

ATTENTION DEFICIT HYPERACTIVITY DISORDER

2020 Edition

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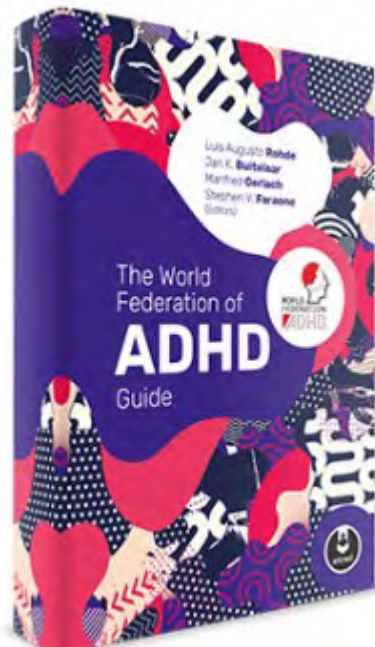
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Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by frequent, pervasive and impairing inattention and/or hyperactivity/impulsivity (American Psychiatric Association, 2013). This chapter summarizes evidence-based data on ADHD, from epidemiology to treatment.

HISTORICAL NOTE

Until recently, two publications competed for the title of providing the first description of ADHD: the fictional *Struwwelpeter*, written by the pediatrician Heinrich Hoffmann in 1845, and the 1902 Goulstonian Lecture, “An abnormal Psychical Condition in Children”, by George F. Still, published in *The Lancet*. There are other ADHD descriptions published between these two. The concept of what we now call ADHD was introduced as a “mental instability” by Désiré-Magloire Bourneville in France in 1885 (Bader & Hadjikhani, 2014). Two other French physicians, Georges Paul-Boncour and Jean Philippe, described a group of abnormal school children who presented symptoms of hyperactivity, impulsivity, and inattention, which would currently be diagnosed as having ADHD and comorbid oppositional defiant disorder or conduct disorder.

Two other authors described ADHD features even earlier—more than two centuries ago. Palmer and Finger (2001) introduced the work of Alexander Crichton, a Scottish physician who had written a text in 1798 entitled “An Inquiry into the Nature and Origin of Mental Derangement: Comprehending a Concise System of Physiology and Pathology of the Human Mind and a History of the Passion and their Effects”, in which he described a clinical condition similar to



For those interested in learning more about different aspects of ADHD, the World Federation of ADHD has a free guide available in the Internet in English, Spanish and Chinese (click on the image to access)

what currently would be described as ADHD in adults. Weikard, a German physician, published a medical textbook in 1775 (*Der Philosophische Arzt*), which included a chapter on attention deficits in which he described symptoms of ADHD like “often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities”, “often has difficulty organizing tasks and activities”, “often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort”. Reports of a condition similar to ADHD can be found even earlier. The oldest is attributed to the Greek philosopher Theophrastus in the 4th century BC (Victor et al, 2018).

After Still’s description, ADHD was believed to be associated with brain lesions and called minimal brain damage (Hohman, 1922; Kahn & Cohen, 1934). Later, recognizing that not all children had physical lesions, it was renamed minimal

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brain dysfunction (Clements & Peters, 1962). In 1934, Kramer-Pollnow described a syndrome called *hyperkinetische Erkrankung* (hyperkinetic disease) characterized by restlessness and distractibility (Sharkey & Fitzgerald, 2007).

In 1937, Bradley described the first effective treatment for ADHD. He 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 International Classification of Diseases, 9th edition (ICD-9) as “hyperkinetic syndrome of childhood” (subsequently called “hyperkinetic disorder” in ICD-10) and in the Diagnostic and Statistical Manual of Mental Disorders, second edition (DSM-2) (“hyperkinetic reaction of childhood”). It was only in 1980 that the role of inattention was recognized and the disorder renamed “attention-deficit disorder with or without hyperactivity” (DSM-III) and subsequently as “attention deficit hyperactivity disorder” (DSM-III-R and DSM-IV).

EPIDEMIOLOGY

Meta-analytic data suggest a worldwide prevalence of ADHD in children and adolescents between 5% (Polanczyk et al, 2007) and 7% (Thomas et al, 2015). Both meta-analyses found high heterogeneity among the studies due to methodological factors, such as different diagnostic approaches, information sources, and whether impairment was considered (Polanczyk et al, 2014).

Prevalence rates vary according to sex. Studies found a male-to-female ratio of 4:1 in clinical samples and 2:1 in general population studies (Polanczyk et al, 2007), suggesting referral biases.

Regarding socioeconomic status, Larsson et al (2014) found that low family income predicted an increased probability of ADHD in a Swedish population cohort. This finding does not necessarily prove that lower socioeconomic status increases the risk of ADHD, it could be the opposite (reverse causation). Since the disorder runs in families and causes various impairments—including educational and occupational problems—that could lead to socioeconomic disadvantage.

Also, prevalence does not seem to vary with ethnicity. The association found in some studies may be related to referral patterns and barriers affecting recognition in particular ethnic groups (Faraone et al, 2015).

Does prevalence vary according to country? Did it increase in the last few decades? Previous meta-analyses show that prevalence neither varies by geographic region nor by the time of publication of the studies (Polanczyk et al, 2007, 2014).



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

ETIOLOGY

Multiple theories about the etiology of ADHD have been proposed, from single-cause explanations to models that characterize ADHD as a multifactorial disorder, including genetic and environmental factors.

Genetic Factors

ADHD is a familial disorder; first-degree relatives of patients show a five- to ten-fold increased risk of developing the disorder themselves when compared with the general population. Twin studies have demonstrated a heritability of 70% to 80% in both children and adults (Thapar & Cooper, 2016; Posner et al, 2020).

A large genome-wide study including 20,000 individuals with and over 35,000 without ADHD found at least 12 different loci, with many genetic risk variants involved in the development of ADHD. Each variant making a small contribution to the risk (Demontis, 2019). These associations account for approximately 22% of the disorder's heritability (Posner et al, 2020).

