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UPDATE ARTICLE

Developments and challenges in the diagnosis and treatment of ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, often associated with other psychiatric comorbidities, functional impairments, and poor long-term outcomes. The objective of this selected review is to describe current advances and challenges in the diagnosis and treatment of ADHD. The disorder is associated with neurobiological underpinnings and is highly heterogeneous in various aspects, such as symptom profiles, cognitive impairments, and neurobiological and genetic features. The efficacy and safety of short-term pharmacological treatments across the life cycle is well studied, but further research investigating long-term treatment, impact of treatment in preschoolers, and non-pharmacological interventions is needed. Future research is also needed to better characterize the neurodevelopmental pathways of the disorder, linking clinical and neurobiological information, less investigated populations, and new interventions.

Keywords: ADHD; heterogeneity; diagnosis; treatment; neurodevelopment

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5% of children and adolescents worldwide.[1] Although symptoms decline with age (65% of the affected individuals present partial remission), only 15% of children with ADHD show full remission in early adulthood, characterizing a chronic disorder.[2,3] Symptoms include age-inappropriate inattentiveness, hyperactivity, and impulsivity.[4] The disorder is highly burdensome, determining 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.[4] Furthermore, it is associated with other psychiatric comorbidities, especially oppositional defiant disorder, anxiety disorder and learning disabilities; it also predicts a diversity of negative outcomes, such as future conduct disorder, antisocial behavior, anxiety and mood disorders, substance abuse, and also physical injuries, traffic accidents, premature pregnancy, sexual transmitted diseases, among others.[5,6]

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ADHD is a cause of significant economic costs to society. A recent systematic literature review suggests that the annual incremental costs of the disorder in the U.S. are at least US$ 143 billion.[7] Despite that, the disorder is still poorly recognized and treated, and there is a lack of public policies developed to address this condition. In the U.S., less than two-thirds of adolescents with ADHD had ever received some kind of treatment.[8] This situation is even more dramatic in low- and middle-income countries. For example, in a community sample of two cities in Brazil that ascertained approximately 10,000 children, 43% of children with ADHD had been previously referred to mental health services, but only 23% had access to some kind of treatment (A Graeff-Martins, personal communication).

The etiology of ADHD has not been completely elucidated.[9] Studies have identified a robust genetic contribution to the disorder, with pooled heritability rate of 76%.[10] Current data indicate that multiple common genetic variants of small effect - including genes of dopaminergic, noradrenergic, serotoninergic and other systems - and possible rare variants, are implicated in the etiology of ADHD.[9] Environmental variables are also known to play a role in the disease etiology. Low birth weight, prematurity, and intra-utero exposure to tobacco are among the environmental factors most strongly linked to the development of the disorder.[9] It is likely that multiple etiological pathways involving different genetic variants and exposures in complex interaction underlie specific neuropsychological characteristics and clinical

symptoms of the disorder (Figure 1). The complexity of the pathways leading to ADHD results in remarkable heterogeneity in many aspects of the disorder, which might be limiting the ability to elucidate the disease etiology.[11]

Various characteristics of ADHD have been summarized by previous systematic reviews.[1,3,9,12,13] The objective of this selected review of the literature is to describe current advances and challenges in the conceptualization, diagnosis, and treatment of the disorder.

Diagnosis

ADHD as a neurodevelopmental disorder

Accumulating evidence supports the notion that ADHD is better understood as a neurodevelopmental disorder characterized by a maturational delay. In the last years, the frequent description of an immature child or adolescent made by parents and teachers has found support in neuroimaging studies.[14] A National Institute of Mental Health longitudinal study provided unique developmental insights into the neurobiology of ADHD. In a landmark report published in 2007, Shaw et al.[15] studied the cortical thickness of 223 patients who had ADHD and 223 typically developing controls. Their results indicated that, rather than a deviation from typical development, ADHD is characterized by a marked delay in reaching peak thickness in many regions and particularly in the prefrontal cortex (median age 10.5 and 7.5 years for the ADHD and control groups, respectively).[15] More recently, the same group extended this finding, suggesting a mirror phenomenon in terms of measures of cortical surface area: among children with ADHD, the median age by which 50% of right prefrontal cortical vertices attained peak area was 14.6 years - in comparison to 12.7 years in the healthy control group.[16]

The developmental aspect of ADHD must be taken into account when characterizing clinical presentation and elaborating new diagnostic criteria. The diagnosis of ADHD is established clinically, based on criteria defined by diagnostic classification systems such as the DSM and ICD. Similar to other psychiatric conditions, there is no ancillary test with sufficient predictive power for the diagnosis of ADHD. Core features of the disorder are developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity (Table 1). Notwithstanding the emphasis regarding the need for a developmental perspective in the assessment of ADHD, limited evidence-based data is available on specific manifestations of the disorder at each period of life.

