Attention-Deficit/Hyperactivity Disorder

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Learning Objectives

Upon completion the learner will be better able to:

- Understand the genetics, neurobiology, and disease course of attention-deficit/hyperactivity disorder
- Detect and diagnose attention-deficit/hyperactivity disorder using DSM-5 diagnostic criteria
- Distinguish attention-deficit/hyperactivity disorder from closely related disorders
- Manage children, adolescents, and adults with attention-deficit/hyperactivity disorder

INTRODUCTION

While attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent mental health disorders in children and adolescents, a substantial number of adults exhibit symptoms of the disorder. As many as one in 25 adults have prominent symptoms of this disorder. Treatment of adults with ADHD differs from treatment of children and adolescents, but there are many overlapping themes and considerations. While the diagnostic criteria are identical across age groups, differing only in the number of symptoms required to make a diagnosis, adults with ADHD tend to manifest symptoms of inattention, impulsiveness, and restlessness more than the others. ADHD in adults can cause substantial functional impairment. Because some features of ADHD overlap across ages and others diverge, we provide a targeted but comprehensive review of the diagnosis and treatment of ADHD in children, adolescents, and adults.

Case Presentation: Abby

Abby is a 7-year-old girl who consistently underperforms her classmates. Abby's teacher, Ms. Henderson, has recently requested a third parent-teacher meeting to discuss her poor scholastic performance. At the first meeting, Abby's teacher was concerned that Abby was experiencing absence seizures because Abby did not seem to listen or pay attention, even when she was called on directly. Ms. Henderson initially dismissed ADHD because Abby is well-mannered, doesn't talk out of turn, and stays in her seat, unlike boys in the class with ADHD. Abby's teacher now reports that the girl will demonstrate a skill or show that she has learned something, but then fail to replicate it. When Ms. Henderson can get Abby to pay attention, the girl clearly has acquired the information, but she seems to omit part of the response or make careless mistakes. Abby asks her teacher to repeat instructions several times for in-class assignments and still has trouble completing multistep tasks. Ms. Henderson turned Abby's seat away from the window, which reduced the number of times Abby was distracted by things happening outside. Abby's mother is continually surprised at these reports since Abby is very well behaved at home. The only potentially troublesome thing that Abby does, according to her mother, is that she spends almost all her waking hours on her iPad. Abby's mother used to try to limit Abby's screen time, but this would cause horrible tantrums. Eventually, Abby's mom simply relented and let Abby use her iPad more or less as much as she wanted.

This discussion is divided into five sections:

- Section 1: Pathophysiology
- Section 2: Diagnostic Criteria and Clinical Features
- Section 3: Differential Diagnosis
- Section 4: Assessment
- Section 5: Management Plan

SECTION 1: PATHOPHYSIOLOGY

In this section, we describe the current understanding of the epidemiology, pathophysiology, and course of ADHD.

ADHD is highly heritable, with twin-based heritability estimates ranging from 70% to 80%.[1] Thus far, only 22% of the disorder's genetic basis has been identified in 12 genome-wide risk loci.[2] The cause of this large mismatch between familial transmission rates and known disorder-associated loci found in genome-wide association studies remains a mystery.[2] The missing genetic basis for heritability is likely due to a combination of epigenetic influences, neurodevelopmental processes, phenotypic variance, and environmental exposures.[2]

According to the CDC, 6.1 million children have been diagnosed with ADHD.[3] Boys are roughly twice as likely as girls to be diagnosed with this disorder (5.6% to 12.9%).[3] ADHD is highly comorbid with other disorders. Specifically, half of children with ADHD also have a behavior or conduct disorder, and approximately a third suffer from anxiety. About 17% of kids with ADHD also have depression, and 14% have autism spectrum disorder.[3]

The prevalence of ADHD in adults is lower than it is in children. The prevalence of ADHD in people ages 18 to 44 is estimated to be 4.4%.[4] As is observed in children, comorbidity rates in adults with ADHD are quite high. The odds ratio of an adult with ADHD also having a mood disorder is as high as 7.5.[5] The odds of also having an anxiety disorder is as high as 5.5, and the odds of also having a substance use disorder is 3. In fact, the number and severity of comorbid mental disorders tends to increase as patients with ADHD age.[5,6] The prominence of mood disorders tends to eclipse underlying ADHD in adults, which may lead to undertreatment. This is particularly unfortunate because perhaps as many as half of children with ADHD will have persistent, clinically significant ADHD symptoms in adulthood.[7]

Meta-analyses have revealed several factors that increase the risk of persistence of ADHD into adulthood. The severity of childhood ADHD appears to be the strongest predictor,[8,9] followed by treatment for ADHD.[8] Of course, ADHD treatment is not believed to be a risk factor such that stopping treatment would be protective. Rather, children with more severe illness are more likely both to receive treatment and to have persistent ADHD. Comorbid major depressive disorder and comorbid conduct disorder are also strong predictors of ADHD symptoms later in life. Comorbid oppositional defiant disorder, intelligence quotient, and single-parent family did not significantly impact adult symptom persistence.[8]

While these numbers strongly suggest ADHD is not simply a disorder found in children and adolescents, adulthood remission is possible. Perhaps as many as one-third of adults with ADHD achieve partial or full remission.[10] Moreover, the persistence of ADHD into adulthood does not necessarily indicate poor outcomes. One estimate suggests one in five boys with ADHD will have poor outcomes in school, social, and emotional behaviors while another one in five boys will have good outcomes.[11] The remaining three in five have deficits in one or more of the three functional domains. Social acceptance and self-perceptions of competence appear to lead to resilience and better outcomes.[12] Hyperactivity and impulsivity are more likely to remit in adulthood, while inattention symptoms are more likely to persist.[13]