Environmental Factors

Many environmental risk factors have been associated with ADHD. However, none are specific to this condition. Due to the high heritability of ADHD, gene-environment interactions might be the main mechanism by which environmental factors increase the risk of developing the disorder. Epigenetics is currently being brought into focus since it provides mechanisms by which environmental risk factors modify gene function (Faraone et al, 2015; Posner et al, 2020).

The following are examples of environmental factors associated with ADHD in meta-analytic or large population studies:

- *Prenatal and perinatal factors*: low birth weight, prematurity—the two more researched, see Franz et al, 2018—in-utero exposure to maternal stress, maternal obesity, hypertension, cigarette smoking, alcohol, prescribed drugs (e.g., acetaminophen, valproate), and illicit substances.
- *Environmental toxins* (in-utero or during early childhood): lead, organophosphate pesticides, and polychlorinated biphenyls.
- *Nutritional deficiencies*: zinc, magnesium, iron, omega-3 polyunsaturated fatty acids.
- *Nutritional surpluses*: sugar, artificial food colorings, low or high IgG foods.
- *Psychosocial factors*: low income, family adversity, harsh or hostile parenting.

It is important to highlight that some of the associations detected might be a product of gene/environment correlations. For example, the association between maternal smoking and ADHD disappears after adjusting for family history of ADHD, which suggests that this association is due to genetic factors that increase the risk for both smoking and ADHD. The same applies to parenting style: a child's behavior may elicit harsh and unsupportive parenting, which leads to an escalation of problems and the development of coercive cycles within families (Posner et al, 2020).

Heritability

Heritability is a difficult to understand concept. There are many misconceptions about what it can and cannot tell us about a given trait. Heritability does not indicate what proportion of a trait is determined by genes and what proportion is determined by the environment. So, a heritability of 0.7 (or 70%) does not mean that a trait is 70% caused by genetic factors; it means that 70% of the *variability in the trait in a population* is due to genetic differences among people.

To clarify this, imagine that height is 80% heritable. This does not mean that only 80% of people have their height genetically shaped. It would also be erroneous to think that a particular height (e.g., 165cm) can be broken down into 132cm of genetically determined growth and 33cm of environmentally caused growth (Lynch K, 2013).

NEUROBIOLOGY

Neurotransmitters

The monoaminergic systems, specifically the dopaminergic and the noradrenergic pathways, have been the most researched in ADHD; they are intimately related to brain processes affected by the disorder. The dopamine system plays an important part in planning and in the initiation of motor responses, activation, switching, reaction to novelty and processing of reward. The noradrenergic system influences arousal modulation, signal-to-noise ratios in cortical areas, state-dependent cognitive processes, and cognitive preparation of urgent stimuli (Faraone et al, 2015).

These systems were implicated in ADHD due to their involvement in the mechanism of action of drugs used in treatment. They have been extensively investigated in genetic studies using candidate gene approaches. Methylphenidate and amphetamines target the sodium-dependent dopamine transporter, atomoxetine targets the sodium-dependent noradrenaline transporter, and both extended-release guanfacine and clonidine target the α_2A -adrenergic receptor. However, the complexity of ADHD pathophysiology extends beyond the dopaminergic and noradrenergic systems. New research has implicated other pathways, such as the nicotinic acetylcholine, glutamate, γ -aminobutyric acid (GABA), serotonin, neurite outgrowth or endosomal systems (Faraone et al, 2015).

Structural Neuroimaging

Many studies have been published in the past two decades on brain structure in ADHD. Earlier studies found a 3% to 5% difference in brain size between individuals with and without ADHD (Castellanos et al, 2002; Durston et al, 2004). Regarding subcortical regions, a meta-analysis reported smaller sizes in the basal ganglia and limbic areas (Frodl & Skokauskas, 2012). The most recent meta-analytic data by the ENIGMA-ADHD Working Group, which includes 36 cohorts and over 4,100 individuals, confirms these differences although noting that they might be more subtle than previously described. Moreover, differences are pronounced only in children and not significant in adults and adolescents (Hoogman et al, 2019).

Several studies found that the ADHD brain matures more slowly than the brain from typically developing children. In an important study, age of peak cortical thickness was delayed among children with ADHD (mean age at peak thickness 10.5 years) when compared with normal controls (mean age 7.5 years) (Shaw et al, 2007). This delay was more significant in the prefrontal regions. In relation to white matter, a meta-analysis of ten diffusion tensor imaging studies showed differences between ADHD and non-ADHD brains (Chen et al, 2016).

Functional Neuroimaging

Task-based fMRI studies in patients with ADHD that used inhibitory control, working memory, and tasks that required attention have shown under-activation of frontostriatal, frontoparietal, and ventral attention networks. The fronto-amygdalar circuits, the limbic brain and the posterior areas of the brain

also seem to be involved. Furthermore, in numerous studies, patients with ADHD show lower activation in reward processing paradigms of the ventral striatum than controls. Also, they present hyperactivation of the somatomotor and visual systems, which is possibly a mechanism to compensate impairment in the functioning of the prefrontal and anterior cingulate cortex (Faraone et al, 2015).

Resting state MRI also suggests that the ADHD brain connects its functional networks differently than the typically developing brain and that some networks related to ADHD mature later (Sripada et al, 2014).

Findings of both structural and functional imaging vary considerably among studies, suggesting that the neurobiology of ADHD is heterogenous, which might be reflected in the multiple symptoms of the condition. Despite evidence that patients with ADHD show differences from the “typical brain”, these biological markers are not sufficiently sensitive and specific to diagnose the disorder or to ascertain if an individual has the disorder.

