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Adult Attention-Deficit/Hyperactivity Disorder Diagnosis, Management, and Treatment in the *DSM-5* Era

Joel L. Young, MD[a,*], and David W. Goodman, MD[b]

ABSTRACT

Objective: To increase awareness of adult attention-deficit/hyperactivity disorder (ADHD) in the primary care community and to provide guidance for the management of this condition. Despite its increasing prevalence, adult ADHD largely remains underdiagnosed and inappropriately treated in the United States. The publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), has provided more clear diagnostic criteria for adult ADHD, but a solid framework supporting the transition of ADHD management from pediatric to adult primary care is lacking.

Data Sources: We searched PubMed and MEDLINE databases (January 1, 1984–June 1, 2016) using combinations of keywords, including *ADHD*, *adult*, *diagnosis*, *prevalence*, *symptoms*, *treatment*, *comorbidity*, *compliance*, and *guidelines*; international treatment guidelines; and the Diagnostic Interview for Adult ADHD websites to identify relevant clinical studies, reviews, meta-analyses, guidelines, and web-based resources describing updates to the *DSM*.

Study Selection/Data Extraction: In total, 143 citations were selected based on their relevance to adult ADHD diagnosis, treatment, major issues, and practice guidelines.

Results: The update on diagnostic criteria in the *DSM-5* may increase the diagnosis of adult ADHD. There are critical differences between childhood and adult ADHD, and specific considerations should be taken with an adult ADHD diagnosis. Adult ADHD is primarily treated with pharmacotherapy assisted by behavior interventions. Caution should be exercised when using stimulants during pregnancy and the postpartum period. Adult ADHD patients often suffer from unemployment, financial difficulties, and an unsuccessful personal life. Adult-specific guidelines may improve adult ADHD treatment.

Conclusions: The successful diagnosis and management of adult ADHD require consideration of many facets including prior medical history and comorbid conditions and use of an individualized, evidence-based treatment approach.

Prim Care Companion CNS Disord
2016;18(6):doi:10.4088/PCC.16r02000
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[a]Rochester Center for Behavioral Medicine, Rochester Hills, Michigan
[b]Johns Hopkins University School of Medicine, Baltimore, Maryland
**Corresponding author:* Joel L. Young, MD, Rochester Center for Behavioral Medicine, 441 South Livernois Rd, Ste 100, Rochester Hills, MI 48307 (Jyoung@rcbm.net).

Attention-deficit/hyperactivity disorder (ADHD) is a common, chronic neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity.[1–3] Once thought to be largely a disorder of childhood, a growing body of evidence suggests that the symptoms of ADHD can persist into adulthood, as 60% of children with ADHD go on to have significant ADHD-related impairments in social, academic, and occupational functioning as adults.[3,4] ADHD affects approximately 4.4% to 5.2% of adults between 18 and 44 years of age[5,6]; however, fewer than 1 of every 5 of these patients are currently diagnosed and/or treated for ADHD.[7,8] There is also an increasing number of adults over the age of 50 years who are seeking assessment for ADHD for the first time, and the prevalence in older adults ranges between 2.8% and 3.5%.[9] Importantly, if left untreated, adult ADHD can lead to significant functional impairments and reduced quality of life (QoL).[7,10–12]

Familial, twin, and adoption studies[13] reported an estimated mean heritability of 76% for ADHD, making it one of the most heritable psychiatric disorders; yet, isolating the dysfunctional genes that predispose or cause ADHD has proven challenging, and research is ongoing.[14] Dysregulation in dopamine and norepinephrine neurotransmission is hypothesized to be involved, and effective pharmacologic ADHD treatments target these pathways; however, the precise mechanisms underlying ADHD pathophysiology remain unclear.[4,14,15] Additionally, a portion of cases may arise due to environmental factors, which play a role in susceptibility.[16] Environmental factors that correlate with an increased risk of ADHD include prenatal tobacco and alcohol exposure, early exposure to various neurotoxic agents (eg, lead) or neurologic insults, and traumatic brain injury.[2,3,16,17]

In the United States, primary care physicians and pediatricians treat the vast majority of patients < 18 years of age with ADHD.[18] Reframing ADHD as a chronic condition and filling the educational gap for patients and health care providers regarding the increasing number of adults in need of treatment for undiagnosed ADHD is of particular importance. There are profound maturational changes in ADHD-related pathology as patients progress through childhood into adulthood, highlighting the need for increased physician support and specialized behavioral interventions during transitional periods.[19] ADHD remains untreated and underdiagnosed in millions of adults in the United States,[5] and adults with ADHD suffer the negative consequences with social dysfunction, educational and occupational underachievement, substance abuse, increased risk of motor vehicle accidents, and legal difficulties.[12,20–23]

While adult ADHD symptomatology differs from the canonical childhood presentations, adults respond well to the same classes of medication used to successfully treat children.[19] The psychostimulants methylphenidate and amphetamine are first-line pharmacologic interventions for ADHD and are proven efficacious in treating ADHD patients of all ages.[19,24] Additionally, adults with ADHD who have been treated with stimulants prior to the age of 18 appear to have significantly better outcomes across broad QoL measurements as compared with

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Clinical Points

- Clinicians should increase their awareness of adult attention-deficit/hyperactivity disorder (ADHD)—which is often underdiagnosed and inappropriately treated—particularly with the publication of the *DSM-5*, now better describing a diagnosis for adults.
- Adult ADHD diagnosis is often complicated by emotional dysregulation and other psychiatric comorbidities and challenged by the lack of standard protocols; the use of adult-specific diagnostic tools may facilitate adequate ADHD diagnosis in adults.
- Adult ADHD is primarily treated with pharmacotherapy assisted by behavioral interventions, with special considerations given to stimulant misuse and abuse, medication use during pregnancy and the postpartum period, and adult-specific health conditions (eg, cardiovascular diseases).

