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Position Statement

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Position Statement

ADHD in children and youth: Part 1—Etiology, diagnosis, and comorbidity

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder. Three position statements have been developed by the Canadian Paediatric Society, following systematic literature reviews. Statement objectives are to:

1) Summarize the current clinical evidence regarding ADHD,
2) Establish a standard for ADHD care, and
3) Assist Canadian clinicians in making well-informed, evidence-based decisions to enhance care of children and youth with this condition.

Specific topics reviewed in Part 1, which focuses on diagnosis, include: prevalence, genetics, pathophysiology, differential diagnosis and comorbid psychiatric disorders and developmental disorders. In addition to database searches, the most recent guidelines of the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network, and the Eunethydis European ADHD Guidelines Group, were reviewed. Because ADHD is a heterogeneous disorder, comprehensive medical assessment for ADHD should always include a complete history, a physical examination, and a thorough consideration of differential diagnosis and related comorbidities. Specific recommendations for information gathering, testing, and referral are offered.

Keywords: *Attention-deficit hyperactivity disorder; Comorbidity; Diagnosis; Etiology*

BACKGROUND

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) classifies attention-deficit hyperactivity disorder (ADHD) as a neurodevelopmental disorder and defines it as 'a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development … and negatively impacts directly on social and academic/occupational activities' (1). Worldwide, ADHD is the third-most-common mental health disorder, after depression and anxiety, affecting an estimated 3.4% of children and youth (2).

ADHD prevalence in the paediatric population has been stable over the past three decades (3) except in the USA (4), where it has increased. Applying the definition of ADHD from the International Classification of Diseases, 10th edition, yields a lower prevalence rate compared with the DSM-5, because the ICD-10 requires criteria be met for both inattention and hyperactivity (5). ADHD is associated with significant adverse outcomes in childhood and adolescence: educational problems (resulting in low rates of high-school graduation and completion of postsecondary education) (6), difficult peer relationships (7)

and increased rates of motor vehicle accidents, accidental injuries, and substance misuse. Risk for substance abuse increases further when ADHD is comorbid with conduct disorder (CD) (8,9). The presence of these comorbid conditions and ADHD is associated with increased mortality risk (10).

Current estimates show that 50% of children with ADHD continue to have symptoms of ADHD in adolescence and adulthood. Predictors of persistence include combined inattention/hyperactivity, increased symptom severity, comorbid major depressive or other mood disorder, high comorbidity (>3 additional DSM disorders), parental anxiety, and parental antisocial personality disorder (11).

ETIOLOGY

ADHD is a disorder with multiple etiologies. Combinations of genetic, neurological, and environmental factors contribute to pathogenesis and its heterogeneous phenotype (12).

Evidence from family, twin, and adoption studies has suggested strongly that ADHD is a highly hereditary, polygenic disorder (13). Gene variants predicting risk for ADHD are important for brain development, cell migration, and encoding for catecholamine receptor and transporter genes (13,14). The identification of gene sets affecting neurotransmitter pathways in the brain (15) has suggested that rare copy number variants or the accumulation of larger deletions and duplications influencing gene transcription are more commonly found in individuals with ADHD (16). (For more information, see the companion statement on special populations in this issue). Ongoing pharmacogenetics research aims to identify genes involved in medication response with ADHD (17).

Noninherited neurological factors affecting brain development or resulting in brain injury have been implicated in ADHD pathogenesis. The contribution of pregnancy and birth complications is mixed, but strong evidence supports greater ADHD risk following in utero exposure to alcohol or tobacco (18) and low birth weight (<2,500 g) (19,20). Hypoxic–anoxic brain injury (21), epilepsy disorders (22), and traumatic brain injury (23–25) also contribute to ADHD risk.

Exposure to environmental toxins (specifically lead, organophosphate pesticides, and polychlorinated biphenyls) has been linked to ADHD symptoms (20,26,27). Except for children experiencing exceptional early deprivation (28,29), a causal relationship between family environment and psychosocial adversity and ADHD is unclear (20,30,31).