Neuropsychological data

It is important to highlight from the start that there is no neuropsychological test with sufficient predictive power to diagnose ADHD. The most widely accepted theory about neuropsychological deficits in ADHD emphasizes deficits on behavioral inhibition (Barkley, 1997), including disruption of working memory, sustained attention, motor control, and affect regulation. Some studies suggest also that there are deficits on non-executive functions such as delay aversion (Sonuga-Barke et al, 2010). In addition, difficulties regulating arousal in response to environmental circumstances are frequent. Clinically, this would mean that ADHD symptoms are exacerbated during lengthy and tedious tasks (Posner et al, 2020).

Regarding cognitive deficits, Frazier et al (2004) found a moderate association between lower reading and IQ scores with ADHD as well as large impairments in arithmetic and spelling performance. These results were found in a meta-analysis of 137 studies with patients of all ages.

Again, the most important finding is the large heterogeneity in the neuropsychological profile of individuals with ADHD. As highlighted by Posner et al (2020): “While some individuals might show an extensive pattern of impairment across different executive functions, others will display profound impairment in a particular executive function (e.g., working memory) but be unaffected in other areas (e.g., the ability to inhibit). Some patients will show no executive function impairment at all.” More importantly, several other disorders might present a heterogeneous pattern of neuropsychological deficits and no specific deficit is pathognomonic of ADHD.

CLINICAL PRESENTATION

ADHD is defined by the presence of a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with normal functioning or development. Manifestations of inattention are numerous, including mind wandering while performing a task, lack of persistence, and disorganization.

fMRI

Functional Magnetic Resonance Imaging (fMRI) measures brain activity by detecting changes associated with blood flow, relying on the fact that cerebral blood flow and neuronal activation go together. When an area of the brain is in use, blood flow to that region also increases. fMRI is a variant of Magnetic Resonance Imaging (MRI) that seeks to measure brain activity and connectivity. It is non-invasive and provides a method to assess brain function.

The experimental designs used in fMRI are resting state and task-based. In resting state fMRI participants are not performing any explicit task, while using a stimulus or performing a task is the characteristic of task-based fMRI. In resting state fMRI the most traditional design consists of instructing participants to keep their eyes closed, not to think about anything in particular and not to fall asleep (Soares et al, 2016).



Click on the picture to view a short clip about ADHD and the brain

Hyperactivity manifests itself as excessive motor activity when not appropriate, fidgeting, tapping, or talkativeness. Impulsivity refers to making decisions or actions without planning. Also, it can appear as social intrusiveness or making important decisions without considering its consequences. It is important to emphasize that these behavioral patterns should not be due to defiance or lack of comprehension (American Psychiatric Association, 2013).

Research about the factor structure of ADHD symptoms across the lifespan, using different information sources (e.g., teachers and parents) and cultures, suggests a two-factor model for ADHD, with inattentive and hyperactive/impulsive dimensions (Bauermeister et al, 2010). DSM-5 (American Psychiatric Association, 2013) suggests that there are three ADHD presentations: predominantly inattentive, predominantly hyperactive/impulsive, and combined. Although this description provides convenient clinical prototypes that have specific associations with functional and behavioral correlates of inattention and hyperactivity-impulsivity symptoms, it does not identify robust subgroups with sufficient long-term stability to justify the classification of distinct types of the disorder (Willcutt et al, 2012). The key symptoms of ADHD are listed in Table D.1.1



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

Table D.1.1 Symptoms of ADHD

Inattention

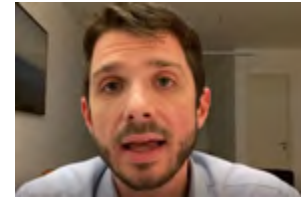
- Difficulty paying attention to details and consequent careless mistakes
- Difficulty sustaining attention in tasks or activities
- Struggling to listen when spoken to
- Struggling to accomplish and to finish tasks or activities
- Difficulty organizing tasks and activities
- Avoidance of tasks that need more mental effort
- Misplacing objects needed to perform tasks or activities
- Distractibility by external stimuli
- Forgetfulness about daily activities

Hyperactivity or impulsivity

- Fidgeting or tapping hands or feet or squirming in seat
- Standing up when expected to remain seated
- Running about or climbing (mostly in children) or subjective feelings of restlessness (mostly in adolescents and adults)
- Inability to play quietly
- Often “on the go”, “driven by a motor”
- Inappropriate talkativeness
- Blurting out answers before a question has been finished
- Difficulty waiting their turn in games or activities
- Interrupting others or intruding

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.

It is important to highlight that children affected by ADHD might be able to remain focused when performing specific tasks such as playing videogames, watching television, or in certain situations which they enjoy. Motivation, relevance, and attractiveness of the task for the child influence the manifestation of symptoms. Also, careful parents might provide structured environments and stimulation for their children with ADHD, creating a situation where symptoms are only evidenced later in adolescence when they become more independent.



Click on the image to view a short clip with Guilherme Polanczyk speaking about the essentials for diagnosing ADHD in pre-schoolers

Differences According to Developmental Stage

The developmental stage must be considered when assessing individual clinical presentations since symptoms vary according to age. Although there are studies showing that current criteria can be used to diagnose ADHD even in 3-year-old children, there are intrinsic difficulties in diagnosing ADHD in preschoolers. A degree of impulsivity and hyperactivity is developmentally appropriate in this age group, which makes it hard to disentangle age-normal from inappropriate hyperactive/impulsive behaviors. Also, since they might not be exposed to substantial environmental demands (e.g., sticking to a task for any length of time), inattention is even more difficult to assess.

In school-age children, inattentive and hyperactive/impulsive symptoms can be detected, particularly in the classroom, in different combinations and varying degrees of severity using information from different sources. ADHD symptoms tend to decline in late adolescence and adulthood—hyperactive/impulsive

Table D.1.2 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.

symptoms lessening more than inattentive ones across development (Rohde et al, 2019). See Table D.1.2.