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 before the age of 6,[17] challenges in the diagnostic procedures include, for example, the impossibility of observation in multiple settings for those children not attending preschool - and subsequent lack of information about pervasiveness. Several studies have shown that currently available criteria reliably identify ADHD in children as young as 2 years old and that these individuals have clinically significant impairment across all relationships and settings.[18]

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 clinically 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).[19] Among the challenges in characterizing ADHD in older individuals, there is the inappropriateness of the description of symptoms (especially hyperactivity/

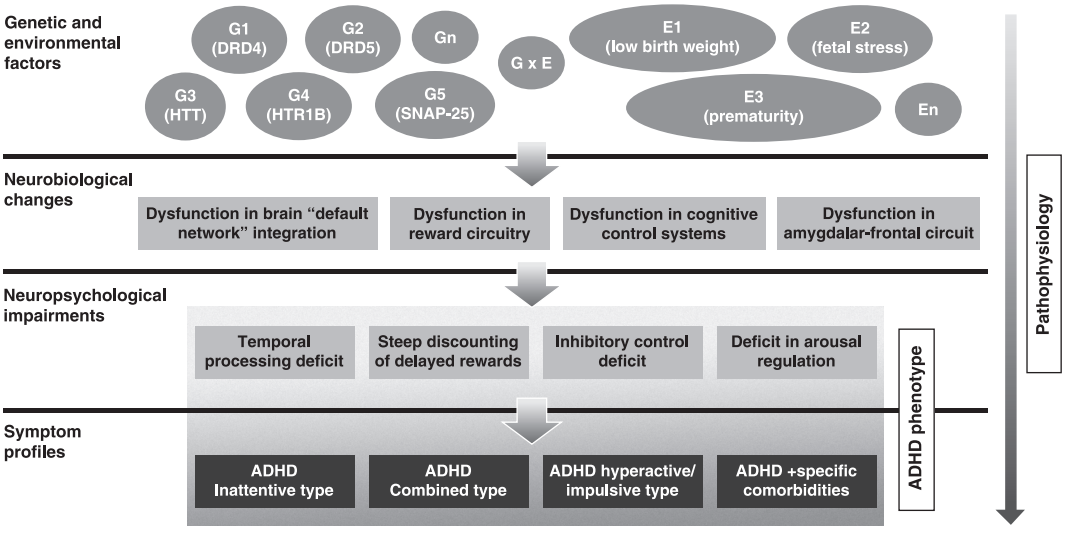

Figure 1 Schematic representation of ADHD pathophysiology. The figure shows the path to ADHD phenotype and the various levels where heterogeneity may occur. Genetic (G1-Gn) and environmental factors (E1-En), and complex gene-environment interactions (GxE) lead to various neurobiological changes, which in turn lead to different neuropsychological impairments and symptom profiles. ADHD = attention-deficit/hyperactivity disorder

Table 1 DSM-IV-TR diagnostic criteria for ADHD

A. Either 1) or 2):
Inattention
1. Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
   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 schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
   e) Often has difficulty organizing tasks and activities
   f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
   g) Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
   h) Is often easily distracted by extraneous stimuli
   i) Is often forgetful in daily activities
2. Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

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

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

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home)
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)

ADHD = attention-deficit/hyperactivity disorder.

impulsivity symptoms) to capture developmental specific clinical manifestation, and difficulties in assessing retrospectively the presence of symptoms in childhood.[20] In addition, the clinical picture in adults might be specifically characterized by symptoms related to executive dysfunctions and emotional impulsivity. More importantly, adults might present substantial impairment even with lower number of symptoms in any of the two dimensions (inattention and/or hyperactivity/impulsivity). Thus, a lower symptom threshold for the diagnosis in adults was proposed for the new version of the DSM - DSM-5.[20]

