhibition was apparent in MPH treated patients after the titration and parallel treatment phase lasting only a total of eight weeks. (Swanson, 2006)

Later analysis of the results of the MPH titration and parallel phases of the study (Ghuman, 2007) revealed that presence of co-morbidities correlated with likelihood of positive response to MPH. Those patients with one or no co-morbidities had a response equivalent in size to that observed in the older children enrolled in the MTA study: (viz: Cohen’s $d$ between 0.89 and 1.0). In the group with a single co-morbidity, by far the most prevalent was the presence of ODD.

In pre-schoolers, higher rates of adverse effects from immediate release MPH and relatively weak efficacy (especially in the presence of multiple co-morbidities) are important findings from these studies. Additionally, the notable failure of the parent training used in PATS during their initial phase also makes management of ADHD in this age-group problematical. After consideration and analysis of all research on use of pharmacotherapies in pre-schoolers, the NICE Guidelines recommend against their use in pre-school children. (National Collaborating Centre for Mental Health, 2009a).

### 5.5.1.2 School-age children

Evidence supports the use of either stimulant therapy or atomoxetine for reduction of ADHD symptoms in school aged children. (McDonagh, 2009; (National Collaborating Centre for Mental Health, 2009a) However, evidence for efficacy of these pharmacotherapies in the inattentive type, as compared to the hyperactive/impulsive, or combined subtypes of ADHD is rather less clear. Many of the studies carried out over the decades have either used earlier DSM classification systems, or alternatively not clearly differentiated ADHD subtypes in their study populations. (McDonagh, 2009)

There are many short term studies confirming efficacy of stimulant therapies but durations of treatment have usually been short and the methodological quality low. Better quality long-term studies with pharmacotherapies are lacking. (McDonagh, 2009) However two such longer-term studies compared immediate release MPH to placebo. (Kupietz, 1988; Ialongo, 1993) Apart from the MTA Study (MTA Cooperative Group, 1999a), there are two further better quality studies (Brown, 1985; Firestone, 1986) which have evaluated immediate release MPH compared with non-drug interventions for periods of nine months to two years. The results of the MTA study are discussed at page 19. The other longer term studies noted some deterioration in effectiveness towards the end of their intervention durations. In one of these studies, the question of adherence to the medication regimen was questioned in the
longer term. (Kupietz, 1988) A further possible cause for this deterioration of beneficial outcomes may lie in the enforced static dose regimes which were used throughout the intervention periods.

As noted in recent neuropharmacology literature, in the last two decades by far the largest advances which have been made in pharmacotherapy for ADHD have been through development of formulation improvements, better drug delivery systems and pro-drug stimulant therapies. The development of new molecules with alternative psycho-activity fundamentals has not occurred. The re-uptake inhibitors, α₂ adrenoreceptor agonists and modafinil do not have the ability to match the powerful functions mediated by psycho-stimulants. (Heal, 2009)

Observational studies have consistently confirmed that sustained release preparations improve both adherence and persistence with stimulant therapies. (Lage, 2004; Marcus, 2005; Sanchez, 2005; Kemner, 2006a; Kemner, 2006b)

Table 8 at page 57 provides a description of the pharmacokinetic profiles of methylphenidate products drawn from the DERP report (McDonagh, 2009)

In short term studies within the school-age group, there is weak evidence that immediate release dextroamphetamine (D-AMP) and immediate release MPH are equivalent in efficacy. Two controlled studies with around 100 patients (Efron, 1997a; Efron, 1997b; Efron, 1998) compared these two products. It was concluded that there were no apparent differences in efficacy between the two products based on children’s assessment (Efron, 1998), or on ratings provided by parents and teachers. (Efron, 1997a) The wider spectrum of neural bioactivity for amphetamine relative to methylphenidate and the lack of substantial systematic research into its efficacy has caused some reviewers to recommend against its use in childhood ADHD. (National Collaborating Centre for Mental Health, 2009a)

A systematic review of six studies investigating the usefulness of atomoxetine relative to placebo in children and adolescents with ADHD has demonstrated that atomoxetine improves ADHD rating scale total scores relative to placebo. (Cheng, 2007) (Standardized mean difference -0.64; 95%CI -0.76 to -0.52) In a meta-regression analysis in this review, a high baseline of ADHD symptoms was associated with greater symptom reduction. Factors associated with smaller amounts of symptom reduction included male gender, co-morbid ODD, and the ADHD hyperactive/impulsive subtype. Young age of patients and high baseline hyperactive/impulsive symptoms was associated with more adverse events while the opposite was true for patients of the inattentive subtype. Common adverse events included appetite decrease, abdominal pain, vomiting, dyspepsia and somnolence. Efficacy and side effects did not appear to be altered by co-morbidities of general anxiety disorder or major depression.

Atomoxetine has been investigated for its efficacy in two non-inferiority studies against immediate release MPH. Regrettably although extending for ten weeks with a total of 228 children, one of these studies (Kratochvil, 2002) has been criticized for unbalanced dosing of the two substances thereby favoring atomoxetine. (McDonagh, 2009) Both studies demonstrated that atomoxetine was apparently non-inferior to immediate release MPH with respect to symptom improvement. (Wang, 2007) However treatment-emergent adverse effects were significantly more frequently seen in the atomoxetine group: (anorexia, nausea,
somnolence, dizziness and vomiting). These effects were described as being of mild or moderate severity. (Wang, 2007)

A more recent study has compared the efficacy of atomoxetine with osmotically-released MPH in a large (N=516) placebo controlled double blind study in children 6 – 16 years of age with any subtype of ADHD. Response rates for atomoxetine (45%) and MPH (56%) were both found to be superior to placebo (24%). (Newcorn, 2008) The response to MPH in this form was significantly better than that observed with atomoxetine. Both medications were described as being well tolerated and there were no significant differences in the extent to which side effects were experienced between the two tested active substances. Using a double blinded crossover technique after the initial six-week study it was found that about half of the initially-MPH-treated patients responded well to both treatments and about two-thirds of the remainder responded preferentially to one treatment or the other.

Potential harms of pharmacotherapies to be balanced against achievable benefits are further discussed at page 40.

5.5.2 Stimulant therapy

When the choice is made to manage ADHD using pharmacological therapies, stimulants are generally considered to be the first line of approach. (AACAP Workgroup on Quality Issues, 2007) There are two stimulant medications currently available, Methylphenidate (MPH) and Amphetamine (AMP).

There is a large body of published research on the benefits of short-term stimulant therapy in relation to ADHD symptoms. In an AACAP practice parameter on use of stimulant therapies in 2002 (Greenhill, 2002) it was noted that symptomatic improvement had been observed in between 65% and 75% of patients randomized to receive stimulants versus only 5% to 30% of those assigned to placebo. This estimate was made from data published up until 1996 in 161 randomized controlled trials of highly variable quality, altogether incorporating a total of 5899 patients.

It is now understood that stimulant effects on human behaviors and cognition are not restricted to sufferers of ADHD, but are equally applicable to the general population. (Arnsten, 2009)

Within the stimulant class there are more studies of MPH than AMP for ADHD. As discussed above, within-subject comparison studies are yet to find significant differences in safety or efficacy of these two groups of stimulants. (Arnold, 2000a) A review of a total of 174 subjects in six small, cross-over studies trialing both MPH and AMP, reported that 48 responded better to AMP, 27 to MPH, and at least 72 to both, representing an 85% overall response rate if both MPH and AMP are tried. (Arnold, 2000a)

There are currently no methods to determine which patients or which symptoms will respond better to one or the other stimulant group. (AACAP Workgroup on Quality Issues, 2007) However more recently, after comprehensive review of data till December 2007, NICE concluded that when compared to placebo, the size of clinical effect is largest for MPH. (National Collaborating Centre for Mental Health, 2009a) In this review, as in others, (King, 2006) it is suggested that if treatment with maximally tolerated doses of MPH fails, then after
review of clinical circumstances, (see page 23) the option remains to switch the patient to an alternative stimulant.

When clinical symptom-reduction response to stimulant therapy has been quantified via rating scales relative to placebo a mean effect size of about 1.0 has been observed. It has been noted that this represents one of the largest effect sizes for any psychotropic medication. (AACAP Workgroup on Quality Issues, 2007)

However, the target for ADHD pharmacotherapy is not solely symptomatic relief. As discussed at page 16, functional impairments attributable to ADHD need to be the primary objective for both pharmacological and non-pharmacological treatments. (Pelham, 2005)

A meta-analysis of social and academic functioning in school aged children receiving MPH with and without accompanying psychosocial treatments has confirmed social functioning improvements of ‘moderate’ mean effect size as a result of stimulant therapy. (van der Oord, 2008) Where the teacher was the informant, it was noted that the effect size for improved social functioning was significantly higher than when parents provided the estimate. Whether or not psychosocial treatments had been added to MPH therapy, improvements in social function were of roughly equal size irrespective of whether improvements had been gauged by parents or teachers.

However with regards the impact of stimulant therapy on academic performance, the results remain controversial. (van der Oord, 2008) In one of the review’s included studies in MPH-responsive children 7-9 years of age without learning or conduct disorders, independent of psychosocial therapies, MPH treatment was found to produce enhanced academic achievement (mean effect size 1.04). (Hechtman, 2004) This positive effect was sustained across a two year trial. However in a meta-analysis of all four studies of academic functioning admitted to this analysis, an overall effect size for improvement in academic function through MPH was found to be small because of the very small effect sizes in the other three studies. (van der Oord, 2008)

There is a largely linear relationship between stimulant dose and clinical response irrespective of the subtype of ADHD. (Solanto, 2009) There also does not appear to be a therapeutic window for response to stimulant therapies. Rather, from the MTA studies, roughly a third of children are likely to have optimal response relative to side effects in each of the dose ranges: < 15mg/ day, >15<34mg/day, or >34mg per day. – However the MTA study found that doses needed to be adjusted (generally upwards) to maintain optimal benefits in relation to side effects. (Vitiello, 2001) It has been suggested that physicians need to titrate doses upwards every one to three weeks, until either a maximum dose is reached, symptoms remit, or side effects limit further upward dose adjustment. (AACAP Workgroup on Quality Issues, 2007)

**5.5.2.1 Methylphenidate (MPH)**

The mechanism by which MPH reduces symptoms of ADHD is not clear. It is believed that concentrations of dopamine and noradrenaline are increased in both the frontal cortex and sub-cortical areas by MPH. (Heal, 2009) MPH inhibits reuptake of dopamine and noradrenaline into pre-synaptic neurons by blocking pre-synaptic membrane dopamine
transporter mechanisms. It also influences presynaptic terminal vesicular transport functions for dopamine stores.