Comorbidity

Individuals with ADHD from clinical and community samples often suffer from other psychiatric disorders. The patterns of comorbidity depend on the developmental stage. The most common comorbid conditions in children are oppositional defiant disorder (ODD), conduct disorder (CD), intellectual disability, learning disorders, language disorders, sleep disorders, enuresis, developmental motor coordination disorders, depressive and anxiety disorders, tic disorders, and autism spectrum disorders.

A meta-analysis found that children with ADHD are 10 times more likely to have CD or ODD, five times more likely to suffer from depression, and three times more likely to have anxiety disorders compared with those without ADHD. There was no significant difference in comorbidity profiles between boys and girls.

In adolescents and adults, eating disorders, substance use disorders, bipolar disorder, and personality disorders are also more frequent. Recently, ADHD has been associated with medical conditions beyond psychiatric disorders such as obesity, asthma and atopic conditions, epilepsy, and diabetes (Rohde et al, 2019).

DIAGNOSIS

Currently, the diagnosis of ADHD, usually following a classification system, predominantly DSM-5 or ICD-11, relies exclusively on a clinical assessment (see table D.1.3 and box in page 10) (American Psychiatric Association, 2013; ICD-11). DSM-5 differs from ICD-11 in that it provides explicit statements of symptoms, other features, and decision rules to determine whether a child qualifies for the diagnosis. DSM-5 is quite prescriptive and allows the creation of diagnostic algorithms useful for research. ICD-11 relies largely on clinicians' experience and subjective judgement (see also Chapters A.3 and A.9 of the eBook).

Sources of Information

Different informants have different perspectives about the individual assessed. Neither DSM-5, nor ICD-11 guide on how to proceed when faced with conflicting data from different sources. Despite a lack of consensus about this matter, the current clinical wisdom is that diagnosis should be based on information from as many sources as possible. Also, it is clear that some informants will be able to evaluate some of the symptoms more accurately than others (e.g., parents can report about their child's development and behavior at home, while teachers, by being constantly surrounded by children of similar age, can better report on differences from peers and about behavior at school) (Rohde et al, 2019). Clinicians should also examine the child, even though symptoms are often absent during the assessment interview. It would be unrealistic to require a child to demolish or run amok in the doctor's office to make a diagnosis of ADHD. Furthermore, examining the child is important to exclude other problems. Adolescents should be asked about symptoms they experienced during childhood. However, they often deny symptoms in the past, interpreting them as normal behaviors or minimizing their impact. Parents' information and school reports may help to determine the age of onset of symptoms.

Table D.1.3 Diagnostic criteria for ADHD according to DSM-5

Criterion	
Number of symptoms needed for 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 • For older adolescents (aged 17 or more) and adults, the threshold is at least 5 symptoms
Age of symptom onset*	<ul style="list-style-type: none"> • Before 12 years of age
Minimal duration of symptoms	<ul style="list-style-type: none"> • 6 months
Pervasiveness	<ul style="list-style-type: none"> • Symptoms present in two or more settings (e.g., school, work, home)
Functioning	<ul style="list-style-type: none"> • There is clear evidence that symptoms cause significant impairment
Sources of information required	<ul style="list-style-type: none"> • Not mentioned
Exclusion of the diagnosis if	<ul style="list-style-type: none"> • 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)
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

*Note that this criterion refers to age of onset of symptoms and not to impairment

ADHD according to ICD-11

Attention deficit hyperactivity disorder is characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood. The degree of inattention and hyperactivity-impulsivity is outside the limits of normal variation expected for age and level of intellectual functioning and significantly interferes with academic, occupational, or social functioning. Inattention refers to significant difficulty in sustaining attention to tasks that do not provide a high level of stimulation or frequent rewards, distractibility, and problems with organization. Hyperactivity refers to excessive motor activity and difficulties with remaining still, most evident in structured situations that require behavioral self-control. Impulsivity is a tendency to act in response to immediate stimuli, without deliberation or consideration of the risks and consequences. The relative balance and the specific manifestations of inattentive and hyperactive-impulsive characteristics varies across individuals and may change over the course of development. In order for a diagnosis of disorder the behavior pattern must be clearly observable in more than one setting.

Unlike DSM-5, ICD-11 excludes ADHD diagnosis when the individual suffers from autism spectrum disorder, disruptive behavior or dissocial disorders.

Additional Investigations

Regrettably, there are no auxiliary tests, investigations, or biomarkers with sufficient predictive power to confirm or exclude this disorder. Likewise, neuroimaging (MRI, PET, SPECT) and EEG are not recommended in routine clinical evaluation, although they may be useful in differential diagnosis in rare cases. Neuropsychological, IQ, and achievement tests are helpful to estimate intellectual impairment, severe executive function deficits, and potential learning disorders (Rohde et al, 2019), which are important for management.

Rating scales are useful to quantify the severity of symptoms and to monitor response to treatment. One of the most widely used is SNAP-IV (Swanson, Nolan and Pelham Rating Scale-fourth revision); for adults, ASRS (Adult ADHD Self-Report Scale) is recommended (see table D.1.4) (Faraone et al, 2015).

Differential Diagnosis

It is essential to conduct a complete physical exam to exclude other clinical conditions (e.g., hyperthyroidism) that might cause inattentive and/or hyperactive/impulsive symptoms, as well as to evaluate visual and auditive acuity and sleep patterns.

Sleep disorders can be the cause, a consequence, or co-occur with ADHD (see Chapter I.4 of the eBook). Several genetic conditions may present with ADHD symptoms (i.e., neurofibromatosis type I, fragile X syndrome). Several psychiatric disorders that can be comorbid with ADHD must be considered also in the differential diagnosis (i.e., generalized anxiety disorder, bipolar disorder, major depression). Although ADHD can be comorbid with PTSD (Spencer et al, 2016), it is important to note that some traumatic events such as sexual abuse or severe neglect might result in a clinical picture that resembles ADHD.