Other challenges in ADHD diagnosis

In addition to frequent developmentally inappropriate symptoms (at least 6/9 in at least one of the dimensions), there are other requisites for the diagnosis of ADHD according to the DSM-IV-TR. One of the most fragile criteria for the diagnosis of ADHD is the requirement of symptoms causing impairment before the age of 7 years (criterion B). This criterion has been retained in DSM editions despite the lack of empirical support, and a systematic review of the literature found 31 studies questioning its validity, especially to older individuals, for whom there can be problems in terms of retrospective recall.[21] Applying this evidence-based approach, the forthcoming DSM-5 will reformulate the criterion, expanding the maximum age at onset to 12 years. This reaffirms ADHD as a disorder of childhood onset, both minimizing false negatives and causing minimal increase in prospectively assessed prevalence rates.[22]

The requirement of some impairment from the symptoms in two or more settings (criterion C) is intended to avoid including situational-specific problems (e.g., only at home). Interestingly, the low concordance between parental and teacher reports (even when focusing on symptoms at school) suggests that, to capture pervasiveness, information should be gathered with both sources.[23] The diagnosis of ADHD is currently excluded in the presence of disorders such as schizophrenia (criterion E). Another change announced for the DSM-5 is the removal of the impossibility of diagnosing ADHD and autism spectrum disorders, as there is sufficient evidence to justify the comorbid diagnosis.[24]

Data converge to confirm that ADHD is a disorder with developmental features that are associated with neurobiological underpinnings. Future research - preferably using longitudinal designs - is needed to better characterize the neurodevelopmental pathways of the disorder, linking both clinical and neurobiological information.

ADHD as a 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, and neurobiological and genetic features (Figure 1).

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.[25] In the case of ADHD, six symptoms are required for an individual to meet diagnostic criteria. 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 types (predominantly inattentive, hyperactive-impulsive, and combined types) is an attempt to deal with the heterogeneity of clinical presentations. Even so, two individuals with identical ADHD subtypes might be similar in as few as three symptoms. In a community sample of 189 individuals with ADHD, a total of 173 combinations of symptomatic profiles were found. Furthermore, it was detected a median agreement between symptoms of 0.61, with 30% of the sample showing an agreement lower than half of the symptoms (G Salum, personal communication). 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.[11] Conversely, a recent comprehensive meta-analyses did not detect significant differences in several assessed areas comparing subjects with different ADHD types (main comparisons between predominantly inattentive and combined types), arguing that these phenotype differences might not be so relevant.[26] Based on these findings and on the low developmental stability of ADHD types, the ADHD working group for the DSM-5 recently proposed the downgrade of the types to current presentation.

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 executive functions, such as: inhibition, working memory, memory span, processing speed, arousal, temporal information processing, response variability; and have also impairments in motivational processes.[27-33] However, the findings of neuropsychological impairments are only of moderate effect sizes and not all individuals with the disorder have these dysfunctions.[27,34] Sonuga-Barke et al.[35] evaluated three neuropsychological domains: inhibitory control, delay aversion, and temporal processing, and found that ADHD children had poorer performance on all domains. However, only 71% of the individuals displayed some deficit, and 70% of those showed just one dysfunction.[35] The results suggest that the three domains are independent components of ADHD and support a triple pathway model for ADHD. Fair et al.[36] recently conducted another study illustrating the neuropsychological heterogeneity in ADHD. They identified distinct neuropsychological subgroups within ADHD children and also within typically developing children.[36] The findings support that ADHD heterogeneity, as well as heterogeneity in typical population, must be considered when trying to elucidate ADHD etiology.

