

IACAPAP Textbook of Child and Adolescent Mental Health

Section D

EXTERNALIZING DISORDERS

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ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Tree climbing
(Vauvau, 2009)

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Although attention difficulties, impulsivity and hyperactivity are common in the general population and may represent transitory or normative developmental patterns, certain individuals have a typical course and combination of symptoms associated with functional impairment, with well-known risk factors, abnormal neuropsychological functioning and neurobiological correlates. These individuals are affected by attention-deficit/hyperactivity disorder (ADHD), one of the most common mental disorders among children and adolescents, with approximately 5% of children under 18 years affected worldwide (Polanczyk et al, 2007). This chapter describes how to identify and treat such individuals.

HISTORICAL NOTE

ADHD has long been described in the medical literature. Heinrich Hoffmann (1809-1894), a German psychiatrist, was the first to describe children whose behavior was marked by impulsivity and hyperactivity. He named this behavioral problem “impulsive insanity” or “defective inhibition”. In 1902 the pediatrician George Still published in *The Lancet* a description of children with motor agitation, attention problems, difficulty in controlling impulses and need for immediate reward (Still, 1902; Figure D.1.1). In his description he attributed the behavioral characteristics to the fact that these children had “no consideration for others” and called the disorder “deficit of moral control”. This historical misconception is emblematic of the stigma associated with ADHD symptoms: affected children are commonly misinterpreted as having control over their behavior and being responsible for their symptoms. In the following decades the syndrome was associated with brain lesions and the disorder was named *minimal brain damage* (Hohman, 1922, Kahn & Cohen, 1934). This label brought to the disorder the status of a biological rather than a moral problem but carried the incorrect assumption that ADHD was the result of a brain injury. Later it was recognized that not all children had physical observable lesions and thus it was renamed *minimal brain dysfunction* (Clements & Peters, 1962). In 1934 Kramer-Pollnow described a syndrome he referred to as *hyperkinetische Erkrankung*

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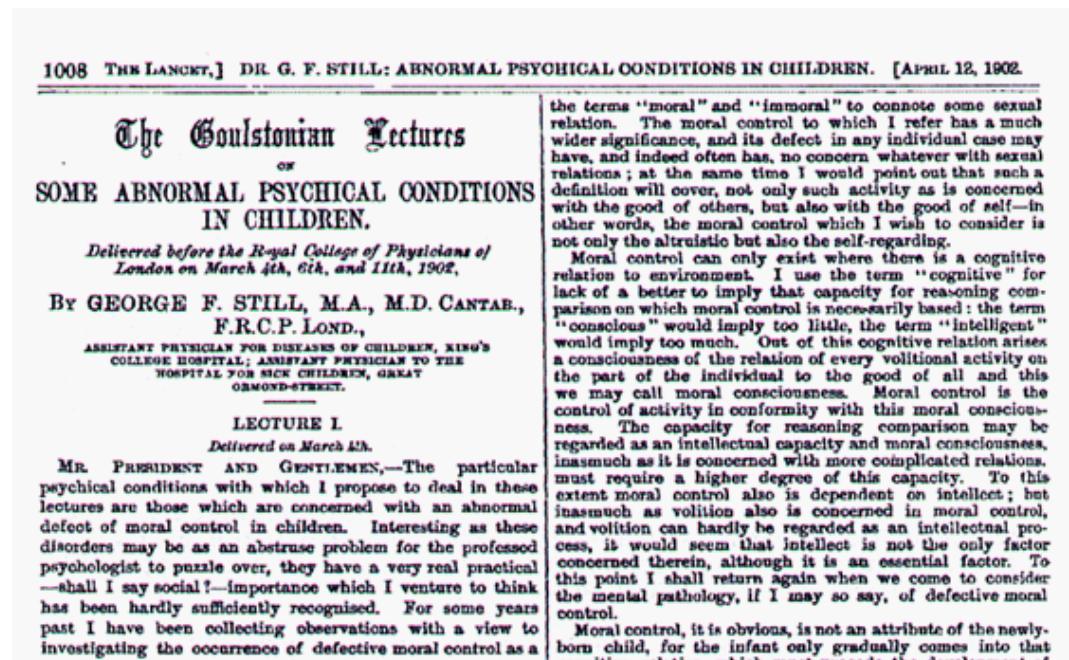


Figure D.1.1

Excerpt from George Still's 1902 paper in which he describes children with ADHD as having a “deficit of moral control”. Reprinted with permission from “Some abnormal psychical conditions in children. Still G (1902). *Lancet*, 1:1008-1012.



Figure D.1.2

Der Struwwelpeter, an illustrated book portraying children misbehaving (“Impulsive Insanity/Defective Inhibition”) by Heinrich Hoffman (1854).

(hyperkinetic disease) characterized by restlessness and distractibility (Sharkey & Fritzgerald, 2007). In 1937 the first effective treatment for ADHD was described by Bradley who reported that benzedrine could decrease hyperactivity and improve attention and academic performance (Bradley, 1937).

Hyperactivity was the symptom used to name the disorder when first included in the World Health Organization’s International Classification of Diseases, 9th edition (ICD-9) as “hyperkinetic syndrome of childhood” (subsequently called “hyperkinetic disorder” in ICD-10) and in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders second edition (DSM-2) (“hyperkinetic reaction of childhood”). It is only since 1980 that inattention was also emphasized and the disorder was reconceptualized as “attention-deficit disorder with or without hyperactivity” (DSM-III) and subsequently “attention-deficit hyperactivity disorder” (DSM-III-R and DSM-IV).

EPIDEMIOLOGY

Prevalence estimates of ADHD vary depending on the criteria used. A recent systematic review pooled data from 102 studies from all over the world and computed a rate of 5% for individuals below 18 years of age, 6% for school age children and 3% among adolescents (Polanczyk et al, 2007). Although estimates were heterogeneous, there was no clear evidence of variation across cultures.

Pooled data confirmed a higher prevalence among males than females, a widely acknowledged clinical observation.

ETIOLOGY AND RISK FACTORS

ADHD is a familial disorder with a strong genetic component. Its heritability (the proportion of variance attributed to additive genetic factors) has been estimated as 76% (Faraone et al, 2005), one of the highest among the mental disorders. Nevertheless, genetic factors alone do not explain the disorder's occurrence. The etiology of ADHD is considered to be multifactorial, that is, multiple environmental, genetic and biological factors play a role in increasing the risk for the disorder.

A number of candidate genes have been associated with ADHD, particularly genes related to catecholaminergic systems, but each gene seems to be responsible for only a small increase in the risk of developing the disorder (Faraone et al, 2005). Furthermore, studies that scan the whole genome without an *a priori* hypothesis, the so called *genome-wide association studies*, did not add new polymorphisms to the current knowledge (Neale et al, 2010). This apparent contradiction between a high heritability and negative results from genome-wide association studies has encouraged research for alternative etiological hypotheses. One possibility is that the disorder emerges from the interaction between genetic and environmental factors (Nigg et al, 2010). In fact, gene-environment interactions have been reported for the interaction between intra-utero tobacco exposure and variations of DAT1 and DAT4 genes (Nigg et al, 2010).