Neuroimaging studies point to ADHD as a disorder of early brain development. Based on volumetric (32) and functional MRI studies (33), differences are found in the structural development and functional activation in the prefrontal cortex, basal ganglia, anterior cingulate cortex, and cerebellum (34). Activity among these areas depends on catecholaminergic brain circuitry (35). Despite weak evidence for deficits in these neurotransmitters, their role is substantiated by their distribution in those areas of the brain involved in ADHD and the positive response of ADHD patients to medications that modulate the neurotransmission of catecholamines (36). A delay in cortical maturation has been documented, with peak cortical thickness attained in the cerebrum at 7 years in typically developing children and at 10 years in those with ADHD (37).

DIAGNOSIS

ADHD remains challenging to diagnose because specific biomarkers and symptom specificity are lacking, the scope for differential diagnosis is large, and comorbidities are often present. Diagnostic improvements in the DSM-5 include criteria that now describe essential behaviours over a broader age range and that natural history is better captured in the lower number of symptoms needed to meet diagnostic threshold in adolescence and adulthood. While some changes occurred between DSM-IV and -5, the same (or similar) questionnaires, rating scales and screening tools (www.cps.ca/en/tools-outils/mental-health-screening-tools-and-rating-scales) can be used to gather diagnostic information from multiple informants. Symptoms must be present across multiple settings and lead to impairment in everyday activities. Key elements of the diagnostic procedure are discussed in several guidelines (38,39) and outlined in Table 1.

Obtaining a diagnosis of ADHD in preschoolers and adolescents can be complicated. Although there is evidence that DSM criteria can be applied to preschool children, it may be difficult to obtain sound observations from nonparent observers (38). Only the Conner's Comprehensive Behavior Rating scale and the ADHD Rating Scales IV have been validated in this age group (40). Before establishing a diagnosis of ADHD and initiating treatment in preschoolers, the American Academy of Pediatrics (AAP) recommends that parents of young children referred for ADHD assessment enrol in a parent training program (38). Such programs can help parents develop age-appropriate developmental expectations and specific management skills for problem behaviours.

Obtaining diagnostic information from multiple informants for adolescents can also be challenging. There are multiple teachers in high school, primary caregivers may have less opportunity to observe their adolescent's behaviours than during childhood, adolescents are less likely to exhibit overt behaviours (e.g., hyperactivity), and adolescent self-reporting often minimizes their problematic behaviours. It is important to establish whether manifestations of ADHD were present at a younger age and to strongly consider substance use, depression, and anxiety as alternative or co-occurring diagnoses.

As with many complex presentations, the differential diagnosis for ADHD can be narrowed considerably by a skillful history

Table 1. Clinical process and 'pearls' in the diagnosis of ADHD: Implementation of guidelines and expert consensus