Relatively little is definitively known about the pathophysiology of ADHD. Much of what is believed about the neurobiology of ADHD is secondary to the action of drugs used to treat the disorder. The main hypothesis in ADHD is related to hypoactive and hyperactive catecholamine systems.[14] Dopamine and norepinephrine synapses release a small, constant amount of neurotransmitter from a so-called "tonic" pool of presynaptic vesicles. The level of the tonic pool is modulated by feedback on presynaptic receptors. When the presynaptic nerve fires, larger amounts of catecholamine are released, which stimulate postsynaptic receptors. Catecholamines in the synaptic cleft either diffuse or are recovered by the presynaptic cell through reuptake transporters. When a person is bored, too little dopamine or norepinephrine is released, which consequently results in inadequate postsynaptic neuronal stimulation. This leads to distraction and impulsivity. Conversely, stress results in excessive neurotransmitter release, which interferes with a person's ability to maintain attention. A modest stimulation of the postsynaptic catecholamine receptors tends to result in guided attention, focus, and organized thoughts and actions.[14] In one hypothesis of ADHD, the tonic pool of catecholamines is abnormally reduced, results in less pre-synaptic receptor tonic feedback and higher phasic release of neurotransmitter. This causes a recurrent state of distraction and impulsivity. Blocking catecholamine reuptake increases the level in the tonic pool and attenuates phasic neurotransmitter release, normalizing

the system.[14] Additional support for this hypothesis derives from linkage studies in adults with ADHD showing polymorphisms in genes that code for proteins in the dopaminergic system, such as the dopamine transporter gene and dopamine receptor genes.[15]

SECTION 2: CLINICAL PRESENTATIONS AND DIAGNOSTIC CRITERIA

In this section, we describe the clinical features and DSM-5 diagnostic criteria for ADHD.

The DSM-5 diagnostic criteria for attention-deficit/hyperactivity disorder[16] are as follows:

A persistent pattern of inattention and/or hyperactivity-impulsivity lasting at least six months that interferes with functioning or development. The nine symptoms of inattention present as a patient who:

1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities
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 in the workplace
5. Often has difficulty organizing tasks and activities
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
7. Often loses things necessary for tasks or activities
8. Is often easily distracted by extraneous stimuli
9. Is often forgetful in daily activities

The nine symptoms of hyperactivity and impulsivity are manifested as a patient who:

1. Often fidgets with or taps hands or feet or squirms in seat
2. Often leaves seat in situations when remaining seated is expected
3. Often runs about or climbs in situations where it is inappropriate, or, in adolescents or adults, often feels restless
4. Often unable to play or engage in leisure activities quietly
5. Is often "on the go," acting as if "driven by a motor"
6. Often talks excessively
7. Often blurts out an answer before a question has been completed
8. Often has difficulty waiting his or her turn
9. Often interrupts or intrudes on others

For children ages 16 and younger, six or more symptoms must be present in one or both categories. For adults 17 and older, five or more symptoms must be present in each category. The DSM-5 bluntly states, "ADHD begins in childhood." Thus, several inattentive or hyperactive-impulsive symptoms must have been present prior to age 12 years. The DSM-IV had previously stipulated a cutoff of age seven, so 12 years reflects a relaxation of this criterion, presumably to enable diagnosis in adults when early life historical information is clouded by poor recall. These changes are likely a response to a large subset of clinicians and researchers who have posed the possibility of a late- or adult-onset form of ADHD.[17-20] The evidence base for this is mixed,[21] but persuasive overall. One of the most strongly supportive studies was documented in a cohort of more than a thousand people followed for nearly 40 years with a 95% retention rate. An astonishing 87% of adults diagnosed with ADHD had normal neuropsychological testing during childhood.[22] Similarly, 85% of participants diagnosed with ADHD as children no longer carried the diagnosis at the end of the study. Notably, the diagnostic criteria in the ICD-11 defines the essential features of ADHD without requiring a precise age of onset, duration, or number of symptoms. This suggests that adult patients who clearly meet criteria for ADHD but do not have a clear childhood history of the disorder may nonetheless require treatment.

The diagnosis of ADHD also requires that several inattentive or hyperactive-impulsive symptoms are present in two or more settings, usually home and school or home and work. This can be challenging to establish because it requires that clinicians interview teachers or other historians outside of the patient's family. Symptoms may be less apparent when the patient is being rewarded for acceptable behavior, has constant stimulation, or is in a novel environment. The American Academy of Pediatrics recommends a *"primary care clinician should initiate an evaluation for ADHD for any child four through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity."*[23] Further, the AAP states, *"Information should be obtained primarily from reports from parents or guardians, teachers, and other school and mental health clinicians involved in the child's care."*

When making the diagnosis, clinicians should specify a combined presentation if inattention and hyperactivity-impulsivity criteria are met or if one symptom group predominates. The DSM-5 replaced the DSM-IV term "subtype" with "presentation" to highlight the fact that symptom clusters may change over time.[24] Mild, moderate, and severe specifiers are not well delineated in the DSM-5 and are largely subjective. It is reasonable to use a validated ADHD scale to assess severity, for treatment planning, and to track response. ADHD scales are discussed in detail in the Assessment section.