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

SCALE (age range)	RATER	COMMENTS
SNAP IV (5–18 years) Swanson, Nolan and Pelham Rating Scale-fourth revision (Swanson et al, 2001)	<ul style="list-style-type: none"> • Self • Parent • Teacher 	<ul style="list-style-type: none"> • A rating scale for symptoms of ADHD and ODD • Sensitive to changes relating to treatment • Short scale: 26 items • Full scale: 90 items • Versions in French, Portuguese, and Spanish
SWAN (5–18 years) Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (Swanson et al, 2001)	<ul style="list-style-type: none"> • Self • Parent • Teacher 	<ul style="list-style-type: none"> • Based on DSM-IV criteria • 26 items • Versions in French and Spanish
ASRS (adults) Adult ADHD Self-Report Scale	<ul style="list-style-type: none"> • Self 	<ul style="list-style-type: none"> • Developed by the WHO • A 6-item version for screening • An 18-item version based on DSM-IV symptoms • Both versions have been translated into many languages

There are steps to be followed by clinicians in the differential diagnoses in these situations:

- Consider the age of onset of the ADHD symptoms and of the symptoms of the other psychiatric problems,
- Examine the trajectory of the symptoms (e.g., some disorders are episodic while ADHD is not), and
- Assess if the symptoms cannot be better explained by the comorbid condition (Rohde et al, 2019).

For example, age-of-onset of symptoms can be clinically relevant when disentangling inattention as manifestation of ADHD or as a symptom of a chronic depressive disorder (e.g., dysthymia). Onset of the inattentive symptoms before the onset of mood symptoms would suggest an ADHD diagnosis.

Relative immaturity. Interest in the relationship between relative immaturity and ADHD has increased recently. Children in the same grade at school are a heterogeneous group with some, born earlier, being older than others, born later. Age difference can be as large as 12 months, representing up to 15% of their young lives. Studies have shown that children who are younger than their classmates are more likely to be diagnosed with ADHD (Caye et al, 2019a). Although the reasons for this are not clear, it could be due to younger (less mature) children being incorrectly diagnosed as having ADHD (false positives), or younger children with ADHD in the same school grade having a more severe clinical presentation, making easier its recognition. Irrespective of the reason, this issue should be taken into consideration not just by clinicians but also by teachers.

Flow of Assessment

The diagnostic process is based on clinical approaches that rely on different sources of information. This process might be conducted using standard psychiatric interviews with the patient and their relatives, and with other appropriate informants, such as teachers (see [Chapter A.5 of the eTextbook](#)).

The interview is designed to elicit the symptoms and understand how they affect the individual's life as well as whether family or social factors may contribute to the symptoms. In addition, it allows capturing relevant medical and family history of mental disorders. The search for impairment in the various areas of life is crucial, such as school and relationship problems with parents and friends. In addition, it is essential to comprehensively search for comorbidities (Rohde et al, 2019).

To assist with diagnosis, particularly in research settings, different standardized interviews can be used with the aim of increasing reliability, such as the [Schedule for Affective Disorders and Schizophrenia for School-age Children \(K-SADS\)](#), or the [Development and Wellbeing Assessment \(DAWBA\)](#). Both can be downloaded from the Internet free of charge and are available in several languages. The K-SADS is a semi-structured interview, that is, it allows clinical judgment by the interviewer who needs to be a clinician trained in the use of the instrument. The DAWBA can be administered by trained non-clinical interviewers, online or by telephone, which is useful in epidemiological research.



COURSE

Until recently, ADHD was seen as a disorder specific to children. The belief was that individuals outgrew ADHD in adolescence. In the last two decades, substantial work has documented its persistence into adulthood in a substantial proportion of cases.

Persistence

There is no consensus on the extent in which ADHD persists from childhood to adulthood. Longitudinal studies following children with ADHD to a mean age of 18 years found rates that varied between 4% and 76% (Caye et al, 2016). A meta-analysis suggested that 15% of childhood cases met full diagnostic criteria by the age of 25, up to 65% showed symptoms causing impairment but did not meet full diagnostic criteria, and 20% showed neither symptoms nor impairment during adulthood (Faraone et al, 2006).

Despite the numerous studies on the trajectory of ADHD during the lifespan, there are only a few reports on childhood risk factors associated with remission or persistence into adulthood. A meta-analysis indicated that severe ADHD, comorbid conditions (such as conduct disorder and major depressive disorder), and treatment for ADHD were the main predictors of persistence. The Multimodal Treatment of ADHD study (MTA) reported that parental mental health problems could be a significant risk factor. However, IQ, socioeconomic status, parental education, and parent-child relationship problems were not associated with persistence (Roy et al, 2016).

Adolescent and Adult-Onset

According to DSM-5 (American Psychiatric Association, 2013), to make a diagnosis of ADHD, symptoms must have been present before the age of 12 (until 2013, before seven years of age). Some studies (Caye et al, 2016; Moffitt et al, 2015; Agnew-Blais et al, 2016) question this and suggest that ADHD may



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

occasionally start during adolescence or even adulthood. Whether ADHD of late-onset may exist or not requires more research (Asherson & Agnew-Blais, 2019).

OUTCOMES

It is widely accepted that ADHD is associated with negative outcomes. A wide range of studies has found that a diagnosis of ADHD is strongly associated with emotional problems and social impairments (Faraone et al, 2015), such as:

- Less ability to cope with stressful events, to express empathy, and to socialize with peers
- More likelihood to bully others, to drop out of school, to be unemployed, to have a lower income, to be involved in accidents—especially motor vehicle accidents—to be convicted of criminal offenses, to be imprisoned, to misuse substances, to have unwanted pregnancies and sexually transmitted diseases, and to die younger.

These negative outcomes result in a worse quality of life and higher suicide rates (Chen et al, 2019; Fitzgerald et al, 2019). In addition, ADHD has a negative impact on families. For example, a Danish study found that having a child with ADHD doubled the chances of parental separation (Kousgaard et al, 2018).