A number of environmental risk factors have been tested for their association with ADHD (Banerjee et al, 2007). Prematurity seems to be the factor most consistently associated with ADHD (Bhutta et al, 2002). Limited evidence also points to intra-utero exposure to tobacco (Langley et al, 2005; Linnet et al, 2003) and low birth weight (Hack et al, 2004; Mick et al, 2002) as possible risk factors. More studies are needed to assess the impact of intra-utero exposure to alcohol and drugs, maternal psychological problems during pregnancy, perinatal and pre-natal complications, traumatic brain injury, duration of breastfeeding, early deprivation and familial and psychosocial factors as well as intrauterine exposure to caffeine (Linnet et al, 2003) and birth in specific seasons of the year (Atladdottir et al, 2007). It is also prudent to remember that no conclusive data exist linking ADHD to food additives, environmental toxins and computer games.

Neurobiology of ADHD

A growing body of evidence has associated ADHD with specific neurobiological deficits. It is important to note however that the neuroanatomical deficits implicated in ADHD cannot be interpreted as *brain damage*; they represent slight differences in mean values when samples of patients with ADHD are compared to controls. Furthermore none of the deficits identified so far are crucial for the development of the disorder, they cannot be linked to ADHD in a causal way and cannot yet be used for diagnostic purposes.

Convincing data exist supporting a frontal-striatal dysfunction in ADHD (Castellanos et al, 2006). According to these data, individuals with ADHD would have deficits in executive functions and inhibitory control that are anatomically associated with thalamo-cortico-striatal circuits. Activity in these

The main risk factors already identified are:

- Genes (DAT1, DRD4, DRD5, 5HTT, HTR1 B, SNAP25)
- Prematurity
- Intra-uterus exposure to tobacco
- Low birth weight

A number of causal agents, both genetic and environmental, can contribute to the development of ADHD. However, each individual risk factor explains only a small proportion of the risk of developing the disorder. None of the risk factors identified are necessary for the development of ADHD, they are non-specific and related to other mental disorders and neurodevelopmental abnormalities as well.

What is the Internet doing to our brains?

In recent years concerns have emerged about the potential harm of Internet use and computer games by children. Click on the picture to view a talk by Professor Paul Howard Jones discussing this issue (26:30).



circuits is mediated by GABA and modulated by catecholamines (dopamine and norepinephrine) (Kieling et al, 2008). In fact the evidence points to a catecholaminergic dysregulation associated with the disorder (Kieling et al, 2008; Taylor & Sonuga-Barke, 2008; Swanson et al, 2007):

- ADHD symptoms are alleviated by dopaminergic and noradrenergic agonists such as methylphenidate, amphetamine and atomoxetine
- A number of genes associated with catecholaminergic systems increase the risk for the disorder
- In animal models it is possible to mimic ADHD symptoms by decreasing catecholaminergic function
- Noradrenaline and dopamine are key neurotransmitters in brain regions associated with ADHD.

A large and well-conducted prospective study has shown that ADHD children show an overall delay in cortical maturation (measured by cortical thickness) when compared to controls (see Figure D.1.3). The delay was more prominent in areas related to attention, particularly the lateral pre-frontal cortex (Shaw et al, 2007).

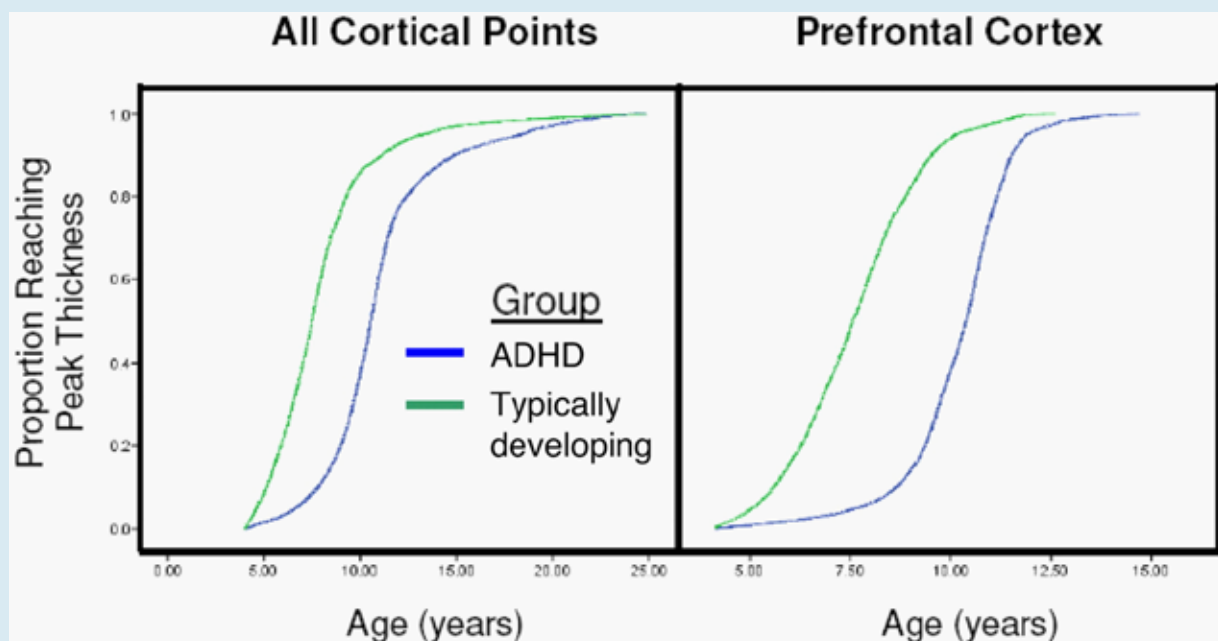


Click on the picture to hear Russell Barkley PhD describe his understanding of executive functions and their relevance for ADHD

CLINICAL PRESENTATION

ADHD is characterized by symptoms of *inattention*, *hyperactivity* and/or *impulsivity*. By definition, onset of symptoms must be early in childhood and differ from what is expected in normal development.

Figure D.1.3 Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (Left) and the prefrontal cortex (Right).



Shaw P et al. PNAS 2007;104:19649-19654 ©2007 by National Academy of Sciences; reproduced with permission.

Inattention refers to a behavioral pattern in which the individual has difficulty initiating, remaining engaged in and completing a task. Inattentive children struggle to organize tasks and activities, to listen when spoken to, to plan or execute actions. Inattention also includes distractibility, forgetfulness, frequent loss or difficulty keeping track of objects. In adolescents and adults it is common to observe distorted time perception; patients commonly underestimate time in relation to tasks to be executed and tend to procrastinate.