While not specific to ADHD, children with the disorder often have mild delays in language, motor, or social development and impaired academic or work performance. However, deficits that only manifest in academic settings are not sufficient for a diagnosis of ADHD. Note that patients with ADHD often have at least one comorbid mental disorder. Therefore, unless a patient meets diagnostic criteria for ADHD solely during a psychotic episode or another disorder that better explains the totality of the patient's symptoms, patients should receive a diagnosis of ADHD in addition to other mental disorders. If symptoms of ADHD manifest solely within the setting of psychosis, depression, mania, etc., the diagnosis of ADHD should remain conditional.[2]

SECTION 3: DIFFERENTIAL DIAGNOSIS

In this section, we review the differential diagnosis of ADHD, which is quite extensive. ADHD symptoms are closely related to oppositional defiant disorder and disruptive mood dysregulation disorder. Children with oppositional defiant disorder are irritable, impulsive, argumentative, inattentive, and refuse to do schoolwork or other tasks requiring sustained mental effort, which overlap with ADHD symptomatology. Moreover, children with ADHD tend to become increasingly oppositional to authority figures when made to perform tasks. Obtaining a thorough history and closely following diagnostic criteria can help differentiate ODD from ADHD or establish both diagnoses in the same person. Patients with disruptive mood dysregulation disorder are highly irritable and lash out against others in more than one domain. Furthermore, disruptive mood dysregulation disorder (DMDD) and ADHD often co-occur.[25] On the other hand, children only with DMDD tend to have intact attention. Their temper tantrums are extreme and abrupt, but this behavior does not indicate impulsiveness.

True intermittent explosive disorder is rare and, like ADHD, children with IED are highly impulsive. Attentional problems are not a core feature of IED and may be a means to distinguish the disorders. Conversely, children with ADHD are not commonly aggressive or violent.

Tourette's disorder that manifests as multiple motor tics (together with vocal tics) and persistent motor tic disorder (without concurrent vocal tics) may be incorrectly perceived as hyperactivity. Motor tics are involuntary and repetitive muscle movements. Blinking, shrugging, grimacing, and body-rocking are common motor tics. Close observation should reveal that even complex motor tics have a repetitive or predictable quality, while the fidgety behavior of ADHD is more random.

Several features of ADHD overlap with autism spectrum disorder, including impaired attention, school and social difficulties, and inappropriate behaviors. Children with pure ADHD lack the more overt features of ASD such as social isolation, blunted facial expressions, and inability to appropriately respond to communication cues or engage in pretend play. Temper tantrums may occur in both disorders, but kids with ASD generally have outbursts when their environment changes unexpectedly or outside their routine. In kids with ADHD, outbursts are driven by poor self-control.

Symptoms of mania, such as hyperactivity, impulsivity, and the inability to concentrate or sustain attention overlap with ADHD. Making matters more complex, people with ADHD may have substantial moods swings or mood lability. Nonetheless, bipolar disorder can usually be distinguished from ADHD in several ways. ADHD usually first presents early in life, and bipolar usually presents later. Manic episodes are just that -- episodic -- and are followed by euthymia or depression. Careful observation will show that symptoms of ADHD that occur in a person with bipolar disorder manifest simultaneously with grandiosity, pressured speech, sleep disturbances, and perhaps psychosis.

Patients with ADHD may be anxious, but the source and focus of anxiety differs from those with generalized anxiety disorder and other anxiety disorders. Patients with anxiety disorders may appear incapable of paying attention to tasks because they are preoccupied with anxious thoughts or specific worries. Patients with ADHD may appear anxious and inattentive because they are rapidly shifting from one activity to another, seeking novelty or pleasure.

ADHD in adults and those with borderline personality disorder exhibit similar clinical features, namely impulsivity, emotional dysregulation, and cognitive impairment, most notably, the cognitive domains of attention-vigilance and verbal learning and memory.[26,27] Moreover, adult ADHD often co-occurs with borderline personality disorder.[26] Patients with borderline personality disorder, unlike those with ADHD, desperately avoid possible abandonment, report chronic feelings of emptiness, and more commonly exhibit self-harm and suicidal behavior.[28]

Various medications and substances can elicit symptoms of ADHD, such as stimulants, bronchodilators, and synthetic thyroid hormone. Likewise, withdrawal from CNS depressants can cause hyperactivity and impulsivity. While certain stimulants are used to treat individuals with hyperactivity (somewhat paradoxically), cocaine, amphetamines, or other stimulants cause symptoms of ADHD in people without the disorder. It is important to note that possible culprits include prescribed medications used as prescribed or misused through inappropriate dose increases or, alternatively, missed doses.

Additionally, and especially important in the diagnostic differential for persons with later age onset of disturbances in attention, impulsivity, and hyperactivity, is consideration of medical conditions. Attentional, behavioral, and cognitive symptoms can occur as sequelae of such diverse conditions as lead poisoning, diabetes mellitus, obstructive sleep apnea, chronic pulmonary disease, hyperthyroidism, and any medical and neurological etiology leading to delirium or dementia.

SECTION 4: ASSESSMENT

In section 4, we describe the screening tools and diagnostic instruments used to detect and diagnose, but first, let's review a clinical vignette.

Case Presentation: Jamal

Jamal is a 26-year-old high-school math teacher. He reports to his primary care physician that he is having trouble grading near-daily homework assignments and frequent tests. His primary symptoms are an inability to stay focused and being easily distracted. Jamal does not want to move to bubble-sheet exams because he strongly believes so much of math education is showing the work. Yet, Jamal cannot seem to concentrate on the work, is often late returning homework, and has even lost a set of student exams somewhere between school and home. Even when Jamal is not working, he has trouble focusing on television or sitting still long enough for pleasure reading. He freely admits that most of his difficulty in staying on top of his work duties is because of his poor time management. While he is patient with his students, he is short tempered with his wife, while waiting in line, or driving in traffic. In fact, Jamal has rear-ended two other cars twice within the past year because of distracted and aggressive driving. Jamal's wife states that he has always been talkative, so much so that he talks over other people, but to a certain point, that is part of her husband's charm. In other cases, it is frustrating to friends and coworkers. His wife is surprised he chose to be a math teacher because her husband has never been very organized or diligent with schoolwork. Jamal mentions that he took Ritalin when he was very young, but when his father lost his job and health insurance, the medication ran out. Jamal filled out the Adult ADHD Self-Report Scale-5 and scored within a range that suggests he has ADHD. The primary care physician referred Jamal to a psychiatrist for formal evaluation.