Despite all the negative outcomes associated with ADHD, some studies give a glimpse of potentially positive aspects. For example, adults with the disorder may have higher entrepreneurial traits (Verheul et al, 2016; Sônego et al, 2020), be more tolerant of risk, more open to new experiences, and more creative (Antshel, 2018; White & Shah, 2011; Boot et al, 2017).

Financial Burden

Large, systematic reviews have estimated the annual cost attributed to ADHD as between \$143 and \$266 billion in the US and more than €1 billion in the Netherlands (Doshi et al, 2012; Le et al, 2014). In Sweden, children with ADHD doubled or trebled the cost to the healthcare system when compared with peers without the condition (Du Rietz et al, 2020). Similar financial burden has been estimated for South Korea and Australia, among others.

TREATMENT

We present here the optimal treatment in an ideal world, something to aspire to. In many cases, however, due to lack of time, resources, skilled clinicians, and for other reasons, shortcuts are made. This is particularly so in low income countries where there is an acute lack of trained personnel. In any case, this should not be a justification for using treatments that are unsafe or have been shown not to be effective.

There are various treatment strategies that can ameliorate ADHD symptoms which are supported by evidence. Given the variation among patients, an individualized treatment plan is needed, taking into account age, comorbidities, severity, family and social circumstances, and preferences of the patient and family. The patient and family must always be involved in this process.

Risk calculator

Click [here](#) to access a risk calculator to estimate the chance of persistence of ADHD from childhood to young adulthood for children aged less than 12 years living in the UK or in the US (Caye et al, 2019b).



Psychoeducation

Because ADHD is a chronic, potentially lifelong condition, psychoeducation is the foundation for any treatment. Clinicians should pay attention to giving information in a way that families can understand, using language, comparisons, and metaphors at the patient educational level and in a culturally sensitive manner. This would include:

- Asking the family and the patient to explain their understanding of ADHD
- Giving an accurate explanation of what is ADHD, debunking myths and misconceptions, which are widespread
- Explaining that there is no “test” to diagnose ADHD, that diagnosis is based on clinical assessment
- Explaining at a level they can understand what causes the disorder
- Listing the various treatment options, including medication, with their benefits and side effects, the likelihood of response, expected course of action, and short and long-term effects
- Discussing pros and cons of the treatment chosen and if treatment is rejected
- With parents’ permission, inform teachers about the disorder and what they can do to support their students
- Informing about self-help resources, support groups, voluntary organizations, websites, and support for education and employment (NICE, 2018).

Non-Pharmacological Treatments

Non-pharmacological treatments may be used as an alternative or as an addition to medication when patients do not respond to the medication or have significant adverse effects, to address certain comorbidities, when patients do not have access to pharmacological treatment or when patients are too young

to take medication (Faraone et al, 2015). This evolves as patients grow up. For instance, parental interventions have more impact on younger children, while psychoeducation regarding substance misuse or motor vehicle accidents is more relevant for adolescents or young adults. A more detailed description of these treatments can be found in [Chapter D.1.1](#) of the eBook.

Behavioral and Psychosocial Treatment

Most guidelines recommend behavioral interventions (especially behavioral parent training) combined with medication. Behavioral interventions are indicated as the first line of treatment mainly for younger children and for those who have mild symptoms and impairment (Caye et al, 2019). However, the more conservative analyses of the literature for school-aged children and adolescents, considering evidence from randomized clinical trials relying on blind evaluations, suggest that effect sizes of ADHD symptoms are not substantial (Rimestad, 2019) but it is important to highlight that they are relevant to improving the quality of parenting and to treat comorbid conditions, especially oppositional defiant disorder and conduct problems (Faraone et al, 2015).

Other psychological approaches used for treating ADHD include behavior classroom interventions, social and organizational skills training, meditation-based therapy, and cognitive therapy. The last three might be particularly suitable for adolescents.

Neurofeedback

Neurofeedback uses reward-based techniques to normalize elements of the patient's electrophysiological profile that are thought to be associated with attention problems (Faraone et al, 2015). In summary, patients are trained to improve their self-control over brain activity patterns while being monitored via EEG obtained when they concentrate on a task (for instance, a simple computer game). Results of research regarding the positive effects of neurofeedback in ADHD are ambiguous at best (Caye et al, 2019).

Computerized Cognitive Training

Cognitive training approaches hypothesize a reduction of ADHD symptoms by enhancing achievement in specific neuropsychological functions related to ADHD (e.g., inhibitory control, attention, working memory). They are usually administered via computers or mobile phones and designed to be appealing to children, similar to videogames (Caye et al, 2019). These interventions train specific functions over multiple sessions, challenging the individual and increasing difficulty as they evolve (Faraone et al, 2015). A meta-analysis found that this treatment shows moderate effectiveness in improving the neuropsychological functions targeted but a less clear impact on the core symptoms of the disorder (Caye et al, 2019). Recently, the US Food and Drug Administration (FDA) approved the first videogame for treating ADHD in children (Kollins et al, 2020). Although promising, more studies are needed before this intervention can be recommended.

Dietary Interventions

Dietary interventions are divided into *exclusions* and *supplements*. Exclusion diets generally target artificial additives (mainly artificial food colorings). They have a positive but small effect, especially in patients that already had food intolerances (Faraone et al, 2015).

Polyunsaturated fatty acids are the supplements with the best positive effects (Caye et al, 2019). The use of other supplements (e.g., vitamins, herbs, homeopathy) is not supported by research evidence (Faraone et al, 2015).

Brain Stimulation

Since the trigeminal nerve conducts afferent inputs to multiple connections in the locus coeruleus, reticular activating system, and nucleus tractus solitarius—areas associated with attention—it is theorized that external trigeminal nerve stimulation may be a non-invasive, minimal risk treatment for ADHD (McGough et al, 2019). Despite having been approved by the FDA, the efficacy of this intervention is supported only by a 5-week randomized controlled trial that involved just 30 patients experiencing active trigeminal nerve stimulation. More studies are needed before it can be recommended.