Oral absorption of MPH is rapid and almost complete, and it undergoes significant first-pass metabolism resulting in low absolute bioavailability. Maximum plasma concentrations are reached one to two hours after administration of a 10mg dose. A relatively short two hour half-life correlates well with a duration of action from one to four hours. (McEvoy, 2010)

MPH has a chiral center, and the d-MPH enantiomer is known to be the pharmacodynamically active substance, and there remains some controversy over the role of the I-MPH enantiomer. (Markowitz, 2008; Quinn, 2008)

5.5.2.2 Amphetamines (AMP)

As with MPH, AMP acts by enhancing the function of central catecholamines, noradrenaline and dopamine. However, as with MPH the precise mechanism by which it alters the symptomatology of ADHD is not understood.

AMP has a chiral center, but unlike MPH, both enantiomers appear to be pharmacodynamically active for moderating symptoms of ADHD. (Arnold, 1976)

The enantiomers of AMP exert action both inside and outside the presynaptic neurons. They are competitive substrates for the noradrenaline and dopamine transporter mechanisms, and thus are actively transported into presynaptic terminals where they can displace catecholamines from newly synthesized, as well as vesicular storage pools.

The released catecholamines are then expelled into the synaptic cleft via the noradrenaline and dopamine transporters without necessarily relying on the firing of the neurons. By virtue of their presence in the synaptic cleft, and their transient occupancy of the noradrenaline and dopamine transporter mechanisms on their way into the pre-synapse, the AMPs also delay clearance of dopamine and noradrenaline from the synaptic cleft. Additionally, the amphetamines are a weak inhibitor of monoamine oxidase: through this mechanism it is believed that the AMP enantiomers may contribute to some further delay in clearance of catecholamines. (Heal, 2009) Finally presynaptic neuronal vesicular storage of dopamine is also influenced by the AMP via modulation of vesicular transport mechanisms.

AMP is readily absorbed orally and is excreted both as unchanged drug as well as with hydroxylated metabolites. The apparent elimination half-life of D-AMP is 6.8 hours, and there is thought that the l-isomer may be excreted at a modestly slower rate than D-AMP. (Patrick, 1997) Excretion is faster in acidic urine, and the half-life can thereby be considerably reduced.

5.5.3 Non-stimulant therapy

5.5.3.1 Atomoxetine

Atomoxetine is a noradrenaline reuptake inhibitor which increases the synaptic concentrations of noradrenaline. Despite the fact that Atomoxetine does not inhibit the dopamine transporter, levels of dopamine are also raised extraneuronally. It is believed that atomoxetine’s effects are substantially localized in the prefrontal cortex in contrast to the broader effects which MPH and AMP exert in subcortical regions. (Heal, 2009)
Taken orally, atomoxetine is almost completely absorbed and is minimally affected by food. It achieves a maximal plasma concentration one to two hours after oral administration. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. It undergoes modest first-pass metabolism. Atomoxetine has a half–life of about 5 hours, and is generally taken once a day in the morning although divided doses may prove to be of benefit.

Further discussion of atomoxetine’s effectiveness is found from page 31 onwards, and harms at page 41.

5.5.3.2 Clonidine

Clonidine stimulates all three of the $\alpha_2$-receptor sub-types in the brain, and its mechanism of action in ADHD is not clear. However it is believed that an optimization of catecholamine modulation occurs in the pre-frontal cortex with administration of clonidine in ADHD. (Arnsten, 2007)

Recently approved for use in ADHD, an extended release formulation has now become available for use either as monotherapy or as adjunctive therapy to stimulant medications.

Orally administered extended release clonidine in the form approved for ADHD treatment produces peak plasma concentrations approximately six hours after administration, (as compared to approximately two hours for non sustained-release clonidine.) Absorption of the extended release dosing form is not influenced by food, and the elimination half-life is around 12 hours similar to the immediate release form of clonidine. However the peak plasma concentration for the immediate release form is approximately twice that of the extended release product.

Clonidine causes dose related decreases in blood pressure and heart rate, as well as relatively frequent somnolence, headache upper abdominal pain and fatigue. At cessation, tapered dosing is recommended to avoid sudden increases in blood pressure.

Despite its only recent approval for use in ADHD, clonidine has been in use for ADHD for more than twenty years. In four out of six available controlled studies by 2007, (Arnsten, 2007) clonidine was described as providing benefits in management of ADHD. Its value relative to stimulants in managing tics disorders in ADHD (Tourette's Syndrome Study Group, 2002) is discussed at page 46. An early meta-analysis of mostly poor quality studies suggested that for symptoms of ADHD, clonidine has a small to moderate effect size, less than that observed with stimulants. (Connor, 1999)

5.5.3.3 Guanfacine

Similar to clonidine, guanfacine stimulates $\alpha_2$-receptors in the brain, and appears to act somewhat preferentially on the $\alpha_{2A}$-receptor subtype. (Arnsten, 2007) These effects in the pre-frontal cortex are believed to underlie the activity of the $\alpha_2$ receptor agonists on ADHD symptomatology. Modulation of catecholamines in this part of the brain is thought to underlie the efficacy of $\alpha_2$-receptor agonists for treating ADHD symptoms.

Guanfacine has been marketed since 1986 for hypertension. It is rapidly and completely absorbed after oral administration. It is liver-metabolized by the CYP3A4 and 5 enzymes, and its effect profile is modulated by inducers and inhibitors of these enzymes. It is renally
cleared, and in its non-sustained release format has a clearance half-life of 17 hours. (Kiechel, 1980)

In a 2001 study, 34 medication-free combined-type ADHD sufferers with tic disorder received either placebo or immediate release guanfacine for an eight week period. (Scahill, 2001) While no significant improvement on a hyperactivity index was noted by parents, an improvement was found on a teacher-rated ADHD rating scale. A significant improvement was also noted on tic severity relative to placebo. A notably high level of side effects was observed in this small study.

An extended release formulation of guanfacine was approved for use in 2009 which provides controlled absorption and less fluctuation of the plasma profile of the parent drug. The company owning the patent on the extended release preparation has sponsored three studies which have explored guanfacine’s usefulness in children with ADHD relative to placebo (Biederman, 2008; Sallee, 2009) as well as in children with oppositional symptoms and ADHD. (Connor, 2010a) These studies have confirmed the effectiveness of guanfacine in reducing ADHD symptomatology over periods ranging from three to eight weeks. Both clinical effect size as well as side effect prevalence appear to be dose related. The effect size at higher dosages exceeds that observed for other nonstimulant treatments but at the cost of substantial side effect levels.

In a study where a total of 259 children were treated with guanfacine, at lower dosages, 46% of children experienced somnolence, sedation or fatigue, rising to 63% at higher dosages relative to 10% experiencing the same side effects with placebo. (Biederman, 2008) While these somnolence/fatigue side effects subsided over time on the medication, there was still a notable proportion in whom at the end of the study, these adverse effects were still apparent: (6-12%). Upper abdominal pain (16%), dry mouth and nausea were also observed at greater levels in groups receiving the higher dose. Cardiovascular adverse events resulted in five of the 259 patients being withdrawn from this study.

Lowered blood pressure and pulse rate effects were noted in most patients enrolled in active arms of these three studies.

A multi-center open-label dose-escalation study of 75 children and adolescents with suboptimal control while prescribed stimulants was undertaken in 2004. (Spencer, 2009) Similar high levels of side effects were observed: (abdominal pain 25%, fatigue 24%, somnolence 19%, headache 20%, irritability 23%.

5.5.3.4 Therapies for ADHD not approved by FDA

5.5.3.4.1 Bupropion

Bupropion selectively inhibits neuronal uptake of both noradrenaline and dopamine. It is a weak selective dopamine re-uptake inhibitor.

It is extensively metabolized during and after oral administration and has a number of active metabolites. The peak level of a key active metabolite after oral administration is approximately three hours, and the parent substance has an elimination half-life of approximately twelve hours and active metabolites around twenty hours.
Some evidence exists that in adults, bupropion when compared with placebo reduces ADHD symptomatology and provides clinical improvements. (Reimherr, 2005; Wilens, 2005a) However little parallel evidence is available to support its use for ADHD in school aged children. (National Collaborating Centre for Mental Health, 2009a)

Bupropion has been associated with dose-related risk of seizures, and when used in children, has caused dermatological reactions twice as frequently as occurred with placebo. (Conners, 1996)

### 5.5.3.4.2 Modafinil

Modafinil is an antinarcotic with mood enhancing properties. It has complex pharmacology. It has weak affinity for the dopamine re-uptake transporter and also does not have affinity for either the noradrenaline or 5HT re-uptake transporters. Modafinil moderately potentiates catecholamine activity in the brain. A major effect appears to be related to 5-HT levels in the brain.

Serious adverse effects observed with modafinil have resulted in the FDA and its parent company recommending that it is not used in children. (Cephalon, 2007)

### 5.5.3.5 Complementary and alternative therapies

The overall extent of use of complementary and alternative medicines in childhood has been estimated using National Health Interview Survey (NHIS) data. From the 2007 NHIS data (Barnes, 2008) it was reported that one in every nine children used such therapies in the twelve months prior to the survey: 2.5% of all US children received such therapies during the previous twelve month period for ‘ADHD/ADD’. In a prestigious US pediatric referral clinic it was noted that 54% of parents reported using these therapies, but that only 11% of parents had discussed their use of these approaches with the child’s physician. (Chan, 2003) Such failures in communication reflect poorly on the nature of intellectual engagement between physicians and the families in their care who are living with ADHD.