This vignette shows many of the symptoms of ADHD that are more prominent in adults. Hyperactivity symptoms in adults manifest as restlessness and excessive talkativeness, including interrupting others. Jamal's driving issues could indicate impulsivity and inattention. He certainly has poor time management skills and is easily distracted.

ADHD is a clinical diagnosis that requires a potentially lengthy and detailed evaluation of symptoms and functional impairment. Clinicians can and should seek reports from parents/guardians, teachers, school counselors, clergy, tutors, and coaches. ADHD symptoms may not manifest similarly in all domains or venues, but the diagnosis requires evidence of symptoms in two or more settings. When reports contradict one another -- for example, parents report severe ADHD symptoms, but teachers do not corroborate the assessment -- the ideal approach is to directly observe the classroom and score the child's behavior using a standardized rubric of direct observation codes.[29] Observation times vary from 15 to 32 minutes. Unfortunately, direct observation requires substantial time and resources, which may not be reimbursed. That said, with the near-ubiquitous availability of cell phone cameras, parents may be able to capture children's behaviors in the home or with peers that the clinician can review during a consultation appointment. For adults, self-report, reports of

spouses/family members, and reports of coworkers/superiors are usually required to make the diagnosis.

Reinforcing the fact that the diagnosis of ADHD is clinical, neuropsychological testing, imaging, and EEG are specifically not recommended for diagnostic purposes because of poor sensitivity and specificity.[2,30-32]

No ADHD rating scale should be used solely for diagnosis; however, they may have a place in screening and monitoring treatment progress. ADHD diagnostic rating scales are separated into two types: narrowband and broadband. Narrowband ADHD instruments for children include the Vanderbilt scales; the Conners scales, including the Conners Rating Scale-revised (CRS-R); and the Conners Abbreviated Symptom Questionnaire; the ADHD Rating Scales (ADHD-RS-V); the Child Behavior Checklist-Attention Problem (CBL-AP) scale; and the Swanson, Nolan and Pelham, or SNAP, scale. Narrowband ADHD instruments for adults include the Adult ADHD Self-Report Scale Symptom Checklist Version 1.1 (Adult ASRS), the Conners Adult ADHD Rating Scales (CAARS), the Adult ADHD Clinical Diagnostic Scale (ACDS), and the Wender Utah Rating Scale. Broadband tools include the Child Behavior Checklist (CBCL), the Behavior Assessment Scale for Children (BASC), and the Brown Attention Deficit Disorder Scales (BADDS), one for children, another for adults. While clinicians must take comprehensive histories and look for comorbid mental disorders, which could be informed by a broadband rating scale, the Agency for Healthcare Research and Quality states that narrowband ADHD rating scales are more accurate. That said, choosing between the narrowband instruments is not straightforward. A meta-analysis comparing several of these instruments found pooled sensitivities of 0.77, 0.75, 0.72, and 0.83 for the Child Behavior Checklist-Attention Problem Scale, the Conners Parent Rating Scale-Revised Short Form, the Conners Teacher Rating Scale-Revised Short Form, and the Conners Abbreviated Symptom Questionnaire, respectively.[33] Respective pooled specificities were 0.73, 0.75, 0.84, and 0.84. Thus, in this group, the Abbreviated Symptom Questionnaire not only had the best psychometric properties, but it was also the easiest to use. While not included in the meta-analysis, the Vanderbilt scales had lower specificity and sensitivity results.[34,35] The Conners Abbreviated Symptom Questionnaire is 10 items. Each item is scored on a simple zero-to-three-point Likert scale. A simple sum of scores greater than 15 suggests ADHD. Normative data for all of these scales are available for children ages five to 18. The only scales that have been validated in younger children are the Conners Comprehensive Behavior Rating Scales, and the ADHD Rating Scale IV are DSM-IV–based scales. DSM-IV versions of these scales that have been tested using DSM-5 criteria have performed well. Thus, older instruments that have not yet been validated using DSM-5 criteria are generally considered acceptable, though this remains unconfirmed. For adults, the instruments with the best psychometric properties are the Conners' Adult ADHD Rating scale (CAARS) and the Wender Utah Rating Scale (short version).[36] However, even these top-performing tools have inherent limitations. Specifically, while the CAARS has satisfactory reliability and validity, in a population of 240 post-secondary students, *"at best, only 72% of all individuals [with ADHD] were identified correctly by the CAARS, and anywhere from 20% to 45% of Clinical Controls were falsely identified as having ADHD."*[37] A third instrument that performs well as a screening tool in primary care is a six-item, self-administered version of the Adult ADHD Self-Report Scale based on the DSM-5.[38] The brief screen has high sensitivity, high specificity, and the results largely agree with the assessments of blinded clinical diagnosticians. Over-diagnosis is still a risk, and any positive screen should be followed by a structured or semi-structured clinical assessment.

Many of these instruments can be used serially to evaluate treatment response.[39] Clinicians are encouraged to choose a scale that has minimal clinically important difference (MCID) information. For example, a change of 27% or more signifies an MCID for the ADHD Rating Scale-IV.[40,41] The MCID for the Clinical Global Impressions-ADHD-Severity score is approximately eight points.[42] Another approach is to choose a scale that reports a Reliable Change Index (RCI).[43] For adults in particular, measures of health-related quality of life can be useful in tracking treatment response in ADHD.