those adult patients who were not treated with stimulants during childhood or adolescence.[23]

Primary care physicians are increasingly becoming responsible for screening for ADHD in undiagnosed adults and coordinating patient management for pediatric patients as they transition into adulthood. Continual access to primary care for patients with ADHD throughout adulthood is critical for improving QoL for these patients and ensuring adherence to treatment regimens.[19] Until recently, physicians have largely lacked adequate resources to diagnose and treat ADHD in adults.[25] Despite the updated guidelines from the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), with criteria to more effectively diagnose adult ADHD in comparison with the previous version (*DSM-IV-TR*),[3,26] a clear framework supporting diagnostics and disease management for ADHD patients as they transition from pediatric to adult primary care is lacking. Owing to the evolving landscape of the diagnostic criteria for ADHD and the number of undiagnosed adults in need of treatment, it is essential to increase awareness in the primary care community about adult ADHD.[27,28] In light of the *DSM-5* criteria revisions in recent years, this review focuses on recognition of symptoms, diagnostic issues, successful long-term patient management strategies, and treatment options in adult ADHD.

METHODS

The objective of this article is to review the major issues, treatment regimens, and guidelines associated with adult ADHD. A systematic search strategy was used to identify relevant studies pertaining to adult ADHD. Searches were limited to English-language articles. PubMed and MEDLINE databases were searched (January 1, 1984–June 1, 2016) using combinations of keywords, including *ADHD*, *adult*, *diagnosis*, *prevalence*, *symptoms*, *treatment*, *comorbidity*, *compliance*, and *guidelines*. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. In addition, the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, National Institute for Health and Care Excellence, European Consensus, and Diagnostic Interview for Adult ADHD websites were searched to obtain international adult ADHD-specific guidelines, along with web-based resources describing updates to the *DSM*. The *DSM-5* and relevant prescribing information for agents of interest were used as primary sources. In total, 143 citations[1–143] were selected based on their relevance to the objective and representation of adult ADHD issues and treatment guidelines, as judged by the authors.

DSM History Leading to the Updated ADHD Nosology

Evolution of ADHD definition. The disorder currently recognized as ADHD first appeared in 1968 in the *DSM-II*.[29] ADHD was originally termed *hyperkinetic reaction of childhood*, implying this disorder was defined primarily by excessive motor activity in children. In 1980, the *DSM-III* included problems with attention, impulsivity, and hyperactivity in the definition and renamed the disorder *attention deficit disorder* (with and without hyperactivity).[29] The term currently in use (*ADHD*) was introduced in 1987 (*DSM-III-R*), and the 3 subtypes of ADHD defined by the presence of excessive symptoms of inattention and hyperactivity-impulsivity (predominantly inattentive, predominantly hyperactive-impulsive, and combined subtypes) were first delineated in 1994 with the publication of the *DSM-IV* (revised in 2000, *DSM-IV-TR*).[29]

ADHD diagnostic criteria update in the DSM-5. The definition of ADHD as reflected in the *DSM-5* published in 2013 represented a 14-year revision process and more accurately incorporates the symptoms of affected adults. This update reflects 2 decades of research supporting the notion that ADHD continues through adulthood for many individuals.[30] Current guidelines now include the addition of specific ADHD examples across the life span and an increase in the age at onset criteria from 7 to 12 years; the latter allows for more ADHD diagnoses because of the broadened age range for the first onset.[31] Additionally, fewer symptoms are now required to establish a diagnosis of adult ADHD; both inattention and hyperactivity-impulsivity criteria have been lowered for those aged 17 years and older by requiring at least 5 of 9 criteria from either domain instead of 6 of 9.[3] Earlier editions of the *DSM* did not include adequate guidance for clinicians to diagnose adult ADHD, and through the adaptation of criteria for adults, children with ADHD can now more easily continue to receive treatment into adulthood.[31,32] Further updates to ADHD nosology include the addition of the autism spectrum as a comorbidity, strengthening of the cross-situational requirement, and the replacement of ADHD subtypes described in *DSM-IV* with corresponding presentations.[3] Lastly, modifiers enabling either the indication of severity (eg, mild, moderate, or severe) or the assessment of the current disease state if full diagnostic criteria are not currently met (eg, in partial remission) are now allowed.[3] Taken together, these updates are better suited to diagnose adult ADHD (Table 1).[3]

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Increasing Prevalence of ADHD in Adults as a Result of *DSM-5*

The US National Comorbidity Survey Replication estimated that 4.4% of adults met ADHD *DSM-IV* diagnostic criteria, with worldwide estimates between 1.2% and 7.3% (data collected between 2001 and 2003).[6,8] However, less than 15% of these adults were receiving pharmacologic or other treatment, suggesting that ADHD remains undiagnosed and untreated in the majority of cases.[5] ADHD is more commonly diagnosed among adult males than females, with an odds ratio of 1.6:1.0.[3] The extension of the age-of-onset criterion from 7 to 12 years in the *DSM-5* has caused a direct increase in the detection rate of ADHD in 12- to 15-year-olds from 7.38% (*DSM-IV*) to 10.84% (*DSM-5*).[36] The corresponding definitive statistics for increased detection of adult ADHD have not yet been made available; however, the *DSM-5* revisions are expected to significantly increase overall ADHD prevalence rates in adults.[37] It is critical for psychiatrists and primary care providers to familiarize themselves with the revised *DSM-5* criteria in order to effectively diagnose ADHD in adults in need of proper treatment.