Hyperactivity is characterized by:

- Excessive physical activity
- Constant feelings of restlessness, making patients incapable of remaining still even in situations in which that is expected
- Non-goal-directed motor activity; that is, activity is purposeless and affects the environment in a negative way (frequently standing up and walking purposelessly when they should remain seated, or move the hands and manipulate small objects when they are expected to remain still)
- Frequent fidgeting or squirming in their seat
- Inability to play quietly
- Talking too much, running around or climbing when it is inappropriate.

Impulsivity refers to difficulty in delaying an action or response even when it is known that this action will have negative consequences. Impulsiveness is associated with the need for immediate over delayed gratification, even when the postponement would lead to better results. Impulsive behaviors manifest themselves as difficulty waiting one's turn to speak, in games and play activities or crossing the street. It can manifest also as a tendency to act without thinking. For example, giving immediate answers irrespective of their accuracy, giving answers not related to the question, or blurting out answers before the question is finished.

Parents may hesitate in accepting an ADHD diagnosis based on the perception that the child is able to remain focused when performing specific tasks such as playing videogames, watching television or in certain situations. It is important to highlight that motivation, the relevance and attractiveness of the task for the child, and the environment largely influence the manifestation of symptoms.

Differences in presentation according to age

Clinical presentation varies according to developmental stage. Table D.1.1 lists the most common symptoms according to age. Evaluation of hyperactivity, inattention, and impulsiveness among *preschoolers* is particularly difficult since these behaviors are normal in this age group; they can be considered abnormal only when they are very severe, pervasive and cause significant impairment of functioning (Byrne et al, 2000). In the school years children with ADHD will frequently draw attention to themselves for their poor school performance and attention problems; they are identified more easily than in preschoolers. Hyperactivity tends to decrease during adolescence or to change into subjective feelings of inner restlessness.

Underestimation of time by ADHD patients

Experiments have shown that individuals with ADHD underestimate the time needed to complete a task. In these experiments, individuals with ADHD and controls were instructed to perform a task (for example sorting books alphabetically and by year of publication); before doing so they were asked how long they believed it would take them to complete the task. Afterwards, time spent to complete the task was recorded and the time actually needed to do the task was compared with the time estimated. Compared to controls, individuals with ADHD underestimated the time needed to complete the task.



For educational videos and other materials, click on the picture to access the American Academy of Child and Adolescent Psychiatry Resource Center on ADHD

Table D.1.1 Changes in ADHD symptoms from childhood to adulthood

	Preschool years	Primary school years	Adolescence	Adulthood
Inattention	<ul style="list-style-type: none"> Short play sequences (<3 min) Leaving activities incomplete Not listening 	<ul style="list-style-type: none"> Brief activities (<10 min) Premature changes of activity Forgetful; disorganized; distracted environment 	<ul style="list-style-type: none"> Less persistence than peers (<30 min) Lack of focus on the details of a task Poor planning ahead 	<ul style="list-style-type: none"> Details not completed Appointments forgotten Lack of foresight
Overactivity	<ul style="list-style-type: none"> “Whirlwind” 	<ul style="list-style-type: none"> Restless when calm expected 	<ul style="list-style-type: none"> Fidgety 	<ul style="list-style-type: none"> Subjective feelings of restlessness
Impulsivity	<ul style="list-style-type: none"> Does not listen No sense of danger (hard to distinguish from oppositionality) 	<ul style="list-style-type: none"> Acting out of turn; interrupting other children and blurting out answers Thoughtless rule-breaking Intrusions on peers; accidents 	<ul style="list-style-type: none"> Poor self-control Reckless risk-taking 	<ul style="list-style-type: none"> Motor and other accidents Premature and unwise decision-making Impatience

Source: Taylor E, Sonuga-Barke E (2008), “Disorders of attention and activity” In Rutter M et al (eds), Rutter’s Child and Adolescent Psychiatry, p. 522. ©Blackwell Publishing Limited, with permission.

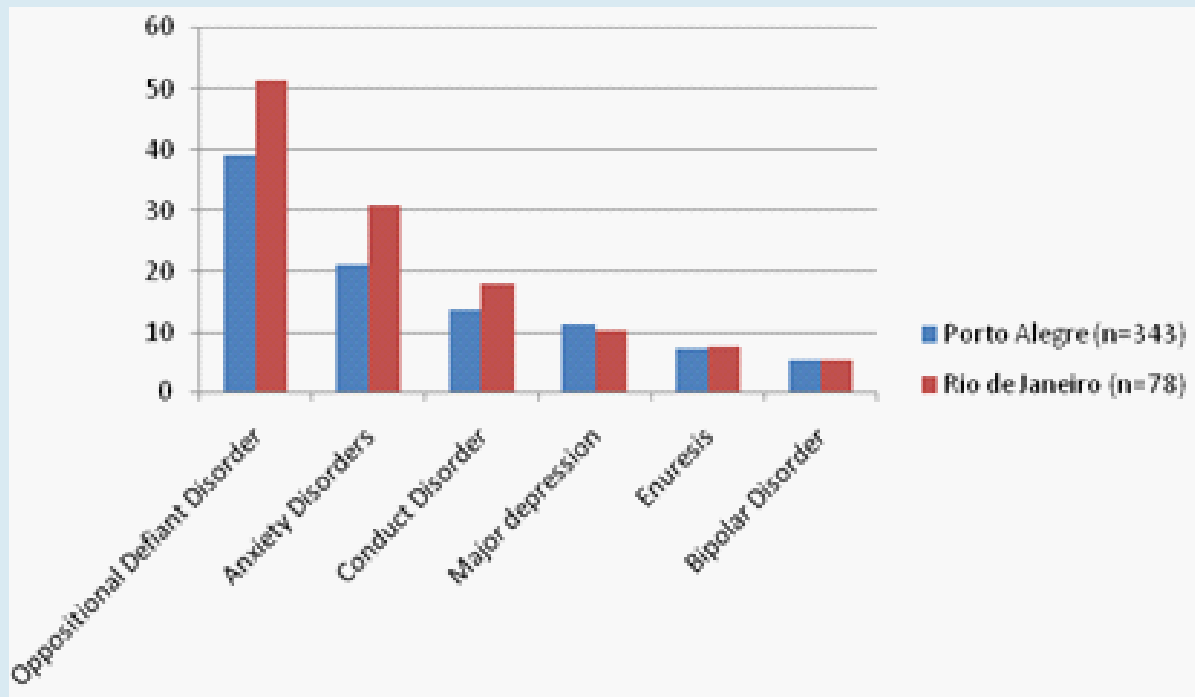
ADHD in DSM-5

Reviews of the DSM and ICD classifications are in progress. Proposals for DSM-5 are not yet finalized. Proposed options include:

- Classifying ADHD under the heading “neurodevelopmental disorders” (together with intellectual disability, communication disorders and autism spectrum disorders, among others), instead of under the current heading of “attention deficit and disruptive behavior disorders.”
- Overall structure. Proposed options are:
 - Keeping the same structure as in DSM-IV (three subtypes: combined, predominantly hyperactive, and predominantly inattentive)
 - Keeping the existing structure but without subtypes
 - Replacing the existing structure with one diagnosis only: “combined ADHD”.
- Predominantly inattentive ADHD.