Lastly, ADHD symptoms can be assessed and tracked through the course of treatment through use of direct tests of attention. These tests are called continuous performance tests. The Conners Continuous Performance Test (CPT) is one such neuropsychological test. It assesses attention-related problems using a task-oriented computerized assessment to measure inattentiveness, impulsivity, and sustained attention.[44] While widely used, its clinical utility in adults with ADHD has recently been questioned.[45]

SECTION 5: MANAGEMENT PLAN

In section 5, we describe the management of ADHD in children, adolescents, and adults. Various organizations in North America, Europe, and Australia have published ADHD treatment guidelines within the past 10 years.[46-51] Almost all available guidelines provide treatment recommendations that vary by age. While the cutoff ages vary by guideline, in general, age groups include preschool (up to 5 or 6 years old), children (from age 6 to 11 or 12), adolescents (up to age 18), and adults. Thus, we review treatment by age range. We also favor newer guidelines over those that were published less recently. Lastly, we give more weight to guidelines that follow more rigorous design standards, namely ones that use systematic reviews and base recommendations on higher quality evidence.

Management of Preschool Children with ADHD

For children ages four and five with ADHD, the first-line treatment is evidence-based parent training in behavior management (PTBM) and/or behavioral classroom interventions. The RCT evidence for efficacy and safety of medication in young children is considered too limited to recommend medication for routine treatment in this age group.[52] That being said, medication may be offered in select cases. If indicated, most guidelines suggest starting with a stimulant medication rather than a non-stimulant.[52] Short-acting methylphenidate is generally the preferred agent for preschool-age children.[47]

Parent Training in Behavior Management (PTBM)

PTBM has been shown to be effective in helping preschool children with ADHD to improve their ADHD symptoms , emotional behavior and social functioning, an effect that was maintained at the four-month follow-up.[53] The cornerstone of PTBM is teaching parents to use positive reinforcement techniques, which involves praising and rewarding appropriate behaviors, providing positive attention to encourage desired actions, and creating a supportive environment for the child. Parents also learn effective discipline strategies, such as setting clear rules, using consistent consequences for misbehavior, implementing time-outs appropriately, and ignoring minor misbehaviors to avoid reinforcing them with attention. PTBM emphasizes improving parent-child interaction by enhancing the quality of their relationship, teaching parents to interact positively with their children, and fostering emotional awareness and regulation in both parents and children.

Typically, PTBM involves 8 or more sessions with a therapist and can be conducted in group settings or with individual families. Parents acquire skills through verbal instruction, video and live demonstrations, role-playing exercises, and practicing skills at home between sessions. Research has consistently shown that PTBM is highly effective in reducing disruptive behaviors in children, improving parent-child relationships, decreasing parenting stress, and enhancing child social skills and academic performance. It is particularly recommended as a first-line treatment for young children with ADHD, before considering medication. successful [47]also [47]

[56,57]Management of Young Children with ADHD (Ages 6 to 12)

For children ages six to 12, US guidelines recommend a medication that has been FDA-approved for ADHD together with PTBM and a behavioral classroom intervention.[47] European guidelines tend to reserve medication for children with more severe ADHD symptoms or when PTBM or behavioral interventions fail.[52] In general, medication is prescribed for children in this age range when the child has no underlying cardiovascular risk factors, no comorbid conditions that would be a relative contraindication to stimulant therapy, and caregivers and school administrators agree to disperse and monitor therapy.[54]

Children with ADHD often receive an individualized education plan (IEP) or a 504 rehabilitation plan. These plans may include placement in special classes, modifying classes with specialized teaching approaches, and providing classroom behavioral supports.

Management of Adolescents with ADHD (Ages 12 to 17)

The primacy of medication used in adolescents with ADHD varies across nations. In the US, medication is considered first-line treatment. Specifically, the guidelines from the American Academy of Pediatrics recommend that adolescents from age 12 to their 18th birthday receive FDA-approved medications for ADHD together with evidence-based training interventions and/or behavioral interventions.[47] Additionally, educational interventions and individualized instructional supports, including school environment, class placement, instructional placement, and behavioral supports, are a necessary part of any treatment plan and often include an IEP or a 504 rehabilitation plan.[47]

Similarly, NICE guidelines from the United Kingdom suggest medication treatment as first-line therapy with cognitive behavioral therapy to be offered if medication is not fully successful in treating symptoms. Other European nations suggest prescribing medications as a second-line therapy or only for moderate or severe symptoms.[52]

Medications in the Treatment of ADHD

Stimulant medications for ADHD include methylphenidate and derivatives and various amphetamine derivatives. The number of stimulant formulations is impressive and available ones include short-acting immediate release, intermediate-acting extended release, and long-acting extended release. Methylphenidate is available in capsule form, orally disintegrating tablet form, chewable form, liquid form, and as a transdermal patch. A helpful guide to all FDA-approved medications, including various methylphenidate formulations, can be found at adhdmedicationguide.com. Given the variety of formulations, clinicians should follow prescribing instructions for the chosen medicinal product. Regardless of formulation—or the FDA-approved medication used, for that matter—it is best to start at a low dose and titrate upward to maximize effectiveness without inducing intolerable side effects.[47] Likewise, extended release stimulants are generally favored over shorter-acting drugs.[55] The one exception is for children ages 4 or 5 who require medication. In young children, immediate-release formulations are preferred.[56,57] Preschool children tend to be more sensitive to the stimulant effects of these drugs which can cause difficulty sleeping, decreased appetite, and irritability.[58] Immediate-release formulations allow for tighter titration than controlled release preparations.