Clinical Presentations of ADHD in Adults

Childhood and adult ADHD exhibit related symptoms; however, there are critical differences between the two. While adults with ADHD tend to experience minimal remission of inattentive symptoms with age, symptoms of hyperactivity/impulsivity tend to dissipate more with age.[38] This decline is associated with partial and, in some cases, full remission of ADHD.[39] Additionally, while there is no accepted system for assessing emotionality in diagnosing ADHD, a recent study[40] reported that 59% of adults with ADHD exhibited emotional dysregulation. In addition to emotional dysregulation, ADHD seems to be commonly accompanied by psychiatric comorbidities such as mood disorders in approximately 38% and anxiety disorders in approximately 47% of adults with ADHD.[6,7,23] ADHD symptoms can be masked by these comorbidities, and untreated ADHD in adults with psychiatric comorbidities results in poor clinical and functional outcomes for patients even if they receive treatment for their comorbid conditions.[7]

Diagnostic Challenges for Adult ADHD

In some cases, adults with ADHD who have been diagnosed in childhood may no longer have access to services and treatment due to loss of coverage during the transition into adulthood.[7] Therefore, timely preparation, good clinician relationships, and parental support are essential to facilitate the process of transition for young adults with ADHD. Conversely, some adults are diagnosed with ADHD without a prior childhood diagnosis. A 2004 survey-based study[7,41] revealed that only 25% of adults currently diagnosed with ADHD had first received a diagnosis of ADHD prior to the age of 18. The absence of a childhood ADHD diagnosis should not disqualify adults with ADHD from being diagnosed, as at least 3 studies[42,44,45] suggest that ADHD impairments may not be evident until adolescence or adulthood for some patients. The extent to which different ages of onset reflect disparate underlying causes of ADHD remains unknown.[36] Individuals with adult ADHD may not have received an ADHD diagnosis in childhood due to inadequate access to care or circumstances that masked ADHD-related functional impairments. Furthermore, adults diagnosed with ADHD later in life may not have been diagnosed earlier because, prior to 2013, the *DSM* criteria were not validated in adults and did not include developmentally appropriate symptoms and thresholds for adults; therefore, many affected adults could not be readily identified by health care professionals.[5] In addition to abatement of ADHD symptoms with age, adults may develop effective coping skills that make their impairments less evident or may choose to work in nonchallenging jobs, which may further mask the disorder.[43] Lack of awareness regarding differences in how ADHD symptoms present in adult versus pediatric patients may explain the prevalence of underdiagnoses of ADHD in adults.[34] Psychiatrists and primary care physicians should therefore be familiar with the presentations of adult ADHD in order to properly manage and treat ADHD and comorbid conditions.

The lack of standardized protocols for adult ADHD diagnosis poses problems for health care professionals and patients alike. There are no accepted biomarkers that are clearly indicative of an ADHD diagnosis; hence, physicians are mostly limited to qualitative assessments of symptoms.[46] Diagnosing adult ADHD can be challenging, and it is important that physicians obtain a detailed psychiatric and physical history to exclude or identify comorbid medical and psychiatric disorders to facilitate effective therapy.[47,48] The psychiatric conditions that commonly compound an ADHD diagnosis include depression, dysthymia, anxiety disorders, personality disorders, bipolar disorder, substance use disorder including nicotine dependence, and eating disorders.[7] As substance abuse is common in adults with ADHD, it is important to assess the risks of potential drug use or criminal behavior before determining the best treatment plan.[47,49] In addition, research suggests that ADHD and autism spectrum disorder frequently copresent in patients. A reported 30% to 50% of individuals diagnosed with autism spectrum disorder also have ADHD symptoms and the reported genetic correlations range from approximately 0.5 to 0.72[50,51] and are associated with a greater degree of impairments in social processing, adaptive functioning, and executive control.[52] Additionally, some classes of medication or substances including anticonvulsants, steroids, antihistamines, nicotine, and caffeine may have side effects that impact attentiveness and mimic ADHD symptoms, further complicating the diagnostic process.[47]

Diagnostic Tools for Adult ADHD

A reliable diagnosis of adult ADHD is incumbent upon a complete detailed clinical history complemented by various rating scales.[47] Ideal key elements include the following:

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Table 1. Criteria and Guidelines for Adult ADHD

Criteria	Description
DSM-5 adult-specific ADHD revisions[33]	• Examples added to the criterion items to facilitate application across the life span • The cross-situational requirement strengthened to several symptoms in each setting • The onset criterion changed from "symptoms that caused impairment were present before age 7 years" to "several inattentive or hyperactive-impulsive symptoms were present prior to age 12" • Subtypes replaced with presentation specifiers that map directly to the prior subtypes • A comorbid diagnosis with autism spectrum disorder is now allowed • A symptom threshold change made for adults, to reflect their substantial evidence of clinically significant ADHD impairment, with the cutoff for ADHD of 5 symptoms, instead of 6 required for those under 12 both for inattention and for hyperactivity and impulsivity • ADHD now placed in the neurodevelopmental disorders chapter to reflect brain developmental correlates with ADHD and elimination of the *DSM-IV* chapter in which all diagnoses usually first made in infancy, childhood, or adolescence
Proposed criteria for ADHD in adults[34]	• Is easily distracted • Makes impulsive decisions • Has difficulty stopping activities or behaviors when they should be stopped • Starts projects or tasks without reading or listening to directions • Does not follow through on promises or commitments • Has trouble doing things in the proper order or sequence • Drives a motor vehicle much faster than others (excessive speeding) or has difficulty engaging quietly in leisure activities • Has difficulty sustaining attention in tasks or recreational activities • Has difficulty organizing tasks and activities
Adult ADHD screen questionnaire (Adult ADHD Self-Report Scale–V1.1)[35]	• How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done? • How often do you have difficulty getting things in order when you have to do a task that requires organization? • How often do you have problems remembering appointments or obligations? • When you have a task that requires a lot of thought, how often do you avoid or delay getting started? • How often do you fidget or squirm with your hands or feet when you have to sit down for a long time? • How often do you feel overly active and compelled to do things, like you were driven by a motor?