Taking into account heterogeneity in neuropsychological and symptom profiles, theoretical models of ADHD have proposed that dysfunctions in multiple pathways may be involved in the disorder, leading to specific impairments.[35,37,38] Nigg & Casey[37] proposed that ADHD may arise from: a) dysfunctions in brain cognitive control systems, b) over-reactivity in nucleus accumbens circuit, or c) under-reactivity in amygdalar-frontal circuit; each leading to related but distinct etiological phenotypes, which are, respectively: a) primary inattentive, disorganized, and ineffective behaviors; b) impulsive, overactive behaviors; and c) impulsive conduct problems, antisociality. Sonuga-Barke, who had previously proposed a dual pathway model (i.e. delay aversion and executive dysfunction pathways),[38,39] recently suggested that three dissociable pathways might be involved in ADHD etiology.[35] The neuroimaging literature has shown that ADHD is related to alterations in several brain systems, including systems involved in attention, cognitive control, emotional, sensorimotor, and reward processes.[12,40-47]. Most of those studies have focused on single process hypotheses and have not addressed the multiple pathways model. Further evaluation of how distinct neuropsychological or behavioral phenotypes relate to differential neural pathways may be particularly relevant to elucidate heterogeneity of ADHD neural substrates.

ADHD heterogeneity is also evident at the genetic level. Genome-wide association studies are inconclusive, but candidate genes studies have found evidence for the association of various genes with elevated risk for ADHD.[48,49] This may suggest that each genetic marker accounts for only a small proportion of heritability, indicating that ADHD arises from a complex interaction of genetic susceptibility and environmental conditions.[50,51] Numerous possibilities of gene combinations added to countless possible interactions with environmental conditions generate pronounced heterogeneity from the genetic point of view.

Therefore, there is compelling evidence that the heterogeneity of ADHD might be one reason for the diversity of findings and lack of replication. It has become crucial that research concerning all aspects of ADHD, such as neurobiology, diagnosis, and treatment, take heterogeneity into account and employ new approaches to deal with this issue.

Treatment

Efficacy of interventions

The recommendations for ADHD treatment indicate multimodal approaches including pharmacotherapy and psychosocial interventions as the most effective. First-line medications for the treatment of ADHD are stimulants (methylphenidate, mixed amphetamine salts, and amphetamine derivatives - lisdexamfetamine and dextroamphetamine). Second-line medications are atomoxetine, tricyclic antidepressants, bupropion, and alpha-agonists.

Meta-analyses and systematic reviews show moderate to large effect sizes of stimulants in short-term reduction of symptoms.[52-56] Most of the studies comparing short and long-acting methylphenidate compounds found no significant differences in effect sizes.[55,57] However, a meta-analysis looking at medications for adults with ADHD found that the clinical response for short-acting stimulants was greater than for long-acting stimulants.[58]

Non-stimulants are considered second-line medications in cases of treatment failure, intolerance or contraindication to stimulants and may be an option in specific cases of comorbidity.[59] There is good level of evidence provided by meta-analysis of efficacy for atomoxetine.[57,60,61] Extended-release clonidine[62-64] and extended-release guanfacine[65,66] are also efficacious options for the treatment of ADHD, alone or in combination with stimulants. Other pharmacologic alternatives evaluated for the treatment of ADHD are modafinil, bupropion,[57] and tricyclic antidepressants,[67] but all of them have showed weaker evidence of efficacy.

Behavioral therapy for ADHD aims to modify the physical and social environment in order to modify behavior. For preschoolers, parent training is the recommended behavioral intervention. This modality of treatment aims to help parents stop inefficacious patterns of interaction with their child by reinforcing child's prosocial behavior and to extinguish unwanted behaviors.[68,69]

A recent meta-analysis examined 40 studies addressing the efficacy of behavior parent training for parents of children of ADHD.[68] A moderate effect size was found regarding the improvement of child behavior and parenting behavior (both measured objectively), and parental perception of parenting. However, these results were observed only immediately after treatment. In a long term (up to 3 years), results remained significant, but with lower magnitude (small effect size). Improvement was more limited for children with associated oppositional defiant disorder or other behavioral problems. Another meta-analysis summarized randomized controlled trials that assessed the efficacy of the following non-pharmacological treatment modalities: restricted elimination diets, artificial food color exclusions, free fatty acid supplementation, cognitive training, neurofeedback, and behavioral interventions.[13] Given the restriction to high-quality trials, six to 15 studies were included for each modality. Authors conducted two sets of analysis: the first considered ADHD assessment by raters closest to the therapeutic setting, and the second considered only probably blinded assessment of the outcomes by the individual studies. According to the first set of analysis, all six modalities of intervention produced significant effects. According to the second set of analysis, only free fatty acid supplementation and artificial food color exclusion produced significant effects, and the effects of the other four modalities were non-significant.[13]