A network meta-analysis of double-blind randomized controlled trials, including data from over 10,000 children and adolescents, revealed large effect sizes for psychostimulants in reducing ADHD core symptoms as rated by clinicians.[59] Studies have also shown that psychostimulants are effective in reducing core symptoms, improving overall quality of life, and reducing functional impairment. Moreover, psychostimulants have been associated with reduced risks of emergency hospital admissions for trauma, suicidal events, substance abuse, criminality, and unintentional injuries. While the short-term efficacy of psychostimulants is well-established, longer-term effects are less clear. Some observational findings have raised questions about the long-term benefits of psychostimulant treatment. However, a randomized placebo-controlled methylphenidate-(dis)continuation study showed significant benefits for those who continued treatment, supporting clinical guideline recommendations for periodic assessment of patients with ADHD to determine the continued need for psychostimulant treatment.[60]

The FDA has also approved four non-stimulant medications for the treatment of ADHD in children: atomoxetine, clonidine extended release, guanfacine extended release, and viloxazine. Of these four, atomoxetine and viloxazine have been approved for the treatment of ADHD in adults. eBoth of these medications are selective norepinephrine reuptake inhibitors, while clonidine and guanfacine are selective alpha-2 adrenergic agonists.

The effect sizes for stimulants are more robust than they are for non-stimulants. [9] The effect size of dexamphetamine, including lisdexamphetamine, and of mixed amphetamine salts, is 1.02 (0.85–1.19) on clinician ratings and 1.07 (0.79– 1.36) on parent ratings using the highest quality data available.[52,59] This is a large effect size. Moreover, the odds ratio of improved clinical global functioning is an impressive 7.71 (5.52–10.77).[52] The standardized mean difference of methylphenidate is 0.82 (0.48– 1.16), 0.78 (0.62–0.93), and 0.84 (0.72–0.95) on teacher, clinician, and parent ratings, respectively and its odds ratio of improved clinical global functioning is 5.57 (3.99–7.79).

Effect sizes for atomoxetine, clonidine, and guanfacine on core ADHD symptoms are medium at 0.56, 0.71, and 0.67, respectively, based on clinician ratings.[59] Clinical global functioning vs. placebo has odds ratios of 2.28, 2.78, and 3.63, respectively. Suitable comparative data are not available for viloxazine, but it did receive FDA approval for ADHD treatment in children and adults and is apparently more effective than placebo.[61] Despite these smaller effect sizes, non-stimulant medications play an important role in the treatment of patients with ADHD and certain comorbidities. Non-stimulant ADHD medications may be considered first-line treatment options in disruptive behavior disorders, tic disorder, Tourette's syndrome, and for patients with substance use disorders, conditions for which stimulants may be unadvisable.[62] Clonidine or guanfacine may be considered when sleep disturbances or significantly low appetite complicate ADHD treatment. These medications appear to have similar efficacy when given day or night but can promote nighttime somnolence.[63] Some evidence supports the use of atomoxetine for ADHD in patients with comorbid anxiety or autism spectrum disorder.[64]

The clinical response to stimulant medications is highly and surprisingly idiosyncratic. About 40% of children respond to both methylphenidate or amphetamine derivatives, but another 40% respond only to one or the other.[61] The most common short-term adverse effects of stimulants are appetite loss, abdominal pain, headaches, and sleep disturbances. Prescribers should also be aware that stimulant treatment may depress growth velocity, particularly at higher doses. The stimulant-treated children may lose 1-2 cm from their predicted adult height.[65] Moreover, stopping the medication does not result in rebound growth.[65] Psychotic symptoms, including hallucinations, rarely occur with prescribed stimulant use, but these adverse events can be extremely disturbing to patients and their caregivers when they do occur.[66]

The risk of adverse cardiovascular events associated with stimulant and non-stimulant ADHD medications is low overall, but should not be dismissed. Teens taking stimulant medications have higher rates of sudden death than peers. Prior to the start of pharmacological ADHD treatment, clinicians should assess the patient's personal and family history of cardiac disease, obtain 12-lead ECG, pulse, and blood pressure measurements, and monitor these values closely, especially early in treatment.

Atomoxetine and viloxazine are associated with drowsiness, decreased appetite, and GI upset soon after treatment initiation. Both drugs carry FDA "black box warnings" regarding an increased risk of suicidal thoughts and behaviors. Interestingly, growth trajectory changes have also been noted with atomoxetine. It is unknown whether viloxazine exhibits the same adverse effect.

The most common adverse events associated with guanfacine and clonidine are abdominal pain, bradycardia, dizziness, dry mouth, headache, irritability, and low blood pressure.[47] The alpha2-agonists are also associated with rebound hypertension, so they should be tapered over at least two to four days when they are discontinued, and perhaps longer.[67] Extended release clonidine, for example, should be reduced by increments of no more than 0.1 mg every 3 to 7 days. Extended-release guanfacine and extended-release clonidine may be used as monotherapy or as an adjunct to a stimulant medication.[68]

Importantly, stimulants exert an effect within days of starting treatment, while non-stimulants may take two to four weeks for full effect. Thus, an adequate treatment trial must be allowed before deeming the patient non-responsive to treatment.