Apart from no change, options considered include:

 - Redefining a “restrictive predominantly inattentive” subtype
 - Creating a new diagnosis of “attention-deficit disorder”.
- Number, content, and distribution of criteria. The options considered include:
 - No change
 - Increasing the total number of symptoms by adding four new impulsivity criteria (often acts without thinking; is often impatient; often rushes through activities or tasks, is fast paced; often has difficulty resisting immediate temptations or appealing opportunities, while disregarding negative consequences).
- Age of onset of symptoms. The options considered are no change or increasing the age of onset of symptoms to be present “on or before age 12” (instead of the current “before age 7”)

Figure D.1.4 Comorbid disorders in community samples of individuals with ADHD in two Brazilian cities

Adapted with permission from Souza et al (2004), "Attention-deficit/hyperactivity disorder and comorbidity in Brazil." *European Child & Adolescent Psychiatry*, 13:245.

Comorbidity

Children with ADHD often suffer from other psychiatric conditions; systematic screening for the presence of other mental disorders is essential. Figure D.1.4 shows the prevalence of comorbid disorders in two Brazilian cohorts of children with ADHD; oppositional defiant disorder, anxiety disorders, conduct disorders and depression are among the most frequent (Souza et al, 2004).

Detection

Much concern has emerged in recent years about over-diagnosis of ADHD in developed countries (Sciutto & Eisenberg, 2007). However, in less advantaged environments ADHD goes frequently unrecognized and untreated. In a systematic review of community studies conducted in Latin American and Caribbean countries, treatment rates among children with ADHD ranged from none to 7% (Polanczyk et al, 2008). In developing and underdeveloped nations, where access to medical care and information is limited, ADHD is usually not detected and parents and families cope with symptoms as well as they can, for example, by avoiding places or situations where they know symptoms will be especially disruptive (like restaurants or shops). Often teachers are the ones that refer children for treatment. In adolescents and adults, comorbidity is often the factor that leads people to seek treatment. Patients may be referred due to problems such as substance misuse, depression or difficulties in inter-personal relationships.

Individuals affected by ADHD and their families commonly misinterpret symptoms as "part of their personality" or their "way of being." In these circumstances, parents are unlikely to seek medical attention unless the behavior is associated with impaired functioning noticed by others, like academic failure; in this case, teachers are the ones who suggest parents to seek treatment.

Table D.1.2 Comparison between ICD-10 and DSM-IV diagnostic criteria for ADHD

	DSM-IV	ICD-10
Number of symptoms needed for the diagnosis	<ul style="list-style-type: none"> 6 or more out of 9 symptoms of inattention OR 6 or more out of 9 symptoms of hyperactivity/impulsivity 	<ul style="list-style-type: none"> 6 or more out of 9 symptoms of inattention AND 3 or more out of 5 symptoms of hyperactivity AND At least 1 out of 4 symptoms of impulsivity
Age of symptom onset	Before 7 years of age	Before 7 years of age
Minimal duration of symptoms	6 months	6 months
Pervasiveness	Symptoms present in two or more settings (e.g., school, work, home)	Symptoms at school are only needed if applicable for the age and developmental level of the child. Fewer symptoms are required to appear at school (2 out of 4 symptoms of inattention and 3 out of 5 symptoms of hyperactivity)
Sources of information required	Not mentioned	Report of parent or teacher (when appropriate) AND direct observation of symptoms OR significant impairment of performance on psychometric tests of attention.
Exclusion of the diagnosis if	Symptoms occur exclusively during the course of 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)	Criteria are met for pervasive developmental disorder, mania, depressive or anxiety disorder or IQ < 50
Possible diagnoses	<ul style="list-style-type: none"> Attention deficit hyperactivity disorder predominantly inattentive type Attention deficit hyperactivity disorder predominantly hyperactive-impulsive type Attention deficit hyperactivity disorder combined type 	<ul style="list-style-type: none"> Disturbance of activity and attention (the general criteria for hyperkinetic disorder must be met, but not those for conduct disorder) Hyperkinetic conduct disorder (when criteria for conduct disorder are also met) Other hyperkinetic disorders Hyperkinetic disorder, unspecified

DIAGNOSIS

The diagnosis of ADHD is exclusively made on clinical grounds and can follow either DSM-IV (American Psychiatric Association, 1994) or ICD-10 (World Health Organization, 1993) criteria. The child's developmental stage must be considered in clinical evaluation as well as symptom pervasiveness (occurrence in more than one environment, like home and school) and clear evidence of clinically significant impairment in social, academic, or occupational functioning. In younger children it is essential to assess the family environment; where there is chaotic or inconsistent parenting, abuse or neglect, children often respond



Click on the picture to view Russell Barkley PhD arguing that the core problem in ADHD is not inattention but a disorder of self-regulation

behaving in ways very similar to those of ADHD. Ignoring this can easily lead to misdiagnosis.

Symptoms listed in the two classification systems are equivalent. However, to fulfill ICD-10 criteria, symptoms must be present in all three dimensions (attention, hyperactivity and impulsivity) while DSM-IV includes hyperactivity and impulsivity symptoms in the same dimension and states that individuals may present symptoms in only one (out of two) dimension. DSM-IV requires at least 6 out of 9 symptoms of inattention or at least 6 out of 9 symptoms of hyperactivity/impulsivity for the diagnosis of ADHD. In both classifications symptoms need to persist for at least 6 months to a degree that is maladaptive and inconsistent with the developmental stage.

According to DSM-IV, there are three possible subtypes based on the presence or absence of specific symptoms in the past 6 months:

- *Combined* (if criteria for inattention and hyperactivity/impulsivity are met)
- *Predominantly inattentive* (if criteria for attention deficit are met but criteria for hyperactivity/impulsivity are not met)
- *Predominantly hyperactive-impulsive* (if criteria for hyperactivity/impulsivity are met but criteria for inattention are not met).

The predominantly inattentive subtype is more frequent among girls and less common in clinic settings because children are less often referred for treatment due to inattention than hyperactivity. This subtype is commonly associated with poor academic performance, cognitive deficits and delayed development. Predominantly inattentive patients are commonly described as disorganized, quiet, dreamers, and as “staring off into space”. The predominantly hyperactive-impulsive subtype is less common both in clinic and community settings. The combined subtype is the most commonly diagnosed subtype in clinic settings. Although all subtypes of ADHD are associated with oppositional defiant behaviors this association is stronger for the combined subtype, making treatment more challenging. Furthermore, the combined subtype is associated with higher functional impairment than the other two types.