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*.

confirming the presence of current impairing ADHD-related symptoms, obtaining school records or speaking with family members to establish a childhood history, evaluating the impairments observed by self and others over the life span, assessing potential medical contributors (pregnancy exposures, repetitive head injuries, concurrent medications), obtaining a complete family history for relevant psychiatric disorders/substance abuse, and eliminating the potential contribution of concurrent acute comorbid psychiatric disorders that may mimic some symptoms of ADHD.[43] The combination of the thorough history with *DSM-5* screening criteria and the utilization of questionnaires proposed by various groups detailed in Table 1 serve as the best-practice guidelines for the proper identification and diagnosis of adult ADHD.[34,53]

Clinical evaluation and rating scales. Adult-specific rating scales are critically helpful in diagnosing adult symptoms and presentations, while also providing metrics for measuring patient response to treatment and changes in QoL.[5] In general, rating scales take 5 to 20 minutes to complete, depending on the scale.[47] While these scales are useful, a critical review of responses is necessary, as patients may preferentially report symptoms in settings in which they are less impaired (ie, tasks that they find easy or interesting), which could diminish or mask their illness. Patients may also rate symptoms based on the experience with compensatory skills, thereby underrating the underlying symptom severity.[5] Diagnostic interviews are critical tools to evaluate the chronicity and pervasiveness of ADHD symptoms and associated impairments and facilitate correct diagnosis of ADHD in adults.[5] Descriptions of some available scales and a diagnostic interview are provided in Table 2.[5,43,47]

Neuropsychological testing. There is considerable interest in using neuropsychological tests as a clinical tool for ADHD assessment, as some adults with ADHD exhibit defined neuropsychological deficits such as impairments in attention, inhibition, and memory.[58,59] Adults with ADHD may display slowed performance in tasks of sustained attention and set shifting, and their use of working memory may be particularly impaired.[60] Neuropsychological testing is typically employed in cases of diagnostic uncertainty or for educational purposes.[5] However, not all individuals with ADHD have quantifiable neuropsychological deficits; therefore, relying on neuropsychological testing exclusively may miss affected individuals.[5,58] Conversely, while some clinicians believe that neuropsychological testing will "sort out the fakers" seeking stimulants, the research suggests that test results from faking may mimic deficits seen in ADHD, further confusing the diagnostic conclusion.[61,62]

Emerging imaging techniques. Advances in structural and functional imaging research have provided new avenues of study for ADHD disease phenotype, progression, treatment, and heritability.[63] Developments in imaging techniques have revealed structural and functional brain differences between individuals with and without ADHD.[63] Recent progress has been made toward understanding how ADHD affects the brain's connectivity through mapping architectural alterations of large-scale brain networks (ie, connectomes)

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Table 2. Selected Adult ADHD Rating Scales

Rating Scale	Description
Screening tools and symptom assessment scales	
ADHD Rating Scale IV[43,47]	Long version and quick screen, originally designed for children and adolescents (aged 12 and above) but has been used successfully in adults
Conners' Adult Rating Scale–Revised[43,47]	• Long, short, and screening versions; self-reports and observer reports; 8 scales • Asks patients about childhood and adult histories • Allows for diagnosis of ADHD by *DSM-IV* criteria, as well as by measuring emotional lability • Good interrater reliability between self-report and physician ratings
Barkley Adult ADHD Rating Scale[54]	• Directly linked to *DSM-IV* diagnostic criteria • Includes both self-report and other-report forms (for example, spouse, parent, or sibling) • Long version and quick screen • Includes a section assessing the newly identified inattentive-only subtype of ADHD
Wender-Reimherr Adult Attention-Deficit Disorder Scale[5,47]	• Measures the severity of symptoms in adults with ADHD using the Utah criteria • Useful to assess mood lability symptoms
Adult ADHD Self-Report Scale Symptom Checklist v1.1[47]	• Official instrument of the World Health Organization, available in multiple languages • An 18-item questionnaire intended for use in patients who are at risk of ADHD; a quick 6-item screening version is also available
Adult Investigator Symptom Rating Scale[5]	• Individual items are paired with the adult-specific prompts contained in the ADHD Clinical Diagnostic Scale • Provides a context basis to questions about symptoms and replacing questions that assess 2 symptom domains with questions that assess only 1 domain • Symptoms rated using a 4-point severity scale (from 0 = none to 3 = severe)
Diagnostic scales	
Adult ADHD Clinical Diagnostic Scale v1.2[5]	• A semistructured 18-item interview to establish the presence of current adult symptoms of ADHD, with suggested age-specific prompts for rating both childhood and adult symptoms • Current symptoms are assessed by examining duration of symptoms using a set of questions for each symptom domain
The Diagnostic Interview for ADHD in Adults[55]	• Based on the *DSM-IV* criteria, it is the first structured European interview for ADHD in adults and takes 1.5 hours to complete • The evaluation of each of the 18 symptom criteria for ADHD, in childhood and adulthood, the interview provides a list of concrete and realistic examples for both current and retrospective (childhood) behavior • Only asks about the core symptoms required to diagnose ADHD and does not cover other comorbid psychiatric conditions
Quality-of-life scales	
Adult ADHD Quality-of-Life Scale[43,56]	• Designed to quantify the quality-of-life consequences of adult ADHD • A 29-item robust scale structure with 4 domains: life productivity, psychological health, relationships, and life outlook
ADHD Impact Module–Adult[5,43,57]	• To evaluate quality of life for adults with ADHD • Comprised 4 global quality-of-life items, 5 economic impact items, and 5 multi-item scales that capture key concepts identified during patient and clinical interviews: living with ADHD; general well-being; work, home and school performance; and daily functioning • Relationships and communication, impact of symptoms—both emotional and daily interference are included

