Luis Augusto **Rohde**
Jan K. **Buitelaar**
Manfred **Gerlach**
Stephen V. **Faraone**
(Editors)

The World Federation of ADHD Guide

BOARD OF THE WORLD FEDERATION OF ADHD

President

Prof. Luis Rohde
Federal University of Rio Grando do Sul
Department of Psychiatry
Porto Alegre, Brazil

Vice President

Prof. Jan Buitelaar
Radboud University
Nijmegen, The Netherlands

Vice President

Prof. Stephen Faraone
SUNY Upstate Medical University
Syracuse, USA

Secretary General

Dr. Declan Quinn
University of Saskatchewan
Saskatoon, Canada

Treasurer

Prof. Manfred Gerlach
University of Würzburg
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Würzburg, Germany

Luis Augusto **Rohde**
Jan K. **Buitelaar**
Manfred **Gerlach**
Stephen V. **Faraone**
(Editors)

The World Federation of ADHD Guide

2019

Cover: Paola Manica
Graphic design, and publishing: TIPOS – design editorial e fotografia

Made by:
ARTMED EDITORA LTDA., a GRUPO A EDUCAÇÃO S.A. company
Av. Jerônimo de Ornelas, 670 – Santana
90040-340 – Porto Alegre – RS
Phone: +55 (51) 3027-7000 Fax: +55 (51) 3027-7070

São Paulo
Rua Doutor Cesário Mota Jr., 63
01221-020, Vila Buarque, Sao Paulo – SP
Phone: +55 (11) 3221-9033

SAC 0800 703-3444 — www.grupoa.com.br

AUTHORS

Luis Augusto Rohde (ed.) – Professor of Psychiatry, Division of Child and Adolescent Psychiatry, Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Brazil.

Jan K. Buitelaar (ed.) – Professor of Psychiatry and Child and Adolescent Psychiatry, Department of Cognitive Neuroscience, Radboud University Medical Centre. Principal Investigator at the Donders Institute for Brain, Cognition and Behaviour, and Head of Karakter Child and Adolescent Psychiatry University Centre.

Manfred Gerlach (ed.) – Associate Professor of Clinical Neurochemistry, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Germany.

Stephen V. Faraone (ed.) – Distinguished Professor of Psychiatry, SUNY Upstate Medical University, Syracuse, New York, United States of America.

David Coghill – Financial Markets Foundation Chair of Developmental Mental Health, Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia.

Dennis van der Meer – Research fellow, NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

Desiree Silva – Professor of Paediatrics, University of Western Australia, Australia.

Francisco R. de la Peña Olvera – Professor of Child and Adolescent Psychiatry, Universidad Nacional Autónoma de México. Head at Clinical Research Department in the National Institute of Psychiatry "Dr Ramón de la Fuente Muñiz", Ciudad de México, México.

Jennifer Richards – Post-doctoral researcher, University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), Groningen, The Netherlands.

Lino Palacios Cruz – Associate Professor of Child and Adolescent Psychiatry, Professor of Faculty of Medicine, Universidad Nacional Autónoma de México. Researcher in Medical Sciences level D of National Institutes of Health, México. Principal Investigator PROMETEO (ADHD) Program, Department of Clinical Epidemiology, National Institute of Psychiatry "Dr Ramón de la Fuente Muñiz", Ciudad de México, México.

Olayinka Olusola Omigbodun – Professor and Head of Psychiatry, Director, Centre for Child and Adolescent Mental Health (CCAMH), College of Medicine, University of Ibadan; Consultant in Child and Adolescent Psychiatry, University College Hospital, Ibadan, Nigeria.

Philip Asherson – Professor of Psychiatry at King's College London, United Kingdom.

Ryan J. Kennedy – Clinical Associate, Brown Clinic for ADHD and Related Disorders, Manhattan Beach, California, United States of America.

Thomas E. Brown – Director of Brown Clinic for ADHD and Related Disorders, Manhattan Beach, California; Adjunct Clinical Associate Professor of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California, United States of America.

Tobias Banaschewski – Professor of Child and Adolescent Psychiatry, Medical Director, Department of Child and Adolescent Psychiatry and Psychotherapy, Deputy Director, Central Institute of Mental Health, Mannheim, Germany.

Wai Chen – Professor of Child Psychiatry, University of Western Australia; Consultant Child and Adolescent Psychiatrist, Department of Health, Western Australia.

Yi Zheng – Professor of Psychiatry, Department of Child and Adolescent Psychiatry, Beijing Anding Hospital, Capital Medical University, Beijing, China.

JUNIOR EDITORS

Brazil

Fausto Campani | **Júlia Stocchero Amaro** | **Márcio Lemos Sônego**

China

He Fan | **Qi Yanjie** | **Huang Huanhuan** | **Qi Junhui** | **Chen Sijian**
Luo Jie | **Yin Shengjian**

Mexico

Adriana Arias Caballero | **Frinné Galicia Moreno** | **Miriam T. Serment Azuara**
Maria Rosa Palacios Heredia

PREFACE

Searching the PUBMED or the Web of Science using the words: "ADHD or Attention Deficit Disorder", your screen will immediately list almost fifty thousand references. If you google: "ADHD/Attention Deficit Disorder book" an equally numerous deluge of titles will be offered instantaneously. Thus, the first question is: Why another book on ADHD?

As part of the current board of the World Federation of ADHD, the organizers of this book thought that our Federation has the unique responsibility to pay special attention to pediatricians, psychiatrists, psychologists and other mental health professionals in Low-Middle Income Countries (LMIC). These colleagues have little or no access to evidence-based information on the disorder. So, this is not simply one more book "in the ocean of the ADHD literature", it is the only book designed with several features to allow easy access by colleagues in LMIC countries. These are as follows:

First, the book will be open access. Professionals from LMICs rarely can afford buying books on specific disorders. Second, it will be an e-book. Distribution of hard copy books is too expensive for distributing to the great majority of professionals in LMICs. Recent surveys worldwide have shown that over 3 billion people globally have a smartphone; 6 billion will have them by 2020. Smartphones are more ubiquitous than clean water, indoor plumbing, and stable electricity. Third, we have prepared versions in English, Spanish, and Chinese, which are the three most commonly spoken languages worldwide, allowing us to reach about 25% of the world's population. Here we would like to thank specially our junior collaborators: Adriana Arias Caballero, Frinné Galicia Moreno, Miriam T. Serment Azuara and Maria Rosa Palacios Heredia from Mexico, He Fan, Qi Yanjie, Huang Huanhuan, Qi Junhui, Chen Sijian, Luo Jie e Yin Shengjian from China, Fausto Campani, Julia Amaro and Marcio Sônego from Brazil for their inestimable efforts.

Fourth, our book focuses on what LMIC professionals need to know about "*the essentials*" for diagnosing and managing ADHD in their daily clinical work. For this reason, we decided for a book with 6 chapters translating what is most relevant when assessing and caring those affected by the disorder and their families, while also including some basic information about epidemiology and risk factors.

Fifth, this book was designed and written by an international team for an international audience. We were very fortunate to have a team of wonderful investigators and clinicians with a long track of experience in different aspects of ADHD writing these six chapters. Our profound gratitude to: David Coghill, Dennis van der Meer, Desiree Silva, Francisco R. de la Peña Olvera, Jennifer Richards, Lino Palacios Cruz, Olayinka Olusola Omigbodun, Philip Asherson, Ryan J. Kennedy, Thomas E. Brown, Tobias Banaschewski, Wai Chen e Yi Zheng. We are proud to highlight that we had in our team representatives from all continents reinforcing the worldwide mandate of our Federation and our respect for diversity.

This book was only possible based on the partnership with our publisher, Artes Médicas that easily and immediately understood the relevance of this proposal and efficiently worked to make it possible. They are also making available with reasonable prices both a printed and an e-version of the book in Portuguese. Our special thanks to the producing team and more specifically to Claudia Bittencourt who worked closely with us in this initiative, making the process smooth and effective.

We are confident that the World Federation ADHD book will be useful clinically for a substantial proportion of health care professionals in LMICs dealing with patients with ADHD. Moreover, we hope that, at the end of the day, ADHD will be more adequately recognized in these countries and that the suffering of these patients and their families will be mitigated by evidence-based interventions that would be feasible to implement in this context.

Luis Augusto Rohde
Jan K. Buitelaar
Manfred Gerlach
Stephen V. Faraone
(Editors)

CONTENTS

1

UNDERSTANDING THE ESSENTIALS OF THE ETIOLOGY OF **ADHD**

Stephen V. **Faraone**
Lino Palacios **Cruz**
Francisco R. de la **Peña Olvera**

For decades, many scientists have been searching for the etiology of attention deficit hyperactivity disorder (ADHD). This search has been motivated by the belief that if we can find the causes of the disorder we may be able to improve our understanding of ADHD psychopathology and discover more accurate treatments or even prevent the onset of this frequently disabling condition. We will consider two sources of etiology: the DNA variants coded in our genome and shared and non-shared environment factors that impact the developing brain.

GENETIC CAUSES OF ADHD

EPIDEMIOLOGY

The first evidence for the heritability of ADHD comes from several studies of families. This work showed that the siblings, mothers and fathers of children with ADHD were at increased risk for the disorder. Figure 1.1 shows examples of early family studies. In Figure 1.1A, the risk to siblings found by Manshadi and colleagues[1] is especially interesting because the ADHD patients in that study were adults. These studies were the first evidence that ADHD might have a genetic

component. They also alert clinicians treating ADHD children that many of the parents of those children will also have ADHD, which could make it difficult for them to carry out instructions about how to implement medical or psychosocial treatments for their children.

Because disorders can cluster in families due to environmental causes such as infections or mutual proximity to toxins, it is essential to consider adoption and twin studies when evaluating the possible genetic component to ADHD's etiology. An example is shown in Figure 1.2. It shows that rates of ADHD are greater among biological relatives of non-adopted ADHD children than the adoptive relatives of adopted ADHD children. The risk to adoptive relatives for ADHD was similar to the risk to relatives of children who did not have ADHD.[2,3] This finding suggests that it is the genetic relationship that mediates the familial transmission of ADHD.

A more powerful method of separating genetic and environmental causes is the twin Study. Twin studies rely on a natural experiment. Identical or monozygotic (MZ) twins share nearly their entire DNA. In contrast, fraternal or dizygotic (DZ) twins share, on average, 50% of their DNA. They are not more genetically similar to one another than ordinary siblings. By studying MZ and DZ twins, one can compute the heritability statistic, which quantifies the fraction of ADHD's etiology that can be attributed to DNA variation. Here and elsewhere we use the term "DNA variation" rather than "genes" because much of our DNA does not consist of genes. Instead, it provides instructions that create special molecules that regulate how genes are expressed.

There have been 37 twin studies of ADHD. For a review, see Faraone and Larsson.[4] When considered together, the twins studies of ADHD lead to a heritability estimate of 74%. This heritability of ADHD does not differ by sex and is the same for inattentive and hyperactive-impulsive symptoms. Twin studies have also been able to test if ADHD is best described as a categorical disorder or a continuous trait in the population. This work suggests that ADHD is best described as a quantitative trait that ranges from nonexistent and mild to moderate and severe. Under this model, the diagnosis of ADHD is the extreme of a trait that occurs in all individuals. As we will discuss later, such data have clinical implications for how one should subthreshold cases of ADHD that are referred to clinical settings.

Twin studies have also been used to shed light on the development and persistence of ADHD from childhood into adulthood. The heritability of clinically diagnosed ADHD in adults is 72%, which is similar to what is found in children.[5] As discussed in by Faraone and Larsson,[4] the heritability of ADHD is stable during the transition from childhood into adulthood, but both stable and dynamic genetic causes affect the expression of ADHD from youth to early adulthood. The stable component is a set of genetic risk factors that influence the expression of ADHD throughout the lifespan. The dynamic causes are genetic effects that turn on and off during development. These dynamic effects likely account for the variable age

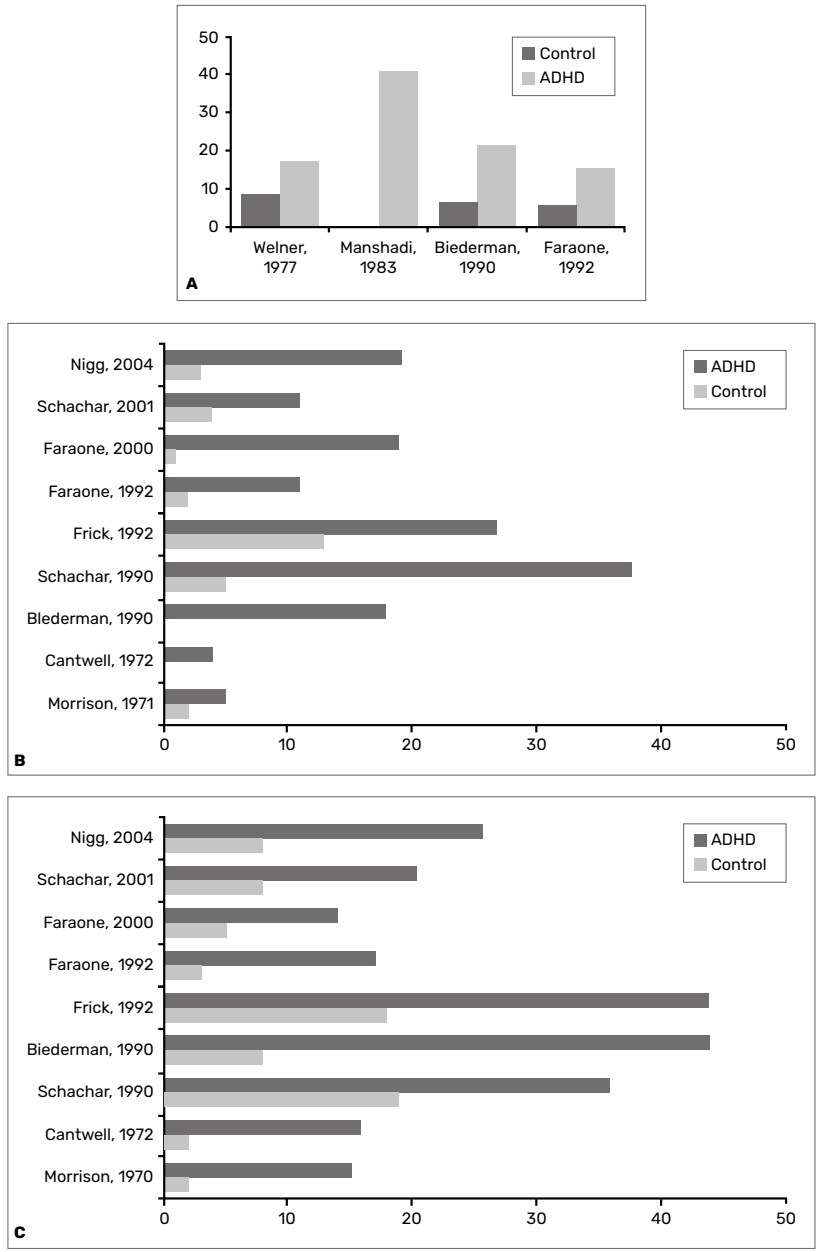


Figure 1.1

(A) ADHD in the siblings of ADHD and control children; **(B)** ADHD in the mothers of ADHD and control children; **(C)** ADHD in the fathers of ADHD and control children.

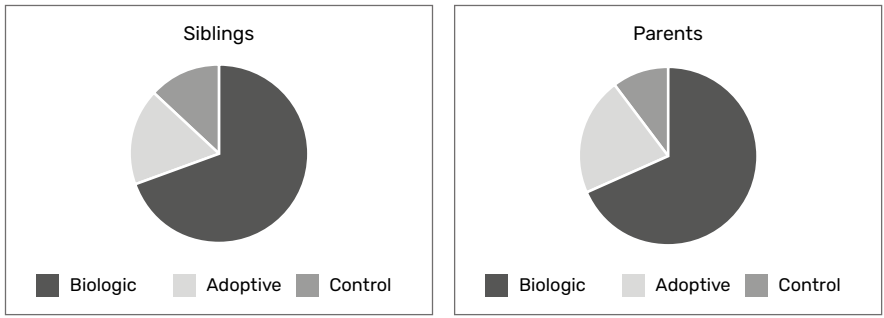


Figure 1.2
Percentage of ADHD in siblings and parents based on adoption studies.
Data from Sprich et al.[3]

at onset of ADHD and for variability in the persistence of the disorder into adulthood. For a review of the genetics of adult ADHD, see Franke et al.[6]

As reviewed by Faraone and Larsson,[4] family and twin studies have taught us much about the familial transmission of ADHD and its comorbid disorders. Both clinical and epidemiological studies have documented that children and adults with ADHD are at increased risk for antisocial disorders, autism spectrum disorders (ASDs), anxiety disorders, mood disorders and substance use disorders. Except for some anxiety disorders, each of these disorders clusters together with ADHD in families. In fact, twin studies of childhood disorders indicate that about half of the comorbidity among these disorders is due to genetic factors. There have been many twin studies of ADHD and ASDs. As a group, they show that these two disorders share genetic risk factors. The fact that ADHD shares genetic causes with other psychiatric disorders is extremely important for clinicians to understand. Such data argue against the idea that when two disorders co-occur, only the "primary" disorder should be treated with the other disorder viewed as a secondary phenomenon. Therefore, current practice suggests that all disorders be treated sequentially starting with the most serious condition.[7]

MOLECULAR GENETICS

In the 1990s, molecular genetic studies of ADHD were mostly limited to candidate gene association studies. The candidate genes were chose based on theories of ADHD's etiology, most of which were driven by the observation that effective drugs for ADHD modulate dopaminergic and noradrenergic circuits in the brain. Association studies pick a genetic marker that is in or near the gene and

determines if one version of that marker is more common in people with ADHD compared with people without ADHD. The marker is either a single DNA base pair known as a single nucleotide polymorphism (SNP) or a longer stretch of DNA made of several SNPs. The DNA variants used as markers usually have no functional significance. They are only used to locate the gene on the genome. When an association is positive, we can conclude that a causal DNA variant is located somewhere near the marker.

In meta-analyses of candidate gene studies, Gizer et al.,[8] found eight DNA variants to be associated with ADHD. These variants pointed to: the serotonin transporter gene (*5HTT*), the dopamine transporter gene (*DAT1*), the D4 dopamine receptor gene (*DRD4*), the D5 dopamine receptor gene (*DRD5*), the serotonin 1B receptor gene (*HTR1B*) and a gene coding for a synaptic vesicle regulating protein known as *SNAP25*. A meta-analysis limited to studies of adults with ADHD found adult ADHD to be associated with *BAIAP2* (brain-specific angiogenesis inhibitor 1-associated protein 2), which regulates the growth of neurons.[9] Both meta-analyses found that although results reached statistical significance, the magnitude of association was small, as indicated by odds ratios less than 1.5.

Considering that the human genome contains about 20,000 protein coding genes along with regulatory regions that moderate the expression of these genes, candidate gene studies are remarkably limited in scope. To deal with that problem, the genome-wide association study (GWAS) was developed. GWAS assays DNA variants across the entire genome to provide information about the association of ADHD to any gene or regulatory element. Because this requires statistical tests of millions of SNPs, very large samples are required to achieve confident results. To achieve this goal for ADHD, a worldwide consortium of researchers banded together to collect a sample of 20,183 people with ADHD and 35,191 controls.[10] The study found that twelve loci on the genome were almost certain to harbor a DNA variant that increased the risk for ADHD. One of these loci is especially interesting because it implicates the *FOXP2* gene. Variants in this gene are known to increase the risk for speech and language disorders.

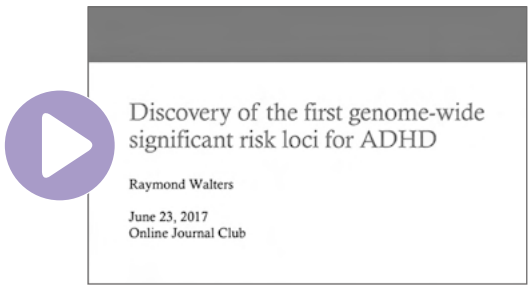
Many of the other loci discovered by the ADHD GWAS implicated genes that are expressed in brain and could putatively be involved in ADHD. None of them, however, were any of the candidate genes that had been studied in the 1990s. Among these, only *SLC9A9* showed a weak association with ADHD. This gene encodes a protein that regulates the recycling of receptors and transporters to the synaptic membrane. Were the researchers in the 1990s wrong about the candidate genes they proposed? Possibly, but we know from GWAS of other psychiatric disorders that we will need very large samples (perhaps hundreds of thousands) to detect most of the DNA variants that increase the risk for ADHD.

Perhaps the most important finding from the ADHD GWAS was the result from a complex statistical analysis that concluded ADHD must be a polygenic disorder. By 'polygenic' we mean that many, many DNA variants (10s or 100s of

thousands) can affect the risk for the disorder. When the ADHD polygenes were analyzed as a single set of genes, Demontis et al.[10] found that the marker SNPs mostly implicated regions of the genome known to have biological significance along with regulatory elements specific to the central nervous system. Each of the polygene variants has a very small effect so many are needed to develop ADHD. This means that everyone carries some ADHD-associated DNA variants but only a few people have enough to be affected with ADHD. You may recall from our discussion of twin studies that ADHD's heritability is 74%. The GWAS data allowed computation of the heritability due to the SNPs forming ADHD's polygenic architecture. It was 22%. This indicates that polygenes account for about one-third of ADHD's heritability.

Discovery of the polygenic risk for ADHD provides a useful tool for studying the genetic overlap between ADHD and other disorders and traits. For example, several population studies have computed ADHD genetic risk scores in youth that were also measured for ADHD symptoms. These studies show that children with a higher genetic risk for ADHD have more ADHD symptoms. This finding confirms the conclusion of twin studies that the genetic susceptibility to ADHD would be a continuously varying trait in the population leading to a wide range of symptom expression. See Faraone and Larsson,[4] for details.

In addition to ADHD symptoms, Demontis et al.[10] correlated ADHD's polygenic risk with 220 disorders and traits. That work, along with other studies, have confirmed reports from family and twin studies suggesting that ADHD shares genetic risk with conduct disorder, major depression and bipolar disorder. Thus, the pervasive psychiatric comorbidity observed in ADHD patients is due, at least in part, to sharing the genetic risk factors comprising ADHD's genetic risk score. In addition to these expected associations, Demontis et al.[10] also found that the genetic risk for ADHD was correlated with the genetic risk for other traits. Positive correlations were observed for obesity and smoking and negative correlations were observed for years of education, college completion, intelligence quotient and subjective well-being. These correlations are consistent with what we have learned from clinical studies of ADHD. Several novel correlations also emerged.



Link in this

https://www.youtube.com/watch?v=sfHDoD01eqc

The genetic risk for ADHD was positively correlated with the genetic risk for coronary artery disease and lung cancer, which suggests that people with ADHD are at risk for these disorders. The ADHD risk score was positively correlated with having a large family and having children at a young age. These findings are consistent with longitudinal studies of the disorder. Higher genetic risk scores for ADHD also predicted a younger age of death of the respondent's mother and father. This finding could be due to ADHD's shared genetic risk for obesity and medical outcomes.

Up to now, we have only been discussing common DNA variants, i.e., those that occur in more than one percent of the population. Our current thinking is that the genetic predisposition for most cases of ADHD is due to these many common variants that constitute the polygenic risk for the disorder. That said, researchers have also discovered rare variants that cause ADHD or symptoms of the disorder. The first information about rare variants came from studies of syndromic chromosomal anomalies such as velo-cardio facial syndrome fragile-X syndrome, Turner syndrome, tuberous sclerosis, neurofibromatosis, Klinefelter syndrome, and Williams syndrome. ADHD symptoms are frequently observed in patients with these conditions.

Although GWAS had been developed to assay common variants, this method can also detect large, rare copy number variants (CNVs). CNVs delete or duplicate a large section of DNA that might contain part of a single gene or several genes in their entirety. Because many of these create large genomic lesions, they seem to have clear consequences for gene functioning. Most studies of CNVs in ADHD have found an increased burden among patients with ADHD compared with controls. These data have been summarized fy Thapar et al.,[11] who reported that deletions and duplications are equally over-represented in ADHD samples. The CNVs found in ADHD studies showed some overlap with the CNVs found in studies of schizophrenia and ASDs. Thapar et al.[11] further showed that ADHD CNVs affected genes in the following biological pathways: respiratory electron transport, organonitrogen compound catabolic process, transmembrane transporter activity, carbohydrate derivative catabolic process, ligand-gated ion channel activity, methyltransferase activity, transmembrane transport and ion gated channel activity.

Another approach to rare variant discovery uses whole genome sequencing or whole exome sequencing. These methods are used to discover rare SNPs, which are called rare single nucleotide variants (SNVs). Because ADHD sequencing studies are still in their infancy, it is too soon to draw firm conclusions about the role of SNVs in ADHD. For a recent review, see Faraone and Larsson.[4]

SUMMARY: GENETIC CAUSES OF ADHD

There can be no doubt now that people with ADHD carry DNA variants that operate via unknown mechanisms to cause inattention, hyperactivity and impulsivity.

Most of these variants are fairly common such that everyone carries some genetic risk for ADHD. This creates a polygenic genetic architecture and supports the idea that the risk for ADHD, and its expression in symptoms, is a continuously varying trait in the population. For clinicians, this means that people who come to clinic with subthreshold symptoms may carry some biological risk for ADHD even though they don't meet full diagnostic criteria for the disorder.

ENVIRONMENTAL CAUSES OF ADHD

EPIDEMIOLOGIC EVIDENCE FOR ENVIRONMENTAL CAUSES OF ADHD

When discussing causation, studies of DNA risk variants have a clear advantage over studies of the environment. Our genome comes into existence prior to our birth. So, when scientists discover an association between ADHD and a DNA variant, it is clear that having ADHD cannot "cause" one to have a specific DNA variant but that having a DNA variant could logically increase risk for ADHD. Studies of the environment are less clear-cut. For example, if a study documents that poverty is associated with ADHD, that could mean that poor nutrition, stress and other concomitants of poverty increase the risk for ADHD. But it is also possible that having ADHD leads to lower levels of education, poorer job performance and thereby increases the risk for parents with high genetic risk for ADHD to live in poverty. Thus, one must always keep in mind the potential for such 'reverse causation' when evaluating environmental risk factors and evaluate whether these have been considered by the relevant studies. That said, keep in mind that when one member of an identical twin pair has ADHD, the risk to the co-twin is only about 50%. Thus, environmental risk factor must contribute to the etiology of ADHD.

Some environmental risks are due to exposures to toxins, lack of nutrients or trauma. Many studies have examined the effects of iron and zinc on ADHD because both of these elements are essential for producing norepinephrine and dopamine in the brain. In a meta-analysis, Scassellati et al.[12] reported that measures of iron deficiency were associated with ADHD. They also found that ADHD was associated with low levels of zinc in the blood. Among the many toxins studied in ADHD patients, the strongest evidence implicates lead contamination. In their meta-analysis, Scassellati et al.[12] found that compared with controls, ADHD cases were more likely to have been exposed to lead.

Many studies have tested the idea that pregnancy and delivery complications (PDCs) might cause ADHD by harming the brain at early stages of its development. Although the literature presents conflicting results, it tends to support the idea that PDCs are risk factors for ADHD. When PDCs have been implicated in ADHD they typically lead to oxygen deprivation and tend to involve *chronic* exposures to the fetus, not *acute* events. Among the most investigated PDCs,

prematurity and low birth-weight are the most studied. A recent meta-analysis of the literature on the association between both very-premature and/or very low--weight babies and ADHD showed a 3 times increased risk for those infants to have ADHD in the future.[13] However, it is important to note that prematurity and low-birth weight are risk factors to other mental disorders. Anyhow, whenever assessing very premature and/or very low birth weight children, clinicians might consider assessing for ADHD.

Maternal smoking during pregnancy has been widely studied as a risk factor for ADHD. It is well documented that smoking during pregnancy places the fetus at risk for birth complications, including low birth weight, which has been associated with ADHD. Maternal smoking also places the fetus at risk for a hypoxia, which has been associated with ADHD. Although Langley et al.'s[14] meta-analysis concluded that children whose mothers' smoked during pregnancy had a 2.4 fold increased risk for ADHD, this is still an area of debate because ADHD and its polygenic risk are known to be associate with smoking behaviors. Thus, mother with ADHD might smoke more than mothers without ADHD and the risk is associated to genetic factors related to ADHD and not to smoking. Those who favor the maternal smoking hypothesis point out that it is a plausible risk factor because nicotine regulates the activity of the dopamine transporter, the site of action of the stimulant drugs that treat ADHD.

People who experience mild traumatic brain injuries (mTBIs) are at risk for developing ADHD. This was the conclusion of a meta-analysis which showed that mTBI associated with ADHD.[15] Another well-documented environmental risk factor is severe institutional deprivation in early childhood. We know this from studies of children who spent the early years of life in Romanian orphanages that offered poor nutrition and nearly no human contact. Many of these children developed ADHD later in life.[16]

Environmental risk factors for ADHD that have been confirmed by meta-analyses include:

- preterm birth,[17]
- prenatal exposure to maternal smoking,[18]
- prenatal methylmercury exposure from maternal fish consumption,[19]
- exposure to lead,[20] and
- perinatal vitamin D deficiency.[21]

From meta-analyses, we can also exclude some environmental factors as increasing the risk for ADHD. These include: sugar consumption,[22] methylmercury in vaccines,[19] maternal thyroid hormone insufficiency,[23] sleep restriction,[24] cesarean section[25] and solar intensity.[26]

It is easy to see how toxic exposures, pregnancy and delivery complications, traumatic brain injuries and severe institutional deprivation could affect the deve-

loping brain and increase risk for ADHD. In addition to such biological adversity, studies have also implicated adverse psychosocial experiences as risk factors for the disorder. Examples of psychosocial stressors that affect children are marital distress, family dysfunction and low social class. In a population study conducted in Ontario, Canada, family dysfunction and low income predicted persistence and onset of one or more psychiatric disorders during a four-year follow-up period. Other potential risk factors for ADHD are low maternal education, low social class, and single parenthood. Several studies show that the mothers of ADHD children have more negative communication patterns, more conflict with their child and a greater intensity of anger than do control mothers and that families of ADHD children are more likely to have higher levels of chronic conflict, decreased family cohesion, and exposure to parental psychopathology. However, most of the environmental factors might act more as unspecific triggers for mental health problems in general than specific environmental risk factors for ADHD. Comparing to medical conditions, stress might be a trigger for gastritis for those with genetic predisposition for this disorder, while acting as a trigger for asthma for those with vulnerability for this disorder.

MECHANISMS FOR THE ENVIRONMENTAL CAUSES OF ADHD

Although we have been discussing genetic and environmental risk factors separately, to fully understand the etiology of ADHD, we must consider how genes and environment work together to cause the disorder. Two mechanistic areas that are of clear theoretical importance are gene by environment interaction and epigenetics.

The DNA variants that increase risk for ADHD do not do so in a vacuum. They reside in cells where they build proteins in response to cellular signals. The environment may generate these signals. Gene by environment interaction occurs when mutant genes only cause disease in the presence of specific signals from the environment. For example, fetal anoxia creates oxidative stress which could trigger a cascade of events leading to abnormal brain development. Those with genetic variants that predispose to lower defenses of oxidative stress will be less able to defend against oxidative stress and more likely to suffer adverse impacts to the brain.

Although there are many studies of gene by environment interaction in ADHD, none of have been consistently replicated to warrant discussion here. One key finding comes from the ADHD GWAS study described in the prior section. There we reported that only 30% of ADHD's heritability could be explained by the disorders polygenic architecture. Some of the other 70% will be accounted for by rare variants but it is likely that a good fraction of heritability will be explained by gene by environment interactions. Unfortunately, these are very difficult to study, as there are many relevant environmental risk factors to study.

Epigenetics refers to a field of study that examines how the environment modifies the genome to change the expression of genes. Epigenetic modifications do not make change to the chemical structure of DNA. Instead, they use mechanisms such as methylation and histone acetylation to change how accessible DNA is to elements required to trigger its expression. Although all cells contain full genomes worth of DNA, every cell only expresses as small subset of that DNA, which is why we have cells with specialized functions such as dopamine neurons and glia. By controlling gene expression, epigenetic events allow for this specialization to occur. The importance of such mechanisms for ADHD is illustrated by the GWAS study finding that much of ADHD's heritability is explained by SNPs in regions that regulate genes rather than in genes themselves. Although there are too few epigenetic studies of ADHD to draw firm conclusions, this area of research is likely to provide insights in the future.[27]

SUMMARY: ENVIRONMENTAL CAUSES OF ADHD

Substantial data from epidemiologic studies implicates the environment in the etiology of ADHD. These data implicate biological assaults on the developing brain such as exposures to toxins, maternal smoking, anoxic birth complications, mild traumatic brain injury and institutional deprivation. Psychosocial stresses such as marital distress, family dysfunction and low social class have also been implicated by epidemiologic studies. Although we expect that gene by environment interaction and epigenetic effects mediate these environmental risks, these areas of research are not sufficiently mature to offer conclusive findings about the etiology of ADHD.

DISCUSSION

Although we have a long road to travel before fully understanding the etiology of ADHD, much progress has been made. We can be sure that some of the risk for

Link in this

http://additudemag.libsyn.com/188-beyond-genes-how-environment-and-lifestyle-impact-adhd

ADHD is inherited and that, for most cases of ADHD, many DNA risk variants are needed before the disorder becomes evident. These risk variants combine and interact with environmental risk factors to create the pathophysiology of the disorder. In the coming decades, scientists will discover more common and rare genetic and environmental risk factors. This process will set the stage for discoveries that will improve treatment and, perhaps, allow for preventive measures.