Medications used for ADHD, but not FDA-approved

Modafinil, a CNS stimulant, has been used for the treatment of refractory ADHD in children.[69] In most cases, the use of modafinil should be reserved as a third line or later therapy and should be prescribed by a specialist in ADHD treatment. While bupropion is not considered a first-line agent in children with ADHD[47], limited evidence suggests it may have efficacy similar to methylphenidate or dexamphetamine with clinician-rated effect sizes as high as 0.96 (0.22–1.69).[52,70] While newer treatment guidelines in the US have omitted tricyclic antidepressants from their recommendations[47,55], imipramine and nortriptyline are still used for the treatment of ADHD in children and may be useful when benefits outweigh the risks, such as for treatment-refractory ADHD.[71]

ADHD Medications in Late-Stage Development

Centanafadine is a novel reuptake inhibitor of serotonin, norepinephrine and dopamine that is being developed for adults with ADHD. Two phase 3 randomized, double-blind, placebo-controlled, parallel-group studies of 200 mg/d or 400 mg/d centanafadine sustained-release tablets showed statistically superior efficacy when compared to placebo.[72] Effect sizes ranged from 0.28 for 200 mg/d to 0.40 for 400 mg/d. Both the overall rate of treatment-emergent adverse events and of serious treatment emergent adverse events was low, as was the potential for abuse. It is not clear when or if the FDA will approve this treatment, however. While no head-to-head trials have been conducted, a matching-adjusted indirect comparison revealed that centanafadine has a more favorable side effect profile compared to several other ADHD medications.[73] When contrasted with lisdexamfetamine, centanafadine showed significantly lower risks of various side effects, including reduced appetite, dry mouth, insomnia, anxiety, nausea, jitteriness, and diarrhea. However, it was less effective in reducing ADHD symptoms as measured by the AISRS/ADHD-RS score. In comparison to atomoxetine, centanafadine exhibited lower risks of nausea, dry mouth, fatigue, erectile dysfunction, reduced appetite, and urinary hesitation, while showing comparable efficacy in symptom reduction. Similarly, when compared to viloxazine ER, centanafadine was associated with lower risks of fatigue, insomnia, nausea, and constipation, with

no significant difference in efficacy. These findings suggest that centanafadine may offer a more tolerable treatment option for some patients with ADHD, particularly those sensitive to the side effects of other medications, while maintaining similar efficacy to non-stimulant alternatives.[73]

Complex ADHD

The Society for Developmental and Behavioral Pediatrics published treatment guidelines for children and adolescents with complex ADHD. They define complex ADHD as patients with an age at onset presentation of <4 years or >12 years; with coexisting conditions that affect neurodevelopmental, mental health, medical, or psychosocial health or development; with moderate to severe functional impairment; in whom the diagnosis is uncertain, and who have an inadequate response to treatment.[74] This definition of complex ADHD is rather broad and conceivably includes most patients with ADHD. Nonetheless, the recommendations made by this society seem to be applicable regardless of whether the disorder is simple or complex. While medication dosage should be titrated to core ADHD symptoms[75], comprehensive treatment planning should focus on reducing functional impairment in addition to symptom reduction.[74] This may be achieved by integrating behavioral parent training, behavioral classroom management, behavioral peer interventions, and skill building into the management plan as appropriate to the patient's age and stage of development. Each functional domain should be considered, assessed, and supported, including home, school, and peer settings.[74] Each visit should include an assessment of ADHD-related symptoms and functioning, psychosocial stressors such as peer victimization and family mental health, and the fostering of the patient's strengths.[74] Comorbidities, such as conduct problems, substance use, poor academic performance, and other mental health symptoms should be identified and treated. The AAP suggests The Barkley Side Effects Rating Scale is particularly useful in tracking adverse events from stimulant medications.[76]

Outcomes are demonstrably better if the first follow-up appointment takes place no later than 30 days after starting medication.[77] Likewise, the more that teachers are involved in reporting on the child's progress, the better the outcomes are.[77] Ideally, clinicians would engage with parents and teachers during the diagnostic phase, and hold frequent progress visits during the first weeks of treatment initiation.

[56,57]Transitioning into Adulthood with ADHD

Children and teens with ADHD have poorer outcomes compared to healthy children their age. Teens with ADHD are two times more likely to be convicted of criminal offenses.[78] Kids with ADHD are overrepresented in juvenile dentation facilities and later, in prisons.[78] Moreover, adults with ADHD are over twice as likely to be perpetrators of physical dating violence, and 65% more likely to be victims of such violence.[78] Not surprisingly, experts recommend intensive treatment for teens with behavioral problems and that all young people with ADHD receive transitional care before they leave high school (or perhaps, college).[79] Indeed, transitional training should begin at age 14 and intensify in junior and senior years of high school.[47] Preparations for this transition should include life skills training, social skills training, and occupational training. Ideally, patients would receive training specific to their individual needs and a formalized hand-off from pediatric to adult providers.[79]

Management of Adults with ADHD

The management of adults with ADHD differs from the management of children and adolescents in important ways. Unlike in younger patients, psychotherapy can be beneficial in adults with ADHD. The expression of comorbid mental disorders tends to be more common and more severe in adults than it is in children overall. While clinicians should certainly consider comorbidities in kids with ADHD, it more directly influences treatment decisions in adults with ADHD.

The FDA-approved stimulant medications for treatment of adults with ADHD include short-, intermediate-, and long-acting methylphenidate; short- and long-acting dexmethylphenidate; and short- and long-acting amphetamines of various kinds. For adults, non-stimulant treatments for ADHD include atomoxetine, viloxazine, bupropion, and nortriptyline.

As in children, treatment effect sizes are slightly better with stimulants than non-stimulant medications.[80] That said, stimulants and non-stimulants have not been tested head-to-head. Stimulants also start curbing symptoms within the first 1-2 hours of treatment initiation; non-stimulants may take from a week to a month to exert an effect.