With the exception of the Canadian guidelines (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA), 2011) supporting the use of melatonin for the treatment of insomnia for children with ADHD, none of the other key guidelines and practice parameters for ADHD management suggest there is value from use of complementary therapies, with one such 2004 international consensus statement affirming that none have proven efficacy. (Kutcher, 2004)

However, a wide range of complementary and alternative therapies remain in use by parents of children with ADHD. From the NHIS data, one in every three to four ADHD patients will have been using complementary or alternative therapies with or without their physician’s knowledge.

### 5.5.3.5.1 Biomedically-based complementary/alternative treatments

A recent review of alternative biomedical treatments (Hurt, 2011) has suggested that there are two such therapies ‘worth a trial’: multivitamin supplementation for example in children with stimulant-decreased appetite, and essential fatty acid supplementation. In the view of these reviewers, two further approaches had enough controlled evidence to be recommended for certain subsamples of patients, namely those where mineral deficiencies
might exist, and where elimination diets could be justified as a result of a documented history of reactions to foods or food additives. These views are controversial.

The potential benefits and difficulties associated with use of elimination diets have been discussed above at section 5.4.3, page 27. A recent publication has provided additional supporting evidence for elimination diets. Under carefully controlled conditions it has been shown that five weeks of a restricted elimination diet can notably improve both parent and teacher evaluations of ADHD symptoms relative to a control group receiving non-specific dietary advice. The effect sizes were substantial (1.1-2.0) in the elimination diet group, and significant relapses were observed on re-challenge of the elimination diet responders. (Pelsser, 2011)

In the case of essential fatty acid supplementation there may be plausible theoretical benefits as a result of generally lower than normal levels of omega-3 fatty acids found in plasma of children with ADHD. (Chen, 2004; Clayton, 2007) There are multiple randomized placebo controlled studies of essential fatty acid supplementation in children with ADHD, but the majority of these studies do not show benefit, and those that do have serious methodological flaws. (Larzelere, 2010) A recent systematic review of essential fatty acids and ADHD concluded that the current evidence does not support use of essential fatty acid supplements as either primary or supplementary treatment. (Raz, 2009)

There has been controversy concerning the potential for zinc deficiency in children with ADHD to hamper the effectiveness of stimulant therapies. (Arnold, 1990) This controversy has resulted in considerable research and comment, (Arnold, 2000b; Akhondzadeh, 2004; Arnold, 2005) culminating in a recent publication (Arnold, 2011) which has concluded that zinc supplementation does not improve inattentive-type ADHD more than placebo; that zinc with amphetamine does not improve ADHD symptoms more than placebo with amphetamine; but that an optimal dose of amphetamine with zinc can be 20% lower than with placebo. These essentially negative results must also be considered in light of additional recent evidence where a random sample of children with ADHD in the United Arab Emirates were found to have blood concentrations of zinc four-fold higher than matched children without ADHD. (Yousef, 2011) As a result of these findings it is important to be especially cautious when parents are wishing to use zinc supplementation for their children, bearing in mind the toxic potential for this particular heavy metal.

In ADHD, no reliable evidence exists to support use of acetyl-L carnitine, flax-oil, pycnogenol, hypericum (St Johns wort), dimethylaminooethanol, immune therapy, herbal treatments, glyconutritional supplements or amino acid supplementation. (Hurt, 2011)

5.5.3.5.2 Melatonin for insomnia

The only complementary/alternative treatment that has been tested in randomized, double blind trials for insomnia in children with ADHD is melatonin. Two well-controlled studies have demonstrated that melatonin is significantly better than placebo at decreasing sleep-onset latency and increasing total sleep time in children treated with stimulants. (Weiss, 2006; Van der Heijden, 2007)

Weiss et al performed a two-phase study in ADHD children six to twelve years of age (n=33) taking stimulants. The study began with a sleep hygiene intervention and patients were
allowed to enter the double-blind, randomized, crossover trial if they continued to have initial insomnia of greater than sixty minutes. Patients were randomly assigned to receive either melatonin 5mg or placebo twenty minutes prior to bedtime for one week. This was followed by a one-week washout period and then therapies were switched. Sleep hygiene reduced initial insomnia to less than sixty minutes in five cases. Combined interventions with sleep hygiene and melatonin resulted in a mean decrease in initial insomnia of sixty minutes. Reduction in initial insomnia of sixteen minutes was seen with melatonin compared with placebo (p<0.01). The treatment responders continued into an open-label follow-up. Sleep duration during the open-label follow-up continue to improve and sleep onset decreased to a mean of thirty-one minutes. (Weiss, 2006)

Van der Heijden et al performed a randomized, double-blind, placebo-controlled trial using melatonin 3mg (<40Kg), melatonin 6mg (>40Kg), or placebo for four weeks in 105 stimulant-free children aged six to twelve years. The primary outcomes included melatonin effects on sleep, behavior, and cognition. They found that sleep onset occurred within twenty-seven minutes with melatonin and was delayed by ten minutes with placebo (p<0.0001). Total time asleep was twenty minutes greater than placebo (p<0.01). There were no statistically significant effects seen on behavior or cognition in the melatonin group. They also conducted a two-year follow-up to evaluate adverse events which did not show significant differences between the 3mg and 6mg doses and placebo. (Van der Heijden, 2007)

Based on the above information and an additional review article (Weiss, 2010), melatonin seems to promote sleep in children with ADHD. It does not seem to improve the behavioral symptoms of ADHD as demonstrated in the study conducted by Van der Heijden and colleagues.

5.5.3.5.3 Non-biomedical complementary/alternative treatments

Use of meditation therapies (Krisanaprakornkit, 2010) and chiropractic (Karpouzis, 2010) for ADHD have recently been reviewed and found to be without generalizable evidence of effectiveness. Biofeedback is another technique which has been examined for its efficacy for ameliorating symptoms of ADHD.

Biofeedback relies on conditioning mechanisms of learning, to train subjects to change physiological activity as a result of real-time feedback. Biofeedback has been used variously to try to regulate muscle tension, skin temperature, the sympathetic nervous system, respiration, and cardiac activity.

Neurofeedback is a specific form of biofeedback which has been investigated systematically for its effectiveness to alter the symptomatology of children with ADHD. (Lofthouse, 2011) Much of the research on neurofeedback effectiveness for childhood ADHD symptoms has been poorly controlled and subject to many confounding factors. In 2005 reviewers of research in this field concluded that the value of neurofeedback was unproven. (Loo, 2005) However, recently more positive appraisals of neurofeedback’s potential have been published (Arns, 2009) with the arrival of a number of better controlled studies. In particular, in the past two years collaborative research from three German specialist child psychiatry centers has reported on a randomized controlled trial which was sufficiently powered to provide evidence for the effectiveness of their particular form of neurofeedback training. (Gevensleben, 2009; Gevensleben, 2010)
Stimulant-naïve children between eight and twelve years of age with any form of ADHD were randomized to receive either neurofeedback or alternatively, attention skills training. The two interventions were designed so that they closely resembled each other, with the amounts and nature of clinical attention being closely matched. Both interventions involved use of a computer ‘game’ with the control group receiving a sophisticated skilling activity involving commercial learning software focusing on visual and auditory perception, vigilance, sustained attention and reactivity. The neurofeedback intervention used two separate feedback animations where, while seated in front of a monitor, children learned to control a simple game through modulating their brain electrical activity. The theoretical basis for the first of the feedback animations involved training of slow cortical potentials both positively and negatively. In the second animation, theta/beta training was involved, with the child learning to reduce theta band activity (4-8Hz) and increasing beta band (13-20Hz) activity.

Both neurofeedback and the control intervention involved blocks of eighteen fifty-minute-long sessions. Two to three double sessions over about three to four weeks, tailored to suit the family’s routine activities were used. After the first eight sessions children in each group were instructed to practice (and log) one of their learned strategies in a specific situation where increased attention control could be important. This exercise was intended to take about ten minutes each day in customary daily-life situations. Parent and child counseling for these activities was matched between groups and equivalent for both the neurofeedback and the control attention skills training interventions.

Both parent and teacher ratings for neurofeedback were significantly superior to those of the attention-skills training group with an effect size of about 0.60. Even more importantly, behavioral effects of the neurofeedback training (relative to control) were maintained in children at a six-month followup, with equivalent numbers of dropouts as a result of either medication commencements or loss-to-followup conditions. (Gevensleben, 2010). The researchers and the families of subjects in this study were unable to be blinded to the intervention conditions. As a consequence it will be important in future for these findings to be confirmed by other workers. (Lansbergen, 2011)

Nonetheless, these important results have led to authoritative commentary suggesting that while neurofeedback techniques may not be as powerful as stimulant medications they may have potential to become a mainstream treatment for ADHD in the future. (Coghill, 2010)

However in 2007 it was noted that costs of neurofeedback training, (where it is available in formats similar to those described by Gevensleben) range from $50 to $200 per hour. (Lofthouse, 2011) As a result, until insurance reimbursement for this form of neurofeedback becomes available, it is likely to remain out of reach for most families.

### 5.5.4 Potential harms of pharmacotherapies

Despite differing modes and durations of action both MPH and AMP share a set of common side effects which are usually mild or temporary, and generally acceptable in the light of the relief from ADHD symptoms achieved.

Milder neurological symptoms such as headache, dizziness and insomnia occur, as do psychological effects such as mood and anxiety symptoms. Gastroenterological symptoms also occur including loss of appetite and abdominal discomfort which contributes to longer
The DERP review (McDonagh, 2009) found a majority of trials of immediate release MPH and AMP in school aged children reported no differences between the MPH and AMP in terms of adverse events. (Arnold, 1978; Elia, 1991; Elia, 1993; Efron, 1997b) However two lesser-quality short term crossover trials reported a greater degree of weight retardation with D-AMP as compared to MPH. (Kauffman, 1981; Sharp, 1999) Studies with sustained release preparations of both MPH and AMP resulted in largely parallel findings.