It is humbling to realize that none of the genome-wide significant variants discovered by GWAS had been predicted by models of ADHD's pathophysiology. The loci discovered challenge the idea that ADHD's etiology will be explained by events that proximally dysregulate catecholaminergic transmission. As suggested by Hess et al.,[28] such dysregulation may be secondary to ADHD's primary etiology. In this model, etiologic events that have effects on early development lead to secondary adjustments by the brain, which dysregulate catecholaminergic systems and cause the symptoms of ADHD.

One of the most remarkable findings from genetic studies, both epidemiologic and molecular, is the conclusion that the diagnosis of ADHD is the extreme of a dimensional trait in the population. This finding suggests that ADHD is analogous to hypertension and that diagnostic approaches should consider defining the full continuum of "ADHD-traits" along with the threshold for defining clinically meaningful manifestations of that trait. Describing this continuum in future diagnostic systems should help clinicians determine how to diagnose and treat patients who fall just below the current threshold for diagnosis. An apt comparison is with intellectual disability (ID). Most forms of ID fall along the normal distribution of intelligence with rare cases being categorically different.[29] A dimensional view of ADHD will change the question "Is ADHD underdiagnosed or overdiagnosed" to "where should we place the diagnostic threshold for ADHD?". Because subthreshold ADHD can be associated with substantial morbidity,[2,30-33] demarcating a diagnostic range that one might refer to as "borderline ADHD" (following the analogy with hypertension), might be useful.

Faraone et al.[34] described two competing models of ADHD's etiology: etiologic heterogeneity and multifactorial causation. Much research shows that ADHD is a clinically heterogeneous disorder as regards the nature and severity of ADHD symptoms, the extent of psychiatry comorbidity, the degree of impairment, the presence of neuropsychological impairments and the course and outcome of the disorder. The etiologic heterogeneity hypothesis posits that clinical heterogeneity is mirrored by heterogeneity in the events that cause ADHD. It predicts that ADHD can be separated into two or more classes having different genetic and/or environmental etiologies.

In contrast to the etiologic heterogeneity model, the multifactorial model posits all cases of ADHD to arise from a single pool of genetic and environmental variables – each of small effect – that combine to produce a vulnerability to ADHD. As cumulative vulnerability increases, the expression of ADHD's symptoms and

impairments becomes more likely. At lower levels of vulnerability, other related conditions may be expressed (e.g., neuropsychological impairments, learning disabilities, emotional dysregulation). The multifactorial model posits that no single factor is required for ADHD to occur. Although under the multifactorial model, all cases of ADHD arise from the same set of risk factors, the set of risk factors impacting specific patients might be quite different. For example, if there are 100 risk factors for ADHD and 50 are needed to develop ADHD, then two patients could have an entirely different set of risks causing their ADHD.

Given that ADHD has been shown to be polygenic and that many environmental risk factors have been discovered, the multifactorial model of ADHD seems more consistent with the data than an etiologic heterogeneity model. Apart from rare cases caused by gross abnormalities of chromosomes, CNVs or SNVs, we do not expect ADHD to be easily subdivided into separate etiologic entities. Figure 3 provides a schematic view of how genes and environment combined to produce persistent ADHD, remitting ADHD and subthreshold forms of ADHD. It seems likely that this view of ADHD is a good guide to the disorder's true etiology, with the understanding that future work will clarify the number of discrete cases due to rare variants and the degree to which gene by environment interaction accounts for the etiology of the disorder.

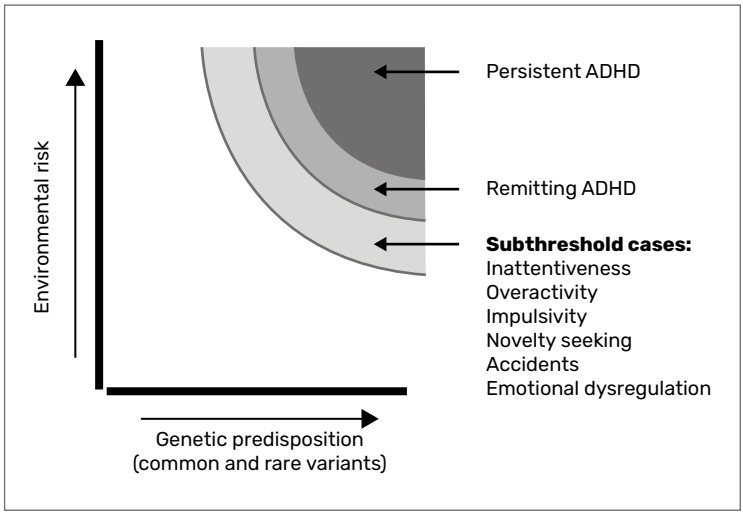


Figure 1.3
Model of the etiology of ADHD.

Conflict of interest statement

In the past year, Dr. Faraone received income, potential income, travel expenses continuing education support and/or research support from Otsuka, Arbor, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA, Ironshore, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In the past year, Dr. de la Peña received income, travel expenses, continuing education support and/or research support from Shire, Springer Edit. and from the Consejo Nacional de Ciencia y Tecnologia, Mexico. In the past year, Dr Lino Palacios Cruz acted as speaker for Novartis and Shire, took part of an advisory board for Novartis and received income, travel expenses and continuing education support from Shire.

Acknowledgements

Dr. Faraone is supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602805, the European Union's Horizon 2020 research and innovation programme under grant agreements No 667302 & 728018 and NIMH grants 5R01MH101519 and U01 MH109536-01.

REFERENCES

1. Manshadi M, Lippmann S, O'Daniel RG, Blackman A. Alcohol abuse and attention deficit disorder. J Clin Psychiatry. 1983;44(10):379-80.

2. Faraone SV, Kunwar A, Adamson J, Biederman J. Personality traits among ADHD adults: implications of late-onset and subthreshold diagnoses. Psychol Med. 2009;39(4):685-93.

3. Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV. Adoptive and biological families of children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry. 2000;39(11):1432-7.

4. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Mol Psychiatry. 2018. [Epub ahead of print].

5. Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. Psychol Med. 2014;44(10):2223-9.

6. Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, et al. The genetics of attention deficit/hyperactivity disorder in adults, a review. Mol Psychiatry. 2012;17(10):960-87.

7. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.

8. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 2009;126(1):51-90.

9. Bonvicini C, Faraone SV, Scassellati C. Attention-deficit hyperactivity disorder in adults: A systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. Mol Psychiatry. 2016;21(11):1643.

10. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for ADHD. BioRxiv. 2017. [Epub ahead of print].

11. Thapar A, Martin J, Mick E, Arias Vásquez A, Langley K, Scherer SW, et al. Psychiatric gene discoveries shape evidence on ADHD's biology. Mol Psychiatry. 2016;21(9):1202-7.

12. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry. 2012;51(10):1003-1019.e20.

13. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics. 2018;141(1). pii: e20171645.

14. Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva Pediatr. 2005;57(6):359-71.

15. Adeyemo BO, Biederman J, Zafonte R, Kagan E, Spencer TJ, Uchida M, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. J Atten Disord. 2014;18(7):576-84.

16. Stevens SE, Kumsta R, Kreppner JM, Brookes KJ, Rutter M, Sonuga-Barke EJ. Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: developmental continuities in gene-environment interplay. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(6):753-61.

17. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002;288(6):728-37.

18. Dong T, Hu W, Zhou X, Lin H, Lan L, Hang B, et al. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Reprod Toxicol. 2018;76:63-70.

19. Yoshimasu K, Kiyohara C, Takemura S, Nakai K. A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/hyperactivity disorder in the childhood. Neurotoxicology. 2014;44:121-31.

20. Goodlad JK, Marcus DK, Fulton JJ. Lead and attention-deficit/hyperactivity disorder (ADHD) symptoms: a meta-analysis. Clin Psychol Rev. 2013;33(3):417-25.

21. Khoshbakht Y, Bidaki R, Salehi-Abargouei A. Vitamin D status and attention deficit hyperactivity disorder: a systematic review and meta-analysis of observational studies. Adv Nutr. 2018;9(1):9-20.

22. Wolraich ML, Wilson DB, White JW. The effect of sugar on behavior or cognition in children. A meta-analysis. JAMA. 1995;274(20):1617-21.

23. Thompson W, Russell G, Baragwanath G, Matthews J, Vaidya B, Thompson-Coon J. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018;88(4):575-584.

24. Lundahl A, Kidwell KM, Van Dyk TR, Nelson TD. A meta-analysis of the effect of experimental sleep restriction on youth's attention and hyperactivity. Dev Neuropsychol. 2015;40(3):104-21.

25. Curran EA, O'Neill SM, Cryan JF, Kenny LC, Dinan TG, Khashan AS, et al. Research review: birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. J Child Psychol Psychiatry. 2015;56(5):500-8.

26. Hoffmann MS, Polanczyk GV, Kieling C, Dos Santos IP, Willcutt EG, Rohde LA, et al. Attention-deficit/hyperactivity disorder and solar irradiance: a cloudy perspective. Biol Psychiatry. 2014;76(8):e19-20.

27. Mill J, Petronis A. Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. J Child Psychol Psychiatry. 2008;49(10):1020-30.

28. Hess JL, Akutagava-Martins GC, Patak JD, Glatt SJ, Faraone SV. Why is there selective subcortical vulnerability in ADHD? Clues from postmortem brain gene expression data. Mol Psychiatry. 2018;23(8):1787-1793.

29. Faraone SV, Ghirardi L, Kuja-Halkola R, Lichtenstein P, Larsson H. The familial co-aggregation of attention-deficit/hyperactivity disorder and intellectual disability: a register-based family study. J Am Acad Child Adolesc Psychiatry. 2017;56(2):167-174.e1.

30. Lecendreux M, Konofal E, Cortese S, Faraone SV. A 4-year follow-up of attention-deficit/hyperactivity disorder in a population sample. J Clin Psychiatry. 2015;76(6):712-719.

31. Faraone SV, Biederman J, Doyle A, Murray K, Petty C, Adamson JJ, et al. Neuropsychological studies of late onset and subthreshold diagnoses of adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2006;60(10):1081-7.

32. Faraone SV, Biederman J, Spencer T, Mick E, Murray K, Petty C, et al. Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? Am J Psychiatry. 2006;163(10):1720-9; quiz 1859.

33. Faraone SV, Wilens TE, Petty C, Antshel K, Spencer T, Biederman J. Substance use among ADHD adults: implications of late onset and subthreshold diagnoses. Am J Addict. 2007;16 Suppl 1:24-32; quiz 33-4.

34. Faraone SV, Biederman J. Neurobiology of attention deficit hyperactivity disorder. In: Charney DS, Nestler EJ, editors. Neurobiology of mental illness. 2nd ed. New York: Oxford University Press; 2004.

2

UNDERSTANDING THE ESSENTIALS OF THE **ADHD** NEUROBIOLOGY

Jan K. **Buitelaar**
Dennis van der **Meer**
Jennifer **Richards**

ADHD is a common neurodevelopmental disorder that typically has onset in childhood, most often between age 6 and 12. Despite thousands of research papers on ADHD are being published each year, our understanding of the neurobiology of ADHD is still limited. It is clear, however, that ADHD is characterized by substantial heterogeneity across many, if not all, levels of analysis. This chapter will review this heterogeneity with respect to the neurobiological mechanisms that underping ADHD, starting with biochemistry and metabolomics, and then continuing with cognition, up to functional and structural alterations of the brain.

NEUROCHEMISTRY AND METABOLOMICS

Knowledge about the neurochemistry of ADHD has thus far largely relied on serendipity and coincidental findings, e.g. from medication studies and work in animal models. Additional evidence for the involvement of those basic pathways comes from genetics as well as first metabolite biomarker studies. For example, a comprehensive meta-analysis of potential biomarkers found several measures, specifically norepinephrine (NE), monoamine oxidase (MAO), 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), zink, ferritin, and cortisol, to be significantly

altered in blood and urine of drug-naïve/drug-free patients with ADHD compared to healthy individuals.[1] Some of the metabolites were also associated with symptom severity of ADHD and/or the response to ADHD medication.

The serendipitous finding that methylphenidate (MPH) treats ADHD symptoms started research into the role of dopaminergic neurotransmission in the pathophysiology of ADHD. This research was soon extended to include norepinephric neurotransmission pathways, since the re-uptake inhibitory action of MPH and other psychostimulants is not selective to the dopamine transporter receptor, but also affects the norepinephrine transporter function. Later, also serotonergic neurotransmission was found to be involved. Thereafter, we review the involvement of other neurotransmission systems in ADHD.

DOPAMINE

The neurotransmitter dopamine is involved in regulation of motor activity and limbic functions, but also plays a role in attention and cognition, especially executive functioning[2] and reward processing.[3] It is a key-contributor to behavioural adaptation and to anticipatory processes necessary for preparing voluntary action following intention.[4] In addition to the fact that the function of dopamine fits well with the signs and symptoms observed in people with the disorder, dopamine circuit dysfunction has been implicated in ADHD based on different experimental evidence.[5] Dopamine-producing cells are localized in the midbrain substantia nigra pars compacta and the ventral tegmental area. From there, three projection pathways can be distinguished: the nigrostriatal pathway, which originates from the substantia nigra and projects to the dorsal striatum (caudate nucleus and putamen); the mesolimbic pathway, which projects from ventral tegmentum to limbic system structures, in particular the ventral striatum (nucleus accumbens), hippocampus, and amygdala; the mesocortical pathway also originating in the ventral tegmental area, which projects to the cerebral cortex, the medial prefrontal areas in particular.[6]

As indicated above, the dopamine transporter – which is the most important molecule in the regulation of dopamine signalling in most areas of the brain – is the main target of stimulants like MPH and also dexamphetamine, the most frequently used prescription drugs for the treatment of ADHD symptoms. These drugs block the dopamine transporter and lead to an increase in dopamine concentration, particularly in the parts of the basal ganglia that are highest in the expression of the transporter, the striatum.[7] This effect is due to the blockade of the transporter molecule in the case of MPH; and due to both transporter blockade and stimulation of dopamine release/block of breakdown through monoamine oxidase in the case of dexamphetamine.[8] The dopamine transporter protein (DAT) and its gene (*DAT1*, official name *SLC6A3*) have thus received most attention in

research of mechanisms underlying ADHD. In animal models, knock-out of the *Dat1* gene produces elevated dopaminergic tone and hyperactivity in the mouse;[9] the latter is also observed upon knock-down of the dopamine transporter in the fruit fly *Drosophila melanogaster.*[10] Implicating the dopaminergic system in ADHD-like behaviour is also the neonatal 6-hydroxy-dopamine lesioned rat model.[11] Neuroimaging studies of the dopamine transporter in humans using positron emission (PET) suggest that more dopamine transporter activity is present in people with ADHD than in healthy individuals,[12] and evidence for depressed dopamine signalling has also been concluded from alterations in dopamine receptors seen in PET. Evidence for disturbances in dopamine signalling have also been suggested by findings of genetic studies. Here, it has again been the dopamine transporter, and in particular a genetic polymorphism in the 3'-regulatory region of the *DAT1* gene, that has been the subject of most studies. Meta-analyses have shown significant associations of this genetic variation in the gene, albeit different versions of the gene were found associated with the disorder in children and adults. Furthermore, an analysis of genetic variants in a larger group of genes involved in ADHD suggested association of this set of genes with the severity of symptoms in children with the disorder.[13]

NOREPINEPHRINE

Norepinephrine signalling is intimately linked to the dopamine system by the fact that norepinephrine is a downstream product of the metabolism of dopamine. Norepinephric neurotransmission regulates important higher cognitive functions such as working memory and inhibitory control, primarily through its projections originating in the locus coeruleus and innervating multiple areas of the cortex, the thalamus, and cerebellum.[5] Especially the innervation of the prefrontal cortex (PFC) by norepinephrine pathways is thought to be important for understanding ADHD. Norepinephrine and dopamine signalling are intimately linked in PFC, i.e. they influence each other in optimizing PFC performance in cognitive tasks.[14] Knowledge about the role of norepinephrine in ADHD mainly comes from the fact that MPH and dexamphetamine inhibit the norepinephrine transporter (NET) in addition to the DAT.[14] Moreover, atomoxetine, a selective NET inhibitor, is effective in the treatment of the cardinal symptoms of ADHD and some of its comorbidities, as are several other prescription drugs with noradrenergic properties, like guanfacine and clonidine[5] While this is clear evidence that altering norepinephrine signalling can ameliorate the symptoms of ADHD, less evidence is available to link it to ADHD neurobiology. This may primarily be due to the concentration of research on the dopaminergic pathways, and the large overlap between dopamine and norepinephrine synthesis and function. No animal models for ADHD based on altering genes involved directly in norepinephrine signalling

have yet been described, but many models actually implicate both dopamine and norepinephrine neurotransmission circuits.[15] PET of the NET has been inconclusive, thus far.[16] Genetic studies of a number of norepinephrine receptors and the NET have not produced convincing evidence for the involvement of these genes either.[17]

SEROTONIN

Serotonin is involved in regulating mood and emotion, and also plays an important role in inhibition, one of the executive cognitive deficits observed in ADHD.[18] The neurons of the raphe nuclei in the midline of the brainstem are the main source of serotonin in the brain. Axons of neurons in the higher raphe nuclei spread out to the entire brain, with strong projections e.g. into the prefrontal cortex, while axons originating in the lower raphe nuclei project to cerebellum and spinal cord. Serotonin signalling is known to affect the regulation of other neurotransmitters, including that of dopamine, which may occur through several mechanisms. Neurotransmission through serotonin was first implicated in ADHD based on paradoxical calming effects of methylphenidate observed in a mouse model lacking the dopamine transporter (DAT). The drug was shown to act by blocking the serotonin transporter in the absence of the DAT in this model. Also, other animal models with altered serotonin signalling show ADHD-like symptoms, inattention as well as hyperactivity.[18] In humans, studies have reported reduced levels of peripheral serotonin in patients with ADHD; but other studies did not find such effects.[18] The exact role of serotonin on ADHD still has to be defined in humans, however. Serotonin neurotransmission may modulate the severity of ADHD symptoms rather than being related to ADHD onset.[13] Other theories suggest that it may be the comorbidity, especially with conduct disorder, obsessive compulsive disorder, aggression and mood disorders (major depression and/or anxiety), rather than the core symptoms of ADHD, which is influenced by serotonin.[18] Genetic studies of the contribution of the serotonergic system to ADHD have not been fully convincing, where it comes to the involvement of serotonin in ADHD. However, the serotonin receptor gene HTR1B and the gene encoding the serotonin transporter (SLC6A4, 5-HTT, SERT) have been implicated in the disorder in meta-analysis.[19] Gene by environment interactions may explain some of the observed inconsistency across studies, as the effect of stress on ADHD symptoms seems to be influenced by genetic variation in the serotonin transporter gene.[20] A recent analysis of a gene-set related to serotonergic neurotransmission suggests that variation in serotonergic genes may be associated with disease severity.[13] Tryptophan depletion, which causes reduction in brain 5-HT synthesis, was found associated with increase of aggression, inattention, and impulsivity.[18] A retrospective pilot study on the administration of precursors of serotonin and dopamine led to promising results

in 85 children and adolescents with ADHD. However, in spite of this supportive evidence for a serotonergic involvement in ADHD, findings from clinical trials with serotonin-noradrenaline reuptake inhibitors (SNRIs) such as venlaflaxine and duloxetine in adults with ADHD are rather mixed (for review, see Banerjee and Nandagopal, 2015).[18]

GLUTAMATE

Glutamate is the most abundant excitatory neurotransmitter in the human central nervous system and is involved in many neuronal functions including synaptic transmission, neuronal migration, excitability, plasticity, and long-term potentiation.[21] The fronto-striatal circuits implicated in impulsivity and compulsivity are notable for their relatively rich glutamatergic receptor density. Glutamatergic projections from the various frontal subregions (orbitofrontal, infralimbic cortex, and prelimbic cortex) to the striatum (and vice versa) play a key role in the regulation of various compulsive behaviours. The signalling effect of glutamate is not dependent on the chemical nature of glutamate, but on how cells are programmed to respond when exposed to it. Because glutamate receptor proteins are expressed on the surface of the cells in such a way that they can only be activated from the outside, glutamate exerts its neurotransmitter function from the extracellular fluid. Consequently, control of receptor activation is achieved by releasing glutamate to the extracellular fluid and then removing glutamate from it. Because there are no enzymes extracellularly that can degrade glutamate, low extracellular concentrations require cellular uptake. Several families of glutamate receptor proteins have been identified and classified as NMDA receptors, AMPA receptors, kainate receptors, and metabotropic receptors.[22] Most, if not all, cells in the nervous system express at least one type of glutamate receptor.

Several candidate genes within the glutamatergic system have been associated with ADHD. For instance, associations have been found for variation in the *GRIN2B* gene with both inattention and hyperactivity symptoms in ADHD. A genome-wide study investigating rare variants found overrepresentation of variants belonging to the metabotropic glutamate receptor genes in several ADHD cohorts.[23] An analysis of a glutamate gene-set showed significant association to severity of hyperactivity/impulsivity of patients with ADHD.[24] Proton-magnetospectroscopy (MRS) studies suggest a possible increase in Glx (a combination of glutamate, glutamine, and GABA) in the striatum across ADHD, obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD), and further, an increased Glx signal in the anterior cingulate cortex in children with ADHD and ASD but a lower Glx signal in adults with ADHD and ASD. This suggests neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan.[25] Glutamatergic agents such as memantine, an antagonist of he NMDA receptor, are of po-

tential value in the treatment of impulsivity in children and adolescents, including ADHD, but large-scale positive trials have not been published yet.

HISTAMINE

Histamine is one of the key neurotransmitters regulating arousal and attention. The cell bodies of histamine neurons are found in the posterior hypothalamus, in the tuberomammillary nuclei. From here, these neurons project throughout the brain, including to the cortex, through the medial forebrain bundle. Histamine neurons increase wakefulness and prevent sleep.[26] In addition, this neurotransmitter is an important agent in (neuro)immune reactions. Interest in the role of histamine in ADHD stems from the observations that allergies have an increased incidence in people with ADHD. Indeed, a recent meta-analysis shows that children with ADHD are more likely to develop asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis than healthy individuals.[27] Conversely, children with allergies appear to have higher ADHD symptom ratings than non-affected children. The histamine H3 receptor subtype is mainly distributed in the central nervous system and functions as both a presynaptic autoreceptor that reduces histamine release and a heteroreceptor that regulates release of other neurotransmitters. Histamine H3 receptor antagonists and inverse agonists increase release of brain histamine and other neurotransmitters. The H3 receptor antagonists have been shown to promote arousal in various species, without the psychomotor activation seen with stimulants.[28] Potent histamine H3 receptor antagonists are currently being developed and tested for the treatment of ADHD.[29]

NICOTINIC ACETYLCHOLINERGIC SYSTEM

Nicotinic acetylcholine receptors are receptor proteins that respond to the neurotransmitter acetylcholine. Nicotinic receptors also respond to drugs, including the nicotinic receptor agonist nicotine. Nicotine use has been associated with improvement in cognition, attention in particular, in different animal species, healthy human volunteers, and patients with ADHD.[30] In addition to the knowledge about the influence of attention, the nicotinic acetylcholine neurotransmission system is also implicated in ADHD through genetic findings: a large study of copy number variants found duplications of the gene encoding the α7-nicotinic acetylcholine receptor (CHRNA7), located in the mutation-prone region on chromosome 15q13.3, to contribute to the risk for the disorder.[31] The nicotinic acetylcholine system may be one of the new targets for the development of alternative drugs for ADHD. Nicotine appears to exert its beneficial effect selectively on behavioural inhibition and delay aversion tasks, which are known to have good discriminant

validity in distinguishing subjects with ADHD from controls. Stimulation of neuronal nicotinic acetylcholine receptors by nicotine may be mediated directly via changes of cholinergic neurotransmission and/or by modulating activity of other neurotransmitters including dopamine, which in turn has a recognized role in the neurobiology of ADHD (see section on dopamine above). Trials of nicotinic drugs demonstrated beneficial effects in adults with ADHD, with evidence for also positive effects on cognitive and emotional domains, although there are no approved medications for ADHD that target nicotinic acetylcholine receptor function.[32]

COGNITION

For many years, cognitive research in ADHD has been dominated by theories about primary key cognitive impairment that would be causal to the development of the disorders (see Box 2.1). This was followed by theories about dual- and triple pathways models (see Box 2.1). Currently, there is consensus that ADHD is characterized by a fragmented pattern of deficits in relatively independent cognitive domains. The classification of these cognitive domains varies by paper, but include inhibition, working memory, arousal, activation, response variability, temporal information processing, memory span, processing speed, decision making and delay aversion.[33,34] We will review executive function and reward processing deficits in particular in more detail below (Box 2.1).

EXECUTIVE FUNCTIONS

Executive functions (referred to as executive function and cognitive control) is a umbrella term for a set of cognitive processes that are necessary for the cognitive control of behaviour. Executive functions include basic cognitive processes such as attentional control, cognitive inhibition, inhibitory control, working memory, and cognitive flexibility. Higher order executive functions require the simultaneous use of multiple basic executive functions and include planning and fluid intelligence (i.e., reasoning and problem solving). Executive functioning deficits in ADHD are seen in inhibitory control, visuo-spatial and verbal working memory, vigilance, and planning.[41]

RESPONSE INHIBITION

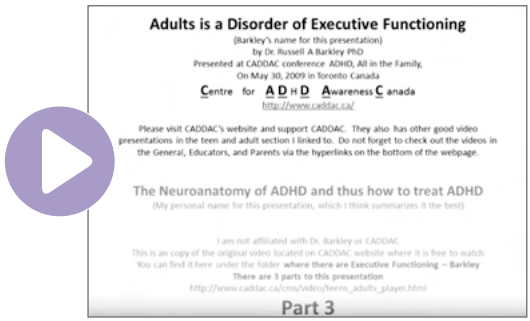
Response inhibition is one aspect of cognitive control. Attention, behaviour, thoughts, and emotions are regulated through inhibition processes executing top-down cognitive control. Response inhibition specifically is the ability to control oneself

Box 2.1
REVIEW OF EXECUTIVE FUNCTION AND REWARD PROCESSING DEFICITS IN ADHA

Key single deficit theories	• Attention deficit[35] • Non-optimal energetic state, in particular activation[36] • Behavioral inhibition[37] • Delay-aversion[38]
Dual pathway theories	Executive functioning deficit ("cold cognition") and reward processing deficit ("hot cognition")[39]
Triple pathway theories	Executive functioning deficit, reward processing deficit, timing deficit[40]

by suppressing or altering intended actions that are no longer required or appropriate. Adequate response inhibition thus enables people to properly adapt to changes in the environment.[42] Impaired response inhibition is central to theoretical models of ADHD.[43] Barkley[37] and others have argued for response inhibition as a central deficit of ADHD in that it affects top-down multiple executive functions, including working memory, self-regulation, internalization of speech and reconstitution. On average individuals with ADHD inhibit their responses more slowly than controls, as reflected in longer stop-signal reaction times and higher error rates. A meta-analysis reported a medium effect-size of 0.62 for the case--control difference in stop-signal reaction time.[44] In addition, a large community study showed that ADHD symptoms in children and adolescents are associated with worse response inhibition and slower response latency.[45]

Response inhibition deficits in ADHD are also observed at the level of the brain. When brain activation is assessed during the administation of response inhibition tasks in the MRI scanner (in socalled functional MRI or fMRI studies),



Link in this

https://www.youtube.com/watch?v=sPFmKu2S5XY

healthy participants activate core network of brain regions involved in response inhibition, including a frontal-striatal and frontal-parietal network.[46] Most consistently, children and adolescents with ADHD show decreased activation in frontal, medial and parietal regions during inhibitions when compared with controls,[47] while for adults with ADHD hyperactivation has also been reported. Relative to comparison subjects, not only participants with ADHD but also their unaffected siblings had neural hypoactivation in frontal-striatal and frontal-parietal networks, whereby activation in inferior frontal and temporal/parietal nodes in unaffected siblings was intermediate between levels of participants with ADHD and comparison subjects.[48] Furthermore, neural activation in inferior frontal nodes correlated with stop-signal reaction times, and activation in both inferior frontal and temporal/parietal nodes correlated with ADHD severity. These neural activation alterations in ADHD are more robust than behavioral response inhibition deficits and explain variance in response inhibition and ADHD severity.[48] Together with alterations in brain activation during response inhibition, individuals with ADHD also had lower functional connectivity within the response inhibition network.

The alterations in brain activations in the inhibition network in unaffected siblings described above indicate that response inhibition may serve as a socalled endophenotype. Endophenotypes are biomarkers that share genetic loading with the disease liability, can be measured in all individuals (both affected and unaffected), and that are assumed to provide greater power to identify disease-related genes than clinical phenoptypes.[49] Since ADHD has strong genetic underpinnings and siblings on average share 50% of their genetic variation, unaffected siblings will on average have more ADHD risk genes than healthy controls. Thus, this suggests that part of the genetic loading for ADHD is mediated by alterations of response inhibition at the behavioural and neural level.

WORKING MEMORY

Working memory is considered to be the most central executive function. Three components of working memory are identified in Baddeley's model.[50] The Central Executive (CE) acts as an attentional controller, coordinating tasks and activities of its two sub-systems: the phonological loop (PL) and the visuospatial sketchpad (VS), both storing modality-specific information. Deficient functioning of the separate systems translates into different performance deficits on cognitive tasks: limitations in storage capacity of the VS or PH subsystems is typically characterised by a decline in task performance with increasing memory load or task difficulty. CE dysfunctioning generally translates into a general performance deficit, stable over different memory loads. Evidence suggests that deficits in working memory are one of the key cognitive impairments in ADHD,[51] with the strongest impairments reported for the spatial domain of working memory, as opposed to

the verbal or phonological domain.[51] Visuo-spatial working memory is subserved predominantly by the inferior and superior parietal areas together with dorsolateral prefrontal regions.[52-56] There is additional evidence of activation in the cerebellum during visuo-spatial working memory tasks.[57,58] The available fMRI studies of ADHD reveal a differential activation pattern in the fronto-striatal areas[59] and reduced activation in the dorsolateral prefrontal areas,[60,61] right inferior and superior parietal lobes,[56,62,63] and right caudate nucleus.[63]

REWARD SENSITIVITY

Reward sensitivity is an evolutionary important construct; because rewards are accompanied by positive feelings, they reinforce reward-linked behaviour. This process of reinforcing behaviour forms the basic principle of learning.[64] Yet, if an individual is highly sensitive to rewards, this can lead to maladaptive behaviour, such as risky behaviour and addictions. Especially during adolescence, reward sensitivity is heightened, which is demonstrated by increased risky behaviour when rewards are at stake.[65] Current theoretical models of ADHD consider altered reward sensitivity to be a key cognitive mechanism.[66,67] In general, studies of reward processing show that individuals with ADHD patients make suboptimal and more risky decisions, prefer immediate compared with delayed rewards[66] and overestimate the magnitude of proximal relative to distal rewards. The greater sensitivity to rewards in individuals with ADHD is further demonstrated by faster behavioural responses to trials which lead to rewards than to non-reward trials in the socalled monetary incentive delay task.[67]

Alterations in reward sensitivity in ADHD have alo been observed at the neural level, using fMRI paradigms. Various brain regions, including the orbitofrontal cortex, medial prefrontal cortex, and the ventral striatum are activated in healthy subjects when receiving or anticipating rewards. Findings in ADHD are mixed, with increased activations in the anterior cingulate and anterior frontal cortex during reward anticipation, and in the orbitofrontal cortex and nucleus accumbens during reward receipt[68] and a community study associating increased activation with impulsivity, a related concept. Other studies in adolescents and (young) adults with ADHD however have reported less striatal activation during reward anticipation compared to controls.

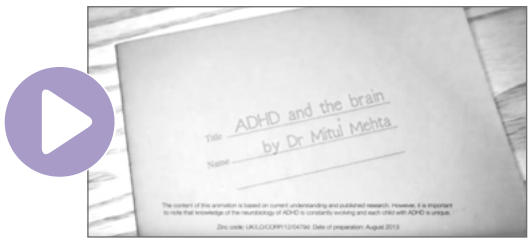
OTHER COGNITIVE DEFICITS

Among other domains that have found to be impaired in ADHD are temporal information processing and timing,[69] speech and language functions,[70] motor control problems,[71] memory span, processing speed, arousal/activation; and reaction

time variability.[72] Slower and more variable reaction times are robust markers of ADHD not only compared to typically developing controls but also to individuals with autism.[73] Last, but not least, it is frequently reported that children with ADHD have on average a lower IQ (about 9 scale points) than controls.[74] This reduction appears to be attenuated in adults with ADHD and is not fully caused by inattentiveness during test performance. This lower IQ may not be specific for ADHD and be found in individuals with other psychiatric disorders as well and might reflect executive deficits that are are assessed as part of the IQ battery tests.

THE AVERAGE INDIVIDUAL WITH ADHD VERSUS INTERINDIVIDUAL VARIATION

All of the above described ADHD case-control cognitive differences were based on group effects. These group effects report on the "average" individual with ADHD but may disguise substantial interindividual variation.[75] Although most individuals with ADHD show deficits in one or two cognitive domains, about 10-25 % have not any cognitive deficit with the test batteries used, and at the other side of the spectrum, only very few show deficits in all cognitive domains[34]. It is further of note that also 10% or more of all healthy controls (without ADHD) present with cognitive deficits in 2-3 domains.[34] This has led to attempts to identify subgroups of ADHD with a more homogenous cognitive profile. One study revealed four cognitive subtypes, the first characterized by high response variability, the second by low performance on memory, inhibition and response speed, the third by inaccurate temporal information processing, and the fourth by sub-optimal arousal. Remarkably, very similar cognitive subgroups were found in a community sample of control children [33]. This supports the view that at least part of ADHD's cognitive heterogeneity is nested within normal variation. Similarly, van Hulst and coworkers[76] identified three neuropsychological subgroups within children with ADHD: a quick and accurate, a slow and variable timing and a poor cognitive control subgroup. The first two of these subgroups were also present in the control



Link in this

https://www.youtube.com/watch?v=4r3XWj269_g

group. Also in adults with ADHD, very similar cognitive subtypes have been identified.[77] It is, however, unclear whether these cognitive subtypes of ADHD have external validity, and for example predict treatment response or course. It is also unclear whether cognitive deficits cause ADHD symptoms and drive the development of the clinical phenotype[38] or reflect the pleiotropic outcomes of risk factors.