Informant

Irrespective of the pervasiveness criterion (presence of symptoms in at least two different settings), it is necessary to have more than one source of information, usually parents *and* teachers. This is because informants (either parents or teachers) observe the child in different contexts, which may influence the occurrence of symptoms, and informants are susceptible to a variety of biases. Parents have a longitudinal view and can give valuable information on their child’s neurodevelopmental trajectory. However, they tend to have more difficulties admitting their children’s problems. Teachers, on the other hand, are in constant contact with a large number of children of the same age, which allow them to easily identify deviant behaviors, and are aware of objective measures of children’s academic performance, which make them more able to detect academic deficits.

Apart from obtaining information from parents and teachers, clinicians should also examine the child, even though symptoms are often absent during the assessment interview. It would be unrealistic to expect observing a child

Controversies about the classification of ADHD

Questions have emerged regarding the classification of ADHD (Rohde, 2008). One relates to the validity and utility of differentiating ADHD into subtypes: subtypes are unstable over time, familial liability seems unspecific, and all subtypes respond to the same drug treatments (Lahey & Willcutt, 2010). Another refers to the need to include functional impairment as a diagnostic criterion because many children with ADHD will have reduced or no impairment because of compensatory skills or extra effort. On the other hand, not including functional impairment as a criterion may lead to over-diagnosis and treatment of children who do not have deficits. A third question relates to the age of onset criterion, that symptoms and associated impairment must emerge before age 7. This is not supported by empirical evidence (Rohde et al, 2000; Polanczyk et al, 2010). In this regard, clinicians should bear in mind that patients must be evaluated individually when considering the need for treatment.

demolishing or running amok in the doctor's office to make a diagnosis of ADHD. Furthermore, examining the child is important in order to exclude other diagnoses. Adolescents should be asked to report symptoms they experienced during childhood. Adolescents often deny symptoms in the past, interpreting such symptoms as normal behaviors or minimizing their impact. Parents' information and school reports may help to determine age of onset of symptoms.

The clinical interview with parents is also important to gather detailed information on peer and family relationships, medical history and investigation for other mental disorders that can co-exist with ADHD. It is important to ascertain whether there is inconsistent or chaotic parenting, abuse or neglect which may lead children to behave similarly to children with ADHD.

Additional investigations

As already mentioned, the diagnosis of ADHD is clinically-based and no additional tests are necessary unless the clinician suspects the presence of other conditions (American Academy of Pediatrics, 2011). The use of rating scales is helpful in quantifying the presence and severity of specific symptoms and monitoring treatment response. Scales can be completed by parents and teachers and are easy to use; in rare cases in which an underlying physical disorder may be suspected, a specialist opinion may be useful, for example, brief or nighttime seizures can occasionally cause attention problems and restlessness that can be misinterpreted as ADHD; in cases where epilepsy is suspected, a neurological evaluation and EEG is required. The use of EEG for the diagnosis of ADHD, although popular in some countries, is not necessary and there are serious doubts about its validity. Likewise, there is usually no need for imaging studies except when a neurological disorder is suspected.

The majority of neuropsychological tests are copyright and expensive, which restricts their use, although specific tests can be of help. Intelligence tests

Although there is significant overlap between DSM-IV and ICD-10 diagnostic criteria, the latter is more restrictive. ICD-10 hyperkinetic disorder is similar to DSM IV combined subtype, a more severe variant of the condition than the predominantly inattentive and predominantly hyperactive-impulsive types (Lee et al, 2008).

Figure D.1.3 The STROOP test



The stroop test is used to measure attention. It takes advantage of our ability to read words more quickly and automatically than naming colors. The cognitive mechanism involved in this task is called directed attention: one has to manage one's attention, inhibit or stop one response in order to say or do something else. It is one of the tests that, despite not being diagnostic, provides data about attentional ability.

Table D.1.4 Selected Scales for ADHD freely available for clinical use

SCALE (age range)	RATER	COMMENTS
SNAP IV (5–11 years) Swanson et al (2001)	<ul style="list-style-type: none"> • Self • Parent • Teacher 	There are several versions: <ul style="list-style-type: none"> • 90-item (full version); rates several dimensions of behavior apart from ADHD and includes SKAMP (to measure severity of impairment at school); it takes about 30 minutes to administer • 31-item version (includes rating of ADHD and oppositional defiant disorder); it takes 10 minutes to administer
SWAN (5–11 years) Swanson et al (2001)	<ul style="list-style-type: none"> • Self • Parent • Teacher 	<ul style="list-style-type: none"> • 26 items
SDQ Strengths and Difficulties Questionnaire (Goodman et al, 2000)	<ul style="list-style-type: none"> • Self • Parent • Teacher 	<ul style="list-style-type: none"> • Measures overall psychopathology, but a subscale can be used to screen ADHD risk • Reasonably sensible when screening “possible” ADHD illness • Available in several languages

(e.g., Wechsler) can be useful in clarifying intellectual deficits or IQ level and its implications. The Continuous Performance Test (CPT-II), Wisconsin Cart-Sorting test, STROOP test, and “Go/no go” tests are useful for research.

Rating scales

While diagnosis cannot be made on the basis of rating scale data alone, using rating scales is good clinical practice for screening purposes, to measure symptom severity and to monitor response to treatment and outcome. There are numerous rating scales that can be either specific for ADHD or for general psychopathology, most have a child, parent and teacher versions. The table below lists some of the rating scales available in the public domain.

COURSE

Growing evidence indicates that ADHD is a chronic disorder and that symptoms often persist into adult life, although disagreement exists about the extent of this; estimates vary across studies – most of the variation may be due to methodological differences such as definition of persistency (presence of symptoms or the full syndrome) and age when individuals are evaluated (Mannuzza et al, 2003). A recent review found a persistency of 15% for young-adults when presence of the full syndrome is considered, and 40-60% when cases in partial remission are included (Faraone et al, 2006).

Persistence of symptoms seems to be associated with severity. Patients with more severe symptoms and combined type ADHD are at higher risk for persistence (Kessler et al, 2005). Durability of symptoms is also associated with negative outcomes such as lower academic achievement (Mannuzza et al, 1997), marital problems and marriage dissatisfaction, divorce, difficulty dealing with offspring (Barkley & Fischer, 2010), lower job performance, unemployment, maintaining job positions below the individual’s potential (Stein, 2008; Mannuzza et al, 1997),

involvement in traffic accidents (Barkley & Cox, 2007) and increased risk for other psychiatric disorders (Mannuzza et al, 1998).

TREATMENT

ADHD interferes with multiple areas of functioning, such as behavior at home, in social situations, school performance; treatment should seek to improve functioning in all these areas. Multimodal interventions with different treatment targets are theoretically optimal, although few studies have directly compared multimodal treatment with pharmacotherapy alone (Abikoff et al, 2004). Many targets for intervention can be enumerated: ADHD symptoms, cognitive deficits and associated behaviors, academic performance, comorbid conditions, parental psychopathology, family and school-based problems. Following assessment, clinicians should decide about targets for intervention and formulate a treatment plan integrating the different modalities needed to achieve all the treatment goals. Treatment plans should be individually tailored to each patient and constantly reviewed and updated according to emerging needs and previous response. A close monitoring of treatment response is required and should include data from different sources, including parents', patients' and teachers' reports of perceived changes following interventions (Pliszka, 2007).