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*.

using techniques such as electroencephalography, functional magnetic resonance imaging (MRI), and diffusion MRI in combination with graph theoretical approaches.[64] Imaging studies[64–67] have revealed several neurologic differences between the brains of ADHD patients and those of healthy individuals. Positron emission tomography showed significant reductions in dopamine transporters and dopamine D_2/D_3 receptors in the striatum and midbrain of ADHD patients relative to healthy control subjects.[64] Decreased volumes of certain brain compartments—including cerebellar regions, subcortical regions, and the total brain matter—have been observed in ADHD patients.[65] ADHD also affects neurodevelopment, demonstrated by imaging-detected delayed maturation of specific brain areas as well as the whole brain functional networks in children with ADHD.[64] In addition, imaging studies have shown that some ADHD patients exhibit differential activation of neural networks relative to healthy controls in response to the same task.[66,67] Finally, the default networks of ADHD patients displayed structural alterations, such as redistribution of regional nodes and lower connectivity.[64]

The neuroimaging field is continually changing, partially due to computational abilities, allowing for the increasingly precise visualization of connectivity.[68] Together, these studies highlight various manifestations of brain network dysfunction in ADHD, shedding light on the pathophysiologic mechanisms in play. However, brain imaging technologies in ADHD are still in their infancy.[64] While accumulating evidence has been establishing a clear correlation between brain structural alterations and ADHD symptoms, a full view of structural and functional connectomes in ADHD is still lacking.[64] In addition, there is no guidance regarding the clinical utility of the imaging findings. With the rapid progression of the field, we can expect the development of

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Table 3. Potential Pharmacotherapy Agents for Adult ADHD Treatment

Medication	Trade Names
Stimulants–immediate release	
Methylphenidate	Ritalin,[71] Methylin,[72] Metadate[32]
Dexmethylphenidate	Focalin[73]
Amphetamine	Adderall,[74] Evekeo[75]
Methamphetamine	Desoxyn[76]
Dextroamphetamine	Dextrostat,[77] ProCentra,[78] Zenzedi[79,a]
Stimulants–extended release	
Methylphenidate	Concerta,[80] Metadate CD,[81] Ritalin LA,[82] Metadate ER,[83] Daytrana,[84,a,b] Ritalin SR,[71] Quillivant XR,[85] Aptensio XR,[86] QuilliChew ER,[87] Methylin ER[88]
Dexmethylphenidate	Focalin XR[89]
Amphetamine	Adderall XR,[90] Adzenys XR-ODT,[91] Dyanavel XR[92]
Dextroamphetamine	Dexedrine Spansule[93]
Lisdexamfetamine dimesylate	Vyvanse[94]
Nonstimulants	
Atomoxetine	Strattera[95]
Guanfacine	Intuniv[96,b]
Antidepressants	
Bupropion	Wellbutrin[97]
Desipramine	Norpramin[98]

[a]Approved for ages 3–16 years, off-label use in adults.
[b]Approved for ages 6–17 years, off-label use in adults.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

imaging-based assays for the future clinical diagnosis and treatment evaluation in ADHD.[64]

Treatment Options for Adult ADHD

First-line treatment–pharmacotherapy. Strategies for treating ADHD are multimodal, and the main treatment goals for patients are to improve symptoms, optimize functional performance, and remove behavioral obstacles.[69] For adults, pharmacotherapy consisting of stimulants or nonstimulants is the mainstay of ADHD treatment (Table 3).[32,47] Several categories of medications (antidepressants, alerting agents, cognitive enhancers) are used to treat ADHD in refractory cases even though this indication is not approved by the US Food and Drug Administration (Table 3).[70]

Adults and adolescents with ADHD have reported that the positive attributes of stimulant medication include improving social relationships, academic/work functionality, and driving and reducing criminal behavior.[23,99–101] Conversely, the negative attributes have been reported to include physical side effects, alterations in perception of sense of self, a loss of personality, stigma associated with medication use, and the inconvenience of taking medication.[99] The commonly prescribed stimulants include methylphenidate and amphetamines that are available in immediate- or extended-release formulations based on the technology of delivery.[32,47] Medication satisfaction studies[102] showed that extended-release medications were preferred by a greater percentage of adults based on the convenience of once-daily dosing. Recent evidence[103,104] suggests that adherence and persistence rates improve in ADHD when using long-acting agents (vs short-acting) and stimulants (vs nonstimulants). Extended-release stimulants are more of an abuse deterrent than their immediate-release counterparts, as they induce less euphoria and render drug extraction difficult.[105] For these reasons, international practice guidelines[101,106,107] recommend extended-release over immediate-release stimulants for ADHD treatment.