BRAIN IMAGING

Brain imaging techniques allow researchers to visualize, measure and analyze the interior of the human brain, i.e. its structure and function, with unprecedented power (see Box 2.2). Alterations have been observed in virtually all neuroimaging modalities applied to the study of the ADHD brain, including structural and functional magnetic resonance imaging (MRI), electroencephalography (EEG), and magnetoencephalography (MEG).

STRUCTURAL MRI

Earlier studies had found that ADHD is associated with a 3-5% smaller total brain size compared to controls[78] due to a reduction of gray matter.[79] Consistent with genetic data suggesting ADHD is the extreme of a population trait, total brain volume correlates negatively with ADHD symptoms in the general population.[80] Meta-analyses further document smaller volumes in ADHD across several brain regions, most consistently in the right globus pallidus, right putamen, caudate and cerebellum. The most recent and largest meta-analysis included in total 1713 participants with ADHD and 1529 controls from 23 sites with a median age of 14 years (range 4-63 years).[81] The results of the mega-analysis (in which not just the case-control differences per site were aggregated but all individual data points were taken in to account) indicated that the volumes of the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume were smaller in individuals with ADHD compared with controls. The effects sizes were small and between 0.10 and 0.19 in terms of Cohen's d. There was no difference in volume size in the pallidum and thalamus between people with ADHD and controls. Effect sizes were highest in most subgroups of children (<15 years) versus adults (>21 years), and case-control differences in adults were non-significant. Psychostimulant medication use or symptom scores did not influence the results, nor did the presence of comorbid psychiatric disorders. The greater case-control differences at younger age and absence of such differences at older age support the brain maturation delay theory for ADHD. This theory states that ADHD is due to a delayed ma-

turation of brain structures that mature earlier in healthy controls, and that brain maturation in ADHD may catch-up at later age.[82] This theory was developed given earlier observations that ADHD is associated with delayed maturation of cerebral cortex. Shaw et al.[83] reported that the age of attaining peak cortical thickness was 10.5 years for individuals with ADHD and 7.5 years for controls. This delay was most prominent in prefrontal regions important for control of executive functioning, attention, and motor planning.[83] The development of cortical surface area was delayed in ADHD, but ADHD was not associated with altered developmental trajectories of cortical gyrification.[84]

Although the work reviewed above suggests that age-dependent decline in the prevalence of ADHD may be due to a late development of ADHD-associated brain structures and functions, most patients with ADHD do not show complete developmental "catch up". Indeed, widespread reductions in cortical thickness have been implicated in ADHD not only in children but also in adults. Findings include both cortical thinning (superior frontal cortex, precentral cortex, inferior and superior parietal cortex, temporal pole, and medial temporal cortex[84, 85] and cortical thickening (presupplementary motor area, somatosensory cortex and occipital cortex).[86]

Changes across age in the brains of ADHD patients are of much interest given the age dependent prevalence of ADHD.[87] Some brain volumetric alterations observed in childhood normalize with age.[88] A longitudinal MRI study found basal ganglia volumes and surface area to be smaller in adolescents with ADHD compared to controls; this difference was fixed and not-progressive over age.[89] In contrast, for ventral striatal surfaces, controls showed surface area expansion with age, whereas ADHD patients experienced a progressive contraction of the surface, which may explain abnormal processing of reward in ADHD.[89]

VOXEL-BASED MORPHOMETRY

Voxel-based morphometry (VBM) analyses (see Box 2.2) on brain scans of adolescents with ADHD observed significantly smaller grey matter volume in 5 clusters located in the precentral gyrus, medial and orbitofrontal cortex, and (para)cingulate cortices, compared to controls.[90] Unaffected siblings of the ADHD probands had also smaller volumes that were significantly different from controls in 4 of these clusters (all except the precentral gyrus). The brain areas that are smaller in ADHD are involved in decision making, motivation, cognitive control and motor functioning, all functional domains that may be affected in ADHD. The alterations in the unaffected siblings indicate the familiality of four of the structural brain differences, supporting their potential as endophenotypes (see above).

Box 2.2
MEASURES OF BRAIN STRUCTURE AND FUNCTION

Neuroimaging has provided a tremendous boost to neuroscience, by enabling a non-invasive study of the brain in health and disease. This chapter describes research into measures of brain structure, activity, and functional network connectivity in individuals with ADHD and control participants. **Structural magnetic resonance** imaging (sMRI) scans are used predominantly to study aspects of brain grey matter, containing neuronal cell bodies and synapses, and white matter, consisting mostly of the myelinated axons that connect brain areas. sMRI scans allow both for assessing the volume of apriori defined volumes of cortical and subcortical volumes and for bottom-up brainwide analyses of brain voxels (voxel-based morphometry-VBM). Finally, sMRI scans enable to quantify various aspects of the cortex, such as cortical thickness, surface area and gyrification. **Diffusion-tensor imaging** (DTI) or diffusion-weighted imaging (DWI) scans make it possible to estimate the location, orientation and functional integrity of the brain's white matter tracts.

Functional MRI (fMRI) takes advantage of changes in the magnetic properties of blood passing through the brain as an indicator of the relative activity of a region over time. The blood-oxygen level dependent (BOLD) signal is usually recorded while subjects perform a cognitive task, and then compared to a baseline recording to isolate the task-associated activity. FMRI data may also be used to study brain functional connectivity by calculating the coherence of activation patterns over time between regions. This may be done with task-based fMRI data, as well as with recordings while individuals are not engaged in any specific task, known as **resting-state MRI** (rsMRI). Studies into functional connectivity have identified several brain networks, collections of regions that are consistently co-activated. The activation of these networks depends on the subjects' current state of mind. For instance, activity in the executive function network is most prominent when performing a working memory task, and the default mode network becoming more active while mind wandering during resting conditions.[93]

Information about brain function can also be obtained by **electroencephalography** or EEG; this is the physiological method of choice to record all of the electrical activity generated by the brain from electrodes placed on the scalp surface, and allows to study the power of frequency patterns of brain oscillations (delta, 1-4 Hz, theta 4-7 Hz, alpha 7-12 Hz, beta 12-30 Hz , and gamma > 30 Hz).

Event-related potentials (ERP) assess the change in electrical activity time-locked to certain cognitive or attentional tasks.

Magnetoencephalography, or MEG, is an imaging technique that measures small magnetic fields produced by the electrical activity in the brain.

Proton magnetic resonance spectroscopy (MRS) is an imaging technique allowing for in vivo quantification of several neurometabolites in small volumes of the brain.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactive tracers for targeting different steps in the process of for example dopaminergic neurotransmission.

DIFFUSION TENSOR IMAGING (DTI)

A meta-analysis of whole-brain analyses DTI studies that combined voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) documented widespread alterations in white matter integrity, especially in the right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum[91] A later meta--analysis on a larger set of TBSS studies found altered white matter microstructure, as reflected in low fractional anisotropy values, in the splenium of the corpus callosum (CC) that extended to the right cingulum, right sagittal stratum, and left tapetum.[92] These findings indicate that altered WM matter tracts that integrate the bilateral hemispheres and posteriorbrain circuitries play a crucial role in the pathophysiology of ADHD.

FUNCTIONAL MRI (FMRI)

Task-related fMRI studies using inhibitory control, working memory, and attentional tasks have documented under-activation of frontostriatal, frontoparietal and ventral attention networks. [94] The frontoparietal network supports goal-directed executive processes while the ventral attention network facilitates attentional reorienting to salient and behaviorally relevant external stimuli. In reward processing paradigms, most studies report lower activation of the ventral striatum in ADHD compared to controls in anticipation of reward 67. ADHD is also associated with hyperactivation in somatomotor and visual systems,[94] which possibly compensates for impaired functioning of the prefrontal and anterior cingulate cortices.[95]

Remission of ADHD has been associated with normalization of abnormalities as measured by activation during functional imaging tasks,[96] cortical thinning[97] and functional and structural brain connectivity.[98,99]

RESTING-STATE MRI

Resting-state MRI studies report that ADHD is associated with reduced or absent anti-correlations between the default mode network (DMN) and the cognitive control network, lower connectivity within the DMN itself, and lower connectivity within the cognitive and motivational loops of the fronto-striatal circuits.[100] In simple words, individuals without ADHD tend to activate in a MRI scan during mindwondering this DMN. When requested to focus or execute an action, connections inside this DMN weaken while connections in the areas needed to the task are activated. This process seems to be disturbed in ADHD. Some previous investigations suggest that individuals with ADHD do not decrease activity in the

DMN as controls while changing from a resting state to a task, making them "work with a background noise".

In summary, both structural and functional MRI imaging findings are very variable across studies, suggesting that the neural underpinnings of ADHD are heterogeneous, which is consistent with studies of cognition. Of note, ADHD has also been associated with more global brain changes (i.e., decrease in total brain volume), as well as with localized brain changes in areas outside the frontal-striatal circuits such as the parietal cortices, thalamus, amygdala, and cerebellum, and altered activation patterns within other networks such as the default-mode network.

NEUROPHYSIOLOGICAL STUDIES. ELECTROENCEPHALOGRAPHY (EEG) AND EVENT-RELATED POTENTIALS (ERP)

Neurophysiological studies, EEG and ERP studies report altered electrical brain activity in relation to several cognitive processes as attention, inhibition, and performance monitoring.[101] In the attention domain, selective attention and continuous performance (CPT) tasks indicate issues with orienting to cues and selection/resource allocation processes to target stimuli, oddball studies indicated stimulus discrimination and evaluation problems, and distraction tasks indicating attention switching/orienting problems. When considering response inhibition tasks, Stop-signal studies have indicated deficits in response inhibition that were often preceded by differences in earlier attentional components. Similar effects were reported for the Go/Nogo task, with the CPT task indicating issues with response preparation and response inhibition. The flanker task has indicated conflict processing and resource allocation issues. Deficient error detection and/or evaluation were identified by attenuated ERN and Pe components in ADHD, with feedback-processing effects also consistently reported. Similarly, atypical patterns of socalled resting-state EEG frequency power have been observed, mostly as increased power of low frequency theta activity and/or decreased power of fast beta activit.[102] Excessive theta-beta ratio, however, cannot be considered a reliable diagnostic measure of ADHD, but may be useful as a prognostic measure.[103]

Longitudinal work has identified consistent neurophysiological patterns related to differential outcomes. Children with ADHD persisting into adulthood show increased beta and reduced frontal theta EEG at rest,[104] and ERP markers for reduced cognitive preparation (CNV) and error processing.[105-107]

MAGNETOENCEPHALOGRAPHY

There are few magnetoencephalography (MEG) studies in ADHD. A study explored neural interactions between auditory cortices and the frontal cortices during

an auditory attention task in adults with ADHD and controls. ADHD was associated with a greater phase coherence in the beta (14-30Hz) and gamma frequency (30-56Hz) range in attend and no-attend conditions compared to controls. Stimulant medication attenuated these differences but did not fully eliminate them. These results suggest that aberrant bottom-up processing may compromise executive resources in ADHD.[108]

PROTON MAGNETIC RESONANCE SPECTROSCOPY

Proton magnetic resonance spectroscopy (MRS) is a non-invasive method allowing for in vivo quantification of several neurometabolites in small volumes of the brain. MRS studies in ADHD and other neurodevelopmental disorders as autism and obsessive compulsive disorder (OCD) are limited by small sample sizes and varying methodology. Nevertheless, some consistent findings were identified in a systematic review:[25] 1. possible increased Glx (which is a combination of combination of Glu, glutamine and GABA) signal in the striatum across ADHD, OCD and autism; 2. increased Glx in the anterior cingulate cortex (ACC) in children and adolescents with ADHD and autism, and 3. decreased Glx in the ACC in adults with ADHD and with autism. This suggests neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan.

RADIOTRACER IMAGING

Radiotracer techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) can provide more direct evidence of altered dopamine binding patterns in the striatum of patients with ADHD. A meta-analysis of SPECT and PET studies investigating striatal dopamine transporter density in individuals with ADHD and matched healthy comparison subjects found that the striatal dopamine transporter density was 14% higher on average in the ADHD group than in the controls.[12] However, there was marked heterogeneity across studies, and density was higher in patients with previous medication exposure and lower in medication-naive patients. Thus, striatal dopamine transporter density in ADHD appears to depend on previous psychostimulant exposure, with lower density in drug-naive subjects and higher density in previously medicated patients.

SUMMARY AND CONCLUSION

ADHD is a highly heritable, multifactorial disorder, in which genetic factors – often in combination with environmental factors – form risk factors for disease onset.

The mechanisms underlying ADHD are complex and can be defined at different levels. Cognitive deficits are often but not always part of the disorder and include problems in executive functioning, reward processing, timing deficits, various aspects of attentional regulation and orientation, perceptual processes, arousal regulation and reaction time variability. The brain alterations seen in ADHD are very heterogeneous, found in all imaging modalities and both in brain structure and brain function and present a mixture of deviancy and delay. Alterations of the fronto-striatal, fronto-cerebellar and fronto-parietal circuits have been most often reported but this certainly is not the whole picture. The fronto-amygdalar circuits and the limbic brain, and the posterior areas of the brain seem to be involved as well. Individuals with ADHD show different patterns of alterations, and a focus on the "average individual with ADHD" and thus on case-control differences can be somewhat misleading and disguise substantial interindividual variation.[75, 109] Single neuroimaging findings have mostly very limited effect sizes.

Sofar, despite clear evidence that individuals with ADHD have brains that at the group level are different from the "typical brain", no single cognitive or biological marker for ADHD has sufficient diagnostic or predictive value to be incorporated in clinical work. There are several explanations for this disappointing situation. First, the clear limitations of our current categorical diagnostic systems as the DSM[110] and ICD[111] that force both clinicians and researchers into a binary decision: ADHD is present "yes or no". In reality, ADHD can be conceptualized better as a high score (but with a still arbitrary cutoff point) on a complex continuous trait with a normal distribution in the population. Second, the reliance on overly simplistic case-control designs in the study of biomarkers that underestimate heterogeneity in both cases and controls.[75] Third, the lack of a stable, agreed upon and biologically valid concept of ADHD, and for matter of any psychiatric disorder,[112] which makes the current classification an even more unclear basis for informed biological research. The way forward is to define biologically more homogeneous subtypes ("biotypes") of ADHD, and such studies are under way but have still to deliver.[114] The Research Domain Criteria (RDoC) project has been initiated to develop and biologically validate new ways of classifying and understanding mental health.[114] RDoC focuses on altered cross-disorder dimensions of functioning that span the full range of human behavior from typical to atypical and aims to integrate many levels of information from genetics/genomics and neural circuits to observable behavior and self-reports. Again, the promise of RDoC to improve understanding of ADHD in terms of varying degrees of dysfunctions in biological systems has still to be realized.

Conflicts of interest

Jan K. Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Medice, Shire, Roche, and Servier. He is not an employee of any

of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. Other authors report no conflict of interest.

REFERENCES

1. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry. 2012;51(10):1003-1019. e20.

2. Nieoullon A. Dopamine and the regulation of cognition and attention. Prog Neurobiol. 2002;67(1):53-83.

3. Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA. 2009;302(10):1084-91.

4. Nieoullon A, Coquerel A. Dopamine: a key regulator to adapt action, emotion, motivation and cognition. Curr Opin Neurol. 2003;16 Suppl 2:S3-9.

5. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011;69(12):e145-57.

6. Ziegler S, Pedersen ML, Mowinckel AM, Biele G. Modelling ADHD: A review of ADHD theories through their predictions for computational models of decision-making and reinforcement learning. Neurosci Biobehav Rev. 2016;71:633-656.

7. Kuczenski R, Segal DS. Stimulant actions in rodents: implications for attention-deficit/hyperactivity disorder treatment and potential substance abuse. Biol Psychiatry. 2005;57(11):1391-6.

8. Kuczenski R, Segal DS. Differential effects of D- and L-amphetamine and methylphenidate on rat striatal dopamine biosynthesis. Eur J Pharmacol. 1975;30(2):244-51.

9. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature. 1996;379(6566):606-12.

10. van der Voet M, Harich B, Franke B, Schenck A. ADHD-associated dopamine transporter, latrophilin and neurofibromin share a dopamine-related locomotor signature in Drosophila. Mol Psychiatry. 2016;21(4):565-73.

11. van der Kooij MA, Glennon JC.Animal models concerning the role of dopamine in attention-deficit hyperactivity disorder. Neurosci Biobehav Rev. 2007;31(4):597-618.

12. Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J Psychiatry. 2012;169(3):264-72.

13. Bralten J, Franke B, Waldman I, Rommelse N, Hartman C, Asherson P, et al. Candidate genetic pathways for attention-deficit/hyperactivity disorder (ADHD) show association to hyperactive/impulsive symptoms in children with ADHD. J Am Acad Child Adolesc Psychiatry. 2013;52(11):1204-1212.e1.

14. Arnsten AF, Pliszka SR. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol Biochem Behav. 2011;99(2):211-6.

15. de la Peña JB, Dela Peña IJ, Custodio RJ, Botanas CJ, Kim HJ, Cheong JH. Exploring the validity of proposed transgenic animal models of attention-deficit hyperactivity disorder (ADHD). Mol Neurobiol. 2018;55(5):3739-3754.

16. Vanicek T, Spies M, Rami-Mark C, Savli M, Höflich A, Kranz GS, et al. The norepinephrine transporter in attention-deficit/hyperactivity disorder investigated with positron emission tomography. JAMA Psychiatry. 2014;71(12):1340-1349.

17. Klein M, Onnink M, van Donkelaar M, Wolfers T, Harich B, Shi Y, et al. Brain imaging genetics in ADHD and beyond – mapping pathways from gene to disorder at different levels of complexity. Neurosci Biobehav Rev. 2017;80:115-155.

18. Banerjee E, Nandagopal K. Does serotonin deficit mediate susceptibility to ADHD? Neurochem Int. 2015;82:52-68.

19. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 2009;126(1):51-90.

20. van der Meer D, Hartman CA, Richards J, Bralten JB, Franke B, Oosterlaan J, et al. The serotonin transporter gene polymorphism 5-HTTLPR moderates the effects of stress on attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry. 2014;55(12):1363-71.

21. Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm (Vienna). 2014;121(8):799-817.

22. Gregory KJ, Noetzel MJ, Niswender CM. Pharmacology of metabotropic glutamate receptor allosteric modulators: structural basis and therapeutic potential for CNS disorders. Prog Mol Biol Transl Sci. 2013;115:61-121.

23. Elia J, Glessner JT, Wang K, Takahashi N, Shtir CJ, Hadley D, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nat Genet. 2011;44(1):78-84.

24. Naaijen J, Bralten J, Poelmans G, IMAGE consortium, Glennon JC, Franke B, et al. Glutamatergic and GABAergic gene sets in attention-deficit/hyperactivity disorder: association to overlapping traits in ADHD and autism. Transl Psychiatry. 2017;7(1):e999.

25. Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: a review of magnetic resonance spectroscopy studies. Neurosci Biobehav Rev. 2015;52:74-88.

26. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol. 2001;63(6):637-72.

27. Miyazaki C, Koyama M, Ota E, Swa T, Mlunde LB, Amiya RM, et al. Allergic diseases in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis. BMC Psychiatry. 2017;17(1):120.

28. Sadek B, Saad A, Sadeq A, Jalal F, Stark H. Histamine H3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. Behav Brain Res. 2016;312:415-30.

29. Moorthy G, Sallee F, Gabbita P, Zemlan F, Sallans L, Desai PB. Safety, tolerability and pharmacokinetics of 2-pyridylacetic acid, a major metabolite of betahistine, in a phase 1 dose escalation study in subjects with ADHD. Biopharm Drug Dispos. 2015;36(7):429-39.

30. Potter AS, Newhouse PA, Bucci DJ. Central nicotinic cholinergic systems: a role in the cognitive dysfunction in attention-deficit/hyperactivity disorder? Behav Brain Res. 2006;175(2):201-11.

31. Williams NM, Franke B, Mick E, Anney RJ, Freitag CM, Gill M, et al. Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. Am J Psychiatry. 2012;169(2):195-204.

32. Potter AS, Schaubhut G, Shipman M. Targeting the nicotinic cholinergic system to treat attention-deficit/hyperactivity disorder: rationale and progress to date. CNS Drugs. 2014;28(12):1103-13.

33. Fair DA, Bathula D, Nikolas MA, Nigg JT. Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD. Proc Nat Acad Sci U.S.A. 2012;109(17):6769-6774.

34. Coghill DR, Seth S, Matthews K. A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. Psychol Med. 2014;44(9):1989-2001.

35. Douglas VI. Stop, look and listen: the problem of sustained attention and impulse control in hyperactive and normal children. Can J Behav Sci. 1972;4(4):259-282.

36. Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neurosci Biobehav Rev. 2000;24(1):7-12.

37. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997;121(1):65-94.

38. Sonuga-Barke EJ, Houlberg K, Hall M. When is "impulsiveness" not impulsive? The case of hyperactive children's cognitive style. J Child Psychol Psychiatry. 1994;35(7):1247-53.

39. Sonuga-Barke EJ. Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. Behav Brain Res. 2002;130(1-2):29-36.

40. Durston S, van Belle J, de Zeeuw P. Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011;69(12):1178-84.

41. Sergeant JA. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. Biol Psychiatry. 2005;57(11):1248-55.

42. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform. 1984;10(2):276-91.

43. Oosterlaan J, Logan GD, Sergeant JA. Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry. 1998;39(3):411-25.

44. Lipszyc J, Schachar R. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc. 2010;16(6):1064-76.

45. Crosbie J, Arnold P, Paterson A, Swanson J, Dupuis A, Li X, et al. Response inhibition and ADHD traits: correlates and heritability in a community sample. J Abnorm Child Psychol. 2013;41(3):497-507.

46. Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev. 2009;33(5):631-46.

47. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry. 2013;70(2):185-98.

48. van Rooij D, Hoekstra PJ, Mennes M, von Rhein D, Thissen AJ, Heslenfeld D, et al. Distinguishing adolescents with ADHD from their unaffected siblings and healthy comparison subjects by neural activation patterns during response inhibition. Am J Psychiatry. 2015;172(7):674-83.

49. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636-45.

50. Baddeley AD. Working memory, thought, and action. New York: Oxford University, 2007.

51. Martinussen R, Hayden J, Hogg-Johnson S, Tannock R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(4):377-84.

52. Awh E, Jonides J. Overlapping mechanisms of attention and spatial working memory. Trends Cogn Sci. 2001;5(3):119-126.

53. Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cereb Cortex. 1996;6(1):11-20.

54. Thomas KM, King SW, Franzen PL, Welsh TF, Berkowitz AL, Noll DC, et al. A developmental functional MRI study of spatial working memory. Neuroimage. 1999;10(3 Pt 1):327-38.

55. Zurowski B, Gostomzyk J, Grön G, Weller R, Schirrmeister H, Neumeier B, et al. Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing. Neuroimage. 2002;15(1):45-57.

56. Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, et al. Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). J Child Psychol Psychiatry. 2005;46(1):94-111.

57. Leung HC, Oh H, Ferri J, Yi Y. Load response functions in the human spatial working memory circuit during location memory updating. Neuroimage. 2007;35(1):368-77.

58. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev. 2000;31(2-3):236-50.

59. Konrad K, Neufang S, Thiel CM, Specht K, Hanisch C, Fan J, et al. Development of attentional networks: an fMRI study with children and adults. Neuroimage. 2005;28(2):429-39.

60. Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD. Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. Am J Psychiatry. 2000;157(2):278-80.

61. Schweitzer JB, Lee DO, Hanford RB, Zink CF, Ely TD, Tagamets MA, et al. Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. Biol Psychiatry. 2004;56(8):597-606.

62. Silk T, Vance A, Rinehart N, Egan G, O'Boyle M, Bradshaw JL, et al. Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. Br J Psychiatry. 2005;187:282-3.

63. Vance A, Silk TJ, Casey M, Rinehart NJ, Bradshaw JL, Bellgrove MA, et al. Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. Mol Psychiatry. 2007;12(9):826-32, 793.

64. Blaukopf CL, DiGirolamo GJ. Reward, context, and human behaviour. ScientificWorldJournal. 2007;7:626-40.

65. Galvan A. Adolescent development of the reward system. Front Hum Neurosci. 2010;4:6.

66. Luman M, Tripp G, Scheres A. Identifying the neurobiology of altered reinforcement sensitivity in ADHD: a review and research agenda. Neurosci Biobehav Rev. 2010;34(5):744-54.

67. Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci Biobehav Rev. 2014;38:125-34.

68. Paloyelis Y, Mehta MA, Faraone SV, Asherson P, Kuntsi J. Striatal sensitivity during reward processing in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(7):722-732.e9.

69. Toplak ME, Tannock R. Time perception: modality and duration effects in attention-deficit/hyperactivity disorder (ADHD). J Abnorm Child Psychol. 2005;33(5):639-54.

70. Tomblin JB, Mueller KL. How can the comorbidity with ADHD aid understanding of language and speech disorders? Top Lang Disord. 2012;32(3):198-206.

71. Fliers EA, Franke B, Lambregts-Rommelse NN, Altink ME, Buschgens CJ, Nijhuis-van der Sanden MW, et al. Undertreatment of motor problems in children with ADHD. Child Adolesc Ment Health. 2009;15(2):85-90.

72. Kuntsi J, Klein C. Intraindividual variability in ADHD and its implications for research of causal links. Curr Top Behav Neurosci. 2012;9:67-91.

73. Tye C, Johnson KA, Kelly SP, Asherson P, Kuntsi J, Ashwood KL, et al. Response time variability under slow and fast-incentive conditions in children with ASD, ADHD and ASD+ADHD. J Child Psychol Psychiatry. 2016;57(12):1414-1423.

74. Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology. 2004;18(3):543-55.

75. Marquand AF, Wolfers T, Mennes M, Buitelaar J, Beckmann CF. Beyond lumping and splitting: a review of computational approaches for stratifying psychiatric disorders. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1(5):433-447.

76. van Hulst BM, de Zeeuw P, Durston S. Distinct neuropsychological profiles within ADHD: a latent class analysis of cognitive control, reward sensitivity and timing. Psychol Med. 2015;45(4):735-45.

77. Mostert JC, Hoogman M, Onnink AMH, van Rooij D, von Rhein D, van Hulzen KJE, et al. Similar Subgroups Based on Cognitive Performance Parse Heterogeneity in Adults With ADHD and Healthy Controls. J Atten Disord. 2018;22(3):281-292.

78. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA. 2002;288(14):1740-8.

79. Greven CU, Bralten J, Mennes M, O'Dwyer L, van Hulzen KJ, Rommelse N, et al. Developmentally stable whole-brain volume reductions and developmentally sensitive caudate and putamen volume alterations in those with attention-deficit/hyperactivity disorder and their unaffected siblings. JAMA Psychiatry. 2015;72(5):490-9.

80. Hoogman M, Rijpkema M, Janss L, Brunner H, Fernandez G, Buitelaar J, et al. Current self-reported symptoms of attention deficit/hyperactivity disorder are associated with total brain volume in healthy adults. PLoS One. 2012;7(2):e31273.

81. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017;4(4):310-319.

82. Rubia K. Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. Proc Natl Acad Sci U S A. 2007;104(50):19663-4.

83. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007;104(49):19649-54.

84. Shaw P, Malek M, Watson B, Sharp W, Evans A, Greenstein D. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012;72(3):191-7.

85. Almeida LG, Ricardo-Garcell J, Prado H, Barajas L, Fernández-Bouzas A, Avila D, et al. Reduced right frontal cortical thickness in children, adolescents and adults with ADHD and its correlation to clinical variables: a cross-sectional study. J Psychiatr Res. 2010;44(16):1214-23.

86. Almeida Montes LG, Prado Alcántara H, Martínez García RB, De La Torre LB, Avila Acosta D, Duarte MG. et al. Brain cortical thickness in ADHD: age, sex, and clinical correlations. J Atten Disord. 2013;17(8):641-54.

87. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed. 2006;8(4):4.

88. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand. 2012;125(2):114-26.

89. Shaw P, De Rossi P, Watson B, Wharton A, Greenstein D, Raznahan A, et al. Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(7):780-9.e11.

90. Bralten J, Greven CU, Franke B, Mennes M, Zwiers MP, Rommelse NN, et al. Voxel-based morphometry analysis reveals frontal brain differences in participants with ADHD and their unaffected siblings. J Psychiatry Neurosci. 2016;41(4):272-9.

91. van Ewijk H, Heslenfeld DJ, Zwiers MP, Faraone SV, Luman M, Hartman CA, et al. Different mechanisms of white matter abnormalities in attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. J Am Acad Child Adolesc Psychiatry. 2014;53(7):790-9.e3.

92. Chen L, Hu X, Ouyang L, He N, Liao Y, Liu Q, et al. A systematic review and meta-analysis of tract-based spatial statistics studies regarding attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev. 2016;68:838-847.

93. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001;98(2):676-82.

94. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169(10):1038-55.

95. Fassbender C, Schweitzer JB. Is there evidence for neural compensation in attention deficit hyperactivity disorder? A review of the functional neuroimaging literature. Clin Psychol Rev. 2006;26(4):445-65.

96. Schulz KP, Newcorn JH, Fan J, Tang CY, Halperin JM. Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. J Am Acad Child Adolesc Psychiatry. 2005;44(1):47-54.

97. Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex. 2007;17(6):1364-75.

98. Mattfeld AT, Gabrieli JD, Biederman J, Spencer T, Brown A, Kotte A, et al. Brain differences between persistent and remitted attention deficit hyperactivity disorder. Brain. 2014;137(Pt 9):2423-8.

99. Francx W, Zwiers MP, Mennes M, Oosterlaan J, Heslenfeld D, Hoekstra PJ, et al. White matter microstructure and developmental improvement of hyperactive/impulsive symptoms in attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry. 2015;56(12):1289-97.

100. Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev. 2014;24(1):3-15.

101. Johnstone SJ, Barry RJ, Clarke AR. Ten years on: a follow-up review of ERP research in attention-deficit/hyperactivity disorder. Clin Neurophysiol. 2013;124(4):644-57.

102. Tye C, Rijsdijk F, Greven CU, Kuntsi J, Asherson P, McLoughlin G. Shared genetic influences on ADHD symptoms and very low-frequency EEG activity: a twin study. J Child Psychol Psychiatry. 2012;53(6):706-15.

103. Arns M, Conners CK, Kraemer HC. A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. J Atten Disord. 2013;17(5):374-83.

104. Clarke AR, Barry RJ, Dupuy FE, McCarthy R, Selikowitz M, Heaven PC. Childhood EEG as a predictor of adult attention-deficit/hyperactivity disorder. Clin Neurophysiol. 2011;122(1):73-80.

105. Cheung CH, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, et al. Cognitive and neurophysiological markers of ADHD persistence and remission. Br J Psychiatry. 2016;208(6):548-55.

106. Doehnert M, Brandeis D, Schneider G, Drechsler R, Steinhausen HC. A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry. 2013;54(3):260-70.

107. Michelini G, Kitsune GL, Cheung CH, Brandeis D, Banaschewski T, Asherson P, et al. ADHD remission is linked to better neurophysiological error detection and attention-vigilance processes. Biol Psychiatry. 2016;80(12):923-932.

108. Heinrichs-Graham E, Franzen JD, Knott NL, White ML, Wetzel MW, Wilson TW. Pharmaco-MEG evidence for attention related hyper-connectivity between auditory and prefrontal cortices in ADHD. Psychiatry Res. 2014;221(3):240-5.

109. Wolfers T, Buitelaar JK, Beckmann CF, Franke B, Marquand AF. From estimating activation locality to predicting disorder: A review of pattern recognition for neuroimaging-based psychiatric diagnostics. Neurosci Biobehav Rev. 2015;57:328-49.

110. American Psychiatric Association. Manual dianóstico e estatístico de transtornos mentais: DSM-5. 5. ed. Porto Alegre: Artmed, 2014.

111. Organização Panamericana da Saúde. CID-10: classificação estatística internacional de doenças e problemas relacionados à saúde. 8. ed. São Paulo: Edusp, 2008.

112. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry. 2012;17(12):1174-9.

113. Wium-Andersen IK, Vinberg M, Kessing LV, McIntyre RS. Personalized medicine in psychiatry. Nord J Psychiatry. 2017;71(1):12-19.

114. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167(7):748-51.

3

ADHD ASSESSMENT ACROSS THE LIFE SPAN

Luis Augusto **Rohde**
David **Coghill**
Philip **Asherson**
Tobias **Banaschewski**

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5% of children and adolescents worldwide.[1] Although symptoms decline with age (up to 65% of affected individuals experience a partial remission), only 15% of children with ADHD show full remission both in terms of symptoms and functional impairment in early adulthood, characterizing ADHD as a chronic disorder.[2] Investigations in adults suggest a prevalence rate around 2.5 to 3%.[3,4]

ADHD is highly burdensome, and carries with it significant functional impairments, such as social and family life problems, low educational attainment and school dropout, low self-esteem, impairment in emotional development, occupational problems, and divorce.[2,4] Furthermore, ADHD is associated with a range of other psychiatric comorbidities, especially oppositional defiant disorder, anxiety disorder and learning disabilities in children and substance use disorders, anxiety and mood disorders in adulthood. It also predicts a diversity of negative long-term outcomes, such as future physical injuries, low academic achievement, traffic accidents, premature pregnancy, sexual transmitted diseases, and criminal behavior, amongst others.[2,4]

ASSESSMENT AND DIAGNOSTIC CLASSIFICATION SYSTEMS

The diagnosis of ADHD is established clinically, based on criteria defined by diagnostic classification systems such as DSM and ICD. Core features of the disorder are developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity. Probably, ICD-11[5] will abandon the operational criteria approach relying only in a prototype presentation (https://icd.who.int/).