The literature is consistent on the effectiveness of stimulant medications and behavioral interventions in the management of the core symptoms of ADHD (American Academy of Pediatrics, 2011). Pharmacotherapy is effective for most children. Behavioral interventions are also valuable as primary treatment or as an adjunct treatment for many children, depending on the nature of coexisting conditions, outcomes targeted and family circumstances (American Academy of Pediatrics, 2011). Treatment plans should include at least one of these two treatment modalities (see Table D.1.5).

The decision to use non-pharmacological versus pharmacological intervention should be based on patient's age, profile of symptoms and disease severity, individual risk for side effects, treatment adherence issues, comorbid disorders, parents' and child's preference, cost, access to medication, and availability of trained therapists.

Education

Clinicians should give adequate information to patients and their families using a language they can understand. The main aims of psychoeducation are to:

- Ensure that patients and their family understand what ADHD is
- Enhance treatment adherence by involving patients and parents in the treatment plan and making sure that they understand the benefits and risks, such as side effects of medication
- Identify barriers to treatment.

Education may also involve school staff; whenever possible clinicians should contact and educate schoolteachers.

Behavior therapy

The effect size of behavioral interventions on ADHD symptoms is smaller than that of stimulant medications (Fabiano et al, 2009). Many guidelines for



Click on the picture to access the excellent guideline on ADHD treatment by the National Institute for Health and Clinical Excellence (NICE)

behavior therapy in ADHD are available (Bauermeister et al, 2006). In general terms, the therapist identifies problem behaviors and collects detailed data on the circumstances that precede and follow such behaviors. Usually behaviors become ingrained when reinforced. After the identification of reinforcing consequences a detailed plan on how to deal with problematic situations is drawn up and a different set of techniques to stop reinforcing unwanted behaviors or extinguish them is implemented (Antshel & Barkley, 2008). Behavior therapy for ADHD almost always involves parents and teachers as well as the child.

Pharmacotherapy

Many medications have been shown to be effective and safe for children with ADHD. Medications can be divided into stimulants and non-stimulants.

Stimulant medications

Stimulant medications (see Table D.1.3) have been used for decades in the treatment of ADHD and are licensed for this purpose in many countries. The efficacy and safety of these drugs have been extensively examined in numerous clinical trials as well as in systematic reviews and meta-analyses (Swanson et al, 2007; Biederman & Spencer, 2008; Adler, 2007; Adler, 2008; Faraone & Buitelaar, 2010; Faraone & Glatt, 2010). Trials consistently show that stimulants are more effective than placebo, with effect-sizes varying from 0.8 to 1.1 and a positive early clinical response in approximately 70% of cases. Most commonly used stimulant medications include methylphenidate, dexamethylphenidate, dextroamphetamine and mixed amphetamine salts. Other agents such as methamphetamine are available in certain countries. Medications are available in different presentations, including short-acting, long-acting and sustained-release. The main advantage of long-acting and sustained-release preparations is that one dose in the morning may sustain effect during the whole day, increasing adherence. However, they are more expensive, which limits their use. No conclusive evidence exists favoring any of the stimulants over others in terms of efficacy and side effect profile.

Stimulant dosage is not weight dependent. Clinicians should begin with a low dose and titrate upward to achieve optimal response (see Table D.1.3). The best dose is the one that leads to maximum benefit with minimal side effects. Although controlled studies that compare different dosing schedules are lacking, some clinicians believe that interrupting medication during weekends and holidays may compromise its efficacy.

Methylphenidate is available in immediate release and sustained release preparations. Immediate release methylphenidate reaches plasma peak levels in 1 to 3 hours after ingestion. Effects last approximately 4 hours; thus a two- or three-times-a-day schedule is necessary for symptom coverage. Methylphenidate SODAS[®] is a long-acting formulation in which half the amount is immediately released and the other half is released after 4 hours. Methylphenidate OROS[®] releases about one quarter of the amount immediately and the rest during the next 9 hours. The two later preparations only require a once-a-day dosage schedule.

There are different amphetamine preparations for ADHD but availability varies between countries. Brand names, dosing and duration of behavioral effect for each of these drugs can be found in Table D.1.3. Lisdexamphetamine has been recently approved for the treatment of children and adults with ADHD in the US,

Parent training

Parents can be trained to constructively deal with their child behavior by teaching them how to reinforce desirable behaviors and extinguish misbehavior. For example, how to set and communicate sensible, appropriate and achievable rules and what to do when the child adheres to the rules or breaks them. The strength of evidence for parent behavior training as the first-line intervention for improved behavior among preschoolers at risk for ADHD is high, while the strength of evidence for methylphenidate is low (Charach et al, 2011).

Table D.1.3 Stimulant drugs available to treat ADHD

Drug	Duration type	Brand name*	Dosage schedule	Approximate duration of action (hours)	Typical starting dose (mg)	Maximum daily dose mg
Methylphenidate	Short-acting	Ritalin Metadate Methylin	BID to TID	3-5	5	60
		Focalin	BID to TID		2.5	20
	Intermediate-acting	Ritalin SR Metadate ER Methylin ER	QD to BID	3-8	10	60
	Extended release	Metadate CD Ritalin LA	QD	8-10	10	60
		Concerta	QD	12	18	72
		Focalin SR	QD	12	5	30
		Daytrana	Patch worn for up to 9 hours		10	30
Amphetamines	Short-acting	Dexedrine Dextrostat	BID to TID	4	5	30
		Adderall	QD to BID	4	5	40
	Intermediate-acting	Dexedrine spansule	QD to BID	10	5	40
	Extended release	Adderal-XR	QD	10	10	30
		Vyvanse	QD	13	30	70

QD: once a day; BID: twice a day; TID: three times a day.

*All may not be available in some countries and brand names may be different.

Canada and Brazil. Lisdexamphetamine is an inactive component (prodrug) that is gradually converted into an active form of dextro-amphetamine in the body. Due to its gradual conversion, effect of Lisdexamphetamine is prolonged – up to 13 hours – thus not needing repeated doses during the day. Another common form of amphetamine approved in some countries for the treatment of ADHD is a preparation of mixed amphetamine salts. It is intermediate-acting and can be taken once or twice a day (see Table D.1.3).