Long-term efficacy and effectiveness

The short-term efficacy of ADHD treatment is well documented, but fewer studies, with variable results, have evaluated long-term efficacy and effectiveness. Poor adherence and difficulties in retention during follow-up are probably some of the reasons for this gap in the literature. However, since ADHD is a lifelong condition, it is fundamental to determine the long-term outcomes of the different treatment modalities. The Multimodal Treatment Study of Children with ADHD (MTA)[70] is a large trial that compared four treatment modalities (behavioral intervention, medication, combined treatment, or routine community) in respect to several outcomes during 14 months (controlled phase) and the subsequent 8 years (open phase). Results indicated that, after 14 months of follow-up, medication alone or combined with behavior intervention had better results on improving ADHD and oppositional defiant disorder symptoms, compared to behavior intervention and community care.[70] Combined behavioral intervention and medication was no better than medication management, but allowed the use of lower stimulant doses. Secondary analysis looked at rates of success defined by a cutoff on the SNAP-IV score at the end of the treatment.[71] Results from the secondary analysis found increased success rates for combined treatment and medication management and confirmed the initial results.[71]

An 8-year follow-up of MTA children, however, did not find differences between the four treatment groups, and children with ADHD combined subtype showed poorer functioning than non-ADHD children, despite the improved outcomes compared with baseline.[72] These results suggest that an initial period of randomly assigned treatment does not change the disorder trajectory. Conclusions from these results are widely discussed. It is possible that: a) treatment was not effective in the long-term; b) medication and behavioral interventions are equally effective; or c) community care is effective in the long-term, and intensive medication management or intensive behavioral therapy improve its effectiveness, but the benefit weakens once the controlled treatment stops.[73] It is also argued that the naturalistic design of the follow-up after 1 year (children returned to community care) may have influenced the results.[74] In conclusion, long-term controlled studies are needed in order to better understand the continuing effects of different modalities of treatment on symptoms and functioning of individuals with ADHD, and also to explore potential moderators of long-term outcomes.

A recent systematic review summarized findings from studies assessing long-term outcomes of treatment vs. non-treatment of ADHD.[75] It was found that ADHD individuals left untreated had poorer long-term outcomes compared to treated individuals in nine major categories, but treatment did not result in normalization. Benefits were more prominent in driving, obesity, self-esteem, social function, academic, and drug use/addictive behavior outcomes. Although the superiority of specific treatment modalities still needs to be further studied, it appears that in general ADHD treatment improves long-term outcomes. However, the field still demands studies to clarify the association between shot-term and long-term effects.

Functional outcomes

Another challenge for ADHD treatment is determining functional outcomes of treatment (e.g., academic and

occupational outcomes). Although few studies have investigated this topic, there is evidence of positive impact on specific outcomes. In regard to academic outcomes, Hechtman et al.[76] found improvement of school performance and homework behaviors in children with ADHD treated with medication associated or not with other treatment modalities (psychosocial treatment or academic intervention). A recent review by Prasad et al.[77] examined children's on-task behavior and academic performance and found that drug treatment improved children's time spent on task and amount of schoolwork they completed. Scheffler et al.[78] also found that medicated children with ADHD had higher mathematics and reading scores. In regard to criminality, during periods under treatment with medication, individuals with ADHD presented lower criminality rates (measured as any conviction for a crime) compared to non-medicated periods.[79] Brook et al.[80] recently studied the relationship between ADHD in adolescence and several outcomes in adulthood, and found that adolescents with ADHD are more likely to have impaired physical and mental health, antisocial personality disorder, impaired work performance, and high financial stress in adulthood. Raman et al.[81] documented that the treatment with stimulants decrease the risk for injuries in children (see slide attached).

In regard to substance use, there is no evidence that medication treatment increases the chance of developing dependence.[75] Results are conflicting with respect to the protective potential of treatment. Biederman et al.[82] found a reduced risk for substance use disorders in medicated individuals with ADHD after 4 years. This was consistent with an earlier meta-analysis.[83] However, a 36-month follow-up of the MTA study[84] and a 10-year follow-up study of a clinical sample[85] found no association between ADHD treatment and rates of substance use. Additional studies assessing large samples and following up participants into adolescence and/or adulthood are necessary to determine whether treatment has a protective effect on substance use rates and development of dependence.