Schedule several office visits to complete the diagnostic evaluation.
Obtain detailed information on prenatal/perinatal events, medical and mental health history.
Obtain developmental/behavioural history (motor, language, social milestones and behaviour, including temperament/emotional regulation and attachment). *(Assessment of developmental milestones is particularly important for diagnosing preschool children because impaired attention and hyperactivity may also be features of a neurodevelopmental disorder.)*
Evaluate family medical and mental health, family functioning and coping styles of primary caregivers. Ask about genetic disorders. Evaluate for comorbid disorder(s) (psychiatric, neurodevelopmental and physical). *(Do comorbid symptoms meet criteria for a separate disorder that is the main diagnosis OR exist in tandem with ADHD as the main diagnosis OR are they secondary symptoms [stemming from the ADHD]?)*
Review academic progress (e.g., report cards, sample assignments) and look for symptoms of a learning disorder (69). *Clinical impressions and use of standardized scales are still the most effective practices for evaluating ADHD symptomatology.*
Obtain standardized behaviour rating scale(s) that evaluate DSM-5 criteria from primary caregivers, teachers and the adolescent being assessed. For a list of screening tools and rating scales to assess impairment, see: www.cps.ca/en/tools-outils/mental-health-screening-tools-and-rating-scales *(Rating scales are not diagnostic of ADHD but they provide subjective impressions to help quantify the degree to which a behaviour may deviate from the norm and can be used to evaluate the effects of interventions in home or school* [70].*)*
Unless indicated by history and physical examination, do NOT: • order laboratory tests, genetic testing, EEG or neuroimaging. • order psychological (standardized assessment of intellectual function and academic achievement skills) neuropsychological or speech-language assessments. • use psychological tests (e.g., TEACH, Continuous Performance Tests [CPT]) or measures of executive function to diagnose ADHD and/or as a means to monitor symptom or functional improvement in daily activities.
Refer to DSM-5 criteria for core symptoms and characteristics of ADHD: 1. Symptoms are severe, persistent (i.e., present before 12 years of age and continuing >6 months), and inappropriate for the patient's age and developmental level. • *Consider the demands and expectations being placed on the child and what the child's innate capabilities are to meet these expectations. What will this child look like over time?* • *The abilities to self-control attention, activity and impulses emerge in a developmental process* (70). *The DSM does not provide for developmental level differences, which may lead to overdiagnosis of ADHD in young preschool-aged children.* 2. Symptoms are associated with impairment in academic achievement, peer and family relations and adaptive skills. • *'Impairment' implies greater severity and frequency of symptoms that interfere with ability to function across major life domains.* 3. If there is a discrepancy of symptoms across settings, it is important to identify why the discrepancy exists. 4. Specify the type of ADHD presentation as per the DSM-5: i) Combined presentation (criteria are met for inattention, hyperactivity-impulsivity) ii) Predominantly inattentive presentation (criteria are met for inattention) iii) Predominantly hyperactive-impulsive presentation (criteria are met for hyperactivity-impulsivity) 5. Specify current severity (mild, moderate or severe) based on the symptoms and degree of functional impairment.
Medical examinations: Perform thorough physical, neurological and dysmorphology assessments (71).

Adapted from references (38,39,72–75). *ADHD Attention-deficit hyperactivity disorder; DSM Diagnostic and Statistical Manual of Mental Disorders.*

and physical examination. Both the symptoms and the context in which they occur require exploration (Table 1).

DIFFERENTIAL DIAGNOSES

The DSM-5 lists 16 conditions or groups of conditions to be distinguished from ADHD, many of which can also occur as comorbidities. A list of developmental and behavioural conditions that are commonly mistaken for ADHD is presented in Table 2 (41).

Conditions comprising the differential diagnosis may be grouped for ease in history-taking. Beginning with disorders considered to be psychiatric, ADHD is often grouped with externalizing conditions associated with visible, often disruptive and aggressive behaviours, such as oppositional defiant disorder (ODD) and intermittent explosive disorder; a disruptive behaviour can be mistaken for hyperactivity or impulsive reactivity. Unipolar internalizing disorders (e.g., anxiety disorder, depression) may be mistaken for inattentive presentation, while mood disorders with mood swings and poor emotional regulation (e.g., bipolar disorder [BD], disruptive mood dysregulation disorder) can mimic all the symptoms of ADHD (combined presentation).

The DSM-5 groups together trauma- and stressor-related disorders. In reactive attachment disorder, social disinhibition may resemble, initially, the impulsivity and social isolation seen in ADHD. However, exploration of the social history and the child's relationships over time can help to distinguish among disorders. Many children with ADHD can make initial social overtures but have difficulty maintaining relationships due to emotional dysregulation. Not specifically listed in the DSM-5 differential for ADHD are adjustment disorders, where emotional and/or behavioural symptoms emerge in response to an identified stressor (e.g., the illness or death of a family member or close friend, a separation or divorce), and to post-traumatic stress disorder. Post-traumatic stress disorder should always be considered with a history of identified trauma (e.g., child abuse) (42).

Children who function at extremes of cognitive development, such as those with ID (see the companion statement on special populations in this issue) or superior intellectual functioning, may be disconnected and inattentive in class, the former because material presented in class may be too difficult, and the latter because school work has already been mastered. In either case, children with learning tasks that are poorly matched to their ability may also become disruptive. Similarly, children with a specific learning or language disorder may show inattention and (at times) disruptive symptoms, when their specific area of difficulty is the focus of class or homework assignments (e.g., the student with dyslexia who becomes inattentive during reading period).