Adverse effects of atomoxetine include appetite decrease, abdominal pain, vomiting, dyspepsia and somnolence. In a recent review and meta-analysis the relevant numbers-needed-to-harm (NNH) were appetite decrease NNH=8.81, abdominal pain NNH=22.48, vomiting NNH=29.96, dyspepsia NNH=49.38, and somnolence NNH=19.41. These estimates of harm were balanced by a number needed to treat (NNT) for treatment response: NNT=3.43 (95%CI 2.79-4.45), and relapse prevention: NNT=10.30 (95%CI 5.89-40.62). (Cheng, 2007)

The other substances currently approved for use in ADHD are the α2 adrenergic agonists, clonidine and guanfacine. These products are associated with a high prevalence of side effects including sedation, irritability and reduction in heart rate and blood pressure. When clonidine is used via trans-dermal delivery, it has been noted that it may result in localized rash, erythema and attendant irritation. (Connor, 1999) For further discussion of harms of guanfacine, see page 36.

The now extensive use of stimulants and atomoxetine for ADHD across the population has led to concerns about rare devastating harms such as sudden unexplained death. There will be continuing controversy and debate about such issues. The development of more reliable epidemiological methods and tools to study and gain estimates of the true frequencies of such outcomes relative to background population incidences is an urgent public health priority. (Vitiello, 2009)

5.5.4.1 Cardiac adverse events

Increased heart rate and pressor effects of stimulant therapies result at least in part from their sympathomimetic activity. (Rapport, 2002) In adults with ADHD who were treated with a wide range of pharmacotherapies, (including stimulants) blood pressure was estimated to rise around 5mmHg, (baseline to end of treatment intervention.) (Wilens, 2005b)

In 2004, a report from the FDA’s adverse event reporting system flagged a possible relationship between ADHD stimulant therapies and sudden cardiac death. (Avigan, 2004) This report recommended close monitoring of this possible association, as well as a black-box warning on stimulant therapy products recommending clinicians consider benefits vs. risks of stimulant therapies in patients with established cardiac abnormalities.

In February 2006, the FDA’s Drug Safety and Risk Management Advisory Committee agreed that a black-box warning describing cardiovascular risks of stimulant drugs used in treatment of ADHD be adopted. (Nissen, 2006) The extensive contemporary use of stimulants (10% of all ten-year old boys in the US) was cited as one of the reasons for this decision even though the exact extent of the contribution of ADHD stimulant therapies to otherwise unexplained deaths was not available.
However in March 2006, the FDA’s Pediatric Advisory Committee agreed (Anonymous, 2006) that labeling and package changes should be made rather than using the proposed black-box warning. It was recommended that possible adverse cardiac and psychiatric events from approved ADHD products including stimulants should be highlighted. In February 2007 it was announced that medication guides had been produced by each ADHD-drug manufacturer. These materials provide further information for patients and their parents/carers about possible risks of these products, as well as advice on precautions that can be taken where a decision to commence ADHD pharmacotherapy has been taken.

In June 2009, a case-control study became available linking sudden death and use of stimulant medications in youths across the US, (Gould, 2009) The FDA responded listing a number of limitations found in this study’s methodology. They also acknowledged that, together with the AHRQ the FDA had sponsored a large epidemiological study to gain further information about risks associated with stimulant medication use in children.

In August 2010 the FDA announced continuing delays in completing this study. Ground-breaking work under way in establishing large enough cohorts for this study, and the essential raw data verification processes had proven to be very challenging. (Anonymous, 2010a)

The FDA have provided recommendations for healthcare professionals concerning adverse cardiac events: (Anonymous, 2010a)

“Follow all the current prescribing information for use of these medications, including:

- Take a medical history for cardiovascular disease in the child and his or her family.
- Perform a physical exam with special focus on the cardiovascular system (including examination for the signs of Marfan syndrome)
- Consider obtaining further tests such as a screening electrocardiogram and echocardiogram if the history or examination suggests underlying risk for, or the presence of heart disease.”

The median death rate for sudden unexplained death in children in the whole population has been reported to be 1.2-1.3/100,000 per year. (Graham, 2010) Extrapolating from adverse drug reporting system data (and making significant assumptions about the duration of individual prescriptions for ADHD pharmacotherapies), a figure of 0.2-0.5 sudden unexplained deaths in children /100,000 per year resulting from ADHD medications has been suggested. (Rappley, 2006) However, it is well known that the FDA’s spontaneous reporting scheme captures only a small proportion of drug-related serious adverse events, and so the real incidence is likely to be significantly higher. Nonetheless, in evaluation of this controversial data, both Canadian (Hamilton, 2009) and European (Graham, 2010) authorities have concluded with the AACAP (AACAP Workgroup on Quality Issues, 2007) that until better data is available, children on ADHD medications are likely to be experiencing the same rates of sudden unexplained deaths as is occurring in the general population.

5.5.4.2 Suicidal behaviors

It has been noted that suicidal events are rarely related to ADHD therapies. However children and adolescents suffering ADHD together with depressive symptoms and more serious forms of ADHD such as conduct disorder, have been associated with significantly higher levels of impulsive completed suicides relative to the general population. (James, 2004) The annual
suicide rate for adolescents with ADHD was reported to be 32 to 39 per 100,000 with a relative risk of 2.91 (95% CI 1.47-5.7) compared with the general population. This review noted that some evidence exists that children treated with MPH may be at lesser risk of suicide attempts than those who are untreated.

Atomoxetine has been suggested as a possible cause of suicidality and suicidal ideation in child and adolescent ADHD patients.

In September 2005, the FDA published an alert regarding suicidal thinking with atomoxetine in children and adolescents. (US Food and Drug Administration, 2005) At that time a combined analysis had been performed on twelve short-term placebo controlled trials of 6-18 weeks duration. In these trials, a total of 1357 patients had received atomoxetine and 851, placebo. In the analysis, the average risk of suicidal thinking was about 4 per 1000 patients receiving atomoxetine, and none in the placebo treated patients. One instance of a suicide attempt had been documented in the atomoxetine treated patients. A similar analysis in adult ADHD and depressed patients found no increased risk of suicidal ideation or behavior. It was noted from these studies that there was a greater risk of suicidal ideation during the first few months of treatment.

At the request of the FDA, Eli Lilly (the owners of atomoxetine) performed a further retrospective analysis of the same trials as well as further studies which had been completed using MPH as a comparator. This analysis was published in 2008. (Bangs, 2008b) While acknowledging that evaluation of suicide had not been an objective of the studies, (and therefore attempts had not been made to specifically elicit information about this kind of adverse event), they confirmed the previously announced findings. For five studies (duration six to nine weeks) in which MPH had been studied in head to head trials with atomoxetine, one of 559 atomoxetine-treated patients and one of 465 MPH patients had been reported to have had suicidal ideation, but no suicidal behavior attempts had occurred.

A follow-up of patients enrolled in atomoxetine studies for more than three years (mean 4.8 years SD 1.1 years) was published in 2009. (Donnelly, 2009) This study included data from 714 patients who had received atomoxetine for more than three years. 11/714 reported suicidal ideation, 2/714 reported suicide attempts, and 1/714 reported suicidal behavior. There were no completed suicides.

### 5.5.4.3 Weight and Growth

Appetite suppression is one of the well recognized side effects of therapy with stimulant drugs. Additionally, increased synaptic levels of dopamine which result from stimulant therapy are known to acutely inhibit growth hormone secretion. (De Zegher, 1993)

There is now general agreement amongst reviewers and commentators that while taking stimulant medication a height deficit of approximately 1cm per year can be expected during the first one to three years of treatment. (Poulton, 2005; AACAP Workgroup on Quality Issues, 2007; Faraone, 2008)

In the MTA study, at the end of the 14 month intervention phase, children receiving the behavior management intervention without stimulant therapy had significantly greater increases in both height and weight relative to those receiving pharmacotherapies. (MTA Cooperative Group, 2004b) Slower growth rates appear to apply to both boys and girls,
and a significant relationship exists between growth in height and weight as a result of pharmacotherapies. (Poulton, 2003; Faraone, 2005a) However, it appears that children with a higher body mass index tend to lose more weight on stimulant medication than children with a lower BMI. (Schertz, 1996)

There are indications that with prolonged childhood ADHD stimulant treatment for two to three years or more, growth velocities tend towards normal for stimulant-treated children with ADHD. (Faraone, 2005a) When children stop stimulant therapies a growth catch-up phase appears to occur. (Klein, 1988) Adults who received stimulant medications in childhood appear to have heights which are comparable to those of normal adults. (Kramer, 2000)

There remains some uncertainty over the extent to which the final adult height and weight of childhood ADHD-stimulant-treated patients might result from periods of lapse in adherence with the medications. During such periods, it might be assumed that rapid catch-up could be occurring during stimulant-free periods. As a naturalistic observation, the MTA study 8 year follow-up for example recorded that only 62% of children taking medication at the 14-month intensive intervention conclusion were still taking medication at the 8-year follow-up, and that only 30% still fulfilled the DSM-IV criteria. (Molina, 2009b) However a recent study observing a ten year follow-up of stimulant-treated childhood ADHD patients in a naturalistic way found little difference in height and weight from control probands observed in parallel across the same ten-year time-frame. For 80% of the ten year observation period, stimulant-treatments were reported to have been continuing in the study group. (Biederman, 2010)

Notwithstanding these findings, the AACAP 2007 practice parameter recommends that patients treated with medication for ADHD should have their height and weight monitored throughout treatment. (AACAP Workgroup on Quality Issues, 2007)

**5.5.4.4 Sleep disturbance, decreased appetite and headaches**

Different therapies used to treat ADHD in children appear to be little different with regards the extent to which they cause sleep disturbances, decreased appetite or headaches. While atomoxetine (a noradrenergic uptake inhibitor) may cause relatively more nausea and sedation than stimulant therapy, there may be a lesser likelihood of these effects from its use. (Sangal, 2006)

A retrospective cohort study of 137 children and adolescents observed over a two year period has provided a recent comparison of these relatively frequently experienced side effects. (Miller-Horn, 2008) Open-label ADHD-monotherapy treatments observed over this period (in roughly equal proportions and without a control group) were: amphetamine/dextroamphetamine extended release (Adderall XR®), amphetamine/dextroamphetamine (Adderall®), osmotic controlled release methylphenidate (OROS-MPH, Concerta®), atomoxetine (Strattera®), and methylphenidate standard release. 25% of children reported side effects during this period, the most common being decreased appetite, insomnia, headaches and tics. Although there were low numbers of observations, there were no significant differences between the five medications in the occurrence of sleep disturbance or decreased appetite.
Children treated with the AMP stimulants or OROS-MPH reported significantly more headaches than those treated with atomoxetine. – In this study 78% of the 137 patients were reported as experiencing improvement in their ADHD symptoms irrespective of which pharmacotherapy they had been receiving.