Treatment of preschool children

Treatment plan for preschoolers must take into account the intensity of symptoms, pervasiveness, but also the velocity and intensity of changes that occur in the brain during this phase. There is scarce data about efficacy and safety of stimulants for this age group, and most of the studies are restricted to methylphenidate.[86] The largest randomized controlled trial conducted for this age period is the Preschool ADHD Treatment Study (PATS),[87] which included 165 children aged 3 to 5.5 years in the medication phase. The inclusion criteria for this study were very rigorous: only children with moderate to severe ADHD-related impairment for at least 9 months were included; it was also required a level below 55 on the Children's Global Assessment of Functioning Scale; and a cross-site panel of clinicians had to agree about the inclusion and exclusion criteria for the enrollment of each participant. Furthermore, all participants underwent a Parent Training phase and only participants with continued impairment were allowed to begin medication.[88] Therefore, children who participated in the study, especially in the medication phase, exhibited severe ADHD, which may explain the high rates of comorbidities they presented.[87] The mean optimal daily dose of methylphenidate (0.7 ± 0.4 mg/kg/day) was lower than the dose recommended for school age children.[87] There were significant reductions in ADHD symptoms, but the effect sizes (0.4-0.8) were smaller than the ones found for school age children. Despite the relative good tolerability of methylphenidate, adverse effects were more frequent.[86] The most common described adverse effects are decreased appetite, stomachache, sleep difficulties, social withdrawal, lethargy, dysphoria, crying, whining, and irritability.

In respect to non-stimulant treatment, there is a randomized controlled trial of atomoxetine in 5- and 6-year old children with ADHD, demonstrating significant improvement in symptom scores compared to placebo.[89] One-third to one-fourth of subjects reported adverse events, which included weight loss, decreased appetite, sedation, and gastrointestinal discomfort, but they were not related to treatment discontinuation.

Group-based parent training is a psychosocial intervention tested for preschool ADHD. Sonuga-Barke et al.[90] performed a controlled trial with 3-year-old children with ADHD, who were randomized to parent training, parent counseling and support, or a waiting list group. They found that parent training significantly improved ADHD symptoms (in clinical and direct observation measures) and mother's sense of well-being, and 53% of children in the parent training group met criteria for recovery by the end of the trial. The beneficial effects of parent training were still present 15 weeks after treatment. Another study by Jones et al.[91] evaluated the effectiveness of parent training for reducing ADHD symptoms in preschool children with ADHD symptoms (not a formal ADHD diagnosis) and conduct problems, and found similar results. Parent training was associated with significant greater reduction in ADHD symptoms, and 52% of children in the parent training group presented symptom scores below clinical threshold by the end of the intervention (against 21% for the waiting list control group). However, Barkley et al.[92] found no effect of parent training on ADHD symptoms in kindergarteners, which may be explained by the low adherence to treatment, inclusion of children with symptom scores above a cutoff in a dimensional rating scale but without a formal diagnosis of ADHD, lack of impaired functioning indicated by parents and teachers, and the training format (delivered in a didactic format). Evidence for the effectiveness of parent treatment for improving ADHD symptoms in preschoolers is still limited and additional controlled trials with children formally diagnosed with ADHD are needed.[86]

Clinical guidelines indicate psychosocial intervention as first-line treatment for preschool children with ADHD. The guidelines by the American Academy of Pediatrics,[17] the

Preschool Psychopharmacology Working Group,[93] and the NICE Guideline[94] recommend specifically group-based parent training, reserving methylphenidate for the more impaired cases or for those children who do not benefit significantly from behavior treatment.[17,86,93,94] Future studies should assess the efficacy and safety of other stimulants, of stimulants compared to parent training, and their short- and long-term effects in this age range, as well as long-term effects of psychosocial interventions.