Non-stimulant medications

Non-stimulant medications are considered second line treatments in case of intolerance, contra-indications or treatment failure. Evidence of effectiveness of these drugs, although not as strong as for stimulants, is good for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (American Academy of Pediatrics, 2011):

- **Atomoxetine** is a selective noradrenaline reuptake inhibitor (SNRI) that appears to cause a secondary increase in dopamine levels. The estimated effect size of atomoxetine for the treatment of ADHD

Long term efficacy of stimulant medication

Although evidence of the short-term effectivity of stimulants is very robust, there are very few data on the longer-term effectiveness of these medications. One of the few long-term trials is the [NIMH Collaborative Multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder \(MTA\)](#). In this study, 579 children with a mean age of 8 years diagnosed with DSM-IV ADHD combined type were randomly assigned to 14 months of systematic medication management, multicomponent behavior therapy, a combination of both, or usual community care. After 14 months, the MTA became an uncontrolled naturalistic study: children were allowed any treatment and followed up even if treatment was abandoned.

Initial results, at the end of the randomized treatment phase (14 months), showed that all groups had improved over baseline. However, methylphenidate proved to be superior to behavioral treatment and to routine community care. Further, the combined treatment did not produce greater benefits than medication alone for core ADHD symptoms.

By the next follow-up, 3 years after enrolment (when participants were about 12 years of age) there were no significant group differences. This result was confirmed in the next two follow-up assessments at 6 and 8 years (when participants were about 17 years old). While differences between the groups had disappeared, the initial improvement was maintained. However, these adolescents still showed significantly more symptoms and impairment than a community control group. Participants still taking medication by 6 and 8 years performed no better than their non-medicated counterparts despite a 41% increase in the average total daily dose (Abikoff et al, 2004; Molina et al, 2009).

The sobering results of the MTA suggest that maintaining a good treatment response probably requires a sustained effort that takes into account long-term academic and behavioral problems commonly associated with ADHD and adapts to the demands of adolescence. Medication may continue to be helpful for some teenagers, but their needs should be re-evaluated periodically. A child's initial clinical presentation, including symptom severity, behavior problems, social skills and family resources, may predict how they will function as teens more so than the type of treatment they receive.



Click on the picture to view James Swanson's talk at the Karolinska Institute about the MTA study and its long-term results (15:00)

(approximately 0.8) is higher than that of other non-stimulant drugs but smaller than for stimulants (Hazell et al, 2011). Atomoxetine can reduce anxiety symptoms in adults and children and is an option for the treatment of ADHD with comorbid anxiety disorders. It is also preferable for patients with a history of substance misuse (or if there are other household members who use drugs because of the risk of diversion). Compared to stimulants, atomoxetine has a slower onset of action but can be taken once daily. Starting dose is 0.5mg/kg/day that can be increased up to 1.2mg/kg/day. The most frequent adverse events are transitory gastrointestinal symptoms, reduced appetite, sleep problems, increased heart rate and blood pressure. Severe but very rare side effects include hepatotoxicity, with increase in hepatic enzymes, bilirubin and jaundice; emergent suicidal behaviors (both suicidal ideation and attempts) have also been reported.

- **Clonidine** and **guanfacine** are alpha-2 agonists with demonstrated efficacy in the treatment of ADHD. Guanfacine is more selective than clonidine causing fewer adverse effects such as somnolence. These medications can also be used for patients with comorbid tic disorders or Tourette's syndrome, in which its efficacy seems to be higher. There are now long-acting formulations for both clonidine and guanfacine available.

- **Modafinil** is a non-stimulant medication used for the treatment of narcolepsy that has been tested for ADHD; its efficacy has been demonstrated in randomized clinical trials.
- **Tricyclic antidepressants** such as imipramine, have also been shown to reduce ADHD symptoms. Nevertheless tricyclic antidepressants are associated with significant side effects, are less effective than stimulant medications and should be used only after failure to respond to two or three stimulants and atomoxetine (AAP, 2011). Tricyclic antidepressants can interfere with cardiac conduction and can cause sudden death; it is important that patients are monitored with electrocardiogram before and during treatment.
- **Bupropion** is considered a third line treatment for ADHD; it can be tried in case of failure of stimulants, atomoxetine and alpha-2 agonists. Bupropion lowers seizure threshold in a dose dependent fashion.

Side effects

Side effects must always be discussed in detail with the patient and parents before prescribing medication. The most common side effects associated with psychostimulants are insomnia, headache, irritability, agitation, nervousness, tremor, loss of appetite, nausea and weight loss. These unwanted effects tend to be mild, dose dependent and transitory. Stimulants can exacerbate tics, psychotic and manic symptoms, and seizures in children at risk for such conditions. Although these disorders are not an absolute contra-indications for stimulants, clinicians should consider alternative treatments such as behavior therapy or atomoxetine (in the case of tics, psychotic symptoms and anxiety) and use stimulants only if the potential benefit is greater than the potential harm. For more information on how to monitor and manage side effects see Table D.1.4.

Controversies have emerged in relation to the safety of stimulants in children with ADHD. The main concerns relate to their effect on growth, the cardiovascular system and risk for abuse or diversion.

Sudden death

There is a theoretical potential for all stimulants to increase the risk of sudden cardiac death and stroke. It is not clear whether this risk is dependent on the stimulant used, the individual's participation in strenuous exercise, or possible underlying cardiac risk factors. Methylphenidate has been associated with sudden cardiac death in individuals with structural cardiac abnormalities but there is no evidence that the frequency of heart attack is higher among those using methylphenidate than in the general population (Elia and Vetter, 2010; Stiefel and Besag, 2010). Several large studies and meta-analyses have shown no evidence that current use of an ADHD drug is associated with an increased risk of serious cardiovascular events. Although the risk cannot be ruled out altogether, the absolute magnitude of such an increased risk is very low (Cooper et al, 2011).

Growth retardation

Stimulants may stunt children's growth and may reduce final adult height. There is no doubt that stimulants reduce growth slightly and this needs to be