Pharmacotherapy issues. Treatment of adult ADHD with psychostimulants consistently yields positive short-term effects; however, confirmation of enduring efficacy is limited, as few trials have evaluated the long-term efficacy and safety of approved ADHD medications for adults.[32] Poor adherence or compliance and presence of other comorbid psychiatric disorders may further complicate the determination of treatment benefits in adults with ADHD.[48] Ineffectiveness and negative side effects are the most common reasons for discontinuing treatment; however, dosing convenience may be another significant factor in adherence.[103] Medication discontinuation or nonadherence is estimated to be between 13.2% and 64% for both children and adults in clinical trial populations over varying lengths of time, with the highest rate found 5 years after treatment initiation, suggesting that adherence negatively correlates with time since treatment initiation.[108] However, it is critical to distinguish between side effect–mediated treatment discontinuation and discontinuation due to symptomatic remission, as improper classification may confound calculations of ADHD persistence rates or adherence.[104]

Formulation-related factors may affect persistence in ADHD treatment. Although definitive evidence in adults is currently lacking, unpleasant taste and difficulty swallowing medication have been reported to negatively impact adherence in children and adolescents with ADHD.[109] Interestingly, difficulty swallowing solid oral dosage forms such as tablets or capsules is problematic for some adults as well as children,[110] and alternative formulations could potentially improve acceptance in those patients. Giving consideration to convenience and acceptability (to patients and family/caregivers) of differing formulations is crucial to potentially improving adherence.[111,112] A variety of newer formulations that circumvent problems associated with swallowing tablets or capsules have been made available (eg, transdermal patch, oral solution, chewable tablet),[113] while others have just recently been approved (eg, long-acting chewable tablet, long-acting liquid, and long-acting orally disintegrating tablet).[87,91,92] While stimulant-based medications have proven effective in treating adult ADHD and the risks of patients developing an addiction to stimulant medications with longer-acting preparations is low,[32,105] the majority of available clinical trial data have been short term and have relied heavily on young and middle-aged adult participants.[32] Further studies that assess the long-term benefits and risks in adults along with the benefits and risks in older adult patients over age 50 are warranted.[9]

Pharmacotherapy for refractory ADHD. While stimulants are highly effective in treating ADHD, responses may vary significantly among individual patients.[114,115] For patients with suboptimal response to 1 stimulant, increasing the dose of their current medication or switching to another

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Prim Care Companion CNS Disord
2016;18(6):doi:10.4088/PCC.16r02000

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stimulant may be a feasible solution.[115] The *d*-amphetamine prodrug lisdexamphetamine could be a stimulant alternative for ADHD patients with unsatisfactory response to methylphenidate or amphetamine.[115] Combining stimulants with a nonstimulant medication such as atomoxetine, guanfacine, or clonidine has shown positive effects among patients who are resistant to stimulants alone.[115] Patients with an insufficient response or intolerable adverse reactions may also switch to a nonstimulant, commonly atomoxetine, as monotherapy.[114] In addition, some medications that are not indicated for ADHD treatment have been used "off-label" for patients who are refractory to their current pharmacotherapy. These medications include the antidepressant bupropion and tricyclic antidepressants desipramine and nortriptyline. All of these agents have demonstrated effectiveness in ADHD treatment in clinical studies.[70]

Cognitive-behavioral therapy. Even though pharmacologic interventions are considered first-line treatments for ADHD, some adults with ADHD are unable to take these medications or continue to experience significant residual and impairing symptoms, which has led to an increased demand for psychosocial approaches targeting ADHD.[116] The cognitive-behavioral therapy (CBT) model—which includes use of higher-level organization and planning, behavioral skills training, and cognitive restructuring—has been instrumental in the treatment of adult ADHD, alone and especially in combination with psychopharmacology.[116] A review of the literature comparing CBT to other psychotherapeutic modalities found that CBT is helpful as an adjuvant to medication in the treatment of ADHD in adults.[117] Indeed, some studies have found CBT to be superior to medication alone.[117] CBT helps reduce impairments resulting from executive dysfunction that is not optimally ameliorated with medication.[117]

Coaching is gaining increasing popularity as an intervention for adults with ADHD. It is a highly individualized intervention in which a personally assigned coach guides the patient in accomplishing tasks and goals.[118] Coaching primarily differs from traditional CBT in that the former is more focused on solving specific problems or reaching specific goals and is more accessible to the patient on an as-needed basis. While clinical data assessing the effectiveness of ADHD coaching are limited, preliminary evidence suggests that this intervention may provide beneficial therapeutic effects when used either on its own or as part of a multimodal treatment package for adults with ADHD.[118]

Impact of ADHD on Adult Life

Outcomes in treated vs untreated adults with ADHD. The outcomes of adult ADHD are best examined in longitudinal studies, which have shown that pharmacologic treatment helped manage ADHD symptoms, decreased the risk of developing comorbid disorders, and improved functional outcomes.[119,120] Missed diagnoses during childhood and the absence of treatment have been associated with an increased risk of substance use disorder, as well as educational, occupational, and social impairments in adaptive functioning.[6,11] Several studies[7,121,122] have demonstrated that adults with ADHD often suffer from educational underachievement, cannot obtain and maintain employment and were less productive due to poor time management, suffered financial hardships, were more likely to engage in criminal activity, were more likely to be divorced, and claimed a greater number of lost workdays. These symptoms can therefore translate into significant financial costs for employees with ADHD and their employers; this is demonstrated by lower household incomes for adults with ADHD compared with the incomes of unaffected individuals.[20,123]

The symptoms of ADHD—including poor listening skills, a tendency to interrupt others, and being constantly active and easily frustrated—can lead to tensions in relationships with family members, friends, and partners.[3] For instance, adolescent women with ADHD in 1 longitudinal study[124] experienced more conflict with their mothers, were involved in fewer romantic relationships, and experienced more depressive symptoms than women without ADHD. Studies[9] in untreated adults with ADHD over age 50 have shown a reduced sense of self-mastery, diminished QoL, and more social isolation compared with age-matched controls.