PHARMACOLOGICAL TREATMENT

Stimulants

Psychostimulants—methylphenidate and amphetamines—are the most studied drugs for ADHD and among the best researched in psychiatry (e.g., table D.1.5). Methylphenidate is the most widely available. They have the limitation of a short half-life, thus requiring two or three doses during the day for optimal benefit—creating considerable practical problems particularly at school. Extended release preparations—which only require a single morning dose—use different mechanisms for slowing down absorption or release. For example, Concerta utilizes an “osmotic pump” mechanism with 22% of the dose available as immediate release.

Although more potent than methylphenidate, the amphetamines are less often used and, due to concerns about potential for abuse, are not commercially available in a number of countries. Apart from immediate release formulations, there are several longer acting, extended release amphetamine products. For example, Vyvanse (lisdexamfetamine) has an extended duration of action (see Table D.1.5).

All stimulants are thought to act, at least in part, through their impact on dopamine and/or noradrenaline pathways. Both neurotransmitters are key modulators of the brain circuits that support attention, reward processing, and activity. Whilst there are similarities between these medications, there are also differences. Methylphenidate and the amphetamines inhibit both the dopamine and noradrenaline reuptake transporters. Amphetamine derivatives also promote the release and reverse pre-synaptic transport of dopamine.

Although Concerta and Vyvanse (lisdexamfetamine) are considered first-line treatment in the majority of international guidelines (see below) and have many

Table D.1.5 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	2-3	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	6-8	10	60
		Concerta	QD	8-12	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	4-6	5	30
		Adderall	QD to BID	4-6	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.

Table D.1.6 Non-stimulant drugs used to treat ADHD

Drug	Duration type	Brand name*	Dosage schedule	Typical starting dose (mg)	Maximum daily dose (mg)
Guanfacine	Extended release	Intuniv	QD	1	age 8-12: 4 13-17: 7
Clonidine	Extended release	Kapway Catapres	BID	0.1	0.4 split in two doses
Atomoxetine	Short acting	Strattera	QD to BID	70 kg or less: 0.5 mg/kg over 70 kg: 40 mg	70 kg or less: 1.4 mg/kg or 100 over 70 kg: 100 mg

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.

similarities, they also have differences. Lisdexamfetamine has both a slightly larger effect size than methylphenidate in clinical trials with children and adolescents, a higher rate of irritability, and a bigger decrease in appetite. Concerta has a quicker onset of action but a slightly shorter duration in pharmacokinetic studies, although there is large inter-individual variability.

Non-Stimulants

There are two classes of non-stimulant medication used in ADHD, the noradrenaline reuptake inhibitor atomoxetine and the α 2-adrenergic agonists clonidine and guanfacine. See table D.1.6. Other medications have been used off-label such as tricyclic antidepressants (imipramine), bupropion (another antidepressant), and modafinil (usually administered to treat narcolepsy), with limited efficacy. Their use for ADHD is not approved in the US and the European Union (Caye et al, 2019). Recently, there is growing interest in the use of cannabinoids.

WHICH MEDICATION TO USE?

Based on Effectiveness

A meta-analysis including 133 studies with 24,000 participants found that psychostimulants were highly effective in reducing ADHD symptoms. Methylphenidate and amphetamines have a slightly different effect according to age group. Methylphenidate achieves a greater improvement in children and adolescents than in adults, while the amphetamines show similar benefit in both age groups. Among non-stimulant medications, atomoxetine produces a moderate improvement in both children and adults. Guanfacine and clonidine, both extended release, lead to a moderate reduction of symptoms in children only (Cortese et al, 2018).

Various well-designed studies, most based on large datasets, have investigated the extent to which reducing ADHD symptoms was associated with better outcomes in real life. They clearly documented the effectiveness of stimulants, mainly methylphenidate, in different functional outcomes such as improved quality of life (Jonsson et al, 2017; Coghill et al, 2017; Coghill, 2010) and higher academic achievement (Lu et al, 2017), reduced criminality (Lichtenstein et al, 2012; Mohr-Jensen et al, 2019), reduced vehicle accidents (Chang et al, 2017), reduced emergency room admissions related to substance abuse or trauma (Quinn et al, 2017; Chang et al, 2014), reduced risk of injuries and brain lesions (Ghirardi et al, 2020; Dalsgaard et al, 2015), fewer sexually transmitted diseases (Chen et al, 2018), fewer suicides (Liang et al, 2018), and reduced mortality rates (Chen et al, 2020).

Based on side Effects

Adverse effects must always be discussed in detail with the patient and parents before prescribing medication. The most common adverse effects of stimulants are insomnia, headaches, irritability, agitation, nervousness, tremor, loss of appetite, nausea, and weight loss. These 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. Most of them can be managed by adjusting the

Table D.1.7 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 retardation
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.1.7 Monitoring and managing medication side effects (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

dose or changing the stimulant drug (see also Table D.1.8). Growth suppression and cardiovascular effects are the long-term adverse effects most relevant.

Growth retardation. Stimulants can stunt children's growth and may reduce final adult height (by up to 4 cm of expected adult height; Greenhill et al, 2019). This risk needs to be discussed with parents and patients, and children's growth monitored regularly while on stimulants. Growth might resume once stimulants are stopped. Thus, ceasing taking the drug during summer school holidays may minimize this risk. Other options include reducing the dose, switching to a non-stimulant medication, or stopping it.

Sudden death. Despite concerns in this regard, several large studies and meta-analyses have shown no evidence that current use of an ADHD medication is associated with an increased risk of serious cardiovascular events. Although the risk cannot be ruled out altogether, its magnitude is very low (Cooper et al, 2011). Nevertheless, as part of the clinical history, it is necessary to ascertain cardiac risk factors. Additionally, heart rate and blood pressure should be monitored at baseline, after each dose change, and every six months. ECGs are not required except when there are cardiac risk factors, particularly a family history of sudden death before the age of 40 years (NICE, 2018). An option in these cases is to prescribe a non-stimulant. Atomoxetine can lead to an increase in blood pressure and heart rate, while guanfacine and clonidine may decrease these two parameters.