The movements associated with autism spectrum disorders (ASDs) (see the companion statement on special populations in this issue) and other neurodevelopmental disorders (e.g., stereotypic movement disorder, Tourette's syndrome) may be mistaken for hyperactivity. Additional social communication deficits and lack of social overtures can help identify ASD, while movement quality (sudden, rapid, nonrhythmic) and distribution (eyes, face, upper body, vocal) may be useful for distinguishing tic disorders (TD).

The DSM-5 also includes conditions (e.g., personality disorders, psychosis, substance abuse disorders [SUDs]) that are seen less commonly in the paediatric population but should be considered when assessing older children and youth. Although these conditions may present with inattention, impulsivity and academic problems, psychiatry or other appropriate mental health services should be arranged. The child's medications should be reviewed carefully for potential to induce ADHD symptoms, anxiety, depression or psychosis.

In addition, medical conditions can mimic inattentive ADHD. These include conditions causing fatigue or pain (obstructive sleep apnea, inflammatory bowel disease), sensory impairments (visual or auditory), chronic health conditions affecting school attendance (such that the child no longer understands or follows what is being taught), and neurological conditions that affect attention and arousal (e.g., epilepsy, post-concussion status). All of these conditions may also co-occur with ADHD; treating an identified medical condition may provide insight into possible comorbid ADHD.

Table 2. Conditions commonly misdiagnosed as ADHD (in decreasing order of frequency)

Learning disorder
Sleep disorder
Oppositional defiant disorder
Anxiety disorder
Intellectual disability
Language disorder, mood disorder, tic disorder, conduct disorder
Autism spectrum disorder
Developmental coordination disorder

Information from reference (41). *ADHD Attention-deficit hyperactivity disorder.*

The prevalence of ADHD in children with epilepsy is two to three times higher than in the general population, and is typically inattentive presentation. ADHD symptoms are generally present at or before the first seizure, suggesting comorbidity as opposed to being secondary to epilepsy or antiepileptic medication. Complicated epilepsy, higher seizure frequency, and earlier age of onset are associated with higher ADHD risk, with these patients mostly showing combined presentation. Antiepileptic medications, especially phenobarbital, and to a lesser extent, phenytoin, carbamazepine, and valproic acid, can affect attention and activity. Newer antiepileptics (gabapentin, tiagabine, vigabatrin, and lamotrigine) may have fewer cognitive side effects (43).

Many genetic conditions (fragile X syndrome, Turner syndrome, tuberous sclerosis, neurofibromatosis, 22q11 deletion syndrome), especially those with accompanying developmental symptoms, show a higher prevalence of ADHD than the general population (44–48). For many, congenital anomalies, significant dysmorphology, seizures or global developmental delay likely will be noted before ADHD symptoms develop. However, in conditions where symptoms and signs are subtle, intermittent or later-developing (e.g., neurofibromatosis, where dermatological findings may increase with age, or syndromes where facial dysmorphology is more apparent over time, or fragile X syndrome), inattention or hyperactivity may be what first brings the child to the physician.

Central auditory processing disorder is a symptom cluster affecting ability to attend to and discriminate among auditory stimuli in the presence of normal hearing and intellect (49). It has been treated with auditory interventions, including preferential seating, sound field systems, personal FM devices, and headphones, but is questioned as a distinct entity because of high comorbidity with ADHD (50).

COMORBIDITY

ADHD, a neurodevelopmental disorder, is most commonly comorbid with other psychiatric and neurodevelopmental conditions (51). The presence of a comorbid disorder can affect symptom presentation, increase symptom severity, and lead to greater functional impairment. Clinicians must be aware of common comorbidities to develop an effective, multidimensional treatment approach, first addressing the condition that is causing the greatest impairment, whether it be the ADHD or a comorbid disorder (52).