A meta-analysis[125] found that ADHD was present among 23% of adolescents and adults with various substance use disorders. ADHD also appears to correlate positively with substance use disorder. Patients with ADHD experience substance use disorder earlier, become addicted more easily, and are hospitalized more often relative to people without ADHD who have substance use disorder.[126] Moreover, adults with ADHD and substance use disorder have increased rates of criminal behavior, imprisonment, and delinquency.[7] Given all of the adverse consequences associated with missed diagnosis of adult ADHD and a relatively high prevalence in the general population,[5] it is important for health care providers to screen for ADHD as part of every psychiatric evaluation, employing the rating scales and criteria in Tables 1 and 2.

Managing ADHD during pregnancy and the postpartum period. With increasing recognition of ADHD as a common condition in adults, specific concerns regarding the use of ADHD medication that are unique to the adult population have arisen. For example, there are concerns about effects of potential fetal exposure in pregnant women taking these medications.[127] Overall, a limited number of studies have evaluated the use of ADHD medications during pregnancy and the postpartum period. Clinical data suggest that orally delivered stimulants may be transferred to breast milk,[128–131] and the use of immediate-release stimulants may be correlated with low milk drug concentrations relative to the established toxic drug level.[130] A register-based study[132] conducted from 1999 to 2010 found that Danish women who used ADHD medication during pregnancy were more likely to experience induced abortion and miscarriage compared with those who were not exposed; however, it remains to be determined whether findings were related directly to ADHD

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medication or if confounding factors associated with use of ADHD medication were also involved.[132]

The consequences of prenatal exposure to methylphenidate remain unclear, although some small sample size studies[133,134] suggest that maternal methylphenidate use may be associated with negative fetal outcomes. CBT offers a suitable alternative to medication that can sustain functioning in some women during pregnancy[134]; however, the benefits of stimulant use may outweigh the risks associated with in utero exposure for some patients.[134] The American Academy of Pediatrics[135] generally recommends breastfeeding of the newborn for at least 1 year, but specific guidance regarding breastfeeding with the use of stimulants is lacking. Importantly, very few human studies have fully explored the effects of ADHD medication on the developing fetus, with disproportionally less known about amphetamine versus methylphenidate.[127] Collectively, evidence suggests that stimulant use during pregnancy is on the rise; therefore, the use of ADHD medication during pregnancy and nursing warrants further research.

Adult ADHD and sleep deprivation. ADHD patients often report sleep and wakefulness disturbances. This disturbance can be related to a close linkage between the brain systems in charge of sleep/wakefulness balance and ADHD symptomatology.[136] While up to 40% of ADHD patients have a sleep disorder,[137,138] the use of stimulants may also cause insomnia and sleep deprivation.[136] Unlike children whose sleepiness may lead to moodiness and aggression, adults with sleep problems often feel drowsy and sluggish.[139] As consequences of sleep deprivation, adult ADHD patients can often be late for work or classes and experience difficulty staying awake and alert for their daily tasks (eg, class, business meeting).[136] Sleep apnea, not uncommon in adults with ADHD, needs to be ruled out in these circumstances. Some adult patients attempt to manage sleep disturbance by using over-the-counter sleep medications or alcohol; however, these approaches are not always effective and may even exacerbate ADHD symptoms.[136]

Solutions to sleep deprivation include regular sleep pattern and, potentially, medication. Sleep hygiene refers to the management of bedtime environmental and behavioral factors, such as maintaining a consistent bedtime and establishing routine, relaxing activities that gradually reduce wakefulness levels (eg, watching TV, listening to music).[136] Patients with ADHD may adjust their stimulant dosing schedules to improve sleep. The stimulant dose should provide sufficient symptom control until evening while avoiding initial insomnia.[136] If the above approaches are unsuccessful or nonapplicable, the patient may use additional medications such as melatonin, clonidine, or tricyclic antidepressants (eg, desipramine and nortriptyline) before bedtime to improve sleep.[136]

Managing medication side effects. ADHD medications are known to cause side effects. These side effects include increases in both blood pressure and heart rate, leading to increasing concerns that prescription stimulant use may be linked to adverse cardiovascular outcomes.[140] However, a recent large population cohort study[141] suggested no increased risk of acute myocardial infarction, sudden cardiac death, or stroke for current ADHD medication users relative to nonusers or infrequent users. In addition, no increased risk was found with any specific medication or longer duration of medication use.[141] While the risks of serious side effects associated with stimulants and nonstimulants for treating ADHD are thought to be low for healthy adults, physicians should exercise caution when prescribing to patients with cardiovascular disease, seizure disorders, and psychosis.[32]