Treatment of adults

Literature about the treatment of adults with ADHD is not as extensive as for school-age children, but a considerable amount of data is already available. Pooled estimation from meta-analysis shows that stimulants decrease adults' ADHD symptoms in short-term bases with a medium to large effect size. When stimulants as a group are compared to placebo, the effect size found is 0.67.[95] Other meta-analyses found effect sizes of 0.9 for methylphenidate,[96] 0.73 for mixed amphetamine salts,[97] 0.8 for lisdexamfetamine (extracted from a single study),[97] and 0.6 for dextroamphetamine.[97] Non-stimulants, when considered as a group, seem to be inferior to stimulants, with pooled effect size of 0.39[53] and 0.59.[95] Meta-analytic data also showed bupropion to be superior to placebo but less effective than stimulants.[58,98,99]

Other non-stimulants were assessed by clinical trials with no meta-analysis yet available. The superiority of atomoxetine to placebo has been demonstrated in a pooled post-hoc estimation combining data from six double-blind trials[100] and also by additional more recent clinical trials.[101-103] Modafinil was not superior to placebo in a well conducted clinical trial that included more than 300 patients.[104] Limited evidence is available for alpha-2-agonists for adults.[105] A randomized, double blind, placebo-controlled trial compared the efficacy of guanfacine with dextroamphetamine for the treatment of ADHD in adults.[106] The study found that guanfacine was similar to dextroamphetamine in reducing ADHD symptoms, compared to placebo, but only guanfacine improved performance on the Color-Word subtest of Stroop, indicating an enhancement of focused attention by guanfacine. A nicotinic agonist has also been studied for treating adult ADHD.[107] A randomized, double-blinded, placebo-controlled trial, with a crossover design, selected adults with ADHD to receive placebo and ABT-894, $\alpha 4\beta 2$ (a subtype of neuronal nicotinic receptors) agonist, or atomoxetine.[107] ABT-894 4 mg twice-daily was comparable to atomoxetine and superior to placebo in reducing ADHD symptoms, but additional studies, with larger sample sizes, greater power, and a parallel design (to avoid results susceptibility to carryover effects) are need to better evaluate the safety and efficacy of this drug.

Psychosocial interventions for adults do not appear to be effective as sole treatment, but evidence shows that they may be effective as adjunctive treatment to psychopharmacological therapy for individuals with residual symptoms.[108] The best evidence comes from a trial conducted by Safren et al.[109] The study enrolled 86 adults with ADHD who were already being prescribed medication and randomized them to cognitive behavioral therapy or relaxation with attentional support. Cognitive behavioral therapy was associated with greater improvement in ADHD symptoms - with improved scores in the ADHD-rating scale, Clinical Global Impression severity, and self-report ADHD scale -, and the benefits were maintained after 12 months of follow-up.

As children and adolescents mature, further studies should be conducted to assess the continuous efficacy of treatment in adulthood, as well as for newly diagnosed individuals. Additionally, new compounds with already available preliminary data should be further tested.

Adverse events

Pharmacological treatment of ADHD may be associated with a range of adverse effects. Adverse effects are mostly mild and/or transitory, and although serious adverse events are rare, they are a subject of concern and debates.[110] The European ADHD Guidelines Group (EAGG) recently reviewed the most common adverse effects and proposed recommendations for clinical management.[111] The most common adverse effects associated with stimulants are reduction of appetite, sleep disturbance, tics, seizures, and psychotic symptoms. The impact of stimulants on growth and its cardiovascular risks prompted significant concerns among clinicians and authorities and debate in the media.

Growth delay is likely caused by inappropriate nutrition due to loss of appetite.[112] A review found deficit in height associated with stimulant use, but also found that the deficit tends to attenuate over time.[112] Some studies also found that growth delay is dose-dependent and can be compensated within 2 years after discontinuing treatment.[112] Recommendations from the EAGG to manage growth deficit involve: managing loss of appetite (high-caloric snacks, medication after meals, late evening meals); monitoring appetite, weight, height and body mass index regularly; alternative options (i.e., medication holidays, pausing medication on weekends); and referring to a growth specialist if necessary.[111] Table 2 displays clinical recommendations for managing appetite loss and growth delay in children treated with ADHD medications.