A synthesis of the operational criteria of the DSM-5[6] for ADHD can be found in Box 3.1. The structure of the operational criteria can be divided in a preamble and the five criteria: symptom list, age-of-onset, pervasiveness, impairment and situations that might exclude the diagnosis.

THE PREAMBLE

The key elements in the preamble are: (a) persistent pattern of symptoms; (b) symptoms interfere with or reduce the quality of functioning or development; (c) symptoms inconsistent with developmental stage and not merely a manifestation of intellectual disabilities or ODD symptoms; (d) a lower symptom threshold for diagnosing ADHD in adults (addressed in the next sub-section – list of symptoms).

The DSM-5 requires a persistent pattern of symptoms to make an ADHD diagnosis. A specific duration of at least 6 months is suggested. This is not an evidence-based criterion. We are not aware of studies addressing the validity of this criterion (i.e. whether the threshold to define persistence could equally be 1, 3, 6, 12 months or more). However, the rationale of the criterion is based on research data suggesting a stable biological vulnerability for the disorder, and based on the recognition that ADHD cardinal symptoms are non-specific and may arise as a short-term response to environmental stressors like family problems or higher school demands. Clinicians should therefore carefully discuss each symptom with patients and their families, considering only those that are frequently present in their daily lives, and have a stable trait-like quality, as positive. This is the reason that different DSM versions have always kept the word '*often*' in front of each one of the 18 symptoms. A failure to set a common understanding with the family on a culturally acceptable definition of what is considered to be frequent makes it impossible to determine the persistent pattern of symptoms requested in the DSM-5.[7]

The symptoms must be inconsistent with developmental stage of the individual under assessment. Previous research clearly identifies ADHD as a dimensional disorder. Thus, clinicians are faced with the difficult task of defining the boundaries of what a typical behavior is for an individual and when a pathological threshold

Box 3.1
SYNTHESIS OF DSM-5 CRITERIA FOR ADHD

A. Either (1) or (2):
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions.
   1. Inattention: Six (or more) symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      For older adolescents and adults (age 17 and older), at least five symptoms are required.
   2. Hyperactivity and impulsivity: Six (or more) symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      For older adolescents and adults (age 17 and older), at least five symptoms are required.
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings.
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder.

was transposed. In this scenario, extensive knowledge on normal human development is crucial for diagnosing ADHD. For example, a lack of knowledge on the acceptable levels (i.e. normal range) of hyperactivity and impulsivity of a preschooler might bias the assessment towards a false positive diagnosis.[7]

DSM-5 has also introduced a new requirement in the preamble. Symptoms should not be best accounted by intellectual disabilities or ODD symptoms. It is clinically important to investigate, for instance, whether a persistent difficulty following instructions is due to inattention or if it is derived by either oppositionality or difficulty in understanding rules owing to a certain level of intellectual disability.

CRITERION A – LIST OF SYMPTOMS

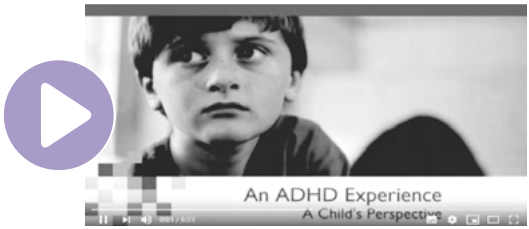
The list of ADHD symptoms in DSM-5 is organized in two dimensions – inattentive and hyperactive/impulsive domains based on previous literature that supported a bidimensional construct for the disorder.[2,7] Nine symptoms are described for

each dimension (see Box 3.2). The list of nine inattentive and nine hyperactive/impulsive symptoms were derived from DSM-IV ADHD field trials. It is important to note that these field trials included predominantly school-age children only from the US. Thus, there is a certain level of uncertainty about its diagnostic performance to capture the latent construct of the disorder in different cultures and in other age ranges (e.g. preschoolers and adults). Indeed, this is a major criticism of the DSM classification, i.e. the lack of a developmentally sensitive perspective. There are convergent findings suggesting different trajectories for inattentive and hyperactive/impulsive symptoms both in population and in clinical samples along the life cycle.

In this regard, DSM-5, for the first time, proposed a different symptomatic threshold for the diagnosis of ADHD in adults. While the threshold was kept at six or more symptoms in one or both dimensions for children, as in DSM-IV, a lower threshold (five symptoms or more) was accepted for adults. This decision reflects previous research demonstrating that adults present significant impairment even with a lower number of symptoms.[4,7] Again, the performance of these different symptomatic thresholds in different cultures was not well tested.

Box 3.2
ADHD SYMPTOMS

1. List of Inattentive Symptoms
   a. Often fails to give close attention to details or makes careless mistakes.
   b. Often has difficulty sustaining attention in tasks or play activities.
   c. Often does not seem to listen when spoken to directly.
   d. Often does not follow through on instructions and fails to finish tasks.
   e. Often has difficulty organizing tasks and activities.
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
   g. Often loses things necessary for tasks or activities.
   h. Is often easily distracted by extraneous stimuli.
   i. Is often forgetful in daily activities.
2. List of Hyperactive/Impulsive Symptoms
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected.
   c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor".
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed.
   h. Often has difficulty waiting his or her turn.
   i. Often interrupts or intrudes on others.



Link in this

https://www.youtube.com/watch?v=w4t4JFKDD6s

CRITERION B – AGE-OF-ONSET

ADHD has been traditionally conceptualized as a neurodevelopmental disorder. Thus, it is not surprising that age of onset in early childhood emerged as a key element in the definitional criteria for the disorder. In the past four decades, experts behind diagnostic manuals have struggled with the lack of evidence to define an accurate threshold for chronological age beyond which symptoms should no longer be considered part of the ADHD syndrome.[2,4,7] Based solely on clinical wisdom, DSM-III[8] introduced ADHD criterion B, which required symptoms to be present before the age of 7 years, and DSM-IV-TR[9] added that impairment must also be present by this same age.

A number of studies have now challenged the utility and validity of this criterion B. The DSM-5 scientific committee decided to change the criterion to require several symptoms before age 12, based on evidence that this threshold would capture almost every case presented in childhood, without raising significantly the prevalence rate. However, recent evidence suggests that the increase in ADHD prevalence rates might not be as insignificant as previously thought with this modification in age-of-onset criterion.[10]

It is important to note that DSM-5 specifies that the age-of-onset criterion refers to symptoms and not necessarily impairment, as was the case for DSM-IV. The reason for this is that ADHD is a highly comorbid disorder in clinical settings and disentangling the source of impairment and its age-of-onset is at best difficult and frequently unfeasible. Impairment may arise later in life when, for example, parental scaffolding is no longer available. More recently, several studies with population samples challenged the threshold for age-of-onset at 12 years of age suggesting the possibility of substantial number of cases with late-onset ADHD after 12 years of age. This is still a controversial area where more research is clearly needed.[11]

CRITERION C – PERVASIVENESS

DSM-5 requires that several ADHD symptoms must be present in at least two different environments. The rationale behind this criterion is to avoid diagnosis in cases where symptoms are manifested in just one environment due to triggers, which are specific to this environment (e.g. ADHD symptoms just at home because of severe family conflicts; or ADHD symptoms just at school owing to excessive demands from the school). However, ADHD is one of the few DSM-5 disorders that require symptoms in multiple settings, and few studies have tested the validity of this criterion.

As pointed out by Willcutt,[12] the presence of symptoms in multiple settings is typically based on ratings from two different adults. Because correlations between raters are low-to-medium in magnitude for ADHD symptoms, a lack of agreement on presence of symptoms may simply reflect measurement error and not necessarily a true absence of symptoms across settings. Furthermore, some children may display impairment in only one setting at one point in time, but in multiple settings later in development when facing more challenging academic and social demands. Nonetheless, it remains likely that some children who meet symptom criteria for ADHD may exhibit significant impairment that is truly restricted to one setting. This pattern may be especially common in groups with predominantly inattentive ADHD presentation because this symptomatic presentation is associated most strongly with difficulties in academic domains that may be most evident at school. Although the reduction of false positive diagnoses is a goal to be pursued, it is not clear why intervention would not be provided to a child who meets all other criteria for ADHD, but significant symptoms are presented in only one setting.

CRITERION D – IMPAIRMENT

There was a strong debate during the development of DSM-5 around the validity of including impairment as a criterion inside the nosological definition of disorders. In the rest of medicine impairment is more frequently embedded in prognosis than in the core definition of disorders. In addition, ADHD is a highly comorbid disorder in clinical and population samples. This profile poses a special difficulty for clinicians in determining if impairment comes from ADHD or its frequent comorbid conditions.[7]

Despite this debate, DSM-5 kept criterion D emphasizing the need for clear interference from the symptoms in functioning. Indeed, since ADHD is better conceptualized as a dimensional disorder (i.e. symptoms reflect a dimensional trait in

the population), failure to incorporate interference of symptoms in functioning as part of the diagnostic criteria for the disorder results in a substantial increase in prevalence rates.

CRITERION E – EXCLUSIONARY CRITERIA

Although ADHD continues to be excluded when inattentive or hyperactive/impulsive symptoms only occur during the course of a disorder with higher diagnostic hierarchy (e.g. psychosis) or when these symptoms are better explained by a different disorder (e.g. mood, anxiety, or substance use disorders), the exclusion of the diagnosis in the presence of autism spectrum disorders (ASDs) was removed.

The literature does not provide any evidence that supports exclusion of an ADHD diagnosis in the presence of ASD. In fact, substantial evidence has shown that ADHD and autism frequently, but not always, coexist, and that the presence of ADHD symptoms in patients with ASD confers distinct clinical correlates from those with pure ASD. Also, stimulants may successfully treat ADHD symptoms in patients with ASD, reassuring the clinical pertinence of the independent diagnosis of these disorders.[7]

A final issue regarding ADHD diagnosis in DSM-5 is the characterization of the current presentation based on the distribution of inattentive and/or hyperactive/impulsive symptoms. The three possible presentations are:

- predominantly inattentive
- predominantly hyperactive/impulsive
- combined

Willcutt et al.[13] conducted an extensive meta-analysis assessing the validity of ADHD subtypes. The absence of major neuropsychological differences between the two most frequent types (predominantly inattentive and combined types) and the lack of developmental stability of ADHD types supported the DSM-5 decision to change the nomenclature from ADHD types to ADHD current presentation. While the word ‘presentation’ denotes the status of the present clinical assessment; ‘types’ denotes a more stable condition. The current ADHD presentation might have some nosological implications. It might depend on the nature of the sample assessed (e.g., inattentive presentation is more common in non-referred samples while combined presentation is more frequent in clinical samples of children), on gender (e.g., inattentive presentation is more common in females) and on developmental stage (see below).[2]

CLINICAL ASSESSMENT ACCORDING TO DEVELOPMENTAL STAGE

The developmental aspect of ADHD must be taken into account when characterizing clinical presentation.

The validity of ADHD among preschoolers has been an area of particular controversy in the literature. Although there is increasing evidence that ADHD constitutes a valid diagnosis even before the age of 6, there are several challenges in making a diagnosis during this developmental period. For example, the difficulties associated with making observations across multiple settings for children not attending preschool – and subsequent lack of information about pervasiveness. In addition, hyperactivity and impulsivity are much more prominent at this stage and inattention might not be so evident due to there being less environmental demands on the child. Thus, it is not surprising that ADHD predominantly hyperactive/impulsive presentation is the most frequent presentation in preschoolers. Several studies have however shown that currently available criteria reliably identify ADHD in children as young as 3 years old and that these individuals have clinically significant impairment across all relationships and settings.[14]

While the combination of inattentive and hyperactive/impulsive symptoms is the most common presentation in clinical samples during school age, inattentive symptoms are more prominent in non-referred samples. Whether this represents an effect of sample origin or gender (e.g., more boys are usually brought to assessment and they present more combined symptoms while girls present more pronounced inattentive symptoms) is still controversial. Another important aspect is that ADHD in school age children is associated with very high rates of comorbid disorders including learning disorders. Up to 70% of the cases in clinical samples present with one or more comorbid conditions.[2,14] When assessing ADHD in school age children, it is important to remember that ADHD symptoms might not be seen during the appointment, since the child is in a very artificial environment with few people in the room, in a situation where performance anxiety might mean that he/she does not portray his/her typical behavior. In addition, school age children with ADHD might focus well during one-to-one activities, especially when highly motivated or the situation is either novel or associated with frequent rewards. Thus, parents frequently report that they doubt the diagnosis since their son/daughter can stay for hours playing videogame or in social media. The explanation of this apparent paradox to families is essential in the process of ADHD psychoeducation (see chapter on “Talking with families”).

Research has also documented the validity of ADHD diagnosis among older adolescents and young adults. Despite the observed age-dependent decline in ADHD symptoms, a substantial proportion of individuals continue to present cli-

nically relevant symptoms as they enter into adulthood. Reduction of hyperactive/ impulsive symptoms is more significant than that of inattentive symptoms (remission in 70 vs. 40% of individuals, respectively).[4] Thus, the most frequent presentation found in adults is ADHD with predominantly inattentive symptoms. Among the challenges in characterizing ADHD in older individuals, there is the failure of the symptom descriptions (especially the hyperactivity/ impulsivity symptoms) to capture developmental specific adult focused clinical manifestations. There are also difficulties associated with assessing retrospectively the presence of symptoms in childhood.[15] In addition, the clinical picture in adults might be also characterized by symptoms related to executive dysfunctions and emotional impulsivity. Since adults might present substantial impairment even with lower number of symptoms in any of the two dimensions (inattention and/or hyperactivity/impulsivity), a lower symptom threshold for the diagnosis in adults was proposed by the DSM-5. Considering the lack of reliability for assessing ADHD childhood symptoms retrospectively in adults and recent findings suggesting a considerable prevalence of late-onset cases among adult individuals with ADHD in population samples,[7] clinicians should put most emphasis when assessing adults for ADHD in a careful characterization of the symptom profile, sustained chronic course and level of impairment associated with ADHD symptoms, and in ruling out other conditions that better explain current inattentive, executive deficit and impulsivity symptoms.

It is also important to recognize that core ADHD symptoms might have a different "dressing" in adulthood. Thus, hyperactivity in adults often manifests itself as inner restlessness or agitation, a sense of continuous restlessness, not being able to relax properly or needing alcohol or drugs to relax or to sleep. Hyperactivity can in the short term be constantly compensated by frequent sporting activities, or constantly finding something to do. Hyperactivity sometimes also manifests itself in excessive talking, an inability to stop talking or carrying out activities, or rattling on and on. ADHD is also described as 'the brake is off ', which is recognized by a lot of patients with hyperactivity.[16]

It is not uncommon in adulthood for attention problems and impulsivity to be more prominent than hyperactivity. A very prominent symptom is feeling quickly impatient or irritable when waiting in queues or traffic jams. Impulsive behavior might manifest as acting without thinking or in blurting things out, spending too much money or spending it too quickly, carrying out plans immediately, resigning from jobs in a flurry, starting relationships quickly, and not being able to postpone the gratification of needs. These behaviors often have consequences for relationships with other people and with employers, as well as for a person's financial situation. Impulsive binges also frequently occur, often to combat restlessness or because of an inability to postpone the gratification of needs. Binge eating may explain why adults with ADHD often suffer from excess weight.[16]

Closely related to impulsivity is the phenomenon of 'sensation- seeking', 'novelty-seeking' or seeking out excitement. This phenomenon manifests itself in the

need for and the seeking out of, new stimuli, variety, excitement, and change. Concrete examples are driving too fast, taking risks in traffic, taking risks in sexual contacts, creating a lot of arguments, seeking or creating an environment with a lot of excitement and variety, often changing position, job, or partner. It is conceivable that people who need excitement and sensation choose professions that meet this need; for example, journalism, free enterprise, or a job involving a lot of travel.[16]

In ADHD, there is also a form of overconcentration or 'hyperfocus', where the extent to which somebody can be distracted is problematic. This phenomenon occurs above all during activities that the patient finds very interesting, such as using the computer or chatting on the internet. Then they can concentrate for hours on end in a very focused manner without a break. It is possible that it is mainly the dynamic 'rewarding' environment of the internet or the games that holds their attention and stimulates hyperfocus. ADHD can thus go hand in hand with both attention deficit and periodic overconcentration, and could therefore be viewed as an attention dysregulation (rather than deficit) disorder. With ADHD there is an inability to focus and to divide attention at the right moment. The problem is not that a patient with ADHD cannot concentrate but that they cannot deploy their ability to concentrate at the moment that it is needed.[16]

THE ROLE OF INFORMATION SOURCES

Extensive data document low levels of agreement between parents and teachers on ADHD symptomatology in children,[2] and divergent data exist on the agreement between self-report and co-informant report on ADHD symptoms in adults.[4] However, no guidance has been provided in any version of the DSM on how to combine data from different information sources during the diagnostic process, besides the more general suggestion in the text (not in the criteria) that assessment should be as comprehensive as possible, including data from teachers whenever possible.[14]

Discrepancies between the different sources and accounts of the child are commonplace. These may occur because the child behaves differently in different settings or is confronted with different impairments in different places, but they can also arise because different people with different views and perspectives and different relationships with the child have provided their descriptions.[14] While research cannot yet inform us on how to combine data from different information sources and how to weight different perspectives, clinical wisdom indicates that:

A the best estimate diagnostic approach should rely on a comprehensive assessment of all available sources;
B some reporters might be in a better position than others to detect some types of symptoms.

Elementary school teachers might have the advantage of knowing well normative behavior for the age-group, and to spend lots of time with children during activities that they are not strongly motivated. Thus, they might be in a good position to detect both hyperactive/impulsive and inattentive symptoms. On the other hand, middle and high school teachers might spend few hours per week with students and might not detect well symptoms that do not disturb classes like inattentive and executive functioning symptoms.

Regardless of their ability to accurately describe their symptoms, it is essential to fully include a child or young person in the assessment process. At the very least it is essential to ascertain their perspective about what it is like to be them. Important aspects include:

- How do they feel their symptoms impact on their lives?
- How is their self-esteem and quality of life?
- How do they feel about their sibling and peer relationships and relationships with parents and other key adults?

ADHD AS AN HETEROGENEOUS DISORDER

It is noteworthy that children with ADHD vary significantly from each other. ADHD, as other psychiatric disorders, is a highly heterogeneous disorder in respect to various aspects, such as symptom profiles, neuropsychological profiles, neurobiological and genetic features.

One aspect of ADHD heterogeneity is related to its clinical presentation. Diagnosis of mental disorders, according to diagnostic manuals, may be assigned from different combinations of criteria listed under the same disorder. In the case of ADHD, six symptoms in either of the two ADHD domains are required for an individual to meet diagnostic criteria during childhood or adolescence. Because the criteria are subdivided into symptom domains (inattention and hyperactivity/impulsivity), it is possible that two individuals diagnosed with ADHD do not have the same group of symptoms. The classification of ADHD diagnosis into current presentation (predominantly inattentive, hyperactive-impulsive, and combined types) is an attempt to deal with the heterogeneity of clinical presentations. Even so, two individuals with the same ADHD current presentation might be similar in as few as three symptoms. This indicates the limited ability of the current clinical diagnostic criteria in defining homogeneous populations, which may be one reason why the field has not yet been successful in finding biological markers of ADHD.[14]

Another facet of ADHD heterogeneity is neuropsychological heterogeneity. ADHD has been shown to be associated with various neuropsychological impairments. Studies have found that, on average, individuals with ADHD, compared to controls, have worse performance in various functions, including: inhibition,

working memory, memory span, processing speed, arousal, temporal information processing, response variability; and have also impairments in motivational processes.[2,4] However, the findings of neuropsychological impairments are only of moderate effect sizes, not all individuals with the disorder have these dysfunctions, and different individuals have a unique profile of such deficits. Coghill et al.[17] evaluated six neuropsychological domains: inhibitory control, memory, delay aversion, decision making, temporal processing and response variability and found that compared to healthy children ADHD children performed poorly at the group level on all domains. However only 75% of these individuals displayed some deficit, none had a deficit on all domains and only 10% had deficits in 4 or more domains. These results suggest that these domains are relatively independent of each other and support the presence of multiple pathways to ADHD. These findings also support the view that ADHD is a heterogeneous condition at the level of neuropsychological functioning, as well as clinical symptoms and impairments, likely reflecting heterogeneity in the aetiology of ADHD."

THE RELEVANCE OF COMORBIDITIES

ADHD is highly comorbid with other psychiatric disorders (70-80% of affected individuals have at least one other disorder). The comorbid profile varies along the lifecycle.[18] The following are among the most common ADHD comorbid conditions in children and they should be assessed routinely: oppositional defiant disorders (ODD), learning disorders, developmental motor coordination disorder, language disorders, intellectual disabilities, sleep disorders, depressive and anxiety disorders, tic disorders, enuresis, conduct disorder and autism spectrum disorders. Although the exact rate of comorbidity with each one of these diagnoses varies considerably in different studies depending on origin of the sample (e.g., referred or non-referred), a meta-analysis of 21 mixed-gender population studies found that children with ADHD were over 10 times more likely to have CD or ODD, whereas they were over 5 times more likely to have depression and 3 times more likely to have an anxiety disorder compared with peers without ADHD. A meta-analysis assessed comorbidity specifically in female children. Main findings suggest that girls with ADHD frequently exhibit comorbid externalizing and internalizing disorders, as boys. In addition, the pattern of comorbidity did not seem to be very different between girls and boys.[19]

In adolescents and adults, other comorbid conditions are also clinically relevant, including: eating disorders, substance use disorders (SUDs), bipolar disorders, and personality disorders. This comorbidity profile complicates diagnostic assessment and differential diagnosis.[16,20,21]

Recent literature has documented that ADHD is also highly comorbid with clinical disorders such as obesity, asthma and atopic conditions, epilepsy, and dia-

betes. The exact mechanisms explaining these comorbid profiles is not yet understood but might be related to general and chronic immune and inflammatory dysregulations.[22]

Clinically, some issues need to be highlighted:

1. the comorbidity with ODD is by far the most common in samples of children and adolescents. Thus, clinical investigation of ODD is mandatory when facing a positive ADHD diagnosis;
2. the presence of some comorbidities like conduct disorder increases the chance of other sequential comorbidities like SUDs. Thus, clinicians assessing adolescents with ADHD comorbid with conduct disorder should give special attention to the assessment of SUDs;
3. some comorbid disorders might reflect a co-occurring diagnosis alongside ADHD in some situations (e.g., SUDs, Generalized Anxiety Disorder – GAD, Depression), or a differential diagnosis in others (e.g., when an adult with Recurrent Major Depression only presents significant inattentive symptoms and executive functioning deficits during the active phase of the mood disorder). Thus, clinicians should assess carefully if the symptoms of the associated disorder explain the ADHD phenotype or co-occur and interact with the ADHD phenotype, making the final phenotype even more complex. In these situations, it is important to ask patients if the main ADHD symptoms occur only in the presence of the symptoms of the co-occurring disorder, or independently of them. For example, it might be clinically relevant in a patient with ADHD and GAD symptoms to try to characterize if the difficulty paying attention in class or at work is related only to worries and dysfunctional thoughts associated to performance or inattention also occurs in moments without anxiety and tension being related to neutral or agreeable thoughts.

ANCILLARY DIAGNOSTIC APPROACHES

As for all other psychiatric conditions, there is no ancillary test or biomarkers with sufficient positive and negative predictive power for the diagnosis of ADHD.[2,4,21]

Some tests can be relevant and valuable to depict an individual's cognitive strengths and weaknesses, but these do not need to be performed routinely. In cases where there are questions about a young person's intellectual impairment, potential learning disorders, or severe executive functioning deficits, additional neuropsychological testing may be warranted. Either a full intelligence test or – when time and resources are scarce – a shortened version should be applied when there are questions about learning progress or classroom adjustment.[18]

There is no evidence that neuroimaging exams (e.g. MRI, SPECT, PET scans) or EEGs should be part of the routine clinical assessment of ADHD, although they might be useful in very specific cases for differential diagnosis. Again, ADHD, as all other mental disorders, is a disorder relying exclusively in clinical assessment.[2,4]

It is appropriate and helpful for clinicians to be trained in the application and interpretation of commonly used scales for ADHD. Although there are numerous different instruments, we give preferences for those that are open-access. For children and adolescents, one option is the SNAP (Swanson[23] – version 4) – IV scale. Although there are some controversies about its psychometric properties in population samples, this scale is helpful for clinicians in:

A initial screening of ADHD symptoms;
B getting information from teachers on ADHD symptoms when a direct contact is not feasible;
C monitoring trajectory of symptoms along the time or during treatment (see Figure 3.1). When using this kind of scale, it is always important to check for adequate and valid translations in your language.

For adults, there is the Adult ADHD Self Report Scale (ASRS) that has two versions: a screener version developed by the World Health Organization (WHO) with six items that is suitable for primary care settings and for a quick screening of ADHD.[24] This version is has been translated in various languages. There is also a long version with the 18 DSM symptoms, probably more useful for specialized settings.[25] Both versions use wording more adequate for adults for assessing symptoms. Recently, a short version adapted for DSM-5 was made available.[26]

A valuable instrument for assessing the diagnosis of ADHD in adults is the DIVA 2.0. This is a semi-structured interview based on DSM-IV-TR that can be downloaded in many languages.[27]

Finally, several apps are available that might help clinicians in assessing and monitoring ADHD.[28] In English, one of the most downloaded is the ADHD test (available at Google Play and Apple Store). In Portuguese, there is the FOCUS TDAH[29] that has both the SNAP-IV and ASRS scales included inside the app and a platform for psycho-education. Although these instruments are open-access, it is important to highlight that none of them has yet its real clinical utility confirmed in well-designed trials.

DIFFERENTIAL DIAGNOSES

A general physical examination is mandatory to exclude clinical conditions that might be causing the inattentive and/or hyperactive/impulsive symptoms. In this

Patient/Client Name: _____

Date of birth: _____

Grade: _____ Type of class: _____

Completed by: _____

Physician Name: _____

Gender: _____

Class size: _____

Date: _____

For each item, check the column which best describes this child/adolescent:

	Not at all	Just a little	Quite a bit	Very much
1. Often fails to give close attention to details or makes careless mistakes in schoolwork or tasks				
2. Often has difficulty sustaining attention in tasks or play activities				
3. Often does not seem to listen when spoken to directly				
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties				
5. Often has difficulty organizing tasks and activities				
6. Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort				
7. Often loses things necessary for activities (e.g., toys, school assignments, pencils or books)				
8. Often is distracted by extraneous stimuli				
9. Often is forgetful in daily activities				
10. Often fidgets with hands or feet or squirms in seat				
11. Often leaves seat in classroom or in other situations in which remaining seated is expected				
12. Often runs about or climbs excessively in situations in which it is inappropriate				
13. Often has difficulty playing or engaging in leisure activities quietly				
14. Often is "on the go" or often acts as if "driven by a motor"				
15. Often talks excessively				
16. Often blurts out answers before questions have been completed				
17. Often has difficulty awaiting turn				
18. Often interrupts or intrudes on others (e.g., butts into conversations/games				
19. Often loses temper				
20. Often argues with adults				
21. Often actively defies or refuses adult requests or rules				
22. Often deliberately does things that annoy other people				
23. Often blames others for his or her mistakes or misbehaviour				
24. Often is touchy or easily annoyed by others				
25. Often is angry and resentful				
26. Often is spiteful or vindictive				

Figure 3.1
SNAP-IV scale.

sense, auditive and visual assessment should be initial steps of any assessment for ADHD. In addition, the sleep pattern should also be investigated. Although sleep problems and disorders are frequent associated features or comorbid conditions in ADHD, sometimes an inadequate sleep quality might itself generate pronounced inattentive symptoms during the day. Other medical conditions like hyperthyroidism should also be excluded. Baseline measures for growth (height, weight) and cardiovascular parameters should be taken, especially when medication treatment is being considered. Referral for genetic examination is recommended if there is a clear developmental delay and/or in case a suggestive phenotype is identified (e.g., fragile X syndrome).

As mentioned above, almost all mental disorders that can co-occur with ADHD need also to be considered in the differential diagnosis, since they can also result in inattentive and/or hyperactive/ impulsive symptoms. In the process of conducting a careful differential diagnosis, some clinical tips might be relevant:

A Consider the age of onset of every disorder – ADHD starts in childhood or adolescence, while most other disorders start later. Exceptions might be ODD and sleep problems.

B Assess the trajectory of symptoms – although ADHD symptoms might suffer the impact of the demands of environment not being always flat along development, the disorder has a more chronic trait-like course. Thus, strong swings of symptoms might suggest other disorders like bipolar disorder where, besides the core manic symptoms, hyperactivity, impulsivity and irritability are episodic. The same applies for ADHD symptoms only associated with depressive symptoms during a major depressive episode.

C Disentangle if the ADHD symptoms are not only intrinsically related to symptoms of another mental disorder (e.g., inattention only as a consequence of dysfunctional thoughts/rumination related to performance as in GAD, or mental rituals of counting as in OCD; inattention and executive deficits following abuse or dependence of marijuana without any previous history of ADHD symptoms).

SUMMARIZING THE FLOW OF THE ASSESSMENT PROCEDURES

In essence, as ADHD is a clinical diagnosis, the assessment will rely in a careful standard clinical interview including all its elements (e.g., chief complaint, current and past symptoms, daily-life, medical history, family history, comprehensive psychopathological review of symptoms, individual strengths). As mentioned above, the final diagnosis will rely on an integrated clinical judgment based on the sum of the information received from different sources from which history was collected (e.g., patient, parents, teachers, significant others) after any disagreements

between sources have been understood and clarified. Questionnaires and direct observations can be helpful to support the assessment and construct a broad view of the strengths and difficulties of the subjects. Information on all domains of daily functioning is crucial to document resilience and impairment. Important areas of potential impact for children include parent–child interactions, parenting practices, and parental stress, as well as school and academic functioning, peer relationships, and engagement in leisure activities.[18] School information can be obtained directly from teachers (by phone, e-mail, written school reports or scales), or through observation in the classroom. In adults, relations with significant others and at functioning at work should also be assessed.[4]

The clinician needs to assess that the child has the requisite number of symptoms, if they are developmentally inappropriate and pervasive across more than one setting, whether they are associated with a significant degree of impairment and cannot be accounted for by an alternative explanation. It is also necessary to consider, and assess for, a wide range of possible comorbid or coexisting disorders, as mentioned above.

Although in primary care this procedure can be easily conducted through a clinical interview, the use of the ADHD module of an interviewer-based semi-structured interview, such as the Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS) or the Development and Wellbeing Assessment (DAWBA) may be helpful in specialized settings. Both have many advantages: The schedules are both available in several languages and can be downloaded from the internet (see K-SADS screener at Advanced Center for Intervention and Services Research [ACISR] for Early Onset Mood and Anxiety Disorders[30] and the various DAWBA translations at Youth in Mind[31]). The K-SADS has several advantages in that it is semi-structured and allows for a normal conversational flow. It also provides probes and examples in everyday life for each symptom, and also operationalizes the word 'often' in most items and reminds the clinician to discriminate ADHD symptoms from those due to other types of psychopathology. On the other hand, the DAWBA is a structured assessment, which means it can be delivered by non-clinicians including graduate students. Thus, it can be used in situations where it is more difficult to access trained clinicians. It can also be administered online (or by telephone) with multiple informants and different versions for different types of informant (parent, teacher, self-report), adding to accessibility in certain situations. Both the K-SADS and the DAWBA offer initial screening questions which if positive are followed up by full sets of questions to assess comorbidities or differential diagnostic problems.[18] The KSADS screener can be available for free. In adults, the use of the DIVA.2 is recommended as an alternative for establishing the diagnosis of ADHD. A comparable diagnostic interview schedule is ACE+.[32] Both DIVA and ACE+ normally require around 1hour to be completed. Current and past ADHD symptoms are investigated in both interviews. Comorbid conditions are not part of the DIVA interview,[16] but a

screen for comorbidities is included in ACE+. A child version of the ACE is also available online in the same site.

It always important to remember that ADHD symptoms will not always be observed during the assessment process, and that an absence of symptoms in the clinic should never be used as a reason to rule out a diagnosis.

An important final part of the assessment process is the sharing of the findings with the patient, the family, and any other important stakeholders. It is helpful to be able to refer back to the phrases and problem definitions that they themselves used at the beginning of the procedure and to link the conclusions to these. When a diagnosis is made, it is important to explain which of the problem behaviors are part of a consistent clinical picture that is a known and valid diagnostic entity and how these fit together. This, of course, also applies to every comorbid diagnosis that is identified. Also to symptoms that may have been judged either not to be clinically significant or to be relevant but not a formal part of the diagnostic criteria, as is often the case for symptoms like irritability, emotional dysregulation and mind wandering; these can be considered to be commonly associated clinical features of ADHD that support the diagnosis. A full psycho-educational discussion of the diagnosis should be provided, such that the patient and parents are equipped with enough knowledge and information about the problems that have been identified and empowered to make use of this in making decisions about and planning treatment and in their daily lives. Any misconceptions and misunderstandings should be identified and carefully reframed (see chapter on talking with families). There should be space for parents to mourn some lost potential of their child and adaptation to new and more adequate expectations, but also room for hope, because ADHD is one of the childhood developmental disorders with the largest possible treatment effects.[18] Indeed, many adults with ADHD have positive, fulfilling and successful lives.