5.5.4.5 Tics

For children with tics, there is roughly a 50% chance that they will have co-morbid ADHD. (Rothenberger, 2007) The MTA study ADHD inception cohort included 11% of children with pre-existing tics. (MTA Cooperative Group, 1999a)

The FDA currently stipulates that most psycho-stimulant therapies are contraindicated for patients who have a tic disorder or a family history of Tourette’s syndrome. (Bloch, 2009) Notwithstanding this FDA requirement, by 2002, other branches of the Federal Government’s health administration had recognized the importance and value of MPH alongside clonidine for treatment of tics and Tourette’s syndrome. (National Institutes of Health, 2002)

The FDA’s requirement for the contraindication came about as a result of a number of case series published from the early 1960’s, culminating in 1982 in a series of fifteen cases where children had developed tics while receiving prescribed psycho-stimulants. (Lowe, 1982) However, it is now believed that it is most likely these observations were the result of confounding, with some commentators suggesting that as many as 20% of children with ADHD suffer from tics irrespective of their stimulant therapy. It is now recognized that symptoms of ADHD typically precede the emergence of tics by some two to three years. (Leckman, 2002)

In a meta-analysis of nine studies involving 477 subjects with ADHD and co-morbid tics, six separate medications were compared for their ability to treat ADHD symptoms and tics. (Bloch, 2009) From the data available it was concluded that MPH offers the most immediate improvement of ADHD symptoms and that it does not seem to worsen tic symptoms. α₂-Agonists offered the best combined improvement in both tic and ADHD symptoms.

Effect sizes of the results from this meta-analysis (both with respect tic, and ADHD symptom reduction) were compared with ADHD symptom effect sizes found in meta-analyses by other researchers (Bloch, 2009):

<table>
<thead>
<tr>
<th></th>
<th>Effect size (ES) for tic reduction</th>
<th>Effect size (ES) for ADHD symptom reduction</th>
<th>Comparison meta-analyses of ADHD symptom effect size (ES) in patients without tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from Bloch et al.</td>
<td>ES=0.28 (0.03 – 0.58)</td>
<td>ES=0.73 (0.53 - 0.94)</td>
<td>ES=0.78 (0.64 – 0.91)</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α₂-Agonists</td>
<td>ES=0.74 (0.44 – 1.04)</td>
<td>ES=0.61 (0.32 - 0.90)</td>
<td>ES=0.58 (0.27 – 0.89)</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>ES=0.32 (0.09 – 0.56)</td>
<td>ES=0.51 (0.09 - 0.56)</td>
<td>Δ ES=0.64 (0.51 – 0.76)</td>
</tr>
<tr>
<td>Desipramine</td>
<td>ES=0.44 (-0.02 – 0.91)</td>
<td>ES=0.80 (0.02 - 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Comparison meta-analyses ‡ Schachter, 2001 (N=2,897): » Connor, 1999 (N=150): Δ Cheng, 2007 (N=1,615)
In addition to the above findings, in a single study in which a combination of both clonidine and MPH was compared against placebo (Tourette's Syndrome Study Group, 2002), the combination significantly improved ADHD symptoms (ES=1.09, 95%CI – 0.72-1.45), as well as tic symptoms (ES=0.75, 95%CI - 0.38-1.12).

5.5.4.6 Hepatotoxicity

Two case reports obtained from the MedWatch system documented hepatotoxicity in patients receiving atomoxetine - Strattera®: (one adult and one child). (McDonagh, 2009) These cases resulted in the following warning being included in the full prescribing information for atomoxetine: “Postmarketing reports indicate that Strattera® can cause severe liver injury. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been rare cases of clinically significant liver injury that were considered probably or possibly related to Strattera® use in postmarketing experience. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions. Reported cases of liver injury occurred within 120 days of initiation of atomoxetine in the majority of cases and some patients presented with markedly elevated liver enzymes [>20 x upper limit of normal (ULN)], and jaundice with significantly elevated bilirubin levels (>2 x ULN), followed by recovery upon atomoxetine discontinuation. In one patient, liver injury, manifested by elevated hepatic enzymes up to 40 times the upper limit of normal and jaundice with bilirubin up to 12 x ULN, recurrent upon re-challenge, and was followed by recovery upon drug discontinuation, providing evidence that Strattera® likely caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. The patient described above recovered from his liver injury, and did not require a liver transplant. However, severe liver injury due to any drug may potentially progress to acute liver failure resulting in death or the need for a liver transplant. Strattera® should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu like” symptoms)” (Eli Lilly & Company, 2010).

A recent publication from Eli Lilly and Co (Bangs, 2008a) provided information on spontaneous adverse event reports which had been recorded in four years since atomoxetine had been launched onto the market. It was reported that 351 such reports had been submitted while 4,328,000 patients had been exposed. Of the 351 cases, 69 were categorized as being unlikely due to the atomoxetine after expert review. Of the remainder which had sufficient information for evaluation, 133 were classed as possibly related, and 3 cases probably related to atomoxetine exposure. 13 cases amongst those possibly related to atomoxetine had AST or ALT levels ≥500u/L, five cases met criteria for Hy’s rule,** (US Food and Drug Administration, 2009) and there were two cases of liver failure amongst those where atomoxetine was possibly related to the injury.

** Hy’s rule is a prognostic indicator of drug induced liver injury and has three components; AST or ALT greater than 3x the upper limit of normal, total bilirubin greater than 2x the upper limit of normal and alkaline phosphatase less than or equal to 1.5 the upper limit of normal.
5.5.5 Common problems with pharmacotherapies

5.5.5.1 Adherence

Parental stresses associated with caring for children with ADHD symptoms are very considerable and often lead to a sense of inadequacy, self-blame, indecision, and continuing doubt or uncertainty about the best pathway forwards for themselves and their child. (Brinkman, 2009) One researcher in an inner-city context found that on average, parents first noted their child’s problems four years prior to obtaining a diagnosis of ADHD. (DosReis, 2009)

Starting and stopping ADHD pharmaco-therapies is common. (Thiruchelvam, 2001; Charach, 2004; Marcus, 2005), and the child’s refusal to take medication is often a significant challenge. The finding from the MTA study that approximately half of the parent-reported adherence to the medication regimen was not borne out by same-day salivary MPH sampling is perhaps partially explained by this point of reality in the homes of children with ADHD. (Pappadopulos, 2009). Knowledge of this observation also is important for clinicians as they work with families to periodically up-titrate dosage levels to gain the best balance of benefits and side-effects from pharmacotherapies.

There is considerably less information available about adherence to psychosocial interventions for ADHD. (Pelham, 2008) However notable failure occurred in a study of a well reputed and carefully documented psychosocial intervention for pre-schoolers identified as being ‘at-risk’ of developing ADHD. The authors reported that up to one third of parents attended no parenting classes and only approximately 13% attended more than half of the sessions. (Barkley, 2000) Additionally in the MTA study acceptable attendance at the behavioral training sessions was set as being 75% of the programs provided. Unfortunately more than a third of the participants allocated to either the ‘behavior’ or ‘combined behavior/medication management’ groups did not achieve the 75% adherence to the behavioral training regime prescribed by the study protocol. (MTA Cooperative Group, 1999b). A further obvious point is the fact that attendance at such training programs does not imply consistent adherence to strategies and tactics taught.

The extent, depth and regularity with which a caring physician has been able to empathically communicate with family members about the condition and its management is a key factor which modulates all subsequent outcomes from either behavioral or medication strategies. (Brinkman, 2009; DosReis, 2009)

Supporting such communication quality, the parents’ indecision and anxiety as they experience their child’s struggle with ongoing functional impairments needs to be fully understood by clinicians.

It has been suggested that it is natural for parents to wish to contrast time on, and off stimulant therapy to help them make decisions about the necessity for ongoing medication. (Brinkman, 2009) The widely discussed concerns for growth compromises of children while taking ADHD pharmacotherapies, addiction fears, and the dismaying knowledge of sudden cardiac death and suicide risk linked to ADHD pharmacotherapies underscores parents’ indecision on all matters related to their adherence to prescribed medication regimes.
The availability of effective once- or twice-a-day dosed pharmacotherapies has been shown to improve adherence, continuity and persistence. (Lage and Hwang, 2004; Marcus, 2005; Chou, 2009) It has been suggested that to some degree this may be due to reduced need for emergency contact with school teachers during the working day, as well as reduced stigma associated with the need to consume medications while at school. (Brinkman, 2009; Hosenbocus, 2009)

5.5.2 Diversion

Diversion of prescribed stimulants into the stream of psychoactive substances in use for non-therapeutic recreational purposes has become a significant contemporary issue.

In a 2003 study of a representative sample of a mid-western college’s students, 2% of undergraduates reported medically prescribed stimulant use in the past year. Of these students who had been prescribed stimulants, 54% had been approached to sell, trade, or give away their medication. (McCabe, 2006). About two and a half times the number of students prescribed stimulants reported illicit use of stimulants during the previous year, representing 5.4% of total respondents.

To explore this issue in the broader population a structured representative sample of civilian non-institutionalized US adults was internet-surveyed using consented adults 18-49 drawn from the Harris Poll online panel. The survey was conducted in 2005 involving 4,297 respondents whose responses were encrypted and password protected.

Past year prevalence of non-medical use of ADHD medications was approximately 2%. When considered by respondents aged between 18 and 25 years, this prevalence was found to be 4.3%. Most users for recreational purposes had never had a prescription themselves but reported use on multiple occasions throughout the previous year. (Novak, 2007) Two-thirds of respondents had received medications from family or friends who gave away some of their prescribed supplies: one third had taken or stolen from friends and family, and one fifth had obtained ADHD medications through fraudulent prescriptions obtained by fabrication of symptoms, or through other means via their physician. 5% had used the internet for supplies.