Because stimulants can potentially increase blood pressure and heart rate, a lot has been speculated about the risk of serious cardiac events of stimulant users. Nevertheless, there is evidence that stimulants are not associated with changes in electrocardiographic parameters or with serious cardiovascular events (meaning sudden cardiac death, acute myocardial infarction and stroke).[113-115] Habel et al.[115] conducted a retrospective cohort study, evaluating electronic health records of 443,198 adults, of whom 150,359 were users of ADHD medications (methylphenidate, amphetamine, or atomoxetine) at baseline. The study investigated cardiovascular events such as myocardial infarction,

Table 2 Management of loss of appetite and growth delay during treatment with ADHD medications[111]

1. Monitor weight, height, BMI, and appetite regularly. Use standardized national charts for monitoring height, weight, and BMI.
2. To reduce appetite loss: give medication after meals, use high-calorific snacks and late evening meals.
3. Alternative for managing appetite loss and/or growth delay:
   a. Discontinue medication during weekends or drug holidays may be useful, but the risk-benefit balance should be carefully considered.
   b. Switch medication to another class or formulation.
4. Refer child to an endocrinologist or growth specialist if weight and/or height values are below critical thresholds.

BMI = body mass index.

sudden cardiac death, and stroke. No evidence was found for the association of current use with increased risk of cardiovascular events, compared with nonuse or remote use (risk ratio of any cardiovascular event for current use = 1.03; 95% confidence interval [95%CI] 0.86-1.24). Similar results were found in another retrospective cohort study that analyzed automated data from health plans from more than 1,200,000 children and young adults.[114] The results showed that current use of ADHD drugs was not associated with increased risk for cardiovascular events (hazard ratio of cardiovascular events for current use = 0.75, 95%CI 0.32-1.85), but the upper limit of 1.85 for the wide confidence interval found requires attention. It is recommended to investigate history of heart disease and family history of sudden death under the age of 40, and to refer the patient to a complete cardiologic evaluation before commencing treatment if either of those is present.[111] Heart rate and blood pressure should be assessed at baseline and monitored regularly during the course of treatment, but there is no evidence to support routine electrocardiogram before prescribing ADHD medication.[111] Table 3 shows recommendations regarding monitoring and managing cardiovascular risk in children and adolescents treated with ADHD medications.

The presence of adverse events should be evaluated and managed carefully when prescribing ADHD medications but, although all effort should be made to avoid exposing patients to unnecessary harm, it is important to adequately treat individuals who need treatment. It is also fundamental to perform a detailed assessment of pretreatment conditions and family history that increases risk for severe adverse events, avoiding negative events that can be anticipated.

Final considerations

There has been a growing investment in research on ADHD over the years. As a result, accumulating evidence supports the validity of the diagnosis. Current data indicate that ADHD is the outcome of deviant developmental processes and complex interactions between genetic variants and environmental exposures. There is no identifiable risk factor at the present moment that is either sufficient or necessary for the occurrence of the disorder. Therefore, it is hypothesized that different combinations of risk factors can lead to ADHD. The underlying etiological heterogeneity is likely to result in heterogeneity in the clinical presentation; countless different combinations of cognitive impairments and behavioral manifestations can be identified in individuals classified under the diagnosis of ADHD.

ADHD is frequently associated with important negative outcomes during development and in adulthood. Therefore, early detection and intervention are fundamental for reducing the burden of the disorder for the individuals, families, and the society. The efficacy and safety of pharmacological agents has been extensively demonstrated for the short-term treatment of the disorder. Less data is available for the long-term treatment and for non-pharmacological interventions. Evidence for the treatment of preschoolers and adults with ADHD is also less abundant. In the near future, long-term follow-up studies, evaluation of less studied populations, and development and assessment of new interventions are expected to contribute to further advance the knowledge about ADHD.

Disclosure

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Table 3 Management of cardiovascular risk during treatment of children and adolescents with ADHD medications[111,113]

1. Before starting ADHD medication:
   a. Conduct detailed interview to investigate personal and familial cardiovascular risk factors. If there is history of risk factors, refer to the child/adolescent's primary care physician or cardiologist.
   b. Measure baseline BP and heart rate. If readings are above normal for age/gender/height ($\geqslant$ 95th percentile), refer to the primary care physician for further evaluation.
   c. Routine ECG is not mandatory.
2. During treatment with ADHD medication:
   a. Repeat BP and heart rate measures at each visit. If readings are above normal for age/gender/height ($\geqslant$ 95th percentile), refer to the primary care physician or indicate drug reduction or drug holiday.
   b. Monitor change in personal or familial history of cardiovascular risk and refer to the primary care physician, if necessary.

ADHD = attention-deficit/hyperactivity disorder; BP = blood pressure; ECG = electrocardiogram.

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