Table D.1.4 Monitoring and managing medication side effects

Side effect	May occur with:	Monitoring	Management
Loss of appetite or weight loss	<ul style="list-style-type: none"> Methylphenidate Atomoxetine Amphetamines 	<ul style="list-style-type: none"> Measure weight before treatment and then every 3-6 months Plot on a growth chart 	<ul style="list-style-type: none"> Avoid taking the medication before meals Give patient and parents dietary advice or refer for dietary advice
Growth retardation	<ul style="list-style-type: none"> Methylphenidate Atomoxetine Amphetamines 	<ul style="list-style-type: none"> Measure height before treatment and then every 3-6 months Plot on a growth chart 	<ul style="list-style-type: none"> Consider stopping medication during weekends and school holidays Consider dosage reduction or stop medication if there is clear evidence of growth suppression
Insomnia	<ul style="list-style-type: none"> Methylphenidate Amphetamines 	<ul style="list-style-type: none"> Gather information about sleep patterns before and after starting treatment 	<ul style="list-style-type: none"> Consider changing the dose schedule avoiding medication in the afternoon Reduce dose Change to atomoxetine
Hepatotoxicity	<ul style="list-style-type: none"> Atomoxetine 	<ul style="list-style-type: none"> Inform parents about risk of liver damage Monitor ALT and AST levels before and after starting treatment 	<ul style="list-style-type: none"> Stop atomoxetine immediately if jaundice or laboratory evidence of liver damage emerges Change to another medication but do not resume atomoxetine
Abnormal blood pressure or cardiac function	<ul style="list-style-type: none"> Methylphenidate Atomoxetine Amphetamines 	<ul style="list-style-type: none"> Before starting medication, collect detailed information about: <ul style="list-style-type: none"> Personal and family history of cardiovascular events (particularly sudden cardiac death) Physical findings suggestive of Marfan's syndrome or long Q-T syndrome At follow up appointments Monitor heart rate, blood pressure and the presence of abnormal murmurs 	<ul style="list-style-type: none"> In case of suspected cardiovascular abnormality refer patient to a cardiologist before commencing medication In case of blood pressure higher than the 95th percentile (or any clinically relevant increase) or arrhythmia/tachycardia, stop the medication and refer to a cardiologist
Seizures	<ul style="list-style-type: none"> Methylphenidate Atomoxetine 	<ul style="list-style-type: none"> Warn parents about risk of seizures 	<ul style="list-style-type: none"> Stop medication. Consider using dexamphetamine.
Tics	<ul style="list-style-type: none"> Methylphenidate Amphetamines 	<ul style="list-style-type: none"> Monitor the presence of tics before and after starting treatment 	<ul style="list-style-type: none"> Reduce/stop the stimulant if tics get worse Discuss with parents and patient the benefits and risks of continuing stimulant treatment Consider atomoxetine
Anxiety symptoms	<ul style="list-style-type: none"> Methylphenidate Amphetamines 	<ul style="list-style-type: none"> Investigate presence of anxiety symptoms before and after starting treatment 	<ul style="list-style-type: none"> Titrate the dose more slowly In case of worsening or emerging anxiety symptoms consider concomitant treatment of anxiety Change to atomoxetine

Table D.1.4 (continuation)

Side effect	May occur with	Monitoring	Management
Psychotic symptoms	<ul style="list-style-type: none"> • Methylphenidate • Amphetamines 	<ul style="list-style-type: none"> • Monitor psychotic symptoms before and after starting treatment 	<ul style="list-style-type: none"> • In case of high risk for, or emerging psychotic symptoms stop stimulants • Consider atomoxetine • If symptoms persist after stopping stimulants treat psychotic symptoms.
Aggressive or hostile behavior and suicidal thinking	<ul style="list-style-type: none"> • Atomoxetine 	<ul style="list-style-type: none"> • Ask patients about suicidal or aggressive ideation or impulses 	<ul style="list-style-type: none"> • Warn parents about risk for such behaviors before starting treatment • Discuss with parents how to keep their child safe from self-harm • If symptoms persists after one month consider changing to another medication
Drug misuse or diversion	<ul style="list-style-type: none"> • Methylphenidate • Amphetamines 	<ul style="list-style-type: none"> • Monitor the number of pills prescribed and gather information about behaviors that may suggest abuse/diversion • Do family members abuse substances? 	<ul style="list-style-type: none"> • Ask parents to monitor or supervise taking the medication • In case of high risk for abuse, suspected abuse or diversion, atomoxetine should be prescribed

discussed with parents and patients. Therefore children's growth ought to be monitored regularly while on stimulants. Growth resumes once stimulants are stopped, stopping the drug during summer holidays may minimize the risk of growth retardation when this is a concern. Other options include reducing the dose, stopping or switching to atomoxetine (Pliszka, 2007).

Abuse and diversion

All stimulant medications have potential for abuse. Abuse and diversion (e.g., selling the medication, giving it to friends or relatives, having it stolen), although rare, has increased in recent years in some countries where stimulants are widely prescribed. Abusers often report using stimulants to increase academic performance but recreational use also occurs. Misuse is more common among those with comorbid conduct or substance use disorders. Household members or college students who abuse substances may also steal the medication from patients if not appropriately protected. Although long-acting stimulants may be less likely to be misused or diverted, atomoxetine should be prescribed in these cases (Faraone & Wilens, 2007).

New therapeutic approaches

New therapeutic approaches are emerging. Neurofeedback, a type of biofeedback that uses electroencephalographic signals to promote self-training of brain activity, has shown some positive initial results (Arns et al, 2009). Another intervention under study is cognitive training (Halperin & Healey, 2011). Cognitive training seeks to improve working memory and executive functions

through a variety of means including computer applications. Omega-3 fatty acid supplementation is also receiving considerable attention; some studies suggest that it improves ADHD symptoms (Bloch & Qawasmi, 2011).

To date there is not enough evidence to support the following interventions for the treatment of ADHD:

- Acupuncture (Li et al, 2011)
- Meditation (Krisanaprakornkit et al, 2010)
- Homeopathy (Coulter & Dean, 2007)
- Physical exercise (Gapin et al, 2011)
- Chiropractic care (Karpouzis et al, 2010)
- *Hypericum perforatum* (St John's wort)(Weber et al, 2008)
- Music therapy (Rickson, 2006)
- Bach flower remedies (Pintov et al, 2005), and
- Elimination diets (Pelsser et al, 2011).

Table D.1.5 Summary of recommendations for treatment

Severity	4–5 years of age	6–11 years of age	12–18 years of age
Mild to moderate	<ul style="list-style-type: none"> • Psychoeducation • Parent training programs • Teacher-administered behavior therapy • If no improvement and symptoms are severe, consider methylphenidate. 	<ul style="list-style-type: none"> • Parent training programs and CBT • If no access to CBT and in severe cases with uncomplicated ADHD: stimulants or atomoxetine • If no response: add stimulants or atomoxetine (first line medications) • If no adequate response or significant side effects: switch to another first line medication (e.g., from methylphenidate to dexamphetamine or to atomoxetine) • If no response and significant comorbidity: try second line medications 	<ul style="list-style-type: none"> • Stimulants or atomoxetine • If no response: add CBT • If no adequate response or significant side effects: switch to another first line medication (e.g., from methylphenidate to dexamphetamine or to atomoxetine) • If no response and significant comorbidity: try second line medications
Severe		<ul style="list-style-type: none"> • Stimulants or atomoxetine, if possible combined with CBT • If no adequate response or significant side effects: switch to another first line medication (e.g., from methylphenidate to dexamphetamine or to atomoxetine) • If no response and significant comorbidity: try second line medications 	<ul style="list-style-type: none"> • Stimulants or atomoxetine, if possible combined with CBT • If no adequate response or significant side effects: switch to another first line medication (e.g., from methylphenidate to dexamphetamine or to atomoxetine) • If no response and significant comorbidity: try second line medications

First line medications: stimulants, atomoxetine
 Second line medications: extended release guanfacine,
 Third line medications: extended release clonidine, tricyclic antidepressants, bupropion

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