Diversion of ADHD Medication

Diversion of stimulant medication (i.e., by selling it, giving it to friends or relatives, having it stolen by others) has increased in the last decades, especially in

high income countries, where stimulants are more often prescribed. While in most of these cases stimulants are used to improve academic performance, recreational use also happens. Parents and patients need to be made aware of this risk and take appropriate precautions monitoring and keeping the medication in a safe place (Faraone & Wilens, 2007). If there are substance misusing individuals in the household, clinicians may consider prescribing long-acting stimulants, which have lower abuse potential than immediate-release stimulants.

Implications of Comorbidities

Specific disorders such as depression and bipolar disorder may present with or exacerbate ADHD symptoms. In these cases, the best course of action may be to treat the comorbid disorder first; the clinician can then assess the ADHD by focusing on the remaining symptoms (Caye et al, 2019).

Generally, stimulants do not exacerbate comorbid tic disorders. However, this can happen in some patients and should be monitored (Caye et al, 2019). If that were the case, treatment with atomoxetine or alpha agonists is an alternative (Pringsheim & Steeves, 2011). It is widely accepted that atomoxetine might be an option when ADHD co-occurs with anxiety disorders due to its positive effect on anxiety symptoms, while stimulants might make them worse.

Table D.1.8 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"> • Psychoeducation & parent training programs • If no access to parent training: stimulants • If no adequate response to a first stimulant or significant adverse effects, switch to a different stimulant • If no adequate response or significant side effects: switch to atomoxetine • If no adequate response or significant side effects, try other medications (e.g., guanfacine, clonidine) 	<ul style="list-style-type: none"> • Psychoeducation & CBT • If no access to CBT: stimulants • If no adequate response or significant side effects: switch to another stimulant • If no adequate response or significant side effects, try atomoxetine • If no adequate response or significant side effects, try other medications (e.g., guanfacine, clonidine)
Severe		<ul style="list-style-type: none"> • Psychoeducation • Stimulants and, if possible, combine with parent training program • If no adequate response or significant side effects: switch to a different stimulant • If no adequate response or significant side effects: try atomoxetine, and after, other medications (e.g., guanfacine, clonidine) 	<ul style="list-style-type: none"> • Psychoeducation • Stimulants and, if possible, combine with CBT • If no adequate response or significant side effects: switch to another stimulant • If no adequate response or significant side effects: try atomoxetine, and after, other medications (e.g., guanfacine, clonidine)

Recommendations by Guidelines

Based on the findings presented, stimulants are the first-line psychopharmacological option in all international guidelines (e.g., Wolraich et al, 2019; NICE, 2018). According to NICE guidelines, the first line pharmacological treatment for children aged five years and over is methylphenidate, either short- or long-acting.

Lisdexamfetamine is the second choice if the patient does not show enough benefit after 6 weeks of treatment with methylphenidate. If poorly tolerated, lisdexamfetamine can be replaced by dexamfetamine.

Atomoxetine and guanfacine can be offered if the patient cannot tolerate or accept methylphenidate or lisdexamfetamine or if there is no improvement in ADHD symptoms after 6 weeks of treatment with methylphenidate and lisdexamfetamine. A summary of treatment strategies according to developmental stage can be found in table D.1.8

SPECIAL CLINICAL ISSUES

Use of Apps to Improve Adherence to Medication

Adherence to medication is always a problem in chronic conditions, particularly in the young. That is also the case for ADHD treatment. A recent meta-analysis identified a growing use of Apps for ADHD (Păsărelu et al, 2020). A pilot study indicated improved medication adherence when using smartphone apps designed to act as a pill reminder as well as providing psychoeducation (Weisman et al, 2018).

Medication Holidays

A double-blind trial randomized children with ADHD into two groups, one taking methylphenidate seven days a week and the other taking it only on weekdays and receiving placebo on weekends. Taking methylphenidate only during weekdays reduced complaints of insomnia and appetite suppression without a significant increase of ADHD symptoms during the weekend or in the first day of school (Martins et al, 2004). Thus, clinicians may consider medication-free weekends in cases where symptoms are pronounced mostly at school or if medication causes significantly decreased appetite or insomnia. Longer drug holidays—e.g., stopping medication during the summer vacation—should be assessed taking into consideration the cost-benefit (i.e., more problem behaviors versus fewer adverse effects). In addition, this allows to test if the child still needs the medication. However, this is an area that needs more research; a clinical trial did not find benefits in relation to height with drug holidays (Waxmonsky et al, 2019).

Pregnancy

There are considerable data showing that ADHD medications are largely safe during pregnancy, although there appears to be a slightly increased risk of pre-eclampsia and of higher neonatal morbidity, especially central nervous system-



There is growing interest in the development of apps to assist with, and monitor adherence to medication and other practical issues. Click on the image to access one such app in Portuguese.

related disorders such as seizures (Cohen et al, 2017; Nörby et al, 2017). Thus, clinicians should make patients who are, or plan to become, pregnant aware of this risk and possibly recommend ceasing medication during pregnancy.

Pharmacogenetics

There are many studies on the role of pharmacogenetics in ADHD using gene-gene, gene-environment, genome-wide associations, neuroimaging, and pharmacokinetic approaches. Currently, there are no genetic markers with sufficient diagnostic accuracy or capable to predict response to treatment to incorporate in daily clinical practice (Zayats & Neale, 2019).

Duration of treatment

There are no evidence-based guidelines about when treatment should cease. Good clinical practice suggests that it is important to assess the need for medication periodically (e.g., once a year) particularly when patients get older, taking into account the response, the young person's opinion, and side effects. A substantial number of patients may benefit from continuing treatment into adulthood (Posner et al, 2020).



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