Disruptive behaviour disorders

ODD and CD comprise the disruptive behaviour disorders, which are characterized by externalizing and aggressive behaviours. Studies report the frequency of ODD/CD comorbidity with ADHD to be as high as 90% (53,54).

Anxiety disorder (AD)/Obsessive compulsive disorder

Anxiety disorders occur in approximately 30% of patients with ADHD (55,56). Children with comorbid AD/ADHD present with more school fears, inattention, poorer social skills, and greater symptom severity (57) compared with ADHD without AD. Further, ADHD symptoms can interfere with a child's ability to engage successfully in cognitive behavioural therapy (CBT) for AD and complicate medication choice, because stimulants may increase anxiety symptoms.

Mood disorders, including bipolar disorder (BD)

Children with ADHD may also experience comorbid depressive symptoms, particularly as they approach adolescence and adulthood. There is increasing evidence of heterotypic continuity between these two conditions, suggesting they may represent the same underlying construct for some children (58). The validity of BD diagnosis, particularly when broadly defined, remains controversial in preadolescent children. Researchers have reported overlapping behavioural symptoms in preadolescent children with ADHD and those with BD that can be challenging to disentangle. The introduction of disruptive mood dysregulation disorder in the DSM-5 may better describe children with extreme mood regulation problems.

Substance use disorders (SUDs)

There is an increase in SUDs as children with ADHD reach adolescence and adulthood (59). It is possible that substance use occurs as an attempt to self-medicate. The treatment of ADHD comorbid with a SUD is complicated by risks for misuse and diversion of prescription stimulants (59). A recent meta-analysis (60) found that stimulant treatment neither contributed to nor prevented future SUDs in youth with ADHD.

Tic disorders (TDs)

The co-occurrence of ADHD and TDs can create challenges due to concerns that stimulants may exacerbate tics. Given that tics wax and wane, it has been difficult to establish whether this relationship between stimulants and tics is causal or coincidental (61,62). Some children with ADHD/TD treated with stimulants are less stressed and experience an improvement in their tics.

Developmental coordination disorder (DCD)

Persistent delays in motor development and coordination are common in individuals with ADHD (63). Fine motor coordination is one of the most impaired areas of motor performance (64). A screening questionnaire and a focused neuromotor exam are important when DCD is suspected (63).

Autism spectrum disorders

(See the companion statement on special populations in this issue).

Specific learning disorder (SLD)

A learning disorder is the most common comorbid condition (51). Approximately one-third of children with ADHD also have an SLD (65). However, children with SLD alone can present with symptoms of inattention because they do not understand what is being taught. A careful psychoeducational assessment can help determine whether the child has SLD as a primary diagnosis or whether the two disorders, ADHD and SLD, are comorbid.

Eating disorders

ADHD symptoms, especially in females, increase risk for eating disorders (66). This comorbidity may underlie difficulties with treatment and remission in some eating disorders (67).

CONCLUSION

ADHD is a heterogeneous disorder. Because paediatricians and family physicians are the first care providers to conduct a medical assessment of children and youth with ADHD, which should always include a complete history, physical examination and consideration of differential diagnosis and possible comorbidities for this disorder, it is essential that their training equips them with the clinical skills needed to assess and manage ADHD and comorbid disorders (68).

RECOMMENDATIONS

- Given the scope for differential diagnosis and frequent comorbidity in ADHD, physicians must perform a comprehensive but directed history and physical examination.
- Collateral information about a child's or adolescent's behaviour should be obtained whenever possible, because core symptoms diagnostic of ADHD are not always observed in the clinical setting.
- Current clinical guidelines do not recommend psychological or neuropsychological testing in ADHD. Such testing should never be used alone to diagnose ADHD or without clinical evaluation by an experienced physician.
- Consider referring to a specialist and subspecialist for diagnosis of complex ADHD, when differential diagnosis and comorbidity are key findings. The limits between what can be handled by a primary care clinician and what should be referred is largely case-based and determined by the expertise and skills of the primary care clinicians involved.
- Residency training programs for paediatricians and family physicians must include ADHD diagnosis and treatment among their explicit learning objectives and take measures to ensure these objectives are being met.

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