Table 4. Key Recommendations for Practice

Key Recommendations for Practice
• All patients who present with significant mental health issues should be assessed for ADHD due to the high rate of prevalence and presence of comorbid psychiatric disorders
• Various criteria, guidelines, and rating scales are available and are appropriate diagnostic tools for ADHD in adults
• Primary care physicians and psychiatrists should thoroughly evaluate prior and current medical and psychiatric history before prescribing ADHD medications to adults. This will help rule out coexisting conditions that may complicate (eg, other psychiatric disorders) or contraindicate (eg, cardiovascular disorders or seizures) treatment
• Health care providers need to heighten their awareness of misuse and diversion by patients, query patients about this, and develop strategies to prevent misuse or diversion of prescribed medications for adult ADHD. These strategies include:
Carefully tracking prescription renewal
Limiting the prescription of immediate-release stimulants
Performing random urine tests to screen for nonprescribed or illicit drugs in high-risk patients
Having stimulants secured away from other family members
Advising patients of the illegality of giving stimulants to others
Scheduling periodic follow-up appointments to gauge medication effectiveness and consistency of daily use
Clinicians should be well aware of pill accumulation at home as a result of inconsistent stimulant use

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Best Practices for Physicians Treating Adult ADHD Patients

An Internet survey[25] of health care providers determined that limited experience in adult ADHD diagnosis and treatment and difficulty in distinguishing ADHD from other disorders are significant barriers to adequate care and management of adult ADHD in both primary care and psychiatry practices. This survey identified a major gap in knowledge and training and further highlights the need to educate all health care providers.[25] In addition to the criteria, rating scales, and screening tools described earlier (Tables 1 and 2), there are also international guidelines[106,142] that provide useful information for adult ADHD management. The third edition of the Canadian ADHD Practice Guidelines[106] provides an Adult Tool Kit and also discusses the specific issues in managing adult ADHD. In addition, the National Institute for Health and Care Excellence guidelines[142] and European Consensus[101] have detailed chapters that cover the diagnosis and treatment of ADHD in adults. Key recommendations for practice are outlined in Table 4.

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CONCLUSIONS

Between 30% and 60% of children with ADHD continue to have significant impairments as adults, and many adults are diagnosed with ADHD without a prior childhood diagnosis.[3,4,7,143] However, adult ADHD as a common neuropsychiatric condition is underrecognized, underdiagnosed, and undertreated. Traditional pharmacologic interventions for ADHD are highly effective in treating adult ADHD, as trial-based data demonstrate sustained responses; however, the effects of long-term, consistent medication use are not known.[32]

If left untreated, adults with ADHD may experience significant functional impairments that can have a detrimental effect on psychological well-being and QoL.[7] It is critical to increase and improve health care professionals' awareness in symptom recognition and management of ADHD throughout the different life stages.[43] Adult ADHD presentations are different from children, with reduced hyperactivity/impulsivity, enhanced inner tension/restlessness,[7,38] and increased comorbid psychiatric disorders and substance use disorders that may complicate the diagnosis.[7] Adult ADHD is primarily treated with pharmacotherapy assisted by behavior interventions, with special considerations given to adult-specific health conditions such as stimulant misuse and abuse, pregnancy and breast feeding, and cardiovascular diseases. Various criteria/guidelines summarized within can help effectively diagnose adult ADHD and highlight issues associated with the management and treatment of ADHD in adults.

The successful diagnosis and management of adult ADHD requires consideration of many facets including prior medical history and comorbid conditions. Improved clinical outcomes can be achieved by treating adult patients with an individualized, evidence-based approach.

Future Directions

Given that long-term trials with adults of all ages are lacking, the long-term benefits versus risks of pharmacologic treatments in adults with ADHD need to be evaluated.[32] Additionally, it is important to design studies that evaluate adult-specific health conditions (eg, pregnancy and cardiovascular disease) and comorbidities (eg, psychiatric and physical disorders) that could potentially occur with ADHD, particularly in adults with ADHD over the age of 50. Strengthening adult-specific ADHD guidelines will provide clearer guidance and improve ADHD management among adults.

Submitted: May 26, 2016; accepted September 15, 2016.

Published online: November 17, 2016.

Drug names: atomoxetine (Strattera and others), bupropion (Wellbutrin and others), clonidine (Catapres and others), desipramine (Norpramin and others), dexmethylphenidate (Focalin and others), dextroamphetamine (Dexedrine and others), guanfacine (Intuniv and others), lisdexamfetamine (Vyvanse), methamphetamine (Desoxyn and others), methylphenidate (Ritalin and others), mixed amphetamine salts (Adderall XR and others), nortriptyline (Pamelor, Aventyl, and others).

Funding/support: Funding for this systematic review was provided by Neos Therapeutics, Inc, Grand Prairie, Texas. Editorial support was provided by Tanmayi Mankame, PhD; Liqing Xiao, PhD; and Jennifer Tyson, PhD of AlphaBioCom, LLC, King of Prussia, Pennsylvania, and was funded by Neos Therapeutics, Inc. Drs Mankame, Xiao, and Tyson report no conflicts of interest related to the subject of this article.

Role of the sponsors: The sponsors had no role in the design, analysis, interpretation, or publication of this study.

Potential conflicts of interest: **Dr Young** reports grants/research support/educational support from Actavis/Forest Laboratories, Alcobra, Allergan, Arbor, Daiichi Sankyo, Neos, NLS Pharma, Otsuka, Pfizer, Rhodes, Shire, Sunovion, Takeda/Lundbeck, and Teva. **Dr Goodman** reports consultancy support from McNeil, Teva, Lundbeck, Janssen US and Canada, OptumInsight (Ingenix Pharmaceutical Services, Inc), Sunovion, Thomson Reuters, GuidePoint Global, Otsuka, Neos, Ironshore, Rhodes Pharm, Novartis, Major League Baseball, National Football League, American Physician Institute for Advanced Professional Studies LLC, Consumer Reports, and the Children and Adults with ADHD Association and receives honoraria from WebMD, Medscape, American Professional Society of ADHD and Related Disorders, Neuroscience Education Institute, Children and Adults with ADHD Association, and Global Medication Education.

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