Abuse potential for drugs is known to be associated with the rapidity of absorption, and rapidity of rise of central drug concentrations followed by rapid clearance. (Kollins, 2008). Thus route of administration, pharmacokinetic parameters and dose each modulate abuse potential. Route of administration in the case of psycho-stimulants is particularly important as it modulates the timing and rate of the dopaminergic response. Thus when stimulants are administered intravenously or intra-nasally they are able to produce a ‘high’ sensation which is generally less pronounced from oral administration. (Volkow, 2003)

Drug formulations for MPH and AMP which provide for extended release produce a slower rise in plasma concentrations over a longer duration, and these features are believed to result in a lesser potential for abuse. (Swanson, 2003) In the case of short and long acting MPH preparations this point has been demonstrated through use of a ‘likeability’ index in which the long acting form was shown to be significantly less ‘likeable’ than the short acting form. (Spencer, 2006)

It is well established that people diagnosed in childhood with ADHD are up to twice as likely to develop a substance abuse disorder relative to people who have never had an ADHD
diagnosis. (Biederman, 2006) The presence of ADHD comorbid with ODD or CD amplifies this risk even further. (August, 2006)

However, rates of non-medical use of stimulants in the 2003 mid-western college population (McCabe, 2006) were significantly different depending on the age when the prescribed stimulants had been commenced. Those students who had had their initial diagnosis of ADHD and prescription stimulants while in elementary school were not more likely to misuse stimulants than members of the general student population studied. However those who commenced prescription use in high school or college were four to eight times as likely to report stimulant misuse compared to the overall student population.

5.6 **Combined behavioral and pharmacotherapies**

Considering the results of the MTA study objectively as discussed at page 19, it is clear that the ADHD symptom-reduction potency of stimulant therapies is such that when psycho-social therapies are added, their incremental additional benefit is very small, at least using available outcome-measurement constructs. Only small benefits were seen in parent ratings of their child’s conduct at the end of treatment after experiencing the combined intervention as compared to medication management alone. This observation is confounded to an unknown degree because parents who had received the behavioral strategies as well as medication could not be blind to the fact that they themselves had invested time and effort into the behavioral interventions.

For reinforcement of this point, a study was carried out to establish whether, after a year of MPH treatment, ADHD patients who during the year had also received an intensive behavioral intervention might have been able to have their MPH therapy ceased successfully during a second year of the study. This study also had a comparison arm of MPH-responsive patients where the behavioral intervention had not taken place at any time throughout the two year period. (Abikoff, 2004) This study was carried out prior to the MTA study between 1990 and 1994 in two sites with a total of 103 patients being enrolled. At the end of the first year, 100% of patients who had received the behavioral intervention were not able to be taken off their MPH. Additionally no incremental benefits at the end of either the first 12 months, or the full 24 months were seen in the group who had been randomized to receive the behavioral intervention as well as the continued MPH treatment beyond MPH alone.

Thus, in considering possible benefits of the combination of behavioral and pharmacotherapies it is important to consider studies where patients are randomized to receive either a behavioral intervention or a medication intervention according to protocol, rather than studying behavioral interventions added on to usual care with a medication.

The NICE reviewers (National Collaborating Centre for Mental Health, 2009a) found five acceptable quality small studies of this kind, (apart from the MTA study), which had been largely carried out prior to 1990. (Gittelman-Klein, 1976; Firestone, 1981; Brown, 1985; Firestone, 1986; Klein, 1997)

It was concluded that the overall results generally favored stimulant medication, but that the strength of effect size remained small. There was no evidence that psychological interventions were better than stimulant medications for any outcome, or at any time point when compared in this way. It was concluded:
“.... it is also the case that stimulant medication for ADHD is not strongly favored over psychological interventions, with the benefits of medication being weakest in comparison with complex psychological interventions.

It also remains unclear whether the beneficial effects of stimulant medication over psychological interventions are sustained after the end of treatment. Accordingly the decision about whether to use a psychological intervention or stimulant medication for ADHD appears to be more balanced. In this context, the choice of first-line intervention might be influenced by factors other than effectiveness, including possible adverse effects of medication and preferences of the child and/or parent.” (National Collaborating Centre for Mental Health, 2009a)
### TABLE 1 - DSM-IV-TR Diagnostic Criteria for ADHD

**A. Either (1) or (2):**

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

**Inattention:**
- Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

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

**Hyperactivity:**
- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- Often has difficulty playing or engaging in leisure activities quietly
- Is often “on the go” or often acts as if “driven by a motor”
- Often talks excessively

**Impulsivity:**
- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (e.g., butts into conversations or games)

**B. Some hyperactive-impulsive or inattentive symptoms that caused impairments 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 clinical 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 Type:**

- 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 Inattentive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

TABLE 2 – Summary of American Academy of Pediatrics assessment and diagnosis considerations in the evaluation of a child with ADHD

1. A primary care provider should initiate evaluation in a child 6-12 years old who presents with academic underachievement and behavioral problems that include inattention, hyperactivity and/or impulsivity since there is a high prevalence of ADHD in school-age children.

2. A diagnosis of ADHD is required to meet DSM-IV criteria which include the presence of functional impairment in two settings and clinically significant impairment of either social, academic, or occupational functioning.

3. When assessing the child, it is important to directly obtain information from parents or caregivers detailing the core ADHD symptoms in multiple settings, what age symptoms began, the duration of symptoms, and the extent of functional impairment.
   a. A range of specific questionnaires and rating scales have been developed to review and quantify the behavioral characteristics of ADHD. (Breen, 1991; Conners, 1997) ADHD-specific questionnaires and rating scales have demonstrated the ability to differentiate children with ADHD from normal, age-matched controls (odds ratio > 3.0; i.e., sensitivity and specificity > 94%). Use of these tools is an option; however, results must be interpreted in the context of the overall evaluation since the results are subject to bias because questions are subjective.
   b. Nonspecific, global questionnaires and rating scales that assess a variety of behavioral conditions are not recommended because they do not differentiate well between children with and without ADHD (odds ratio < 2.0 in studies differentiating children referred to psychiatric practices; i.e., sensitivity and specificity < 86%).

4. When assessing the child, it is important to directly obtain information from the classroom teacher or other school professional detailing the core ADHD symptoms, settings, the duration of symptoms, the extent of functional impairment, and comorbid conditions. School-based multidisciplinary evaluations should be reviewed by the provider whenever the evaluations occur. Input from after-school care centers and programs can provide additional information. Information should be obtained from settings other than the home for the home-schooled child as well.
   a. Teacher ADHD-specific questionnaires and rating scales have demonstrated the ability to differentiate children with ADHD from normal, age-matched controls (odds ratio > 3.0; i.e., sensitivity and specificity > 94%). (Green, 1999) Use of these tools is an option; whether these scales provide additional benefit beyond narratives or descriptive interview informed by DSM-IV criteria is not known.
   b. Teacher global questionnaires and rating scales that assess a variety of behavioral conditions are not recommended because they do not differentiate well between children with and without ADHD (odds ratio < 2.0 in studies differentiating children referred to psychiatric practices; i.e., sensitivity and specificity < 86%).
   c. Discrepancies between different settings evaluated are common and do not preclude the diagnosis of ADHD. Some reasons for differences may include: levels of expectation, levels of structure, behavioral management skills, and/or other environmental circumstances.

5. Assessment of comorbid conditions should be included in the evaluation of the child with ADHD since as many as one-third of children with ADHD have one or more comorbid conditions.
   a. A variety of psychological and developmental disorders frequently coexist with ADHD in children; examples include: oppositional defiant disorder, conduct disorder, anxiety disorder, and depressive disorder.

6. Routine use of other diagnostic tests is not indicated to diagnose ADHD.
   a. Current evidence suggests that other diagnostic tests contribute little to establish the diagnosis of ADHD and does not support the routine use of blood lead levels, thyroid hormone levels, brain imaging studies, electroencephalography, or currently available continuous performance tests.

References: (Breen and Altepeter, 1991; Conners, 1997; American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2000)
TABLE 3 – Diagnostic and post-diagnostic recommendations from the United Kingdom NICE (National Collaborating Centre for Mental Health) guideline on diagnosis and management of ADHD in children, young people and adults

**DIAGNOSIS**

1. Appropriately trained and qualified healthcare professionals, including a specialist psychiatrist or pediatrician, should make the diagnosis of ADHD based on the combined evaluation of:
   a. a full psychosocial and clinical patient assessment, including the discussion and comparison of what behavior/symptoms occur in different everyday settings,
   b. a full developmental history and psychiatric history, and
   c. reports and assessments from observers regarding the patient’s mental state.

2. Rating scales (e.g., Conners’ rating scales, Strengths and Difficulties questionnaire) or observational data alone are not sufficient to make a diagnosis of ADHD, but are valuable adjuncts that can be useful when there is doubt about patient symptoms.

3. In addition to meeting DSM-IV or ICD-10 (hyperkinetic disorder) diagnostic criteria for ADHD, a diagnosis of ADHD requires confirmation (by interview and/or direct observation) that the symptoms of hyperactivity/impulsivity and/or inattention:
   a. cause at least moderate psychological, social, and/or educational/occupational impairment in more than one setting, and
   b. occur in two or more important settings (e.g., social, family, educational, occupational). Assessment should take into consideration the patient’s needs, coexisting conditions, physical health and personal circumstance in all settings. An additional key priority for children and young people should be a mental health assessment of parents and caregivers.

4. ADHD is a consideration in all age groups, with symptom criteria for a diagnosis of ADHD adjusted for age-appropriate changes in behavior.

5. Whenever possible, opinions and feedback from children and young people should be considered when determining if impairment as a result of ADHD symptoms is clinically significant.

**POST-DIAGNOSIS**

Healthcare providers should consider providing educational materials based on positive parenting and behavioral techniques (e.g., self-instruction manuals, videos) to all parents and caregivers of all children and young people after they are diagnosed with ADHD.