When a child does not fulfill the criteria for a diagnosis of ADHD, an alternative explanation for the problem behavior needs to be offered. This could be another diagnosis or a description of an imbalance between the burden on a child and its overall maturation or capacities. General advice on how to get help to lower the burden or increase coping skills then needs to be offered.[18]

COMPLEMENTARY INFORMATION FROM GUIDELINES

There are several guidelines available in the literature that can help clinicians in the assessment of ADHD. We have presented two of them since they are both open access and were updated in 2018. Although each guideline has its peculiarities, these two do not bring information that is markedly different from the one presented above, but they can be good reference for systematizing an ADHD assessment. The last revision of the National Institute for Health and Care Excel-

lence (NICE) ADHD guideline was launched in March 2018. Besides important rules regarding diagnosis (e.g., do not forget to assess parent mental health when assessing ADHD in children), the NICE guidelines offer relevant information on recognition, identification and how to give support for those affected by the disorder, their families and carers. The NICE guideline can be downloaded at National Institute for Health and Care Excellence.[33] The 4th edition of the Guidelines of the Canadian ADHD Resource Alliance (CADDRA) was launched in February 2018. Whilst this guideline was not as rigorous in its development as that NICE guidelines it contains probably the most comprehensive open access tools for helping clinicians systematize the ADHD assessment procedures. It provides useful flowcharts specific for assessment in each developmental stages (children, adolescent and adults). It also provides a specific chapter addressing comorbidities and differential diagnoses that is helpful for clinicians since it offers some tables with potential overlapping symptoms and not overlapping symptoms of the co-occurring disorders. The CADDRA guidelines can be downloaded at Canadian ADHD Resource Alliance.[34]

Conflicts of interest

Luis Augusto Rohde has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Eli Lilly and Co., Janssen, Medice, Novartis and Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by Dr Rohde have received unrestricted educational and research support from the following pharmaceutical companies: Eli Lilly and Co., Janssen, and Novartis. Dr Rohde has received authorship royalties from Oxford Press and ArtMed and travel grants from Shire to take part in the 2018 APA annual meeting and from Novartis to take part of the 2016 AACAP annual meeting. David Coghill reports grants from The European Union FP7 Programme and Shire; honoraria from Shire, Eli-Lilly, Novartis, and Janssen-Cilag; acted as an advisor to Shire and Lundbeck; and received royalties from Oxford University Press. Prof. Coghill was a member of British Association for Psychopharmacology ADHD, Depression and Bipolar Disorder Guideline groups. Tobias Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, PCM scientific, Shire and Viforpharma. He received conference support or speaker's fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. King's College London received payments for work conducted by Philip Asherson: consultancy for Shire, Eli-Lilly, Novartis, Lundbeck and Medice; educational and/or research awards from Shire, Eli-Lilly, Novartis, Vifor Pharma, GW Pharma, and QbTech; speaker at events sponsored by Shire, Eli-Lilly, Janssen-Cilag, Medice and Novartis.

REFERENCES

1. Polanczyk G, Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942-8.

2. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention--deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.

3. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. Atten Defic Hyperact Disord. 2017;9(1):47-65.

4. Asherson P, Buitelaar J, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. Lancet Psychiatry. 2016;3(6):568-78.

5. World Health Organization. ICD-11: international classification of diseases 11th revision: the global standard for diagnostic health information. Geneva: WHO, 2018. Disponível em: https://icd.who.int/. Acesso em: 23 nov. 2018.

6. American Psychiatry Association. DSM5: diagnostic and statistical manual of mental disorders. 5th ed. Washington: APA, 2013.

7. Rohde LA, Kieling C, Salum GA. Current diagnostic criteria: DSM, ICD and future perspectives. In: Banascheswki T, Coghill D, Zuddas A. Oxford textbook of attention deficit hyperactivity disorder. Oxford: Oxford University Press, 2018.

8. American Psychiatry Association. DSM-III: diagnostic and statistical manual of mental disorders. 3rd ed. Washington: APA, 1985.

9. American Psychiatry Association. DSM-IV-TR: diagnostic and statistical manual of mental disorders. 4th ed. Washington: APA, 2011.

10. Coghill D, Asherson P, Faraone SV, Rohde LA. The age of onset of ADHD. In: Girolamo G, McGorry PD, Sartorius N, editors. The age of onset of mental disorders: etiopathogenetic and treatment. [S. l.]: Springer International Publishing, 2018.

11. Caye A, Sibley MH, Swanson JM, Rohde LA. Late-onset ADHD: understanding the evidence and building theoretical frameworks. Curr Psychiatry Rep. 2017;19(12):106.

12. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012;9(3):490-9.

13. Willcutt EG, Nigg JT, Pennington BF, Solanto MV, Rohde LA, Tannock R, et al. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. J Abnorm Psychol. 2012;121(4):991-1010.

14. Dias TG, Kieling C, Graeff-Martins AS, Moriyama TS, Rohde LA, Polanczyk GV. Developments and challenges in the diagnosis and treatment of ADHD. Braz J Psychiatr. 2013;35 Suppl 1:S40-50.

15. Matte B, Rohde LA, Grevet EH. ADHD in adults: a concept in evolution. Atten Defic Hyperact Disord. 2012;4(2):53-62.

16. Kooij S, Asherson P, Rösler M. ADHD in adults: assessment issues. In: Banascheswki T, Coghill D, Zuddas A. Oxford textbook of attention deficit hyperactivity disorder. Oxford: Oxford University Press, 2018.

17. Coghill DR, Seth S, Matthews K. A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. Psychol Med. 2014;44(9):1989-2001.

18. Danckaerts M, Coghill D. Children and adolescents: assessment in everyday clinical practice. In: Banascheswki T, Coghill D, Zuddas A. Oxford textbook of attention deficit hyperactivity disorder. Oxford: Oxford University, 2018.

19. Tung I, Li JJ, Meza JI, Jezior KL, Kianmahd JS, Hentschel PG, et al. Patterns of comorbidity among girls with ADHD: a meta-analysis. Pediatrics. 2016;138(4). pii: e20160430.

20. Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatry. 2017;17(1):302.

21. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240-50.

22. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. Eur Child Adolesc Psychiatry. 2017;26(9):1093-1103.

23. Swanson JM. SNAP-IV 26-item teacher and parent rating scale. Hamilton: Collaborative Mental Health Care, [s. d.]. [capturado em 27 nov. 2018]. Disponível em: http://www.shared-care.ca/files/Scoring_for_SNAP_IV_Guide_26-item.pdf.

24. National Comorbidity Survey. Adult ADHD self-report scales (ASRS) [Internet]. [Boston]: Harvard Medical School, c2005. [capturado em 27 nov. 2018]. Disponível em: https://www.hcp.med.harvard.edu/ncs/asrs.php.

25. Canadian ADHD Resource Alliance [Internet]. Adult ADHD self-report scale (ASRS-V1.1) symptom checklist. [Toronto]: CADDRA, 2012. [capturado em 27 nov. 2018]. Disponível em: https://www.caddra.ca/cms4/pdfs/caddraGuidelines2011ASRS.pdf.

26. Harvard College. [Internet]. Adult ADHD self-report screening scale for DSM-5 (ASRS-5). [Boston]: Harvard College, 2017. [capturado em 27 nov. 2018]. Disponível em: https://www.hcp.med.harvard.edu/ncs/ftpdir/adhd/ASRS-5_English.pdf.

27. DIVA Foundation: diagnostic interview for ADHD in adults. [Internet]. Home. The Hague: DIVA Foundation, [c2018] [capturado em 27 nov. 2018]. Disponível em: http://www.divacenter.eu/DIVA.aspx.

28. Powell L, Parker J, Robertson N, Harpin V. Attention deficit hyperactivity disorder: is there an app for that? suitability assessment of apps for children and young people with ADHD. JMIR Mhealth Uhealth. 2017;5(10):e145.

29. PRODAH: Programa de Transtonos de Déficit de Atenção/Hiperatividade [Internet]. Focus: aplicativo de suporte ao manejo do TDAH em adultos, crianças e adolescentes. Porto Alegre: UFRGS, [c2018]. [capturado em 27 nov. 2018]. Disponível em: www.focustdah.com.br.

30. Advanced Center for Intervention and Services Research (ACISR) for Early Onset Mood and Anxiety Disorders [Internet]. K-SADS-PL DSM-5. Baltimore: Kennedy Krieger Institute, 2016. [capturado em 27 nov. 2018]. Disponível em: https://www.kennedykrieger.org/sites/default/files/library/documents/faculty/ksads-dsm-5-screener.pdf.

31. Youth in Mind. DAWBA [Internet]: information for researchers and clinicians about the development and well-being assessment. [S. l.]: Youth in Mind, [c2018.]. [capturado em 27 nov. 2018]. Disponível em: http://dawba.info/.

32. Psychology Services Limited. ADHD. [Internet]. [S. l.]: Psychology Services Limited, c2018. [capturado em 27 nov. 2018]. Disponível em: https://www.psychology-services.uk.com/adhd.htm.

33. National Institute for Health and Care Excellence [Internet]. Attention deficit hyperactivity disorder: diagnosis and management. London: NICE, 2018. [capturado em 27 nov. 2018]. Disponível em: https://www.nice.org.uk/guidance/ng87.

34. Canadian ADHD Resource Alliance [Internet]. Canadian ADHD practice guidelines. 4th ed. Toronto: CADDRA, 2018. [capturado em 27 nov. 2018]. Disponível em: https://www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf.

4

ESTABLISHING A PSYCHOSOCIAL PLAN TO MANAGE **ADHD**

Thomas E. **Brown**
Ryan J. **Kennedy**

Effective treatment for ADHD involves a variety of psychosocial interventions, even when medication treatments are also being used. The most important intervention is education of the patient and family about what ADHD is, how it impacts an individual, and what interventions are available for effective treatment. This education can help to correct prejudices and misunderstandings that may otherwise undermine participation in treatment. Chapter 6 of this book provides useful information about talking with patients and their families about myths and facts about ADHD.

This chapter begins with information about recently emerging changes in understanding of ADHD that may be incorporated into education of patients, family members, and educators, as well as health care professionals and mental health providers. It is important for all those who provide support and treatment for those with ADHD to have accurate and up-to-date understanding of ADHD. The chapter then moves on to describe a variety of additional psychosocial interventions that may be utilized for treatment and support of ADHD in children, adolescents and adults.

This chapter is not weighted with evidence-based recommendations as much as other chapters in this e-book. This is because, as was noted by Watson et al.[1] and by Barkley,[2] there is presently relatively little in empirical research literature or meta-

-analyses of psychosocial interventions for ADHD that are methodologically sound and adequately attentive to both beneficial and adverse effects. Yet despite the lack of evidence from rigorous empirical studies and meta-analyses, the following psychosocial interventions can be adapted by clinicians to provide helpful care for children, adolescents and adults with ADHD. It is generally agreed that combined psychosocial and medication treatments are usually optimal for care of those with ADHD, However, even when medication treatment may not be utilized or available, the following interventions may be useful.

EDUCATION OF PATIENTS AND FAMILIES ABOUT UPDATED UNDERSTANDING OF ADHD

Described below are five basic facts about ADHD important for patients and families to understand. Clinicians may adapt and utilize these descriptions for their conversations with patients and family members. Additional information available online or in selected videos or publications is included within this section of text and in the reference section at the end of this chapter.

ADHD IS A COMPLEX DISORDER OF THE BRAIN'S COGNITIVE MANAGEMENT SYSTEM

The disorder currently identified as ADHD has long been associated with chronic difficulty in paying attention as well as impulsive and hyperactive behavior. More recent research has expanded that behavioral model to recognize that ADHD is associated with developmental impairments in the brain's cognitive management system, its **executive functions.** Although current diagnostic criteria for ADHD do not explicitly refer to "executive functions", many symptoms included in the present list of diagnostic criteria are related to executive functions.

These executive functions develop slowly starting in early childhood; they are not fully matured until the late teen years or early twenties. These cognitive functions mature and come "online" only gradually over the long course of development from early childhood to early adulthood. Assessment of impairments in EF should always be in comparison to others of comparable age.

Several models and various rating scales have been proposed to describe executive functions impaired in ADHD.[3-5] Most of these include impairments related to the following cognitive functions as described by Brown:[6]

1 **Activation:** organizing tasks and materials, estimating time, prioritizing tasks, and getting started on work tasks. Patients with ADHD describe chronic difficulty with excessive procrastination. Often they will put off getting

started on a task, even a task they recognize as very important to them, until the very last minute. It is as though they cannot get themselves started until the point where they perceive the task as an acute emergency.

2 **Focus:** focusing, sustaining focus, and shifting focus to tasks. Some people with ADHD describe their difficulty in sustaining focus as similar to trying to listen to the car radio when you drive too far away from the station and the signal begins fading in and out: you get some of it and lose some of it. They say they are distracted easily not only by things that are going on around them but also by thoughts in their own minds. In addition, focusing on reading poses difficulties for many. They may generally understand the words as they read, but often have to read the material over and over again to fully grasp and remember the meaning.

3 **Effort:** regulating alertness, sustaining effort, and working with adequate processing speed. Many with ADHD report that they can perform short--term projects well, but they have much more difficulty with sustained effort over longer periods of time. They also find it difficult to complete tasks on time, especially when required to do expository writing. Many also experience chronic difficulty regulating sleep and alertness. Often, they stay up too late because they can't shut their head off. Once asleep, they often sleep like dead people and have a big problem getting up in the morning.

4 **Emotion:** managing frustration and modulating emotions. Although the most current version of the manual used for psychiatric diagnosis does not recognize any symptoms related to the management of emotion as an aspect of ADHD, many with this disorder describe chronic difficulties managing frustration, anger, worry, disappointment, desire, and other emotions. They speak as though these emotions, when experienced, take over their thinking the way that a computer virus invades a computer, making it impossible for them to attend to anything else. They find it very difficult to get the emotion into perspective, to put it to the back of their mind, and to get on with what they need to do.

5 **Memory:** utilizing working memory and accessing recall. Very often, people with ADHD will report that they have adequate or exceptional memory for things that happened long ago, but great difficulty in being able to remember where they just put something, what someone just said to them, or what they were about to say. They may describe difficulty holding one or several things "online" while attending to other tasks. In addition, people with ADHD often complain that they cannot retrieve from memory information they have learned when they need it, though they may recall it later.

6 **Action:** monitoring and regulating self-action. Many people with ADHD, even those without problems of hyperactive behavior, report chronic problems in regulating their actions. They often are too impulsive in what they say or do and in the way they think, jumping too quickly to inaccurate con-

clusions. People with ADHD also report problems in self-monitoring for the context in which they are interacting. They fail to notice when other people are puzzled, hurt, or annoyed by what they have just said or done and thus fail to modify their behavior in response to specific circumstances. Often, they also report chronic difficulty in regulating the pace of their actions, in slowing themselves down or speeding up as needed for specific tasks.

THOSE WITH ADHD FOCUS WELL IN A FEW SITUATIONS, BUT NOT IN MANY OTHERS

Impairments of ADHD vary from one situation to another. Virtually all those diagnosed with ADHD have a few activities or tasks in which they have no difficulty exercising those same executive functions in which they are consistently impaired for most other tasks they encounter. For example, students who chronically struggle to sustain attention in school may have little or no difficulty in sustaining focus and effort for hours to play a particular sport or to make art or music, to construct with Legos, to play video games, or to do mechanical tasks.

Often parents or teachers challenge those with ADHD asking "If you can focus so well and work so hard for this activity, why can't you just make yourself focus and work that way for your schoolwork and other tasks that you know are important?" Usually the response is "I can focus well for activities I'm really interested in. I can't focus like that well for tasks that are just not interesting for me." This can make ADHD appear to be a simple problem of failure to exercise "willpower" when the disorder is really not a problem of willpower. It is a result of inherited problems in the dynamics of the brain's chemistry.

One college student once explained this with a sexual metaphor: "Having ADHD is like having 'erectile dysfunction of the mind.' If the task you're faced with is something that really interests you, you're 'up for it' and can perform. But if the task is not interesting to you, you can't get up for it and you can't perform. It's just not a willpower kind of thing."

ADHD IS USUALLY INHERITED AND TENDS TO RUN IN FAMILIES

Many twin studies have shown that one out of four individuals with ADHD is likely to have a parent with ADHD; those who do not have a parent with the disorder are likely to have a sibling, grandparent, uncle or aunt with ADHD. These family members may not have been diagnosed because this disorder was not adequately understood in earlier years and, even today, many medical and mental health professions are not adequately trained to recognize and diagnose it. ADHD is not due to any one gene; it is related to multiple genes.

ADHD OCCURS IN BOYS, GIRLS, MEN, AND WOMEN AT ALL LEVELS OF INTELLIGENCE

Years ago, ADHD was seen as a problem occurring only in little boys who were hyperactive. It is now clear that ADHD occurs in many individuals who are not hyperactive. Although it is more often recognized in males, it also is found in a significant number of girls and women. High intelligence is not a protection against ADHD. Many with ADHD are very bright, but still struggle a lot in exercising executive functions described above which are essential for success in school, work and many activities of daily life.

THOSE WITH ADHD OFTEN HAVE ADDITIONAL PROBLEMS IN LEARNING OR EMOTIONS

A very large percentage of children, teens and adults with ADHD have one or more additional problems such as anxiety, depression, sleep difficulties, substance use disorders, obsessive compulsive disorder, autism spectrum disorders, and/or specific learning disorders in reading, math or written expression. One of these other problems may be identified first, possibly overlooking the underlying ADHD. Or the ADHD may be recognized while another underlying disorder is not noticed or treated. Russell Barkley and Thomas Brown[7] have written about unrecognized ADHD in persons diagnosed with other disorders and Brown[8] has edited a handbook on ADHD complicated by additional disorders. If another impairing disorder is present, it may be important for that additional disorder to be directly treated concurrent to the ADHD.

EDUCATION ABOUT ADHD NEEDS TO BE AN ONGOING PROCESS

Education of patients and families about ADHD is not accomplished in one or several conversations. It should be an ongoing process that needs to address changing concerns as the individual with ADHD encounters different challenges and tasks of development over time. Education is important for helping those with ADHD to understand themselves and to improve their abilities to cope with emerging challenges. Education is also important for helping parents and other family members to respond with understanding and compassion to the changing challenges presented by the family members with ADHD.

Below are some resources that may be useful to parents, teachers and others interested in getting additional updated educational information about ADHD.

ONLINE SOURCES OF INFORMATION ABOUT ADHD

One valuable resource for parents of children and teens with ADHD as well as adults with ADHD is the website of CHADD (www.chadd.org), the U.S. advocacy and support organization for children and adults with ADHD. CHADD also sponsors and is linked to the National Resource Center on ADHD which provides a rich collection of information on ADHD for children and adults with ADHD. This resource center is not commercial; it receives support from the U.S. Centers for Disease Control and Prevention. It offers videos, print information and specialists available during specified hours to respond to questions about ADHD. The National Resource Center on ADHD website is free and available 24/7 in 10 languages: Arabic, Chinese (simplified), Chinese (traditional), English, French, Hebrew, Japanese, Portuguese, Spanish, and Vietnamese.

Another valuable web resource for parents seeking online information and help about children and teens with ADHD and/or learning issues is the website www.understood.org. It offers a wealth of valuable, readily understandable information in videos and print in both English and in Spanish to help parents better understand and help their children of various ages who suffer from attention and learning issues. It is free and available 24/7.

SUPPORTIVE ENVIRONMENT AND ROUTINE IN FAMILY LIFE

Although ADHD is usually inherited, the environment in which a child grows up has a substantial impact on how much ADHD impacts that individual and family. Because they tend to be slower than many of their peers to develop self-management skills, most of those with ADHD tend to need more support and structure in daily life than do many other of the same age. They usually benefit from consistent and clear expectations for morning routine to prepare for school or work. In comparison to others of similar age, they often need more supervision for getting homework and chores completed, for limiting excessive use of screen time, and for maintaining a reasonable bedtime and adequate sleep.

Link in this

http://www.chadd.org/about-chadd/national-resource-center.aspx

Those with ADHD also need recognition and encouragement of their strengths. Many get very frequent feedback from parents, teachers and peers about what they are doing wrong and how they are not doing what is expected. It is easy for them to learn to think of themselves as less capable than others their age and less able than they actually are. Parents can strengthen self-esteem and positive motivations when they identify and support specific strengths and talents of their children, providing them opportunities to develop and be recognized for those abilities.

For some this may involve encouragement to join sports teams or to take lessons and practice to strengthen talents in art or music. Others may have interest in making craft projects or cooking or doing mechanical tasks. When parents encourage and show pride in abilities and accomplishments of their children, they can strengthen the self-esteem and positive motivations of their son or daughter with ADHD and counter some of the discouraging negative feedback they may often receive, especially if their ADHD is not adequately treated.

Maintaining a supportive environment and routine in a family with one or more children who have ADHD is especially challenging when one of the parents has untreated ADHD. Despite very positive intentions, that parent may find it very difficult to maintain routines for self as well as for the rest of the family. If a parent of a child with ADHD has undiagnosed and untreated ADHD that is problematic, it may be very helpful for that parent to seek evaluation and treatment for his or her own ADHD. Taking such action is consistent with the "growth mindset" described below.

"MINDSET" IN THOSE WITH ADHD

In her book, *Mindset*, Carol Dweck[9] introduced the term "fixed mindset" to describe those who feel that they have been born with certain intelligence and abilities which sometimes may bring praise and success, but, at other times is simply insufficient and there is not really anything they can do to change their situation. It is as though they consider themselves a "finished product" unable to develop beyond their present level. She contrasts this with the "growth mindset" which assumes that one can work to develop and improve one's abilities, even after times where one has been unsuccessful. This mindset sees the self continually as "a work in progress" where change is possible through effort and persistence.

Some children are often praised by parents and teachers who say things like 'Oh, you did that so well, you're so smart, you have so much talent" as though the good performance was simply the result of natural talent. In contrast, when a child is praised for having worked hard to do a good job, the emphasis is upon the effort, not alone on given talent and abilities. When results are disappointing, the person with the growth mindset can be more readily helped to focus on how performance can be improved to try for a better future outcome.

Many children with ADHD experience such persistent and powerful negative feedback from those around them that they learn to think of themselves with a "fixed mindset" in which they understand themselves as doomed to frustration and mediocrity, unable to make any significant change in their ability to cope with challenges they encounter.

Cultivation of a growth mindset has been demonstrated to be helpful to any individual. It can be especially helpful for those who need to cope with impairments of ADHD. More detailed explanation and examples about how parents, teachers and others can help to nurture development of a growth mindset are provided in Dweck's book which is also available online as a free audio book.

SUGGESTIONS TO HELP PARENTS DEVELOP EFFECTIVE DISCIPLINE FOR CHILDREN 2-12 YEARS

In his book *1-2-3 Magic: 3 Step Discipline for Calm, Effective and Happy Parenting* and in videos, Thomas Phelan[10] has described a simple practical system which many parents and teachers have found helpful for encouraging their children to behave. His system can be very helpful in dealing with children who have ADHD. Phelan[10] begins by reminding parents that children should not be treated as reasonable little adults who will change their behavior in response to reasonable parental talk about what to do and why they should do it. He claims that many parents and teachers make two major mistakes in dealing with children: they do too much talking and show too much emotion, both of which tend to encourage the child to persist in the very behavior the parent is trying to stop.

The 1-2-3 system involves the parent saying "1" when a child starts an unwanted behavior, but not saying anything more about it. If the child persists in the unwanted behavior, the parent simply says "2" without any additional comment. If the child persists in the unwanted behavior, the parent says "3" and tells the child to go to serve a time out which is usually no longer than one minute for each year of the age of the child.

Phelan's books and videos suggest practical ways parents can deal with the many real-life problems that come up when the child refuses to go to his room, keeps coming out, continues to argue, etc. But he emphasizes the need for the parent consistently to avoid getting caught up in talking to the child or acting emotionally upset while using the system. He also encourages the parent to avoid any debriefing or other additional discussion of the incident after the child has returned from time out.

His system also provides tactics parents can use to encourage their children to start doing tasks or behaviors the parent wants them to do. Examples include getting up and out in the morning, cleaning rooms and eating, doing homework,

and getting to bed at night. Multiple strategies proposed include a particular kind of praise or other rewards for good behavior, charting for a reward system, using a kitchen timer, docking the child's allowance or other privileges for failure to comply, or allowing the child to face natural consequences of failure to comply.

The principles Phelan[10] advocates are based on sound psychological principles, a good sense of humor, and considerable common sense. He also reminds of the need we all have for positive reinforcement, shared fun, times without evaluation, active listening and "plain old affection." In addition, he notes that some children suffer from emotional or behavioral problems including ADHD and that parents of some of those children may need to seek professional help for themselves and their children to deal with their more complicated situations. However, the principles of 1,2,3 Magic work quite well even for many children with ADHD and/or related problems.

Many of the approaches described above are ingredients found in parent training as part of behavior interventions, one of the most used evidence-based psychosocial interventions for ADHD in children.[11] The World Health Organization, World Psychiatric Association and the International Association of Child and Adolescent Psychiatry and Allied Disciplines developed an open access manual for behavior interventions to treat children with ADHD and externalizing disorders[12] in primary care settings available in English, Spanish and Portuguese (go to loja.grupoa.com.br, search for *Guia para compreensão e manejo do TDAH da World Federation of ADHD* and click on Material complementar to download).

FOR PARENTS AND PROFESSIONALS DEALING WITH PRETEENS AND TEENAGERS

Chris Zeigler Dendy[13] offers valuable information and a very practical and sensible approach in her 2017 book *Teenagers with ADD, ADHD and Executive Function Deficits* as well as on videos available on her website. Drawing on her years of experience as a teacher, a school psychologist and as a parent of a son with ADHD, Dendy[13] begins with recognizing that "Most parents of these preteens and teens feel isolated and receive little support and understanding from most others… When their children struggle, parents may experience a great deal of anxiety and self-doubt." She also notes that with appropriate supports and treatment, most of these teens and their parents make it through this difficult period successfully. She understands the stresses experienced by many parents of children with ADHD. She also recognizes the importance of encouraging hope in those who care for those with ADHD and those who have ADHD.

Some of the principles Dendy[13] describes and recommends to parents of teens with ADHD include the following:

1 Choose your battles. Ignore minor misbehavior and focus on more important issues.
2 When making corrections, talk about the specific behavior that is unacceptable now without also complaining about a list of grievances from the past.
3 Use brief, reasonable consequences for misbehavior. Long punishments are not usually effective. Except for serious offenses, restrictions lasting a day or a weekend are usually as effective as those that go on for a week or more.
4 If your teenager breaks your trust and doesn't handle freedom responsibly, discipline him with an appropriate consequence. A few weeks later, give him a second chance.
5 Avoid overreacting when your child disobeys you or gets into trouble. If you're enraged, you might give yourself some time to calm down while saying something like: "This is not acceptable and I'm very angry. I want to think about what you did and what your consequence will be. Then I'll come talk with you in a few minutes."
6 If your child blows up, lower your voice and propose taking a break. If an adult gets loud, a frustrated teenager is likely to get more aggressive and less able to think reasonably.
7 Nurture yourself. When you are frustrated or upset with your child talk with your spouse, another friend or a relative who will be understanding and supportive. Seek professional help if you need someone else who can understand ADHD, the stresses of raising a child with ADHD, someone who may be able to offer some useful suggestions.
8 Practice forgiveness for your teenager, for those who have misunderstood your teen, and for yourself.

EMOTIONS AND CONFLICT IN INDIVIDUALS AND FAMILIES WITH ADHD

Current diagnostic criteria for ADHD include no mention of problems with emotions as an aspect of ADHD. Yet most individuals with ADHD and those who know them are very much aware that emotions and struggles with and between various emotions are a critical component of daily life for those with ADHD. In *Smart but stuck: emotions in teens and adults with ADHD*, Thomas Brown[14] has described a variety of ways in which emotions tend to be problematic for those with ADHD and their families.

Emotional conflicts within a person suffering from ADHD can powerfully affect their willingness to seek and utilize needed treatment as well as many other aspects of their daily life. Likewise, emotional dynamics between individuals, couples and within families can provide strong support and powerful demoralization

for those with ADHD and those with whom they live and interact. Any clinician seeking to understand and provide care for these people needs to be sensitive to the complex and often changing dynamics in emotional interactions of those who need and try to utilize treatment for ADHD.

If they have adequate resources, treatment services for those with ADHD and their families may offer counseling or psychotherapy for individuals, couples or families when emotional issues become especially problematic. Yet, support for recognizing and dealing with emotional aspects of ADHD may also be provided by the tone and content of education offered in the course of evaluations, follow-up sessions, and in literature and educational information provided. One example of emotion-laden stress is conflict between parents of a child with ADHD.

PARENTS MAY DIFFER IN THEIR APPROACH TO DEALING WITH A CHILD WHO HAS ADHD

In *Outside the Box: Rethinking ADD/ADHD*, Thomas Brown[15] has described how parents of children with ADHD often become polarized into extreme positions and spend much time and energy accusing one another of being too harsh or too lax in dealing their child. One parent may argue that the child is suffering considerably from impairments related to ADHD and needs much more support and understanding rather than confrontation and punishments. The other may argue that the child needs to be punished promptly and more firmly for misbehavior or failure to do assigned tasks so he can learn eventually to discipline himself. Often their arguments can lead each of these parents to ignore the truth of the other's concerns and to argue a more extreme form of their own position.

In such situations both parents are likely to need help to stop and remind themselves and one another that both of them love the child and that both of them are arguing something that may be quite true. However, their task is to put their heads together to decide in each specific situation how best to deal with that particular situation in a way that will help their child to feel loved, but also to behave more appropriately. Sometimes more understanding and support are needed and, at other times, the more pressing need may be for both parents together to confront the child and to enforce their expectations more effectively. Sometimes developing a more effective strategy may require consulting with trusted friends or family members or a professional who understands both ADHD and stresses of parenting of a child with ADHD.

Additional resources for addressing emotional conflicts in ADHD relationships are found in Russell Barkley's *When an Adult You Love Has ADHD1*[6] and in Gina Pera's *Is it You, Me, or Adult A.D.D.? Stopping the Roller Coaster When Someone You Love Has Attention Deficit Disorder.*[17]

PARENT SUPPORT FOR STUDENTS IN ELEMENTARY AND MIDDLE SCHOOL

Parental support for education of their children with ADHD is important. One means of support is for the parent to provide the child's teacher with factual information about ADHD and about their specific child. Some teachers have a very good general understanding of ADHD in children at the grade level they are teaching, but most have been provided very little education about ADHD and how they can provide a supportive learning environment for children with ADHD. Even if the teacher has some general information about ADHD, it can still be helpful to the parent to provide more specific information about their particular child with ADHD.

Early in each academic year a parent can talk briefly with their child's new teacher to describe how that student's ADHD tends to affect their work in school. This might include mention of specific interests, strengths and difficulties as well as techniques that parents or previous teachers have found helpful in working with that student. The parent might also ask the teacher to suggest any particular strategies that might help to maintain efficient communication between parent and teacher.

In addition, the parent might share with that teacher a few selected pieces of printed information from the CHADD National Resource Center website or from the Understood.org website. Another resource is an article "ADHD: From Stereotype to Science" written by Thomas Brown specifically to update teachers on how new understandings of ADHD can be helpful to teachers in their classroom. This article is free and available in the articles section of www.BrownADHDClinic.com.[18] A few pieces of such literature could be especially helpful if the teacher is interested in getting more updated information about ADHD. However, it is important for the parent to offer this information as "something I found interesting and helpful" and not as though the parent is assuming the teacher to be completely uninformed about ADHD.

Communicating with teachers in middle school or high school may be more difficult because in most schools at those grade levels each student has not just one primary teacher, but a number of different teachers each for a different subject area. Parents who want to talk with each teacher who works with their student may need to make several different visits to the school. Sometimes those teachers may be willing to write a few brief comments on a weekly form which asks each teacher to note whether this student with ADHD has handed in all assigned work over the past week and whether the student has been coming to class each day adequately prepared.

Getting such a report from each teacher can allow the parent to reward their student for good performance and to provide incentives to improve work over the coming week. This approach is called daily/weekly behavior report card. Re-

cent studies have documented its effectiveness in reducing ADHD behaviors at school.[19] This intervention can foster communication between parents and teachers about behaviors at school helping to promote a more comprehensive coverage for interventions based on token-economy and reinforcements. For a quick explanation on the use of daily behavior report cards, see the video in this page. However, it important that a parent not burden a teacher with requests for excessive paperwork on a regular basis.

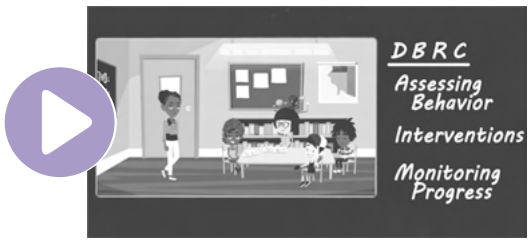
For students with ADHD in elementary, middle school or high school, parents often need to play an important role in supporting and monitoring homework. Most basic is monitoring the student's keeping track of what homework has been assigned and when it is due. Many students are reluctant to make use of a daily planner where they write down each assignment for each class, but this may need to be a requirement if they are not able to keep track of their assignments in any better way.

Also essential is helping the student to find a good time and place to do homework without getting caught up in distractions such as TV, surfing the net, or communicating with friends by phone, email, texting or social media. This may be done by having specific monitored hours for homework when those distractions are not allowed while also having planned breaks as needed.