A large meta-analysis of 51 RCTs in adults with ADHD suggests amphetamines exert a greater treatment effect than methylphenidate.[59] On the other hand, adult patients are more likely to stop treatment with amphetamines because of treatment-related side effects compared to methylphenidate. Unlike in children, amphetamines may be considered first-line agents for ADHD treatment in adults; however, treatment may be limited by adverse events. Thus, clinicians may consider methylphenidate and amphetamines reasonable first-line choices in adults using patient preference and comorbidities to inform treatment selection. The duration of action among stimulants does not seem to significantly affect clinical benefit.[59] That said, longer-acting medications may be associated with lower abuse potential.

Since non-stimulant medications are available, it may be prudent to offer patients with a history of substance use disorders one of these medications as first-line treatment. Atomoxetine and viloxazine are reasonable choices under these circumstances.[81] Bupropion can be tried instead if atomoxetine fails to achieve clinical goals. The possible one exception to this order – bupropion only after atomoxetine and viloxazine —is in patients whose substance of choice is nicotine and who desire smoking cessation treatment.[82] Ideally, the substance use disorder should be stabilized before started ADHD treatment. ADHD treatment efficacy may be reduced in the context of active substance use.[83]

Again, non-stimulant medications may take time to exert full benefit. Moreover, these drugs should be started at lower doses and increased as tolerated. This means it could take some months to reach the highest tolerated dose with atomoxetine, viloxazine, and bupropion. Once at the maximum tolerated dosage, treatment should be allowed to continue for at least four to six weeks before discontinuing for lack of effect. If stimulant medications must be used as a third-line pharmacological treatment in adult patients with ADHD and substance use disorder, long-acting stimulants are likely safer options than immediate-release forms. The relatively rapid-onset kinetics of immediate-release forms may lead to a "rush" which can be triggering in patients with a propensity to substance abuse.

Atomoxetine and viloxazine may also be reasonable first choices in patients with ADHD and prominent anxiety[84] or depressive symptoms.[85,86] In patients with particularly troublesome or prominent ADHD symptoms, a stimulant added to an SSRI or SNRI may be beneficial.[87,88] In general, the SSRI or SNRI should be started first and the dose stabilized before starting the stimulant. Skipping atomoxetine or viloxazine and offering a trial of bupropion is another option for patients with ADHD and a depressive disorder.

Patients with bipolar disorder should be on a stable and effective dose of a mood-stabilizing agent before starting a stimulant medication. Stimulants appear to increase the risk of mania in ADHD patients with poorly controlled bipolar disorder but pose no increased risk in those on stable treatment.[89]

Any time a patient receives both a stimulant medication and an SSRI or SNRI, there is a risk of serotonin syndrome. Serotonin syndrome is a potentially life-threatening condition that manifests as mental status change and neuromuscular and autonomic hyperactivity. Because of their association with various adverse events, tricyclic antidepressants such as nortriptyline should be reserved for treatment of refractory symptoms in select patients.

Psychosocial Interventions in the Treatment of ADHD

Children and Adolescents

With the exception of PTBM, psychosocial and psychological treatments for ADHD have repeatedly failed to provide robust benefits in children. Unblinded clinical trials have yielded robust effect sizes from treatments with cognitive behavioral therapy, organizational skills interventions, cognitive training, and neurofeedback; however, blinded studies of the same treatments found little to no effect.[52]

The European ADHD Guidelines Group estimated the impact of blinding on results in their series of meta-analyses of non-pharmacological treatments for ADHD comparing what they termed the "most proximal" outcome, i.e., rated by persons closest to treatment delivery and, therefore, the most vulnerable to lack of blinding. They compared those ratings with the measure judged by the group consensus to be most blinded rater. The EAGG meta-analyses found proximal rater effects were considerably larger than blinded rater effect sizes. Also, the scale of this discrepancy varied by treatment type in that it was largest for interventions where blinding was most challenging to implement. On the one hand, these results demonstrate the importance of blinding by design and by reporter. On the other hand, unblinded outcome measures may reflect clinically relevant changes that are not detected by the blinded raters.[52]

Adults

Unlike children, adults with ADHD may benefit from adjunctive cognitive behavioral therapy. [1]In general, the addition of CBT to medication improves outcomes in adults with ADHD compared to medication alone.[90,91] However, the benefits of CBT may be limited to improvements in organizational skills, self-esteem, and executive functioning rather than core ADHD symptoms specifically.[90-92] Indeed, some authors argue that CBT should be reserved for adult ADHD patients with deficits in executive functioning, and a structured manualized CBT program be used specifically.

Dialectical behavioral therapy may be helpful for patients who have difficulty regulating their emotions, are impulsive, or who have strained interpersonal relationships. Unfortunately, the effect sizes of dialectical behavioral therapy have been small.[93] Small RCTs have failed to show a benefit.[94]

Adults with ADHD may respond well to life skills training, peer coaching or life coaching.[95] In contrast to CBT, coaching and training are task-specific. For example, adults may benefit from learning time management skills, goal setting, and problem-solving.[96] Patients learn how to organize their home, school, and work environments to complete tasks. Furthermore, patients can be taught how to prioritize those tasks and fully complete one task before moving on to the next.

CONCLUSION

ADHD is a mental health disorder that was previously thought to only affect children and adolescents, but clearly persists into adulthood in most. In fact, recent research suggests the existence of a late-onset or adult-onset form of ADHD. If it is detected and diagnosed, ADHD can be effectively managed with pharmacological interventions and, in many cases, psychosocial interventions. Diagnosis requires the input of multiple informants across various venues, such as home, school, or work. While ADHD assessment tools can be helpful for screening or to track treatment progress, they are not substitutes for a thorough mental health evaluation. Therefore, the proper diagnosis of ADHD can be time-consuming and resource intensive. Nonetheless, adequate ADHD treatment can improve outcomes and functional trajectories. Indeed, early intervention may be able to reduce the emergence of comorbid conditions later in life.

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