Reference: (National Collaborating Centre for Mental Health, 2009a)
TABLE 4 - Summary of prevalence of selected co-morbidities in children with ADHD

<table>
<thead>
<tr>
<th>Comorbid disorder</th>
<th>Estimated prevalence (%)</th>
<th>Confidence limits for estimated prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>35.2</td>
<td>27.2 - 43.8</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>25.7</td>
<td>12.8 – 41.3</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>25.8</td>
<td>17.6 – 35.3</td>
</tr>
<tr>
<td>Depressive Disorder</td>
<td>18.2</td>
<td>11.1 – 26.6</td>
</tr>
</tbody>
</table>

Reference: (Green, 1999)

TABLE 5 - Prevalence of selected co-morbidities in children with ADHD

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>ODD</th>
<th>CD</th>
<th>Anxiety/depression</th>
<th>Learning difficulties</th>
<th>Language impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD predominantly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inattentive type</td>
<td>11.1</td>
<td>3.7</td>
<td>21.3</td>
<td>13.9</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>ADHD predominantly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperactive-impulsive</td>
<td>36.3</td>
<td>8.0</td>
<td>11.5</td>
<td>2.7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD combined type</td>
<td>49.8</td>
<td>21.5</td>
<td>24.9</td>
<td>10.9</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>ADHD all types total</td>
<td>26.5</td>
<td>9.6</td>
<td>20.8</td>
<td>11.3</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

Reference: (Wolraich, 1998)
TABLE 6 – Summary of American Academy of Pediatrics Clinical Practice Guidelines for treatment of ADHD in the school-aged child

1. Primary care providers should establish an overall strategy for diagnosis and long-term management of ADHD as a chronic condition in their practice.
   a. ADHD is common among school-age children (4%-12%).
   b. ADHD is a chronic condition. As with any chronic condition, it requires child-specific treatment plans and goals to be developed that include monitoring care over time with a specific follow-up plan.
   c. Part of patient management should include parent and patient education to familiarize them with ADHD and the ways it can affect learning, behavior, self-esteem, social skills, and family function.
   d. It is important for the provider to keep current and know how to refer/connect families or caregivers of individuals with ADHD to community resources available that provide support and/or education.

2. When developing appropriate target outcomes, the provider should collaborate with the child, parents, and school to agree on at least 3 – 6 key targets/desired changes to guide management.
   a. The primary goal is to maximize function; e.g., less disruptive behavior as well as improved academic performance, independence, self-esteem, safety and relationships with family members, teachers and peers.
   b. Goals should be realistic, attainable, and measurable. As goals change, the method of treatment and monitoring should adapt as needed.

3. The treatment management of a child with ADHD should include stimulant medication and/or behavior therapy as appropriate to improve target outcomes.
   a. Behavioral interventions are valuable for primary and adjunct treatment of ADHD and should be individualized according to comorbid conditions, targeted outcomes/goals, and family circumstances.
   b. Behavioral interventions share principles while using different techniques/strategies that can be combined into an overall comprehensive management plan. Examples of effective behavioral techniques include: positive reinforcement, time-out, response cost, and token economy.
   c. Stimulant medication is highly effective to manage core symptoms of ADHD for most children. Begin with a low dose and titrate upward because there is marked inter-individual variability in the does-response relationship.
   d. For children on stimulants, evidence supports a trial with a different stimulant in children who fail to respond or cannot tolerate the medication. When tried in a systematic way, at least 80% of children will respond to one of the stimulants.

4. Providers should assess the accuracy of diagnosis and possibility of undiagnosed comorbid conditions when a child with ADHD does not respond to treatment. Use of the selected treatment plan and adherence to that plan should also be evaluated.
   a. Examples of situations that may lead to lack of treatment response include: unrealistic target outcomes; lack of information regarding behavior of the child; incorrect diagnosis; undiagnosed or inadequately managed comorbid conditions; non-adherence to treatment plan; or a treatment failure.
   b. True treatment failure can be considered when: a patient does not respond to 2 or 3 trials of stimulant medications at maximum dose without side effects or with intolerable side effects at any dose; a patient’s behavior is not controlled by behavioral therapy or combination therapy; and when a comorbid condition interferes with the management of the ADHD.

5. Periodic, systematic follow-up of the child with ADHD should occur with monitoring focusing on targeted outcomes and medication adverse effects. Information should be gathered from the parents, teachers, and child.
   a. Adherence to the treatment plan should be reviewed at each follow-up.
   b. Methods for follow-up with patients may include office visits, phone calls, and written reports. Feedback from schools can be obtained using methods such as office interviews, phone conversations, teacher narratives, and periodic behavior report cards/checklists.
   c. Providing information and support at frequent intervals such that the child and family are able to make informed decisions promote the child’s continuing well-being. Monitoring frequency will vary with the extent of dysfunction, complications and adherence. Once stable, an office visit every 3 – 6 months creates the opportunity to assess behavior, learning, and potential side effects.

Reference: (AAP: Subcommittee on Attention-Deficit/Hyperactivity Disorder - Committee on Quality Improvement, 2001)
### TABLE 7 - A listing of commonly used ADHD pharmacotherapies, their dosing forms, durations of action as well as indications of their relative costliness

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Examples</th>
<th>Strengths/Dosage Form</th>
<th>Duration (hours)</th>
<th>Split, Sprinkle or Dissolve</th>
<th>Monthly Cost (Brand, Generic)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin&lt;sup&gt;®&lt;/sup&gt; 5 mg</td>
<td>5, 10, 20 mg tab</td>
<td>3 – 4</td>
<td>Split</td>
<td>$111 / $38</td>
</tr>
<tr>
<td></td>
<td>Methylin&lt;sup&gt;®&lt;/sup&gt; 5 mg</td>
<td>5, 10, 20 mg tab</td>
<td>3 – 4</td>
<td>Split</td>
<td>$45 / $38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5, 5, 10 mg chew tab</td>
<td>3 – 4</td>
<td>Split</td>
<td>$669</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg/mL, 10 mg/mL OSOLN</td>
<td>3 – 4</td>
<td>N/A</td>
<td>$714 / $449</td>
</tr>
<tr>
<td></td>
<td>Dextmethylphenidate</td>
<td>Focalin&lt;sup&gt;®&lt;/sup&gt; 2.5 mg</td>
<td>2.5, 5, 10 mg tab</td>
<td>3 – 6</td>
<td>Split</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin SR&lt;sup&gt;®&lt;/sup&gt;</td>
<td>20 mg ER tab</td>
<td>(highly variable)</td>
<td>No</td>
<td>$179 / $66</td>
</tr>
<tr>
<td></td>
<td>Methylin ER tab&lt;sup&gt;®&lt;/sup&gt;</td>
<td>10, 20 mg ER tab</td>
<td>3 – 8</td>
<td>No</td>
<td>$120 / $56</td>
</tr>
<tr>
<td></td>
<td>Metadate ER tab&lt;sup&gt;®&lt;/sup&gt;</td>
<td>20 mg ER tab</td>
<td>3 – 8</td>
<td>No</td>
<td>$89 / $56</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin LA&lt;sup&gt;®&lt;/sup&gt;</td>
<td>10, 20, 30, 40 mg ER cap</td>
<td>7 – 9</td>
<td>Sprinkle</td>
<td>$165</td>
</tr>
<tr>
<td></td>
<td>Methylin CD&lt;sup&gt;®&lt;/sup&gt;</td>
<td>10, 20, 30, 40, 50, 60 mg ER cap</td>
<td>7 – 9</td>
<td>Sprinkle</td>
<td>$205</td>
</tr>
<tr>
<td></td>
<td>Metadate CD&lt;sup&gt;®&lt;/sup&gt;</td>
<td>30, 40, 50, 60 mg ER cap</td>
<td>7 – 9</td>
<td>Sprinkle</td>
<td>$226</td>
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<tr>
<td></td>
<td>Concerta&lt;sup&gt;®&lt;/sup&gt;</td>
<td>18, 27, 36, 54 mg ER tab</td>
<td>10 – 12</td>
<td>No</td>
<td>$189</td>
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<tr>
<td></td>
<td>Metadate, Transdermal</td>
<td>Daytrana&lt;sup&gt;®&lt;/sup&gt;</td>
<td>10, 15, 20, 30 mg transdermal patch</td>
<td>10 – 12</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Dextmethylphenidate</td>
<td>Focalin XR&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5, 10, 15, 20, 30, 40 mg ER cap</td>
<td>9 – 12</td>
<td>Sprinkle</td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Generic only</td>
<td>5 mg/5 mL OSOLN&lt;sup&gt;®&lt;/sup&gt;</td>
<td>4 – 6</td>
<td>Split</td>
<td>$38 / $298</td>
</tr>
<tr>
<td>Mixed Amphetamine Salts</td>
<td>Adderal&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5, 7.5, 10, 12.5, 15, 20, 30 mg tab</td>
<td>4 – 6</td>
<td>N/A</td>
<td>$259 / $66</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Dexedrine Spansules&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5, 10, 15 mg ER cap</td>
<td>(highly variable)</td>
<td>6 – 10</td>
<td>Sprinkle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Amphetamine Salts</td>
<td>Adderal XR&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5, 10, 15, 20, 25, 30 mg ER cap</td>
<td>10 – 12</td>
<td>Sprinkle</td>
<td>$251 / $174</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Vyvanse&lt;sup&gt;®&lt;/sup&gt;</td>
<td>20, 30, 40, 50, 60, 70 mg cap</td>
<td>10 – 12</td>
<td>Dissolve</td>
<td>$183</td>
</tr>
<tr>
<td><strong>FDA Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera&lt;sup&gt;®&lt;/sup&gt;</td>
<td>10, 18, 25, 40, 60, 80, 100 mg cap</td>
<td>24</td>
<td>No</td>
<td>$209</td>
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<tr>
<td>Clonidine ER</td>
<td>Kapvay&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.1, 0.2 mg ER tab</td>
<td>12</td>
<td>No</td>
<td>$161</td>
</tr>
<tr>
<td>Guanfacine ER</td>
<td>Intuniv&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1, 2, 3, 4 mg ER tab</td>
<td>8 – 14, up to 24 at higher doses</td>
<td>No</td>
<td>$193</td>
</tr>
<tr>
<td><strong>Non-PDA Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapres&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.1, 0.2, 0.3 mg tab</td>
<td>4 – 6</td>
<td>Split</td>
<td>$127 / $12</td>
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<tr>
<td></td>
<td>Catapres-TTS&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.1, 0.2, 0.3 mg transdermal patch</td>
<td>7 days</td>
<td>N/A</td>
<td>$277 / $163</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Tenex&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1, 2 mg tab</td>
<td>6 – 8</td>
<td>Split</td>
<td>$179 / $22</td>
</tr>
</tbody>
</table>

Key: Cap = Capsule; ER = Extended release; N/A = Not applicable; OSOLN = Oral solution; Tab = Tablet; — = No generic or no brand available.