Some students benefit from talking with a parent daily about what homework needs to be done, what priority to give specific tasks and how to reasonably budget time for task completion. Many students also benefit from help in organizing notebooks and papers with occasional cleanouts. Some may also need parental help in gathering resources or library materials for special projects.

Parents may also help students review for tests and exams. For older students, test review might be more productive in study groups where just a few students meet together. Prior to meeting, they may divide up content to be covered in an upcoming test so that each student agrees to study one chunk of the material very closely and then quiz other members of the study group about that particular segment.

Regardless of the age of the student, parents can be helpful in offering encouragement and occasional rewards for effective work on homework. They may



Link in this

https://www.youtube.com/watch?v=vSUyjZrh-W4

also offer some commiseration when the homework burden is especially heavy or boring.

Some parents find it works better for them to arrange to have a tutor help their student with homework in subject areas where the parent lacks the time or information needed to be helpful. The tutor may be a slightly older student, a neighbor or another family member who has the patience and ability to support the student without being overbearing. If the family can afford it, parents may want to hire a professional tutor.

It is often frustrating for parents as they try to help their child with ADHD manage homework. Especially as the son or daughter enters adolescence and is struggling to feel and act more independently, parents need to try to manage a reasonable balance between doing enough to support their young student effectively while also trying to avoid excessive "micromanaging" of homework and routines in ways that create excessive resistance or encourage "learned helplessness" and excessive dependency.

SCHOOL, COLLEGE AND UNIVERSITY ACCOMMODATIONS FOR STUDENTS WITH ADHD

ADHD-related Impairments of executive function cause some students with ADHD and/or learning disorders to struggle with requirements in their schooling. Even if they are quite bright and taking medication for ADHD, these students may be unable adequately to demonstrate what they are learning unless allowed special accommodations in class requirements or test-taking procedures. This may be due to slow processing speed, inattention to details, impulsive responding, and/or impaired working memory.

Some countries such as the U.S. have laws or other regulations that require specific accommodations for such students once they have adequate documentation of their disability. Some other governments do not currently offer such legal protections. Clinicians should learn what accommodations are mandated for students in the country where they practice and what documentation is needed to establish eligibility.

Some countries and some examinations used in many nations require documentation such as standardized IQ and achievement testing to establish eligibility for accommodations for testing. If legal protections are not mandated, clinicians and parents may be able to negotiate specific accommodations with teachers or officials in a given school, college or university to obtain needed accommodations for specific deserving students.

Thomas Brown[15] has summarized possible accommodations that may be helpful for students with ADHD:

- Elementary, middle school and high school students:
  1. Extended time for completing timed tests or examinations (usually 1.5 of the usual)
  2. A minimally-distracting environment in which to take the exam.
  3. Alternate seating of the student in the classroom, e.g. closer to teacher
  4. Use of a calculator for math or computer for written work
  5. More frequent reports from school to home, possibly daily report forms
  6. Behavioral interventions such as point system to reinforce good behavior
- College or university students:
  1. Extended time for completing timed tests or examinations (usually 1.5 of the usual)
  2. A minimally-distracting environment in which to take the exam.
  3. Access to power point presentations offered in class or a copy of lecture notes.
  4. Permission to record lectures so the student can prepare more adequate notes.
  5. Peer notetaker to provide notes of lectures to supplement the student's notes.

Extended time for taking tests and exams is the most frequently requested accommodation among students with ADHD and/or other learning problems. Some students with ADHD tend to rush too quickly as they take tests, as though the goal were to finish as quickly as possible. Yet many, though not all, students with ADHD need to work slowly and have great difficulty in demonstrating what they have learned when they are tested under tight time limits. Often, they need to re-read passages of text repeatedly in order fully to grasp what the exam question is asking for.

On math tests, those with ADHD often need more than the usual time to go back and check their calculations so they can correct careless errors or possible misunderstanding of the problem due to their not paying enough attention to details. Likewise, many with ADHD need extended time for tests that require written expression. They may have good ideas about what to write, what information to provide, but many with ADHD have much difficulty in organizing their information and in translating their thoughts into sentences and paragraphs.

EMPLOYMENT ACCOMMODATIONS FOR ADULTS WITH ADHD

Some adults with ADHD need accommodations in their work setting to help compensate for their impairments of executive function and to protect them from discrimination based on their disability. Some governments have laws that prohibit

discrimination in employment. Under provisions of such laws, those with ADHD or learning disabilities that significantly impair them, relative to the average person, in important life activities may be protected from discrimination in job recruitment, hiring, job assignments, pay, lay off, firing, training, promotions and benefits. Such laws may also offer some accommodations for those with ADHD or learning disabilities to allow them to work more effectively.

It is important for clinicians to be aware of what protections and accommodations may be provided by laws in the country where they practice. It is also important for clinicians to caution patients about disclosing their ADHD diagnosis to their current or potential employer until they have accurate information not only about what accommodations are provided by local or national laws, but also about policies and practices in how their specific employer understands and implements such accommodations. Regardless of what may be required by law, if employees with ADHD impulsively disclose that diagnosis and request or demand certain accommodations they believe are due to them, their supervisor or employer may respond in ways that ultimately penalize the employee with discriminatory practices or with termination not easily remedied.

SELF-MANAGEMENT AND COPING STRATEGIES FOR ADULTS WITH ADHD

In their *Adult ADHD Tool Kit*, Russell Ramsay and Anthony Rostain[20] provide detailed descriptions of a variety of strategies that can be helpful to adults as they work to overcome chronic ADHD-related problems with disorganization, procrastination, excessive distractibility and forgetfulness in a variety of day-to-day functions. Here are some examples:

1. Devote 10 minutes daily to defining your To-Do list, but list no more than 2-5 items; so completion of the tasks remains manageable.
2. Use a daily planner where you write scheduled appointments, work and school commitments, as well as personal, recreational, and self-care tasks.
3. Review your daily planner at the start of your day or the night before.
4. Predict the most likely distractions or barriers that could get you off task and devise ways to avoid them.
5. Plan for physical activity, adequate rest, and regular meal times.
6. Consider that you really can follow through on your plan despite feeling discomfort with it (even if you're not in the mood to do a task, consider that you can start and finish it).
7. Set up automatic payments systems for recurring bills and automatic reminders for tasks.

8 Before taking on a new project, assess whether it is really feasible or if you should decline.
9 Go through incoming mail daily and throw out things you don't need.
10 For a task you need to do, but want to avoid, start by dedicating just 10 minutes to it with the option to continue beyond that time limit if you feel ready. Often getting started is the most difficult part of the task.

HELPING TEENS AND YOUNG ADULTS IMPROVE SOCIAL SKILLS

Many, though not all, teens and young adults with ADHD struggle to make and sustain friendships and comfortable relationships with peers and/or adults. Such difficulties are especially common among those whose ADHD may be complicated by characteristics of Autism Spectrum Disorder. Elizabeth Laugeson[21] has published *The Science of Making Friends* where she describes in text with an accompanying DVD an excellent intervention developed in the Program for Education and Enrichment in Relational Skills (PEERS) at the University of California-Los Angeles.

This program has used scientific methods to break down complex, seemingly sophisticated, social skills into concrete rules and steps for social behavior that can become similar to what is naturally used by teens and young adults who are usually successful in social interactions. The PEERS program involves teens and young adults who want to improve their social skills in a structured course which involves the young people in a series of group instructional sessions and activities while their parents participate in a concurrent series of sessions.

Parent sessions are intended to help the parents to understand and support the evidence-based rules and methods being taught to their sons and daughters. The intention is to help the parents become effective "coaches" for their teens and young adults as they develop social skills being taught and practiced in the program.

Vignettes, texts, and role plays provided in the PEERS program help participants to learn specific ways to find good friends, have good conversations and meet new people, how to organize get-togethers with friends, and how to handle things like bullying, teasing and other social problems. Unlike most other programs intended to provide social skills training, this program has been empirically tested and found to be effective for most participants in ways that tend to have lasting benefits.

Laugeson's book provides a useful guide for parents who may want to adapt the PEERS methods for coaching their own son or daughter. That book also provides guidance for clinicians who may want to offer these methods to groups of interested parents with their teen or young adult sons or daughters who are seeking support for enhancing their development and improvement of social skills.

PARENT-TEEN THERAPY TO IMPROVE EXECUTIVE FUNCTION DEFICITS AND ADHD

A different approach to working with parent and teen together (in dyads or groups) focuses not on making and sustaining friendships, but on helping parents and teens to collaborate in improving their interactions focused on the adolescent's executive function and ADHD impairments. Primary focus of this program is on improving parent-teen interactions to support the teen's developing executive functions and autonomy to deal effectively with homework and related tasks. Margaret Sibley[22] describes this excellent manualized program in her book *Parent-Teen Therapy for Executive Function Deficits and ADHD.*

Unlike many didactic approaches, this program is firmly grounded in the *Motivational Interviewing (MI)* approach which emphasizes therapist-family *partnership* in equal relationships between therapist and family members; therapist *compassion and empathic acceptance* of parent and teen as they are, despite their ongoing ambivalence about making changes and despite possible differences in their values from values of the therapist; and *evocation: drawing reasons and ideas for change from the family* rather than from a therapist imposing a plan for change on parents and teens.

Sibley's book provides detailed guidance and materials for a therapist to offer a menu of specific modules from which parent and teen together can select which modules will best fit their current needs and concerns. This program developed at Florida International University provides practical suggestions for the therapist to offer content and a process to address the expressed concerns of the parent and teen and to adapt those to their particular aims and circumstances.

ADDITIONAL RESOURCES AND CONCLUDING COMMENT

Additional resources for developing psychosocial interventions for those with ADHD and their families are listed in the reference list for this article.

This chapter closes with two brief comments: it is generally understood that the combination of finely tuned medication with carefully tailored psychosocial treatments is the usually the best intervention for those with ADHD. However, it is also true that if medication treatment for ADHD is not accompanied by competent education of patient and family, as well other psychosocial supports, treatment is not only less effective, but medication treatment is often not continued by the patient on a sustained basis, despite the fact that ADHD is usually a chronic disorder.

Conflicts of interest

Dr. Brown is a consultant for Ironshore, Shire, Sunovian, and Supernus. He receives publication royalties from Yale University Press, American Psychiatric Publishing, Routledge, Jossey-Bass/Wiley, and Pearson. Dr. Kennedy reports no potential conflicts of interest.

Links to resources online

- https://www.additudemag.com
- http://brownadhdclinic.com
- http://www.chadd.org
- https://www.understood.org/en/learning-attention-issues/child-learning-disabilities/add-adhd
- https://www.understood.org/en/learning-attention-issues/child-learning-disabilities/add-adhd/adhd--explained-a-28-minute-primer

For parents and professionals

- http://adhdlectures.com/lectures.php?catindex=3

Parent training: 1-2-3 Magic by Dr. Phelan

- https://youtu.be/xDmAsO-uDfg

Organization & planning

- http://www.homeroutines.com
- https://mindnode.com/mindnode/ios
- https://itunes.apple.com/us/app/listastic-shared-to-do-task-lists/id1025619367?mt=12

Coaching

- https://edgefoundation.org
- http://addca.com/adhd-coach-training/Faculty-Details/david_giwerc_mcc

American Academy of Pediatrics resource toolkit for clinicians

- https://www.nichq.org/resource/caring-children-adhd-resource-toolkit-clinicians

CADDRA e Toolkit for clinicians & professionals

- https://www.caddra.ca/etoolkit-forms/

REFERENCES

1. Watson SM, Richels C, Michalek AP, Raymer A. Psychosocial treatments for ADHD: A systematic appraisal of the evidence. J Atten Disord. 2015;19(1):3-10.

2. Barkley RA. Adverse events associated with behavior management training for families experiencing parent-ADHD teen conflict. The ADHD Report. 2018;26(2):1-5.

3. Barkley RA. ADHD and the nature of self-control. New York: Guilford Press, 1997. p. 335.

4. Brown TE. Brown attention-deficit disorder scales: for adolescents and adults. San Antonio: The Psychological Corp., 1996.

5. Gioia GA, Isquith PK, Guy SC, Kenworthy L. BRIEF-2: behavior rating inventory of executive function. 2nd ed. Lutz: Psychological Assessment Resources, 2015.

6. Brown TE. A new understanding of ADHD in children and adults: executive function impairments. New York: Routledge, 2013.

7. Barkley RA, Brown TE. Unrecognized attention-deficit/hyperactivity disorder in adults presenting with other psychiatric disorders. CNS Spectr. 2008;13(11):977-84.

8. Brown TE. Developmental complexities of attentional disorders. In: Brown TE. ADHD comorbidities: handbook for ADHD complications in children and adults. Washington: American Psychiatric Pub., 2009. p. 3-22.

9. Dweck CS, Gavin M. Mindset: the new psychology of success. Rego Park: Gildan Media Corp., 2009.

10. Phelan TW. 1-2-3 magic: 3 step discipline for calm, effective and happy parenting. 6th ed. Naperville: Sourcebooks, [2016].

11. Caye A, Swanson JM, Coghill D, Rohde LA. Treatment strategies for ADHD: an evidence-based guide to select optimal treatment. Mol Psychiatry. 2018. [Epub ahead of print].

12. Bauermeister JJ, So CY, Jensen PS, Krispin O, El Din AS; Integrated Services Program Task Force. Development of adaptable and flexible treatment manuals for externalizing and internalizing disorders in children and adolescents. Rev Bras Psiquiatr. 2006;28(1):67-71.

13. Dendy CAZ. Teenagers with ADD, ADHD and executive function deficits. Bethesda: Woodbine House, 2006.

14. Brown TE. Smart but stuck: emotions in teens and adults with ADHD. San Francisco: Jossey Bass, [2014].

15. Brown TE. Outside the box: rethinking ADD/ADHD in children and adults: a practical guide. Arlington: American Psychiatric Publications, [2017].

16. Barkley RA. When an adult you love has ADHD: professional advice for parents, partners, and siblings. Washington: American Psychological Association, 2017.

17. Pera G. Is it you, me, or adult A.D.D.? stopping the roller coaster when someone you love has attention deficit disorder. San Francisco: 1201 Alarm, 2008.

18. Brown TE. Special topic: ADHD: from stereotype to science. Educational Leadership. 2015;73(2):52-56. Disponível em: http://www.brownadhdclinic.com/wp-content/uploads/2016/02/ADHD_From_Stereotype_article1-1.pdf. Acesso em: 15 nov. 2018.

19. Iznardo M, Rogers MA, Volpe RJ, Labelle PR, Robaey P. The effectiveness of daily behavior report cards for children with ADHD: a meta-analysis. J Atten Disord. 2017:1087054717734646. [Epub ahead of print].

20. Ramsay JR, Rostain AL. The adult ADHD tool kit: using CBT to facilitate coping inside and out. New York: Routledge, 2014.

21. Laugeson EA. The science of making friends: helping socially challenged teens and young adults. Hoboken: John Wiley & Sons, 2013.

22. Sibley MH. Parent-teen therapy for executive function deficits and ADHD: building skills and motivation. New York: Guilford; 2016.

5

ORGANIZING AND DELIVERING TREATMENT FOR **ADHD**

David **Coghill**
Wai **Chen**
Desiree **Silva**

Following diagnosis, all children with ADHD will require some form of intervention and most will require treatment over a relatively prolonged period of time. Before starting a child on medication for ADHD, it is important that both the treating doctor and parent (carer) have a good understanding of the child's ADHD; a full history which includes environmental exposures and stress in pregnancy and early childhood; exclusion of conditions that may mimic ADHD (although can often be associated with ADHD), a thorough assessment with includes information from several sources, and an assessment of comorbidities associated with ADHD. Managing ADHD can be a complex task where good communication with your patient, family and other allied professionals will greatly enrich this journey.

Studies agree that there are currently significant variations in the delivery of ADHD care both between (e.g. Hinshaw et al.[1]) and within countries and even within specific regions of a country (e.g. Australian Comission on Safety and Quality in Health Care[2]). Unfortunately attempts to explain the reasons behind these within and between country variations in care have been largely unsuccessful.[3] Clearly the availability of medications will impact on prescribing patterns but differences in the way services are funded will also make a difference. Some countries like the USA rely almost completely on privately delivered healthcare services whilst services are almost all publicly funded in others (e.g. UK, Scandinavia). Whilst others have

a mixed private/public approach (e.g. Germany, Australia), there are wide variations across countries with respect to the balance between these two systems. There are also considerable differences in the way that doctors are trained. While in some countries child and adolescent mental health services see most of the children with ADHD, in others it is mainly through paediatrics.

In countries where ADHD is still under recognized, under diagnosed and under treated, it seems likely that most of those referred for treatment will be at the more severe end of the ADHD spectrum, present with high levels of comorbidity and have a wide range of impairments that impact significantly on all aspects of their lives.

Whilst we strongly endorse the use of evidence based clinical practice guidelines in determining what care and treatment should be delivered, we also recognise that even the best guidelines struggle to clearly describe how to deliver this care within routine clinical practice. Therefore, the purpose of this chapter is to unpack the evidence about using medications to treat ADHD and translate this into a more usable format that will help the clinician develop and implement clinical pathways in their everyday practice. Much of this work stems from the work conducted with the European ADHD Guidelines Group (EAGG)[4-8] translating their guidelines and those from others into our own day to day clinical practice.[9] We will attempt here to describe clearly an implementable version of the evidence-based guidance and strategies for initiation, monitoring, and maintenance of medications for ADHD.

The National Institute for Health and Care Excellence (NICE)[10] and other authorities have supported the development of structured stepped care pathways for the management of ADHD. The most typical shared care will be for the specialist team to monitor care and adjust treatment depending on response, adverse effects and any comorbid problems and for the primary care team to prescribe medication and, sometimes, monitor growth and blood pressure as required in between the specialist appointments. Whilst this is a sensible approach, it is clearly not suited to all healthcare systems. However, rather than dismiss the concept, it may be more helpful to try and see whether any of the concept could helpfully transferred into your own healthcare system. In this vein, and as it is not possible to draw up one set of recommendations that will fit all systems, we suggest that the most effective way of reading this chapter is in a problem-solving rather than problem-finding mode. We recognise that not everything we suggest will be possible in every setting, however if you think something may be helpful spend some time thinking about how you can make it, or something similar, work within your clinical environment.

MANAGING ADHD

The purpose of this chapter is to provide a framework for organizing ADHD care with the hope that this can help reduce variability in the care described above. The rest of the chapter is divided into eight main sections, which will focus on:

1 Medications available for treating ADHD
2 Understanding how ADHD medications work and how to use them effectively
3 Deciding on the initial targets for treatment
4 Starting treatment with medication
5 Monitoring treatment and side effects
6 Adjusting and switching treatments
7 Special circumstances
8 Unlicensed medications for ADHD

In each section, we will break down the guidance into the tasks that have to be addressed at each stage of the clinical process. The advice should not be seen as prescriptive and, as noted above, we suggest that it is used to stimulate discussion within teams and services and to facilitate problem-solving any barriers to practice and aid the development of evidence-based care pathways that can work within their own particular systems and circumstances.

MEDICATIONS AVAILABLE FOR TREATING ADHD

Both stimulant and non-stimulant medications are licensed for the treatment of ADHD. Not every medication is available in every country. The broadest range of medications is available in North America whilst in some low and middle-income countries, no medications are licensed to treat ADHD and those that are licensed in other countries are unavailable. In this chapter, we will focus on the most common medications as these are also the best studied and understood. At the end of the chapter we will briefly discuss other medications that are sometimes used off-label to treat ADHD.

The most frequently used medications in most countries are the psychostimulants comprising methylphenidate, dexamfetamine/amphetamine and several other amphetamine derivatives. Racemic amphetamine was the first stimulant medication used to treat ADHD since the seminal observations of Bradley in 1937. Methylphenidate is the most widely available medication for ADHD across the world. It is licensed in the US and in most European countries as part of comprehensive treatment programs in children (over 6), adolescents and adults. There are several different extended release formulations of methylphenidate that are differentially available across the globe. Although more potent than methylphenidate, the amphetamines are less used in most countries and due to concerns about abuse potential and diversion are not commercially available in many countries. Whilst mixed amphetamine salts are popular in the USA, immediate release dexamfetamine is the most common amphetamine across the rest of the world.

There are several long acting extended release amphetamine products available in the US but these are not widely available in other countries. Lisdexamfeta-

mine, an amphetamine pro-drug, which has an extended duration of action due to the prodrug mechanism, is a more recent addition to the ADHD medications and is now licensed in several parts of the world. Three non-stimulant medications are licensed for treating ADHD. Atomoxetine, and extended release formulations of guanfacine and clonidine. The extended release formulations of guanfacine and clonidine are the only medications with a specific indication within their license for co-administration alongside the stimulants.

UNDERSTANDING HOW ADHD MEDICATIONS WORK AND HOW TO USE THEM EFFECTIVELY

Having a good understanding of psychopharmacology in relation to the neuroscience of the brain, neural circuitries, attention networks, receptors and neurotransmitters can significantly enhance the effective drug management of ADHD. This is particularly the case in the presence of comorbid conditions, which for ADHD is the rule than the exception. The reasons are fourfold:

1. The actions of dopamine (DA) and/or noradrenaline (NA) (sometimes termed 'norepinephrine (NE)' interchangeably) and the medication dose-response relationships in ADHD do not follow a linear relationship; in fact, they often track in an inverted-U shape curve (see Figure 5.1).[11]
2. Individuals vary considerably regarding the actual dosage required for optimal drug response, duration of action, frequency of dosing and tendency to experience rebound effect (i.e. symptoms more intense than baseline) when a medication starts to wear off. Importantly for the stimulants, the clinical effects vary between individuals, independent of a patient's weight; and are different from many other medications used within paediatric populations.
3. The presence of comorbidities such as anxiety, depression and autism spectrum disorder can influence the side-effect profiles of medications; and how a given dosage of drug impacts on the therapeutic window, within which treatment responses become optimal.
4. Some children require combination treatment instead of monotherapy in order to gain full control over their problems. These may include a combination of inattention, hyperactivity, impulsivity, emotional dysregulation, mood, anxiety and tics. A prudent and judicious selection of appropriate agents to yield a combination therapy (instead of uninformed polypharmacy) is predicated upon sound knowledge of psychopharmacology.

All currently licensed ADHD medications are thought to act, at least in part, through their impact on DA and/or NA. Both DA and NA are key modulators of the key brain circuits that support attention, reward processing, and activity

levels and which are thought to underpin ADHD. As described by the inverted U-shaped curve mentioned above, both too little and too much DA and NA result in sub-optimal cognitive functioning and are implicated the development of side-effects and impairments. ADHD is associated with lower levels of DA and NA; but too much DA is thought to be a key cause of psychotic symptoms, and excessive NA can lead to anxiety, agitation or aggression. A key aim of medication treatment is to optimise neurotransmission through the important, predominantly glutamatergic, brain circuits, which function sub-optimally in ADHD. These medications correct the levels of DA and NA, which modulate and correct the suboptimal glutamatergic transmissions.

Whilst there are similarities between the medications, there are also key differences. This is the reason why some people respond better to one medication than another (and also why some have adverse effects with one and not another). Methylphenidate and the amphetamines inhibit both the dopamine (DAT) and noradrenaline reuptake transporters. These transporters' function is to remove DA and NA from the synaptic and extra synaptic spaces. Blocking reuptake, increases the amount of available DA and NA, that engages dopamine (D1) receptors, thereby improving neurotransmission by reducing the amount of 'noise' and interference (DA) and boosting the 'signal' (NA). Atomoxetine only inhibits the noradrenaline reuptake transporter, however it also increases levels of both NA and DA in the prefrontal cortex (because in the prefrontal cortex, almost all

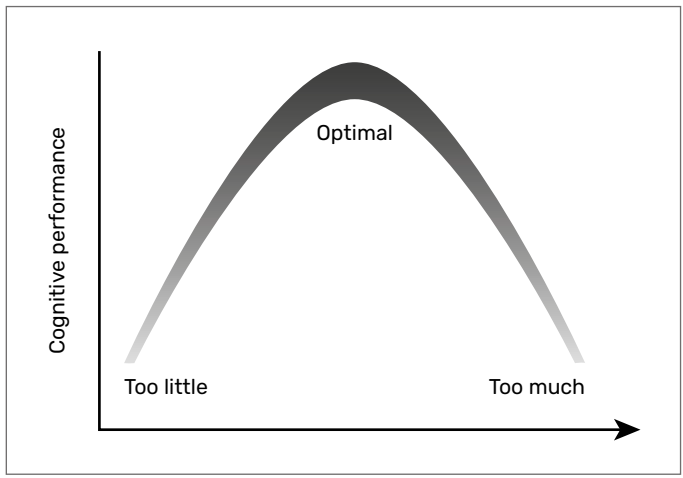


Figure 5.1
The inverted U-shaped influence of noradrenaline (NA) and dopamine (DA) on prefrontal cortex.

DA is actually taken back up by the NA transporter). Clonidine and guanfacine (G) are direct alpha2A receptor agonists; and, therefore, mimic NA action at the postsynaptic alpha2A receptors and improve glutamatergic neurotransmission by reducing 'noise' and interference.

Dopamine receptors

There are two main DA receptors, each of which has different levels of affinity for DA. In ADHD treatment, D1 and D2 receptors are relevant:

1. The *D1 receptors* have high affinity for DA, and therefore are engaged at relatively low concentrations of DA. At optimal concentration, D1 transmission reduces excess activity in the neural network, reducing distractibility and improving concentration. Excessive D1 activity can lead to deterioration in cognitive functions.
2. *D2 receptors* have a lower affinity with DA than D1 receptors, requiring higher concentrations of DA for activation. At moderate levels of *phasic DA neuronal firing,* D2 activity enhances reward and motivation, and improves cognitive performance. Some children and adults can be extremely sensitive to D2 activation, this in turn can result in cognitive decline along with emergence of agitation, irritability, and paranoia or hallucination symptoms in extreme cases.

It is therefore important that stimulant medications are carefully titrated to doses that ensure both optimal levels of D1 and D2 activity and continued effectiveness across the course of the day. Over- or under -dosing or marked fluctuation in dose levels across the day can compromise drug response, leading to deterioration of symptoms and cognitive functioning.

Link in this

http://adhd-institute.com/disease-management/pharmacological-therapy/mode-of-action/

In children with autism spectrum and anxiety disorders, the therapeutic window of stimulants tends to be narrower and shifted to left. For this reason, these children are more often sensitive to medications and require lower doses to avoid side-effects such as over-focusing, agitation, anxiety and aggression. The general advice for commencing medication in ADHD individuals with comorbidities is to "start low and go slow".

Noradrenergic receptors

In the NA system, the alpha 2A receptors have a high affinity with NA and are engaged at low concentrations of synaptic NA. Selective alpha 2A agonists like clonidine and guanfacine enhance neuronal 'signals', and this effect also follows an inverted U shape dose-response curve, as illustrated in Figure 5.1. The optimal balance between DA and NA synaptic concentrations results in an optimal balance between D1 and alpha2A activity,[11] which can improve working memory and cognitive performance. However, excessive NA concentration leads to activity in the low affinity NA receptors, such as beta and alpha1 receptors.[12] This can result in agitation, anxiety, fear, arousal, aggression and rage.

From a clinical perspective understanding the neurobiology pathways provides some explanation on (1) why careful dose titration of stimulant and psychotropic medications is essential; (2) why combination of stimulants and antipsychotic can reduce emotionality, anxity, agitation and aggression – given that stimulants target D1 and alpha2A receptors, while anti-psychotics target D2 receptors; (3) why guanfacine and clonidine – alpha 2A agonists – have a role in ADHD management as a monotherapy or combination therapy.

The relevance of pharmacokinetics of drug preparations

Having explained why it is pivotal to titrate the correct dosage of medication in relation to the inverted-U response curve, we now turn to how different preparations of drugs can determine fluctuations in the blood levels and symptoms across the day.

Both methylphenidate and amphetamine are available as immediate release and extended release formulations. But the patterns of availability differ widely across the world. Different extended release preparations utilise different mechanisms for slowing down absorption or release into the cirulation compartment.[5] For example Concerta ('OROS MPH') utilises an 'osmotic pump' mechanism – with 22% of the dosage available as immediate release from the coating of the capsule. Also as around 20% of the dose is not released by the 'pump' mechanism, this proportion does not add to activity. Taking this into account, and because these formulations were designed in a way that the extended release portion is adequate to continue the effects of the immediate release portion, it is suggested

that they are dosed such that the patient is given an equivalent immediate release dose. For example to switch from 10mg IR methylphenidate three times a day you would need to prescribe 45mg of Concerta. Similar conversions are available for other formulations.[13]

Figure 5.2 illustrates the pharmacokinetic profiles of some common ADHD medications. Evidently, the twice daily use of IR methylphenidate leads to larger peaks and troughs throughout the day. This may induce a marked 'on-and-off effect': with side-effects at the peaks; but break-through and rebound symptoms in the troughs. Extended release preparations tend to yield a smoother profile, with larger 'area under the curve' (AUC), thus greater action effects.

When you review treatment response, it is therefore critical to ask the patient and carer about symptom control throughout the day, and not just a global impression for the whole day. We recommend asking about medication response within 3 or 4 hour-windows thorough the day, in order to titrate the dosage probably across these windows throughout the day. We therefore also recommend that you study the pharmacological profiles of each medication you prescribe.

The next section will focus on the specific ADHD medications and how to use them.

DECIDING ON THE INITIAL TARGETS FOR TREATMENT

Although medications are not the only treatment for ADHD, they are often very effective in reducing the core symptoms of ADHD (inattention, distraction and/or hyperactivity). They may also improve self-esteem, school performance, family functioning, interactions with friends, memory, performance, mood and sleep.

Most children with ADHD presents with multiple additional problems beside their core ADHD symptoms and impairments. This means that it is usually necessary to decide which problem or problems should be tackled first. Sometimes the decision is simple (e.g. child protection concerns or significant suicidality clearly outweigh most other problems), but in many circumstances the choice depends on a combination of severity (actual and perceived), relative importance (to the child, their parents, the school, and the clinician), the availability of an evidence-based treatment, and a combination of rational and pragmatic clinical decision-making. For example poor peer relationships and academic functioning with low self-esteem are often judged to be secondary to ADHD symptoms, in which case it would seem sensible to treat the ADHD symptoms first and observe the impact of this on the other difficulties).

It is very important to be clear and explicit about the overall goals of treatment, what order they will be tackled and also to identify expectations that may not be realistic. In this way patient and parental expectations are more easily met and managed and compliance with treatment is likely to be higher.

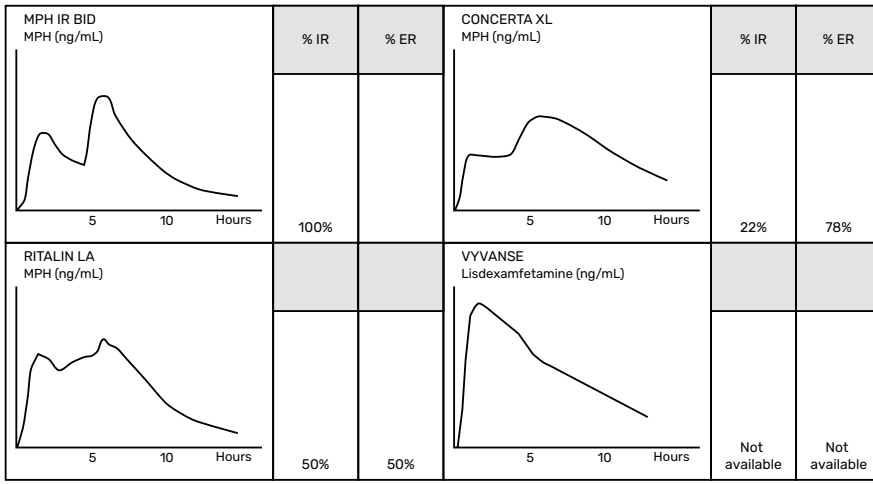


Figure 5.2
Plasma levels of methylphentidate and amphetamin over time with different preparations and their immediate release and extended release proportions.

Broad targets for treatment in ADHD include:

- Core ADHD symptoms both at home and at school
- Oppositional and disruptive behaviour in the home
- Oppositional and disruptive behaviour in at school
- Academic problems
- Parent–child relationship and communication problems
- Peer relationships
- Other associated symptoms (e.g. anxiety, mood instability, depression, motor coordination problems, specific learning disorders, speech and language problems, etc.)

Whilst medications are most effective at treating the core symptoms, they can also impact positively on other problems. When choosing targets for intervention it is important to start to think about how outcomes will be assessed and to take baseline measures so that any changes can be accurately identified.

Psychoeducation forms the cornerstone of all treatment approaches to ADHD and, when medication is to be part of a treatment programme it is essential that the psychoeducation includes giving accurate advice about the medications, their potential effects, positive and negative, the likelihood of response, expected time-

-course of action and understanding of not only the short term but also long-term effects. Every clinician who is prescribing or monitoring ADHD medications needs to have these facts at their fingertips with a script ready to share with patients and their families at a pace that allows them to listen and in a language that they can understand. Whilst it can seem dull and repetitive to give the same story several times a day, week after week, it is important to remember that whilst you have heard the story many times it is new to the patient and they typically only get to hear it once. Time spent explaining things carefully at this stage can pay big dividends later on in terms of acceptance and adherence with treatment recommendations.