1 Dextroamphetamine and short-acting mixed amphetamine salts are FDA-approved for ADHD in children 3 years or older; other medications (except where noted) are FDA-approved for ADHD in children 6 years or older.
2 Tablets that may be split are not always scored. Scoring may vary by manufacturer.
3 Open and sprinkle on teaspoonful of unheated, soft food. Do not crush or chew.
4 Open capsule and dissolve contents in glass of water. Do not crush or chew.
5 Average monthly costs based on April 2011 cash price of 1 independent and cash discount price of 4 chain pharmacies in South Carolina using “average daily dose” for relative comparison.
6 Check availability before prescribing; compounding is an alternative.

Reference: Refer to the SCORxE Evidence-Based Best Practices for the Management of Attention-Deficit/Hyperactivity Disorder (ADHD) in Pediatric Primary Care in South Carolina 16-page Summary April 2011 available at: [http://www.sccp.sc.edu/SCORxE](http://www.sccp.sc.edu/SCORxE)
### TABLE 8 – Pharmacokinetic profiles of methylphenidate products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses per day</th>
<th>Time to peak (hours)</th>
<th>Duration of action (hours)</th>
<th>Delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate-release methylphenidate</td>
<td>2-3</td>
<td>1-2</td>
<td>3-4</td>
<td>Immediate release tablet</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metadate ER&lt;sup&gt;®&lt;/sup&gt;</td>
<td>2-3</td>
<td>~ 4-5</td>
<td>8</td>
<td>Wax-matrix vehicle tablet</td>
</tr>
<tr>
<td>Methylin ER&lt;sup&gt;®&lt;/sup&gt;</td>
<td>2-3</td>
<td>~ 4-5</td>
<td>8</td>
<td>Wax-matrix vehicle tablet</td>
</tr>
<tr>
<td>Ritalin SR&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1-2</td>
<td>~ 3-4</td>
<td>8</td>
<td>Wax-matrix vehicle tablet</td>
</tr>
<tr>
<td><strong>Long-acting (biphasic pharmacokinetic profiles)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphentin&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;: 1.7-2.6 2&lt;sup&gt;nd&lt;/sup&gt;: ~4.5</td>
<td>10-12</td>
<td>Multilayer-release system: 40% immediate; 60% delayed</td>
</tr>
<tr>
<td>Metadate CD&lt;sup&gt;®&lt;/sup&gt;, Equasym&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;: 1.5 2&lt;sup&gt;nd&lt;/sup&gt;: 4.5</td>
<td>8</td>
<td>Errand Diffucaps: 30% IR &amp; 70% ER beads released from capsule</td>
</tr>
<tr>
<td>Ritalin LA&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;: 1-3 2&lt;sup&gt;nd&lt;/sup&gt;: 4-5</td>
<td>8-10</td>
<td>Spheroidal Oral Drug Absorption System (SODA): 50% IR; 50% delayed-release beads released from capsule</td>
</tr>
<tr>
<td>Concerta&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;: 1-2 2&lt;sup&gt;nd&lt;/sup&gt;: 6-8</td>
<td>12</td>
<td>Osmotic Release Oral System (OROS): 22% IR tablet coating; 78% released from tablet utilizing osmotic pressure</td>
</tr>
</tbody>
</table>

<sup>a</sup> Information obtained from product labels.

<sup>b</sup> Not available in the United States.

Reprinted with permission from Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder 2009, Drug Effectiveness Review Project, Oregon Health Science University (McDonagh, 2009).
FIGURE 1 - Diagnosis and Evaluation of the Child with Attention-Deficit/Hyperactivity Disorder - Clinical Algorithm

1. Child 6 to 12 years of age presents with parent (or other caregiver) or teacher concerns about academic underachievement and/or specific behaviors OR clinician assesses these conditions during health supervision screening.

2. Assessment of the child by the primary care clinician includes:
   - Standard history and physical examination
   - Neurological examination
   - Family assessment
   - School assessment

3. Meeting ADHD criteria using the DSM-IV must include whether symptoms interfere with functioning and performance in more than one setting and last longer than 6 months.

4. Does child meet DSM-IV criteria for ADHD?
   - yes → Go to Box 8
   - no → 5

5. Is there evidence of developmental variation or problem or alternative conditions?
   - yes → Assess and treat
   - no → Reassessment of patient/parent concerns

6. Reassessment of patient/parent concerns

7. Continued from Box 4

8. Associated conditions (coexisting conditions) may include:
   - Learning/language disorders
   - Oppositional Defiant disorder
   - Conduct disorder
   - Anxiety
   - Depression
   - Other conditions

9. Are there symptoms of associated conditions?
   - yes → Assess for coexisting conditions
   - no → 10

10. Diagnosis of ADHD

11. Educate patient/parent and treat

12. Can presence of coexisting conditions be confirmed?
   - yes → Diagnosis of ADHD and coexisting conditions
   - no → Return to Box 10

13. Educate patient/parent and treat

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FIGURE 2 – General Principle and Key Questions concerning diagnosis of ADHD – Drawn from the UK NICE guideline on diagnosis and management of ADHD in children, young people and adults. (National Collaborating Centre for Mental Health, 2009a)

**General Principle:** The diagnosis depends on the evaluation of two necessary components, both of which are required to trigger the use of this guideline. The first is the presence of the symptom cluster of age-inappropriate levels of inattentive, hyperactive and impulsive behaviors; the second is the presence of significant clinical and psychosocial impairments. Other key criteria include onset during childhood and situational pervasiveness. Behaviors and symptoms that are restricted narrowly to one environmental setting only (for example, school), or one set of impairments (for example, educational attainment alone) would not be considered sufficient ground to make the diagnosis.

**Q:** Should ADHD be recognized in the presence of pervasive developmental disorders/autism spectrum disorders?

*Summary Statement:* ADHD can be diagnosed in the presence of pervasive developmental disorders.

**Q:** Should ADHD be recognized in the presence of general learning disability?

*Summary Statement:* ADHD can be recognized in the presence of a general learning disability, with behavioral symptoms compared to a group of similar mental age.

**Q:** How should impairment be judged

*Summary Statement:* Impairment should be pervasive and enduring, affecting several aspects of life.

**Q:** Should the age of onset before 7 years be strictly applied?

*Summary Statement:* ADHD should be diagnosed in some cases where onset is dated between the ages of 7 and 12 years

**Q:** Should some kinds of etiology be excluded?

*Summary Statement:* In the current state of knowledge, ADHD should be considered whenever diagnostic criteria are fulfilled, regardless of the presence of any specific etiological factors

**Q:** Should the same definitions be used for both genders?

*Summary Statement:* In current knowledge, the same diagnostic criteria should be applied to males and females.

**Q:** Can the diagnosis be made on the basis of observation alone?

*Summary Statement:* The diagnosis of ADHD should not be made on the basis of observational data alone.

**Q:** How should social, cultural and economic circumstances and factors be taken into account in making the diagnosis of ADHD?

*Summary Statement:* Social, cultural and economic circumstances should always be evaluated by an expert and whenever possibly by a multi-disciplinary team.

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FIGURE 3 - Treatment of the school-aged Child with Attention-Deficit/Hyperactivity Disorder - Clinical Algorithm

1. Child presents with diagnosis of ADHD
   See Clinical Practice Guideline, Diagnosis and Evaluation of the Child with Attention-Deficit Hyperactivity Disorder

2. Clinician Parent/Child and Teacher:
   A. Identify target outcomes,
   B. Develop comprehensive treatment plan
   C. Assess responses to treatment plan

3. Is response to treatment plan adequate
   no → Go to Box 2
   yes → Clinician monitors routinely

4. Clinician monitors routinely
   yes → Go to Box 2
   no → Go to Box 2

5. Is response to treatment plan adequate
   yes → Go to Box 2
   no → Go to Box 2

6. Clinician should periodically provide systematic follow-up to monitor target outcomes and adverse effects

7. 1. Consider adding stimulant medication.
    2. Reinforce behavior therapy

8. 1. Is child on stimulant medication
    no → Go to Box 2
    yes → Go to Box 2

9. 1. Consider adding stimulant medication.
    2. Reinforce behavior therapy

10. Go to Box 2C

11. Have all stimulant medications been tried?
    no → Go to Box 2
    yes → Go to Box 2

12. 1. Consider adding stimulant medication.
    2. Reinforce behavior therapy

13. Go to Box 2c

14. 1. Is adherence to stimulant medications or behavior therapy poor?
    no → Go to Box 2
    yes → Go to Box 2

15. Go to Box 2B,C

    2. Reinforce behavior therapy

17. Continues from box 16

18. Is the diagnosis correct?
    no → Exit guideline and seek appropriate treatment
    yes → Go to Box 2

19. Were coexisting conditions missed?
    no → Go to Box 2
    yes → Go to Box 2

20. Clinician evaluates and treats coexisting conditions

21. Are target symptoms appropriate?
    no → Go to Box 2
    yes → Go to Box 2

22. Clinician considers second-line medications after all stimulants have been tried

23. Yes

24. Go to Box 2

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6 REFERENCES


Li, D, Sham, PC, Owen, MJ and He, L (2006). "Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD)." Hum Mol Genet 15(14): 2276-84.