Starting treatment with medication

When should we start a medication treatment for ADHD? This used to be a question that was guaranteed to spark a heated debate between clinicians in the USA and Europe. Europe was more conservative and generally medication was reserved for those with severe ADHD and behavioural parent training was preferred for those with mild to moderate symptom and impairment. Whilst there is still a stronger preference for parent training approaches in Europe and many other parts of the world than the US, the differences are now less stark. For example, the most recent NICE guidelines acknowledge the difficulty assessing severity of ADHD and suggest that medication can be considered as a first line treatment for ADHD as long as there is also some effort to provide environmental modifications and provide advice and support about appropriate parent management techniques. [10] When a decision is made to start a medication treatment for ADHD, it is important to think about which medication to use first. This will obviously depend on availability. It is of course very important to take into account any relative contra-indications to ADHD medications. These include: high risk for psychosis, glaucoma, hypertension, and known cardiac risk such as a familial history of congenital arrhythmia.[4]

Choosing the first medication

As noted above there are several medications and several formulations licensed for the treatment of ADHD. It is therefore important to think about the effect size of medication, order in which these should be usually prescribed and under what circumstances these general rules should be broken. Taken together the evidence from clinical trials suggests that there are few differences in overall efficacy, safety and tolerability between methylphenidate and the amphetamine medications (including lisdexamfetamine) but that these psychostimulants are, – at least at the group level, – more effective than the non-stimulants licensed for use in ADHD (atomoxetine, guanfacine and clonidine).[11,14,15] Most guidelines conclude that,

where available, a psychostimulant will generally be the first-choice medication and we would agree with this position. There are circumstances where a clinician may feel it appropriate to start with a non-stimulant medication (atomoxetine, guanfacine or where these are not available clonidine), such as: a current or past history of substance misuse; the presence of tics or anxiety or where there is a strong preference within the family to avoid stimulants. These are relative preferences rather than absolute contraindications to stimulants, and the presence of any one of these conditions should not preclude the use of a stimulant medication.

Amphetamines and methylphenidate appear to be equally effective and have similar adverse event profiles[14] and both are available in many countries as immediate release short acting and extended-release preparations. Where cost is important, and a stimulant is being thought of, the cheaper and more flexible immediate-release preparation will often be the first choice.[5] In low-middle income countries, this might be the only option for primary care physicians. In some countries such as Australia, the government has mandated that a short-acting medication has to be tried first, and that this may only be changed to the intermediate-acting or longer-acting medications if it the short acting does determines significant side effects and the child requires a longer cover during the day. Thus, it is very important to be familiarized with pharmacodynamics and pharmacokinetics properties of this presentation. However, an extended-release methylphenidate preparation or the long acting amphetamine prodrug lisdexamfetamine are also often considered as first-line treatments where: financial constraints are less important; in circumstances where it is deemed important to reduce stigma and increase privacy as is often the case for adolescents; where poor compliance needs to be addressed or when it is particularly important to reduce the chance of diversion. In practice, many clinicians now start with an extended-release preparation and those that still initiate treatment with immediate-release methylphenidate will usually switch most patients to an extended release preparation after titration when the dose is stabilized.

Which extended-release or long acting preparation is chosen will depend first on what is available locally and also on the desired profile of action required across the day. In Europe, regulatory issues restrict the use of lisdexamfetamine to patients who have failed to have an optimal response to methylphenidate. In other countries, it can be considered as a potential first line treatment.

Titrating on to ADHD medications – general principles

Treating ADHD is easy, treating ADHD well takes a lot more skill and effort.

There is strong evidence that ADHD medications are very effective at reducing core ADHD symptoms and that, in many cases, both symptoms and functional impairments can be reduced such that and residual impairment is minimal.[5] For

this to happen, it is essential that the patient be treated with the right medication at optimal doses. Not every patient will respond to every medication and, for the stimulants, it is not possible to predict what the optimal dose will be before starting treatment. It is therefore necessary to individually titrate patients onto each new medication whilst carefully measuring both their response and any adverse effects.

Key to a successful titration is the routine use of standardized instruments to measure treatment response and to also routinely assess for adverse effects. There are a wide range of measures available for assessing treatment response. We suggest the SNAP-IV[16] rating scale as the main measure of ADHD symptoms and response to treatment. It is freely available for clinical use[17] and is most effective when used as a clinician-rated semi-structured interview with parents and patient as the informants. We have found this to be more reliable than the parent rated questionnaire as it allows the clinician to enquire about particular symptoms when it is not clear how persistent, pervasive they are in day to day life. We have also found that when parents are going through a more difficult period with oppositional behaviours they sometimes over score severity of ADHD symptoms as a way of indicating their distress and need for support. For this reason we started to use the oppositional defiant disorders section of the SNAP-IV at every clinic appointment in addition to the standard ADHD questions. This gives parents an opportunity to first discuss their child's oppositional behaviours allowing them to then give a clearer and less prejudicial account of the ADHD symptoms. We also suggest that teacher ratings, using the ten-item SKAMP questionnaire (Murray et al.[18]),[19] are also collected at each appointment. We have found that asking parents to both deliver and pick up the SKAMP from school maximises response rates.

Whilst there is no need for patients starting on ADHD medications to have an ECG (except for the tricyclic antidepressants – see section **"**Other medications used off license to treat ADHD"), all patients or carers should be questioned about potential cardiac risk factors (past cardiac disease, familial history of arrhythmias, unexpected sudden death of a first degree relative before the age of 40 years, frequent syncope on exercise, excessive breathlessness on exercise) and have a cardiac examination (auscultation, blood pressure and cardiac frequency). For adverse effects, it is helpful to use a standardized set of questions that document presence or absence of common adverse effects and to note, where an effect is present, whether or not it is impairing. A list of general side effects expected with ADHD medications are listed in Box 5.1. Pulse, blood pressure, height, and weight should be measured and charted against age- and gender-matched norms. The Dundee ADHD Care Pathway contains a sample pro forma for collecting and recording this type of information in Coghill et al.[20]

It is essential that these measures are first taken at baseline, prior to the first dose of medication, in order that change can be assessed accurately. This is especially important for potential adverse effects as many children with ADHD will have issues with sleep, mood dysregulation, irritability.

Box 5.1
SUMMARY OF MEDICATION ADVERSE EFFECTS

Stimulant medications – methylphenidate, amphetamines, lisdexamfetamine
Relatively common adverse effects include: insomnia; decreased appetite; weight loss; nervousness; agitation; anxiety; low mood; nightmares; stomach pain; nausea; vomiting; dizziness; palpitations; headache; vision problems; tachycardia; hypertension; sweating; skin rash; numbness, tingling, or cold feeling in hands or feet. Whilst some may settle after 2-3 weeks, they need to be monitored and alternative medications considered if they are getting worse. Less common side effects include: exacerbation of motor and vocal tics, aggressiveness/hostility (especially when medication is wearing off) and psychosis.

Non-stimulant – atomoxetine
Relatively common adverse effects include: nausea (which usually settles after a few weeks); dry mouth; appetite loss; insomnia; fatigue; constipation; dizziness; erectile dysfunction; somnolence; abdominal pain; urinary hesitation; tachycardia; hypertension; irritability; abnormal dreams; dyspepsia; ejaculation disorder; increased sweating; vomiting; hot flushes; sensation of tingling, tickling; menstrual disorder; weight loss; depression; sinus headache; dermatitis; mood swings. Uncommon but important adverse effects include suicidal ideation and liver failure.

Non-stimulant – guanfacine
Relatively common adverse effects include: somnolence; dizziness; dry mouth; constipation; nausea; headache; stomach pain; weight gain; irritability. If sedation and somnolence occurs, it is recommended that medication be given at night. It is important for patients to be advised to contact a health professional if they are experiencing more severe adverse effects including: severe dizziness; slow heartbeat; fainting or psychiatric symptoms or mood changes (such as depression, hallucinations, or thoughts of suicide).

Titration on to methylphenidate

Whilst almost all clinical guidelines stress the importance of titration when initiating medication treatments for ADHD, few give any advice about the practicalities of titration in a routine clinic setting. Whilst there are several approaches to titration on to methylphenidate, we believe that a dose optimization titration method is the most effective. Here the child is started on a low dose of methylphenidate (e.g. 5 mg of immediate release twice or three times a day, or the equivalent of an extended-release preparation). Baseline measures are recorded as described above and the child is reviewed after 1-2 weeks (either in person or by telephone), at which time the measures are repeated. If the child has improved, and there is no room for further improvement, one option is to continue treatment at the same dose. It is however not uncommon for parents to report that symptoms have been optimised after the initial dose, because they have been surprised by how much the

symptoms have improved, only to realise later that there was actually still quite a lot of room for improvement. For this reason, we have tended to increase the dose until there is clearly no improvement between doses and then revert to the lowest dose with the maximum benefit and least adverse effects. [9]

When there is still some room for improvement, the dose is increased to the next level (e.g. from 5 to 10 mg immediate release) and the patient is again reviewed after 1 to 2 weeks. It is usually best to start a new dose over a weekend, so that parents are the first to evaluate both the positive effects and new or worsening of adverse effects.

Titration is continued until there is either no further room for improvement, there are significant adverse effects, or the maximum routine dose is reached (usually 20 mg three times daily for immediate release methylphenidate). For younger and smaller children (< 25 kg), we pause the titration at 15 mg as tolerability problems are more common above this dose in this group of children. However, if there are no adverse effects at this point, we will, cautiously, increase the dose if clinically indicated.

Whilst guidelines such as those from the European ADHD Guideline Group recommend a maximum daily dose of around 100mg methylphenidate, [4] we recommend that doses higher than 60mg are normally only considered when there is already a clear, but not yet optimal, response to the 60 mg dose.

How do you know when treatment is optimised? Whilst it is important to look at each case on its own merits, we are able to give some general guidance about the interpretation of scores on the SNAP-IV (and SKAMP) rating scales (Table 5.1). The easiest way to interpret these scores is to calculate the mean score per item. Then one is aiming to achieve a score of <1 for the total score and the hyperactive/impulsive and inattentive subscales.

By the end of the titration period the clinician will decide whether the patient:

1 has responded best to a particular dose;
2 has responded but cannot tolerate the optimal dose due to adverse effects, and either:
   – shows an acceptable response, with no or tolerable adverse effects at a lower dose or,
   – does not show an acceptable response at a lower dose
3 has not responded at any dose

Whilst this approach to titration is acceptable to most families, there is a less intensive strategy which may be more practical in some situations. Here parents give an initial 5 mg dose of immediate release methylphenidate on a weekend/holiday morning and introduce a cognitively demanding task about one hour later, and observe the general effect. If there are no adverse effects this can be followed by a 10 mg dose on another weekend/holiday morning (and 15 mg on another in te-

Table 5.1
CLINICAL INTERPRETATION OF SCORES FROM THE SNAP-IV RATING SCALE

SNAP-IV Rating Scale score				Post-treatment monitoring
Total score (range 0–54)	**Mean item total score[a]**	**Subscale[b] score (range 0–27)**	**Mean item subscale score[a]**	**Clinical interpretation**
0–18	≤1	0–9	≤1	Very good/optimal response: symptoms well within normal range
19–26	<1.5	10–13	<1.5	Good response: symptoms within normal range but may be improved
27–36	1.5–2	14–18	1.5–2	Response still clinically significant: symptoms just outside normal range and response probably inadequate. Need to assess other factors
37–54	>2	19–27	>2	Inadequate response: many symptoms still observed. Need to assess other factors

[a] Calculated by dividing the total/subscale score by the number of items (18 for the total; 9 for each subscale); [b] Inattention or Hyperactivity/Impulsivity subscales.
SNAP-IV, Swanson, Nolan and Pelham-IV Rating Scale.

enagers). Parents then draw conclusions about tolerability and likely effect. If this is favourable the trial can be extended to mornings during the school week with the teacher measuring effect with a standardized rating scale (e.g. the SKAMP). Where effectiveness is established, it is still necessary to try to optimize dose and again one should aim for maximum response, with minimal adverse effects at the minimum dose. It is important to remember that some adverse common effects such as loss of appetite or sleep problems can be managed by adjusting routines or the timing of doses.

Titration on to dexamfetamine

A titration on to dexamfetamine can follow the same procedures described for methylphenidate but with reduced doses (5 mg methylphenidate ≈ 2.5 mg dexamfetamine). As the half-life of dexamfetamine is somewhat longer than that of

methylphenidate, some children only require twice daily dosing whilst others still gain benefit from the addition of a third dose.

Titration on to lisdexamfetamine

A similar approach to that described for methylphenidate can be used with lisdexamfetamine with a starting dose of 30 mg, increased to 50 mg and then to 70 mg once daily as required. Unlike for methylphenidate, where it is possible to calculate the appropriate dose for switching between immediate release and extended release preparations, this approach is not possible for lisdexamfetamine and dexamfetamine. Due to important differences in the pharmacokinetics and pharmacodynamics, it is not possible to calculate equivalent doses for these two medications. So, whilst a positive response to dexamfetamine does suggest that a patient is likely to respond to lisdexamfetamine, it is still necessary to independently titrate when switching between the two medications. Treatment response and adverse effects should be assessed in the same way as described above for methylphenidate.

Titration on to atomoxetine

Atomoxetine is prescribed for children and adolescents in a dose per weight (mg/kg) and is therefore generally simpler to titrate than the stimulants. The standard protocol for titration on to atomoxetine is to start at a dose of 0.5 mg/kg, once daily for a week. The purpose of this first week is to reduce difficulties with initial adverse effects (especially nausea, which is very common but usually transient). The dose is then increased up to 1.2 mg/kg and continued at this dose. For older adolescents and adults, the maximum dose is capped at 100 mg/day. Whilst many of those who are going to show a response will report some positive effects after three to four weeks, a small but significant number of patients are late responders. We therefore recommend that patients are made aware of this when starting on atomoxetine and that treatment is continued for 12 weeks before a decision about response/non-response is made. When there is a partial response on 1.2 mg/kg, it is acceptable to increase the dose up to 1.8 mg/kg. (Up to a maximum of 100 mg/day). Where there has been no response after 12 weeks, we will usually switch to an alternative treatment. Treatment response and adverse effects are again assessed using the same protocols that were described for methylphenidate.

Titrating on to extended release guanfacine and clonidine

Extended release guanfacine is designed to be taken once daily and this can be either in the morning or evening. The recommendation is to begin at a dose of 1 mg/day. Adjustments should be done in increments of no more than 1 mg/week

depending on response. For children, our practice is to initiate treatment at the recommended dose of 1mg for one week and then increase to 2mg for another week. Whilst there are a very small number of patients who do respond to these very low doses, the main purpose of this phase is to assess potential adverse effects (especially somnolence, bradycardia and hypotension). We then increase the dose to 3mg and reassess for clinical response after another six weeks. If there is no response at this dose, it is unlikely that response will occur at a higher dose. Where there has been a partial response at 3mg, we will increase doses to 4mg (and further for adolescents). Clinical trials identified a dose- and exposure-related response for both clinical improvement and several adverse events (hypotension, bradycardia, sedation). To provide a balance between benefits and risks, it is recommended that the target dose range is between 0.05 and 0.12 mg/kg/day with a total daily dose between 1-7 mg (See Table 5.2). Following discontinuation of guanfacine it is possible for patients to experience increases in blood pressure and heart rate. It is therefore important to instruct patients and their caregivers not to discontinue their medication without consulting their doctor. Pulse and blood pressure should be monitored when reducing the dose or discontinuing this medication. Good practice is to taper the dose down in decrements of no more than 1 mg every 3 to 7 days to avoid possible rebound hypertension. For those living in hot countries, it is also very important to pay close attention to hydration status as dehydration may result in more extreme degrees of hypotension and bradycardia.

Table 5.2
RECOMMENDED TARGET DOSE RANGE FOR THERAPY WITH EXTENDED RELEASE GUANFACINE

Weight	**Target dose range (0.05 – 0.12 mg/kg/day)**
25-33.9 kg	2-3 mg/day
34-41.4 kg	2-4 mg/day
41.5-49.4 kg	3-5 mg/day
49.5-58.4 kg	3-6 mg/day
58.5-91 kg	4-7 mg/day
>91 kg	5-7 mg/day

Doses above 4 mg/day have not been evaluated in children (ages 6-12 years)
Doses above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)

Clonidine has been less well studied as a treatment for ADHD and is only licensed for use in the USA which is also the only country to have an extended release formulation of clonidine. In other countries clinicians may use immediate release clonidine, usually as an add on medication, but in some countries where other ADHD medications are not available it may be used as a monotherapy. It is difficult to give firm advice about titration and dosing as this has not been well studied. Starting doses are usually around 0.1mg/day increasing up to around 0.3mg/day. One problem with immediate release clonidine is the short duration of action and it would require at least four time a day dosing to achieve coverage across the day. When using clonidine similar precautions to those described for guanfacine should be followed. Note that clonidine and guanfacine should *never* be used in combination.

MONITORING ONGOING TREATMENT AND SIDE EFFECTS

Having established and stabilized an effective and optimized medication treatment, it is important to put a system in place to monitor ongoing treatment. Whilst a proportion of patients will continue to do well with minimal attention, many will require closer monitoring, either to ensure clinical response continues to be optimal or to minimize the impact of adverse effects. Whilst it is also essential to monitor and manage comorbidities, this is beyond the scope of the current chapter and we will restrict our discussion to the impact of comorbidities on medication treatments (see section "Special circumstances").

Several studies including the influential Multimodal Treatment of ADHD (MTA) study have reported that the long-term outcomes for ADHD treated in a community are much less positive than those reported in short term clinical trials.[21,22] We have argued that this is likely to be due to the reduced focus on adjusting treatment according to accurately measured clinical outcomes in routine practice.[23] As with chronic physical illnesses like diabetes, asthma and hypertension, close monitoring of psychiatric symptoms can significantly improve outcomes.[24] There is preliminary evidence that this is also the case for ADHD.[9] We therefore

Link in this

https://www.additudemag.com/straight-answers-are-medications-safe/

recommend that both treatment response and adverse effects are routinely monitored for the duration of treatment and that their assessment is allocated adequate time and consideration. We also recommend getting feedback from teachers and young people, as well as parents.

We have demonstrated that is not necessary, from a clinical perspective, for senior medical staff to conduct all follow up visits. Indeed, it is possible for junior medical staff and nurses to provide high-quality care with an adequate protocol through a well organised clinical pathway.[9] The same protocol, assessment schedule, and measurement tools used when initiating and titrating on to medication can be used for continuing care clinics.

It is good practice to routinely and regularly make sure that an individual continues to require their medication. This is most often conducted by a trial off medication. As noted above, when stopping guanfacine and clonidine, it is good practice to taper the dose down gradually over a period of several days to avoid possible rebound hypertension. For the stimulants and atomoxetine, it is acceptable to stop them abruptly without dose tapering. It is generally recommended that an individual has a planned withdrawal from medication at least once a year while on stimulants to assess whether symptoms and impairment return. This is usually carried out in the long school holidays, as it does not interfere with their school work. A continued need for medication is more difficult to demonstrate with atomoxetine in view of its different mechanism of action and in particular because it has a more long-term pharmacodynamic effect. If a short withdrawal of atomoxetine results in a recurrence of symptoms, then one can conclude it should be restarted. If, however, symptoms do not immediately return after a short-term withdrawal, it is still possible that they will return after a longer break. The problem for many families is that if symptoms do return after a moderate to long withdrawal, even when atomoxetine is restarted it may take several weeks for the symptoms to resolve again. This might be a problem for families considering that it might take some time to get another appointment at the clinic. There is no simple solution other than to ensure that withdrawal is monitored closely, and that the patient has quick and easy access to the clinic as required. Evidence from discontinuation studies suggest that for guanfacine there is often also a somewhat extended period before full symptoms return although the timescale is somewhat shorter than seen for atomoxetine.

Adverse effects of medication

Although there are several adverse effects associated with ADHD medication, some of them, such as sleep difficulties and irritability may already be present before starting on medication. Stimulants are tolerated well in the short term when used optimally. As long-term randomized, placebo controlled studies are not feasible and long-term naturalistic studies are limited by absence of controls, there

are still significant gaps in the literature, although this scenario is improving.[25] The effect on growth is often a reason for worries for parents and the most recent data does suggest that long term stimulant medication is associated with a modest reduction in adult height of around 2.5 cm.[21] A summary of adverse effects for stimulant and non-stimulant medication is shown in Box 5.1. Non-stimulants have less effect on appetite but can result in somnolence rather than the insomnia that is more common with stimulants. Indeed, somnolence is the most frequently reported adverse effect for guanfacine and clonidine. The safety of the stimulants and atomoxetine have been comprehensively reviewed.[26,27] Atomoxetine has a black box warning for suicidal ideation. Whilst the association between suicidality and atomoxetine is unclear and occurrence is rare, it is important to monitor during treatment. It is our policy to ask about suicidality, which is more common in ADHD, at every visit irrespective of what treatment is being prescribed. Atomoxetine can rarely cause reversible liver damage (1 in a million), which most typically presents as jaundice. If this occurs, medication should be discontinued, and patient reviewed urgently.

It is also important to continue to monitor and chart growth, weight, heart rate and blood pressure throughout treatment and to make appropriate accommodations and referrals should these deviate significantly from expected age and sex adjusted norms. The issue of switching medications as a consequence of adverse effects is discussed in section "Adjusting and switching treatment" below. For further suggestions about the management of adverse effects see Graham et al.[6] e Cortese et al.[8] The risk of serious cardiovascular adverse effects secondary to ADHD medications is low[28] especially where an efficient cardiac screen has been conducted prior to starting treatment. It is also advised that patients are asked about cardiac symptoms (excessive breathlessness or chest pain on exertion and frequent syncope) at each follow up visit.[7] There are however still valid concerns for the psychostimulants and atomoxetine about increases in pulse and blood pressure. For most, these increases are moderate, however a minority do develop iatrogenic hypertension. Whilst this can be managed by reducing or stopping the ADHD medication, this will often result in problematic return of symptoms. Following a full clinical evaluation and investigation of hypertension, another option is to add in or switch to guanfacine or clonidine (which lower blood pressure) or to treat the hypertension.[7] Of course, this cannot happen unless the problem is identified. It is therefore essential that pulse and blood pressure is taken at each follow-up visit and the results should compared to age, sex and height standardised charts.[9]

ADJUSTING AND SWITCHING TREATMENT

Where there is a failure to respond to a particular treatment or when a patient is unable to tolerate a particular treatment due to adverse effects, it is necessary to

consider either adjusting or switching treatment. In general, whilst the problems may have been recognized within primary care, such alterations to the treatment plan should usually be carried out by specialists within child and mental health services or paediatrics. This is particularly true when non-response is expected as there are several general considerations that need to be addressed before a decision can be made about the most appropriate clinical response. These include reviewing dosage (always ensure an adequate dose has been applied before switching treatment), addressing compliance issues (motivational interviewing may help compliance and if on an immediate-release preparation try an extended-release one), and diagnosis. It is also important to ensure that apparent non-response is not actually due to a co-existing disorder or problem that is not currently being treated. These and other questions that should be considered before switching treatments are described in Box 5.2.

For stimulants the general rule is that 70% of patients have a strong clinical response to methylphenidate and 70% to an amphetamine with between 90 and 95% responding well to one or the other (of course not all of those with a good clinical response can tolerate that medication). Whilst it is sometimes the case that a patient who has adverse effects to one stimulant will have similar problems with the other, this is by no means always the case. When a patient has failed to respond or has had intolerable adverse effects to their first stimulant, it is usually ok to consider switching to the other class (i.e. from methylphenidate to an amphetamine or from an amphetamine to methylphenidate). Of course, some patients, particularly those with adverse effects, will be uncomfortable about such a switch and their wishes should always be taken into account.

For those who have failed to respond to both stimulants classes a switch to one of the non-stimulants (atomoxetine or extended release guanfacine [or extended release clonidine in the US]) will often be the most appropriate choice. As there

Box 5.2
QUESTIONS YOU SHOULD ASK BEFORE CHANGING TO ANOTHER DRUG

- Have I titrated properly?
- Is the patient at the maximum dose?
- Is this drug/preparation working well at any times during the day?
- Have I got good enough information from school?
- Are parents and school in agreement about the effects of the drug?
- Am I targeting the right symptoms?
- Is there a behavioural explanation for the drug "wearing off"?
- What else is going on in patient's life / family life?
- Is the medication working but effects limited by side effects?
- Have I missed any comorbidity?
- Is the diagnosis right?

are no data to help predict who will respond to any of the ADHD medications, each new medication must be tried and tested one drug at a time. For those who have a partial response to a stimulant, it may be appropriate to consider adding in an alpha 2 agonist (guanfacine or clonidine), which have a very different adverse event and safety profile compared to one of stimulants and atomoxetine making combination treatment much safer than adding atomoxetine to a stimulant.

SPECIAL CIRCUMSTANCES

When ADHD occurs in association with other disorders some adjustment to the treatment plan may be required. Whilst there is often few formal evidence on which to base these decisions, the following recommendations can be made:

ADHD + depression

The clinician should determine which disorder requires to be addressed first. If it is the depression that is causing the most severe impairments and concern, then usual treatment guidelines for depression should be followed, after which, the ADHD symptoms can be addressed following the principles outlined above. Where the ADHD is to be treated first, stimulant medication, if required, should be titrated carefully as this may further lower mood. Otherwise treatment should follow the usual pathway with secondary treatments being offered for depression should this not resolve with treatment of the ADHD. The potential for drug × drug interactions should be remembered. This is particularly relevant for atomoxetine and fluoxetine, both of which are metabolised by CYP2D6 and co-prescription can lead to increased levels of both drugs.

ADHD + anxiety

Whilst there is some evidence to suggest that those with ADHD with comorbid anxiety disorders do not always respond as well to methylphenidate as those without, this is not the same as saying that stimulants are ineffective in the presence of anxiety, and anxiety is certainly not a contraindication. The MTA study reported no adverse effects of anxiety on medication response for core ADHD or other outcomes but did suggest that parent rated outcomes for those with comorbid anxiety were improved by the addition of psychosocial treatment.[29] There is some evidence to suggest that atomoxetine may reduce anxiety symptoms in the presence of ADHD and it may therefore be considered in such cases. However, a further assessment of additional psychological stresses on the child is always in order, and if these cannot be simply alleviated, then psychological treatment may have more to offer than repeated trials of medication.

ADHD + tics

Comorbid tics may sometimes be worsened by stimulants. This is not inevitable, and stimulants are sometimes useful even for the hyperactivity seen in Tourette's syndrome. Guanfacine and clonidine are alternatives, since both, have demonstrated to reduce tics in addition to their effectiveness in ADHD.[30] Atomoxetine is also an option which appears less likely to exacerbate tics than stimulants. Where guanfacine, clonidine and atomoxetine are ineffective at reducing the tics and they continue to cause significant psychosocial impairment or where methylphenidate, whilst effective for the core ADHD symptoms, is exacerbating tics (and where a dosage reduction does not lead to an improvement), the use of a tic-reducing medication either as a monotherapy or in parallel with ADHD medication (e.g. aripiprazole, risperidone, pimozide, tiapride, SSRI's) seems to be indicated. Some drug interaction checkers warn against the combination of stimulants with the alpha--2-agonists guanfacine and clonidine for possible heart rhythm problems. In general, the risk would appear to be low, however particular care should be taken in cases of pre-existing vulnerability; i.e. where there is personal or family history of arrhythmias, cardiac malformations, or sudden unexpected death.[31] Also, the risks for rebound hypertension after a sudden stopping of the alpha-2-agonists when given alongside a stimulant may be increased and therefore due care should be exercised with slower tapering of the alpha-2-agonist should it need to be stopped. Behavioural therapy may also be helpful for tics and obsessive symptoms.

ADHD + autism spectrum disorder

It is always appropriate for these, usually complex, cases to be seen by a multidisciplinary team of specialist services. There is little trial evidence, but we suggest that where ADHD is comorbid with autism, a trial of medication for the symptoms of ADHD should be considered. Medications should be started at the lowest practical dose and titrated slowly and carefully as these children are more likely to suffer from adverse effects, even at low doses. Stimulants are often the most helpful with the strongest evidence for methylphenidate. Atomoxetine, clonidine, guanfacine, and even risperidone and aripiprazole may have their place. Behavioural therapy, targeting the ADHD symptoms, is also widely applicable.

ADHD + substance misuse

There is little in the way of research evidence to guide clinicians when treating those with ADHD and an established substance-misuse disorder. Treatment plans should address both disorders and should include psychosocial interventions aimed at reducing substance misuse and preventing relapse. There are indications that effective treatment of core ADHD symptoms may enhance effective treatment of substance misuse. Pharmacological therapies for ADHD should be star-

ted with caution and under close supervision. Atomoxetine is unlikely to be abused and extended-release stimulants or lisdexamfetamine are less capable of being abused than their immediate-release counterparts. In some regions (e.g. Western Australia), patients who take un-prescribed medications are not allowed stimulant medications and need to have evidence of this through regular drug testing.

OTHER MEDICATIONS USED OFF LICENSE TO TREAT ADHD

Bupropion

Bupropion, an antidepressant, has been shown to be better than placebo in treating ADHD symptoms in children. Its efficacy is however smaller than that of stimulants. Bupropion can cause nausea, insomnia, and palpitations; it can also trigger tics and cause dermatological reactions, such as rash and urticaria, which may be severe and require discontinuation. Bupropion also increases the risk of seizures, but this effect is minimised if the dose is maintained within 300 mg/day.

Tricyclic antidepressants

Imipramine, desipramine, nortriptyline, amitriptyline and clomipramine have all been demonstrated to be superior to placebo for the treatment of ADHD symptoms, but they are less effective than stimulants. They are rarely used due to realistic concerns about potential cardiotoxicity. Sudden and unexplained deaths have been reported in children receiving therapeutic doses of tricyclic, most often desipramine and they are also very dangerous in overdose. Despite these concerns, there may still be a limited place for tricyclics in countries where no other ADHD medications are available. Whilst the clearest evidence for efficacy relates to desipramine, the potential for sudden death limits its use and it may be prudent, if a tricyclic is to be used at all, to consider imipramine or nortriptyline ahead of desipramine. A starting dose of between 10-25 mg once a day is usual, this can be

Link in this

https://www.youtube.com/watch?v=rD9qK8-sMGQ

gradually raised after several days to b.i.d. dosing and then further adjusted based on clinical effects and adverse effects. The patient should receive a complete physical examination with ECG recording before starting treatment. Treatment should be considered only if the following limits are not exceeded on the ECG: 200 msec for the PR, 120 msec for the QRS, and 450 msec for the QTc, and the heart rate should be regular and not higher than 100 bpm. If there is personal history of arrhythmias, dizziness, fainting, palpitation, or heart abnormalities, a more thorough evaluation by a cardiologist is appropriate. Family history of sudden unexpected death or life-threatening arrhythmias should be reason for avoiding use of tricyclic medication. Clinical effects may become evident after a few days, but full response may take weeks and the dose usually needs multiple adjustments. The usual therapeutic dose is between 0.7 and 3.5 mg/kg/day. The ECG, pulse, and blood pressure should be monitored when a steady state is reached (usually after 4-5 days of treatment) and each time the dose is increased above 3 mg/kg/day. Abrupt discontinuation can trigger withdrawal symptoms, such as nausea, vomiting, headache, lethargy, flu-like symptoms. To prevent withdrawal symptoms, the medication should be tapered off gradually, decreasing the dose by 10-25 mg every 2-3 days until complete discontinuation.

Atypical antipsychotics

Whilst there is limited evidence to support an effect of atypical antipsychotics on aggressive behaviours, especially in the context of autism spectrum disorder, there is no evidence to suggest that these are effective medications for treating ADHD. In addition, the evidence that children and adolescents treated with atypicals are at increased risk of serious adverse effects including dystonias, dyskinesias and metabolic syndrome is convincing.

Conflicts of interest

Prof. Coghill reports grants from The European Union FP7 Programme and Shire; honoraria from Shire, Eli-Lilly, Novartis, and Janssen-Cilag; acted as an advisor to Shire and Lundbeck; and received royalties from Oxford University Press. He was a member of British Association for Psychopharmacology ADHD, Depression and Bipolar Disorder Guideline groups. Professors Silva and Chen report no conflict of interest.

REFERENCES

1. Hinshaw SP, Scheffler RM, Fulton BD, Aase H, Banaschewski T, Cheng W, et al. International variation in treatment procedures for ADHD: social context and recent trends. Psychiatr Serv. 2011;62(5):459-64.

2. Australian Comission on Safety and Quality in Health Care. Attention deficit hyperactivity disorder medicines dispensing 17 years and under. In: Australian Comission on Safety and Quality in Health Care. Australian atlas of healthcare variation. Sydney: Australian Commission on Safety and Quality in Health Care, 2015. Cap. 4.10, p. 249-256.

3. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. Lancet Psychiatry. 2018;5(2):175-186.

4. Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, et al. European clinical guidelines for hyperkinetic disorder -- first upgrade. Eur Child Adolesc Psychiatry. 2004;13 Suppl 1:I7-30.

5. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, et al. Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry. 2006;15(8):476-95.

6. Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, et al. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry. 2011;20(1):17-37.

7. Hamilton RM, Rosenthal E, Hulpke-Wette M, Graham JG, Sergeant J, European Network of Hyperkinetic Disorders. Cardiovascular considerations of attention deficit hyperactivity disorder medications: a report of the European Network on Hyperactivity Disorders work group, European Attention Deficit Hyperactivity Disorder Guidelines Group on attention deficit hyperactivity disorder drug safety meeting. Cardiol Young. 2012;22(1):63-70.

8. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry. 2013;54(3):227-46.

9. Coghill D, Seth S. Effective management of attention-deficit/hyperactivity disorder (ADHD) through structured re-assessment: the Dundee ADHD Clinical Care Pathway. Child Adolesc Psychiatry Ment Health. 2015;9:52.

10. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management. London: NICE, 2018.

11. Huss M, Chen W, Ludolph AG. Guanfacine extended release: a new pharmacological treatment option in Europe. Clin Drug Investig. 2016;36(1):1-25.

12. Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2012;51(4):356-67.

13. Coghill D, Sinita E. Pharmacology for ADHD, tourette syndrome and autism spectrum disorder. In: Huline-Dickens S, editor. Clinical topics in child and adolescent psychiatry. London: Royal College of Psychiatrists, 2014. p. 74-93.

14. Hodgkins P, Shaw M, Coghill D, Hechtman L. Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. Eur Child Adolesc Psychiatry. 2012;21(9):477-92.

15. Savill NC, Buitelaar JK, Anand E, Day KA, Treuer T, Upadhyaya HP, et al. The efficacy of atomoxetine for the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a comprehensive review of over a decade of clinical research. CNS Drugs. 2015;29(2):131-51.

16. Swanson JM. SNAP-IV 26-item teacher and parent rating scale. Hamilton: Collaborative Mental Health Care, [s. d.]. Disponível em: http://www.shared-care.ca/files/Scoring_for_SNAP_IV_Guide_26-item.pdf. Acesso em: 16 nov. 2018.

17. Bussing R, Fernandez M, Harwood M, Wei Hou, Garvan CW, Eyberg SM, et al. Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: psychometric properties and normative ratings from a school district sample. Assessment. 2008;15(3):317-28.

18. Murray DW, Bussing R, Fernandez M, Wei Hou, Garvan CW, Swanson JM, et al. Psychometric properties of teacher SKAMP ratings from a community sample. Assessment. 2009;16(2):193-208.

19. Wigal SB, Gupta S, Guinta D, Swanson JM. Reliability and validity of the SKAMP rating scale in a laboratory school setting. Psychopharmacol Bull. 1998;34(1):47-53.

20. Coghill D, Lim SC, Gomez Flores L, Seth S, Dunlop G, Geddes A, et al. Dundee ADHD continuing care proforma (revised). Dundee: University of Dundee, 2015. Disponível em: https://discovery.dundee.ac.uk/en/datasets/dundee-adhd-continuing-care-proforma-revised. Acesso em: 16 nov. 2018.

21. Swanson JM, Arnold LE, Molina BSG, Sibley MH, Hechtman LT, Hinshaw SP, et al. Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry. 2017;58(6):663-678.

22. Langley K, Fowler T, Ford T, Thapar AK, van den Bree M, Harold G,et al. Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. Br J Psychiatry. 2010;196(3):235-40.

23. Banaschewski T, Buitelaar J, Coghill DR, Sergeant JA, Sonuga-Barke E, Zuddas A, et al. The MTA at 8. J Am Acad Child Adolesc Psychiatry. 2009;48(11):1120-1; author reply 1123-4.

24. Knaup C, Koesters M, Schoefer D, Becker T, Puschner B. Effect of feedback of treatment outcome in specialist mental healthcare: meta-analysis. Br J Psychiatry. 2009;195(1):15-22.

25. Craig SG, Davies G, Schibuk L, Weiss MD. Long-term effects of stimulant treatment for ADHD: what can we tell our patients? Current Developmental Disorders Reports. 2015;2(1):1-9.

26. Reed VA, Buitelaar JK, Anand E, Day KA, Treuer T, Upadhyaya HP, et al. The safety of atomoxetine for the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a comprehensive review of over a decade of research. CNS Drugs. 2016;30(7):603-28.

27. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs. 2008;22(3):213-37.

28. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, et al. Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine. CNS Drugs. 2017;31(3):199-215.

29. March JS, Swanson JM, Arnold LE, Hoza B, Conners CK, Hinshaw SP, et al. Anxiety as a predictor and outcome variable in the multimodal treatment study of children with ADHD (MTA). J Abnorm Child Psychol. 2000;28(6):527-41.

30. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry. 2011;20(4):173-96.

31. Vitiello B. Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatr Clin N Am. 2008;17(2):459-74, xi.

6

TALKING ABOUT **ADHD** WITH PATIENTS AND THEIR FAMILIES

Luis Augusto **Rohde**
Olayinka Olusola **Omigbodun**
Manfred **Gerlach**
Yi **Zheng**

Attention-Deficit/Hyperactivity Disorder (ADHD) is at the same time one of the most prevalent and the most controversial mental disorder of childhood. This chapter aims to discuss some doubts and myths families frequently have about Attention--Deficit/Hyperactivity Disorder (ADHD). The authors provide simple ways for pediatricians, family doctors and mental health professionals in Low-Middle Income Countries (LMIC) to translate current scientific knowledge about the disorder to families using examples in an accessible language.

Following a search of the scientific literature and Internet sites for patients with ADHD and their families, ten most frequent doubts and myths about ADHD were identified and are listing as follows:

1. ADHD is not a real disorder, everybody has a bit of it!
2. There are no brain abnormalities or dysfunction in ADHD.
3. How can a child who spends hours focused in a videogame have ADHD? Isn't ADHD just a new name for laziness or lack of willpower?
4. ADHD is a disorder caused by demands of the modern society.
5. How can my child have ADHD if he/she is not hyperactive?
6. Is ADHD my fault for not giving enough discipline to my child?
7. ADHD only occurs in children.

8. How about the future? Will my child always will have ADHD?
9. Children with ADHD are less intelligent.
10. Children who take ADHD medication are more likely to abuse drugs when they become teenagers.

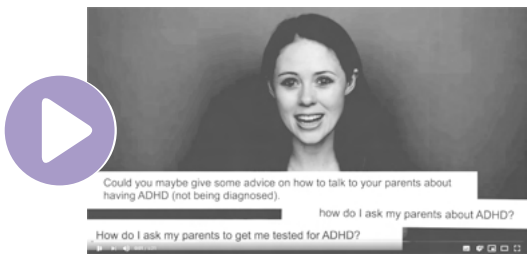
Pediatricians, family doctors, mental health professionals in LMIC are overloaded with clinical work, making it difficult for them to have enough time during appointments with patients with ADHD to fully address their concerns and doubts about the disorder. However, not addressing these issues poses a great risk for treatment adherence. A robust literature documents that compliance with medical recommendations depend on clear understanding about the disorder, risks of treatment and no treatment.[1] Since patients with ADHD might have some symptoms like forgetfulness and impulsivity and personal traits like high risk-taking that interfere even more with treatment adherence, addressing their doubts is essential. Otherwise, they are left to get information about the disorder from the Internet and/or lay media and this does not always portray ADHD adequately.[2] However, exceptions that can be shared with families as seen on website with link.

At the end of this chapter, several ways we and others describe ADHD to patients and families are presented. However, let's begin by addressing the 10 myths/frequent doubts!

THE 10 MYTHS/FREQUENT DOUBTS ABOUT ADHD

ADHD IS NOT A REAL DISORDER? EVERYBODY HAS A LITTLE BIT OF IT!

Probably there is no month without a report in one of the major newspapers/magazines worldwide or TV shows portraying ADHD as a disorder that is not real, or as a condition invented by the pharmaceutical industry to sell medication. Several



Link in this

https://www.youtube.com/watch?v=YsREaxPHlZU

authors, mainly from areas like social psychology, also argue that ADHD is not a valid disorder.[3] This situation brings a lot of confusion, uncertainty and fear for families facing a diagnosis of ADHD for the first time.

In a close look on these articles, the core arguments made tend to be: a) Everybody has a touch of inattention and/or hyperactivity; b) there is no biological marker for the disorder. The first issue will be tackled here and the second will be addressed in the next section.

Data from neuroimaging and genetic studies, as presented in previous chapters and in the literature,[4] clearly indicate that ADHD is dimensional and not a categorical condition. A categorical condition is one which is, either present or absent. Examples are an infection by bacteria where either we have the infection or not. Pregnancy is also a categorical medical condition as there is either a pregnancy or not. There is nothing in between.

Inattention, hyperactivity and impulsivity are distributed in the population on a continuum (see video), similar to other medical variables like blood pressure, cholesterol and glucose levels. To define a condition on a dimension, a cutoff point is established whereby the chance for impairment increases above the cutoff. Persons with ADHD are at the end of this continuum in a zone where the intensity of symptoms is associated with impairment in their lives, such as a proneness for accidents, unexpected pregnancy or sexually transmitted disorders in adolescence, and higher academic failure among others.[5]

Everybody has a level of blood pressure, but this does not make hypertension, which is defined as a blood pressure above a certain threshold clearly associated with impairment, an unreal disorder! In the mental health arena, there are several other examples of dimensional disorders like depression and social anxiety and generalized anxiety. Again, the fact that most people tend to have some level of performance anxiety does not make those with extreme levels of constant performance anxiety unleashed by small triggers and associated with other symptoms like insomnia, muscle tension and emotional suffering not deserving of an assessment, diagnosis and care.

Link in this

https://www.youtube.com/watch?v=rqOBvsGtTb0

That said, it is always important to check that the threshold is set at the right point and that pressures from families, society or private interests like those from the pharmaceutical industry are not influencing the cut off point.

Finally, the definition of ADHD is not only based on the severity of symptoms causing impairment but also on the pervasiveness of them in different settings of life. This approach will help to differentiate ADHD from conditions that are a reaction to specific triggers in the environment such as inattentiveness only in the classroom setting because of an inadequate teaching method.

THERE ARE NO BRAIN ABNORMALITIES OR DYSFUNCTIONS IN ADHD

Probably, the most cited argument against the validity of ADHD is that science has never found a brain abnormality that exists in all individuals affected by the disorder. This is a true assertion used in wrong way. Science will never find a single brain abnormality in all ADHD brains.

This is why: ADHD is a syndrome, which means that individuals with the disorder have different profiles of symptoms in one of the two dimensions that characterize the disorder, inattention and hyperactivity/impulsivity. In some populations, impulsivity and hyperactivity form different dimensions and we have three and not two dimensions. We call this phenomenon phenotypic heterogeneity meaning that, as not all humans are equal, not all patients with ADHD have the same symptoms. Thus, we have some brain abnormalities that are probably related to a specific group of symptoms in each of these dimensions. Whenever a group of patients with ADHD have a scan in a Magnetic Resonance Imaging (MRI), differences are detected in their brains compared to individuals without ADHD, but the same brain abnormality is not present in all brains due to the phenotypic heterogeneity. Figure 6.1 below, illustrates a picture of what information ADHD research provides so far and what additional information is needed. Imagine that each point represents a specific characteristic of the brain of one individual (e.g., thickness of the pre-frontal cortex). In Figure 6.1A, you have where we are. When you calculate the mean of the thickness of the pre-frontal cortex of individuals in group 1 (ADHD), it is significantly lower than the one for group 2 (individuals without ADHD), but, as you can see, several individuals with ADHD (group 1) have the same thickness of the pre-frontal cortex than those of individuals without ADHD (group 2). They are probably different in other structural and/or functional brain characteristics compared to individuals without ADHD. The challenge is to have a composite measure including several structural and functional brain characteristics that can separate groups as in Figure 6.1B. With better scans, larger samples of patients and sophisticated new data analytic techniques as machine learning, we are getting closer!

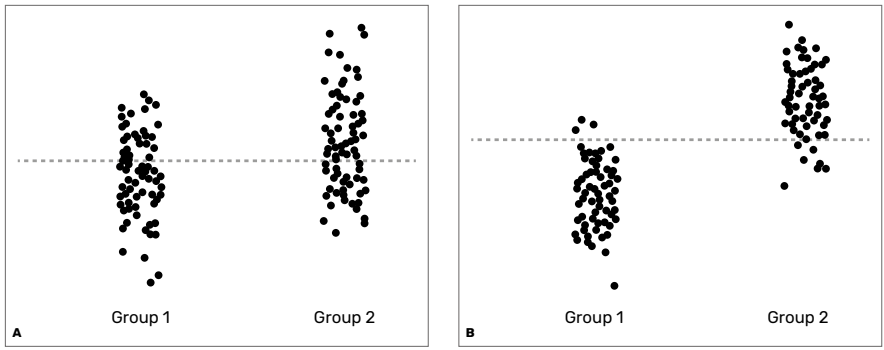


Figure 6.1
Statistical significant between group differences **(A)** and group differences with sufficient magnitude to inform biomarkers **(B)**.

Regarding group differences between individuals with ADHD and typically developing subjects, a group of investigators led by colleagues in the Netherlands recently published a mega-analysis comparing more than 1700 brain scans of subjects with ADHD with around 1500 brain scans of individuals without ADHD. They found that several brain areas were different as a group in subjects with ADHD. Specifically, the volumes of the several parts of the brain such as the accumbens, amygdala, caudate, hippocampus, putamen, and the total brain volume were smaller in individuals with ADHD compared with controls.[6]

Finally, it is always important to remember that if the lack of a single brain abnormality in all ADHD brains is a valid argument to exclude ADHD from "the hall of medical disorders", we must exclude all other mental disorders too! There is no unitary brain abnormality in all patients with autism, schizophrenia, depression, bipolar disorder, dementia or anxiety disorders.

HOW CAN A CHILD WHO SPENDS HOURS FOCUSED IN A VIDEOGAME HAVE ADHD? ISN'T ADHD JUST A NEW NAME FOR LAZINESS OR LACK OF WILLPOWER?

The ability to focus attention and inhibit an action is strongly modulated by motivation. Thus, almost everybody, including the great majority of those affected by ADHD, can pay attention even for long periods of time when motivated. Our current understanding of brain mechanisms indicates that areas of our brain related to attention and the ability to orchestrate the execution of functions are flooded by an excitatory substance called dopamine in situations associated with motiva-

tion.[7] Playing videogames or in other highly motivating situations, individuals with ADHD frequently can focus pretty well.

The problem in ADHD is the ability to focus and inhibit motor response or movement in day-by-day activities where the level of stimulation is not high enough to keep the brain activated as needed. A 10-year-old typically developing child can pay attention in class even when the topic is not tremendously interesting for him/her. In other words, his/her default brain mechanisms associated with attention do not need a high energetic state to operate, although they might operate even better when stimulated. Individuals with ADHD do not achieve the energetic level to execute functions without moderate to high motivation due to impaired brain structure, function and/or neurotransmitters unbalance. More important, since these mechanisms cannot be voluntarily turned on, we are not dealing with an issue of willpower. The idea that people with ADHD should just try harder might be compared to ask someone with poor eyesight to try harder to see well.

Another aspect that gives families the impression that ADHD is a problem of willpower is that people with ADHD might work better under some optimal level of stress. Thus, it is not uncommon for hyperactive children to sit still in the doctor's office during the whole appointment or extremely inattentive adolescents might focus for studying at the end of the school year. Several investigations have documented that an optimal level of activation/stress helps pre-frontal cortex work better due to discharge of a brain substance called noradrenaline.[8] Again, under these circumstances, individuals with ADHD might achieve the energetic threshold needed to execute things that they cannot achieve under normal circumstances. For this reason, we did not rule out a diagnosis of ADHD just based on the lack of hyperactivity/ impulsivity or inattention in the doctor´s office.

That said, it´s important to recognize that some level of effort is always needed to overcome obstacles imposed by disorders. Even if the impaired brain mechanisms could be improved with medication, a level of effort will always be needed. Here, we can use an analogy with a situation where someone has a mild stroke in brain areas commanding left hand movement. Without physiotherapy exercises, the patient will probably not recover hand movement. This is the reason why combined treatment in ADHD, even if it is just in the format of psychoeducational interventions, is important in ADHD.

ADHD IS A DISORDER CAUSED BY MODERN SOCIETY DEMANDS

In the last two or three decades, sufficient knowledge was accumulated clearly indicating that ADHD runs in families and that genetics play a major role in the transmission of the disorder.[9] As discussed in a previous chapter, we now have sufficient research data to even indicate the first sequences in our DNA that is responsible for a very small part of this genetic susceptibility.[10]

Thus, the evidence of a genetic based disorder is against the idea of a disorder caused by modern society demands. Moreover, there is substantial medical literature describing what is now called ADHD since the beginning of the previous century. Reports of clinical presentations like ADHD can be traced to writings in ancient Greece.[11]

Additionally, one of the most cited studies in the entire literature on ADHD assessed more than 100 papers addressing the frequency of the disorder in countries from all continents. The main findings showed that both the frequency of the disorder is similar in culturally very different countries and the prevalence is not different between North-America and Europe, reinforcing that culture does not cause the disorder.[12]

A variant of this myth is the one that the frequency of the disorder is increasing in the population in the last decades due to modifications in our society that is only focused on performance. Our group conducted a large review of the literature (more than 130 studies) across the last three decades on the frequency of the disorder and clearly documented that there is no increase worldwide in the rates of the disorder during this time period in population samples (see Figure 6.2).[13] Recently, authors from Sweden replicated the same finding in a population sample of more than 19200 twins assessed at 9-years of age from 2004 and 2014.[14]

However, it is important to note that the modern understanding of mental disorders suggests that they are determined by the interaction between genes and environment.[15] Therefore, the environment plays a role in the manifestation of ADHD symptoms. In this way, an individual with a strong genetic predisposition for ADHD might present symptoms independently of the environment while people with low genetic predisposition for the disorder might never manifest symptoms even in a very demanding environment. The demands of the environment might be more relevant for those halfway between these two extremes. Thus, the modern western demand of higher inhibitory control, planning and focus to be successful is not the cause of the disorder, but can trigger ADHD symptoms in those with the genetic vulnerability while a supportive environment can buffer genetic predisposition.

HOW CAN MY CHILD HAVE ADHD IF HE/SHE IS NOT HYPERACTIVE?

People tend to associate ADHD with a stereotype of a young boy who never stops! However, as discussed in the first chapter, ADHD is composed of symptoms in one of the two dimensions: inattention and/or hyperactivity/impulsivity. Thus, while some individuals might have predominantly hyperactive symptoms, others have predominantly inattentive symptoms and there are people with symptoms in both dimensions.

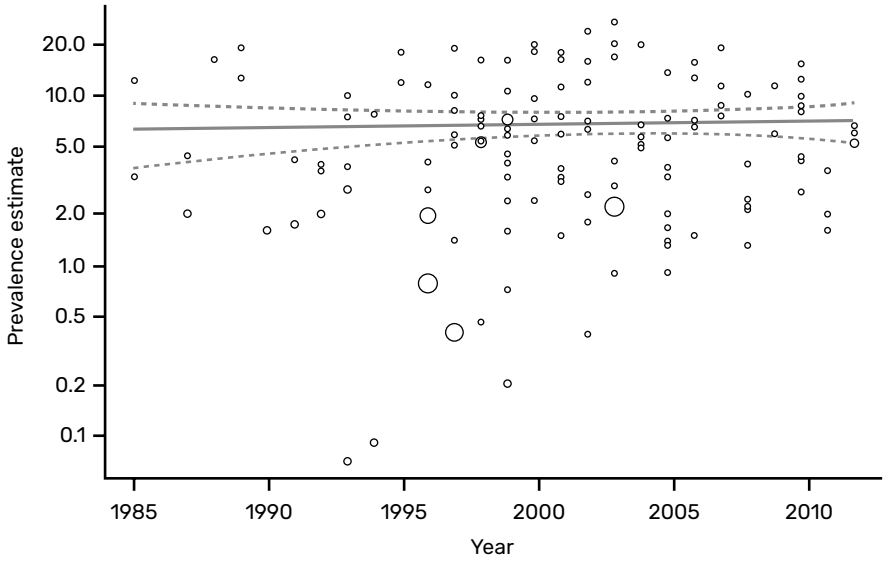


Figure 6.2

Prevalence of ADHD in different studies according to their date of publication. Each point represents the frequency of ADHD in a given study. The solid line represents the predicted mean prevalence for each year across the 3 decades. The dashed lines represent the 95% confidence interval bounds).

From: Polanczyk et al.[13] Permission granted by Oxford University Press. Reproduction prohibited.

Young children in pre-school years tend to present more hyperactive symptoms since attentional demands are not yet high. In school age children, we see more frequently the combination of symptoms in both dimensions. Hyperactivity tends to decrease during development. Thus, a child who was extremely hyperactive/ impulsive in the pre-school years could present with a combination of attention problems and hyperactivity in school years and then might turn out as an adolescent/ young adult with predominantly inattentive problems and executive deficits.[5]

Interestingly, there is a gender effect in the manifestation of symptoms. Females tend to present more inattentive than hyperactive symptoms. Boys tend to present more hyperactive or a combined profile of symptoms. Since hyperactive and impulsive symptoms tend to cause more visible impairments, ADHD tends to be recognized more in males.

A common doubt parents have is how symptoms so different as inattention and hyperactivity might be part of the same disorder. The brain mechanisms related to the disorder suggest that deficits of inhibitory control are essential in the disorder, although not the unique mechanism. Thus, if the brain areas responsible for "our

brakes" (e.g., prefrontal cortex and associated areas) are impaired or immature in ADHD, it is easily understandable that people affected by the disorder will be more impulsive and active. But how inattention is related to inhibitory deficits? To focus attention on the most important issue in a given moment such as a teacher during a class, people needs to inhibit a huge number of other stimuli in the environment that are competing for attention like a classmate fidgeting in the chair or a car honking outside. Even inner thoughts like what to do next are constantly competing for our attention. So, inhibitory skills are essential for focusing attention in one stimulus. However, there are issues for which there is no clear answer yet like:

- Why some people manifest preferentially one set of symptoms instead of the other?
- Why inattention is more frequent than hyperactivity/ impulsivity in females?

One current hypothesis is that among the several genes conferring susceptibility for ADHD, groups of them would be related to deficits in inhibitory control or deficits in executive functions. These genes would interact, by mechanisms not understood yet, with another group of genes that might be responsible for the type of symptoms constellation manifested.

IS ADHD MY FAULT FOR NOT GIVING ENOUGH DISCIPLINE TO MY CHILD?

We, as parents, have a sense of feeling guilty for whatever happens to our children. In the past, mental health professionals helped to make the situation even worst, by blaming mothers for everything in their offspring from autism and schizophrenia to bad behavior. ADHD is a disorder caused by the interplay of genes and environment that impairs normal maturation/development of some areas of the brain and/or their communication. This idea of parents causing ADHD is a variation of the one already discussed that modern environment causes ADHD.

However, as said about the environment, parenting might buffer or accentuate the force of the genes conferring the susceptibility to the disorder. A frequent additional problem here is that ADHD runs in families. Thus, it is not uncommon that one or both parents also have ADHD or had the full syndrome in the past and attenuated symptoms currently. Some investigations suggest that around 30% of the families that search assessments for ADHD in their children have at least one parent with ADHD.[16] In this case, it might be more difficult for them to provide a more structured environment for their children with ADHD. Thus, pediatricians and primary mental health professionals dealing with children should always screen for ADHD in parents when assessing a child with the disorder, as well as

mental health professionals dealing with adults should have to screen for ADHD in the offspring if a positive ADHD diagnosis is made in an adult parent.

ADHD ONLY OCCURS IN CHILDREN

Three decades ago, there was a belief that ADHD was a childhood disorder and that biological modifications associated with puberty would make children outgrow the disorder. Investigations all around the world now demonstrate that ADHD can be detected in adolescents and adults and the prevalence rate in adulthood is around 2.8%.[17]

The clinical presentation might be different in adults compared to children with more prominent inattentive symptoms and deficits in executive functions determining symptoms like procrastination. Impulsivity and emotional regulation problems might be more important than hyperactivity.[18] This difference in clinical presentation in adults is now recognized in the diagnostic criteria for the disorder. The new version of the diagnostic system of the American Association of Psychiatry (DSM-5)[19] suggest that a lower threshold of inattentive and hyperactive/impulsive symptoms for diagnosing ADHD is needed in adults than the one needed in children.

Recent investigations have even demonstrated that ADHD might be present in older adults. A study in the Netherlands documented a prevalence rate of ADHD around 2.8% in older adults (60 years of age or older).[20]

HOW ABOUT THE FUTURE? WILL MY CHILD ALWAYS HAVE ADHD?

From an era where we believed that children would outgrow the disorder, we moved to a time where ADHD was considered a "life sentence" for all. As usual, the true probably is not in any of the extremes. Although there is no consensus on the exact persistence rate of ADHD from childhood to adulthood, a significant group of children with ADHD will continue to present symptoms and impairments in adulthood. Some studies suggest a rate around 50%.[21] We know that the persistence depends on how you define the disorder in adulthood (presence of full syndrome, partial symptoms, or only impairment).

Recent research suggests that persistence of the full ADHD syndrome in adulthood depends on several factors like the severity of the symptoms in childhood, presence of co-occurring child mental disorders and parental mental disorders like depression.[21]

That said, it is important to recognize that there is a significant proportion of children with ADHD that become adults without the disorder. This might be related to maturation of the brain areas involved in the disorder.

CHILDREN WITH ADHD ARE LESS INTELLIGENT

This is a stigma frequently shown to people affected by the disorder. Due to the interference of ADHD symptoms in academic achievements, affected individuals frequently have a perception that they are not intelligent! See below an essay written by a 10-year-old boy with ADHD that had never been diagnosed. The teacher requested students to write an essay the describing themselves.

> *Hello, I am Peter (fictitious name) and I will tell my story. I am stupid, more or less ugly and I don't know how I am in the 4th grade. My mother even says that I'm not good at all, she does not know why I came to this world.*
>
> *I am an idiot, do not have ideas, only waste others' money, and the only thing I know how to do is play soccer. In sum, I suck, I did not have to born.*

There is no evidence that ADHD is related to intelligence. Since assessment of executive functions and working memory is part of some IQ batteries and these neuropsychological functions are affected by ADHD, results from these batteries might be flawed in the sense of estimating a lower potential IQ than real. Persons with ADHD can have cognitive problems, an average IQ and high cognitive abilities.[22]

See other potential stigmas associated with ADHD in this link.

CHILDREN WHO TAKE ADHD MEDICATION ARE MORE LIKELY TO ABUSE DRUGS WHEN THEY BECOME TEENAGERS.

Currently, it is not clear if ADHD by itself increases the risk of abuse/dependence on substances or the risk is associated with some disorders that tend to travel with ADHD like conduct disorder. [23,24]

Link in this

https://www.youtube.com/watch?v=ji0hg1LduU8&t=14s

At the same time, although it is yet controversial if ADHD treatment with medication can really decrease the risk of future substance abuse or dependence[25] as no longitudinal data suggests that people with ADHD treated with medication have a higher risk than ADHD people not treated with medication to develop substance use problems.

On the other side, although we now have substantial evidence that treatment with medication might bring acute benefits including in outcomes that really matter for people like decrease of accidents, higher academic test scores, lower rates of pregnancy and sexual transmitted disorders in adolescence and even mortality, clear long-run benefits of treating ADHD with pharmacological and non-pharmacological interventions yet need to be fully demonstrated.[26]

HOW TO EXPLAIN ADHD TO FAMILIES?

Based on everything discussed up to now, we offer one model, among several others available in the literature, to introduce ADHD to families.

After the assessment process, considering that we have enough evidence from both the described profile of symptoms and the medical, developmental and family history of the child/adult patient for a diagnosis of ADHD, we need to discuss ADHD with the patient and/or his/her family.

Our starting point is to ask the patient and/or parents/family to describe what they understand as ADHD. This is an important stage since it allows us to recognize and discuss some of the above-described misunderstandings about the disorder since they are part of the patient/family culture and values.

We normally begin stating that there is no biological marker for ADHD, as there is no one for any mental disorders. Thus, the diagnosis relies on the clinical assessment. Second, we describe ADHD as a dimensional disorder making analogies with medical conditions like hypertension, diabetes and hypercholesterolemia. This initial approach is relevant for informing the patient why sophisticated neuroimaging or even simple electroencephalogram (EEG) would not be needed in the diagnostic process and to connect ADHD to medical conditions.

At this stage, we review with the patient the data from symptoms reported in the clinical interview or in scales collected with the patient/family/school, as well as data from the medical, developmental and family history that corroborates our clinical hypothesis of ADHD.

We move then to characterize what constitutes ADHD. We state that ADHD is a disorder of the development of the brain caused by the interplay of our genes with environmental factors. Analogies with medical conditions like asthma or gastritis might help here. Individuals who have a propensity in their genes for asthma when facing modifications in the weather or increase in allergens in the environment might have asthmatic attacks. This approach helps families to un-

derstand that although ADHD is a biological disorder, their action might buffer the symptoms or increase them. This might be important to motivate them for future parent training interventions.

We then describe ADHD as an immaturity or dysregulation of the chemicals in brain areas that are responsible for "our brakes" and for coordinating our ability to plan and execute actions. We localize these areas in the front of our brains emphasizing that our modern understanding of brain suggest that its functions are much more dependent on interactions among diverse brain areas than the action of an isolated area. Different analogies here might help such as the one with the brake fluid of the car and how a dysregulation in this fluid will make the brakes not working properly. Then, we present the idea how a failure in the brake system can determine symptoms as different as inattention and hyperactivity, as discussed above.

Another interesting analogy is the one between the conductor of an orchestra and our frontal brain areas. If frontal areas that act as the conductor for other areas (musicians) do not work adequately by immaturity or chemical dysregulation, the orchestra (brain) will not play properly independent on how well the musicians are individually (how intact other brain areas are).

Although it might be seen as a time demanding process for appointments in primary care or in a pediatric office, this process is essential to foster initial understanding about ADHD and compliance with any proposed management plan in a disorder where adherence to treatment is one of the biggest problems, as already mentioned[1]. Indeed, this whole talk might not take more than 10-15 minutes.

CONCLUSION

This chapter aims to provide a guideline for clinicians to address some of the common doubts and misunderstanding patients with ADHD and their families have about the disorder. It might even be indicated to families to read before or just after an ADHD diagnosis, stimulating them to share their questions with their mental health professionals.

Conflicts of interest

Luis Augusto Rohde has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Eli Lilly and Co., Janssen, Medice, Novartis and Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by Dr Rohde have received unrestricted educational and research support from the following pharmaceutical companies: Eli Lilly and Co., Janssen, and Novartis. Dr Rohde has received authorship royalties from Oxford Press and ArtMed and travel grants from Shire to take part in the 2018 APA annual meeting and from Novartis to take part of the 2016 AACAP annual meeting. Olayinka Omigbodun, Manfred Gerlach and Yi Zheng do not have conflict of interest to disclosure.

REFERENCES

1. Khan MU, Kohn M, Aslani P. The need for a paradigm shift in adherence research: the case of ADHD. Res Social Adm Pharm. 2018. pii: S1551-7411(18)30374-7. [Epub ahead of print].

2. Ponnou S, Gonon F. How French media have portrayed ADHD to the lay public and to social workers. Int J Qual Stud Health Well-being. 2017;12(sup1):1298244.

3. Timimi S, Timimi L. The social construction of attention deficit hyperactivity disorder. In: O'Reilly M, Lester JN, editors. The Palgrave handbook of child mental health. Basingstoke: Palgrave Macmillan, 2015. p. 139-157.

4. McLennan JD. Understanding attention deficit hyperactivity disorder as a continuum. Can Fam Physician. 2016;62(12):979-982.

5. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention--deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.

6. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017;4(4):310-319.

7. Berridge KC, Kringelbach ML. Pleasure systems in the brain. Neuron. 2015;86(3):646-64.

8. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6(6):463-75.

9. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240-50.

10. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for ADHD. BioRxiv. 2017. [Epub ahead of print].

11. Victor MM, Silva BS, Kappel DB, Bau CH, Grevet EH. Attention-deficit hyperactivity disorder in ancient Greece: The Obtuse Man of Theophrastus. Aust N Z J Psychiatry. 2018;52(6):509-513.

12. Polanczyk G, Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942-8.

13. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014;43(2):434-42.

14. Rydell M, Lundström S, Gillberg C, Lichtenstein P, Larsson H. Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample. J Child Psychol Psychiatry. 2018;59(8):863-871.

15. Geschwind DH, Flint J. Genetics and genomics of psychiatric disease. Science. 2015;349(6255):1489-94.

16. Rohde LA, Szobot C, Polanczyk G, Schmitz M, Martins S, Tramontina S. Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? Biol Psychiatry. 2005;57(11):1436-41.

17. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. Atten Defic Hyperact Disord. 2017;9(1):47-65.

18. Asherson P, Buitelaar J, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. Lancet Psychiatry. 2016;3(6):568-78.

19. American Psychiatric Association. Manual diagnóstico e estatístico de transtornos mentais: DSM-5. 5. ed. Porto Alegre: Artmed, 2014.

20. Michielsen M, Semeijn E, Comijs HC, van de Ven P, Beekman AT, Deeg DJ, et al. Prevalence of attention-deficit hyperactivity disorder in older adults in The Netherlands. Br J Psychiatry. 2012;201(4):298-305.

21. Caye A, Spadini AV, Karam RG, Grevet EH, Rovaris DL, Bau CH, et al. Predictors of persistence of ADHD into adulthood: a systematic review of the literature and meta-analysis. Eur Child Adolesc Psychiatry. 2016;25(11):1151-1159.

22. Brown TE, Reichel PC, Quinlan DM. Executive function impairments in high IQ adults with ADHD. J Atten Disord. 2009;13(2):161-7.

23. Serra-Pinheiro MA, Coutinho ES, Souza IS, Pinna C, Fortes D, Araújo C, et al. Is ADHD a risk factor independent of conduct disorder for illicit substance use? A meta-analysis and metaregression investigation. J Atten Disord. 2013;17(6):459-69.

24. Groenman AP, Janssen TWP, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: a meta-analysis. J Am Acad Child Adolesc Psychiatry. 2017;56(7):556-569.

25. Groenman AP, Oosterlaan J, Rommelse NN, Franke B, Greven CU, Hoekstra PJ, et al. Stimulant treatment for attention-deficit hyperactivity disorder and risk of developing substance use disorder. Br J Psychiatry. 2013;203(2):112-9.

26. Arnold LE, Hodgkins P, Caci H, Kahle J, Young S. Effect of treatment modality on long-term outcomes in attention-deficit/hyperactivity disorder: a systematic review. PLoS One. 2015;10(2):e0116407.