

# Attention deficit hyperactivity disorder

## *Epidemiologic, pathophysiologic, diagnostic and treatment perspectives*

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### **ABSTRACT**

Although attention deficit hyperactivity disorder is a common child psychiatric disorder, the epidemiology and pathophysiology of attention deficit hyperactivity disorder is variable in different studies. Attention deficit hyperactivity disorder and comorbid disorders in children aided both by attention deficit hyperactivity disorder diagnostic criteria and assessment scales entails a comprehensive neuropsychiatric interview plus collection of information from different sources. Although psychosocial and behavioral therapies are of great therapeutic values, the psychopharmacological drugs are often used in the treatment of patients with attention deficit hyperactivity disorder. With a combined approach, a substantial proportion of patients with attention deficit hyperactivity disorder (90%) show good recovery. The patients with attention deficit hyperactivity disorder need careful evaluation and appropriate long-term treatment in order to prevent subsequent negative consequences. In rapidly developing countries, the researchers should carry out studies, which explore different aspects of attention deficit hyperactivity disorder in children, adolescents and adults.

**Keywords:** Attention deficit hyperactivity disorder, prevalence, psychopharmacological drugs, psychosocial-behavioral therapies, integrated treatment.

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Attention deficit hyperactivity disorder (ADHD) afflicts approximately 5% of school children and persists in 30-50% of adults. It is the most common childhood neuropsychiatric disorder that has early onset. It is characterized by 3 core features, which are inattention, impulsivity and overactivity. Attention deficit hyperactivity disorder is known to coexist with many neuropsychiatric disorders that posit etiological, diagnostic, prognostic, treatment, and research dilemmas. Attention deficit hyperactivity disorder is heterogeneous and often causes diagnostic confusion. The worldwide projected prevalence of ADHD is variable. Attention deficit hyperactivity disorder is reported to cause variable distress not only among sufferers but also their immediate family members. While exploring the wellness in children

with ADHD, one study recommended that there is a need to understand the contexts and everyday circumstances under which ADHD children and their families achieve well-being.<sup>1</sup> Unlike the scientific community, the lay public thinks this syndrome to be very controversial. This public attitude is mainly attributed to over diagnosis of ADHD among children based on superficial reports and a dramatic increase in stimulant use coupled with growth retardation and potential abuse and dependence. According to their views, ADHD is a "myth" rather than a disease.<sup>2</sup> Despite all these criticisms, we feel that ADHD needs continuing research that should explore its different aspects. In particular, the research should bring favorable changes both in the parental perceptions and the public mind. Parental

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knowledge regarding ADHD is reported to have positive impact on enrollment rate and good drug compliance.<sup>3</sup>

**Prevalence of ADHD.** In sharp contrast to Arabian Gulf countries, there are several studies<sup>4-16</sup> from western countries, which have projected variable prevalence rates of ADHD. The London study carried out in 1990 reported the lowest prevalence rate of ADHD namely 2%.<sup>13</sup> However, the highest prevalence rate of ADHD are 9.5-16% and 13% reported from Puerto Rico in 1988<sup>8</sup> and United States of America inner cities in 1989.<sup>9</sup> All the studies used the Diagnostic and Statistical Manual of Mental Disorders, III (DSM-111) diagnostic criteria for ADHD. In the year 1998, Goldman and colleagues have reported a 5% prevalence rate of ADHD in children.<sup>17</sup> The inconsistent prevalence rate of ADHD could be attributed to several factors, which include differing definitions, diagnostic criteria, pervasiveness of symptoms required, sources of information, sampling characteristics, study settings, patients age groups and lack of both sensitive assessment scales and diagnostic laboratory tests. Additionally, the cultural factors also affect the prevalence of ADHD.<sup>18</sup> Attention deficit hyperactivity disorder affects both genders but preferentially men. The reported male to female ratio is 5:1. The prevalence of ADHD in the female population is now changing<sup>19</sup> attributable to the progressive refinements in diagnostic systems in particular the enhanced emphasis on attention component. As ADHD in girls as compared to boys manifests less aggressive and disruptive behaviors but more attention difficulties, therefore, they are likely to be under diagnosed and perhaps under treated. The prevalence of ADHD in adults is not known. Approximately 60% of children with ADHD carry their symptoms into adolescence and adulthood. According to one estimate, if the prevalence of ADHD in children is 6%, approximately 2% of adults may have ADHD.<sup>20</sup> In another study, it was found that in a given age group ADHD appears to decline by 50%, approximately every 5 years. It was further revealed that if the prevalence of ADHD in children is assumed to be 4%, the estimated rate of adult ADHD based on the exponential decline extrapolation will range from 1% at age 20 to 0.05% at the age 40.<sup>21</sup> In addition to definition of remission, however, age is the most important factor associated significantly with decline in total ADHD core symptoms. Notably, the symptoms of hyperactivity and impulsivity tend to decay at a higher rate than the inattention features.<sup>22</sup> Attention deficit hyperactivity disorder is not an exception and a similar decay or improvement has been reported in the symptomatology of antisocial behavior and alcoholism. This progressive improvement in symptoms may reflect either continuing maturation of brain or nonspecific

changes in ADHD.<sup>23</sup> The ADHD, a public health problem, is linked with antisocial and addictive behaviors in adolescents and adults. These behaviors have devastating negative consequences such as crimes, educational impoverishment, relationship difficulties and other problems. In rapidly developing countries, there is a need to assess the magnitude of ADHD in children, adolescents and adults.

**Pathophysiology of ADHD.** Attention deficit hyperactivity disorder is caused by multiple speculative etiologies<sup>24,25</sup> and researchers have proposed a variety of models to explain the pathophysiology of this disorder. According to one model, investigators have found faults both in self-regulation and motivation.<sup>26</sup> At evolutionary level, ADHD is conceptualized as a disorder of communication/language.<sup>27</sup> Further, both a maturational lag in brain development and cortical hypo-arousal as evidenced by an increased electroencephalograph absolute theta activity and relatively reduced posterior beta activity are 2 underlying mechanisms of adolescent ADHD.<sup>28</sup> Additionally, researchers have found hypofrontality during executive functioning in the patients with ADHD that also supports dysmaturational pathogenesis in ADHD.<sup>29</sup> Similarly, frontal attention networks are implicated in the pathology of ADHD.<sup>30</sup> Further, ADHD has been viewed in the light of the cognitive-energetic model comprising of 3 components that include cognitive processes, energetic pools and management or executive function system. Sergeant found deficiencies in response organization, activation and efforts and executive functions in ADHD. Similar results were also reported in the patients with oppositional and conduct disorders.<sup>31</sup> By and large, the neural substrates identified in several areas of the brain are implicated in the pathogenesis of ADHD.<sup>26,32</sup> Based on 3 separate but interrelated neural systems, such as the sensory attention, the motor intentional, and the arousal activation, the researchers reported that impairments in attention, intention and arousal are the bases for the development of ADHD.<sup>33</sup> Prenatal and perinatal injuries are reported to damage striatum connections with frontal cortex among patients with ADHD.<sup>34</sup> Viral encephalitis is also reported to cause ADHD.<sup>35</sup> Further, unlike schizophrenia, ADHD patients have relatively specific impairments in frontal lobe functions as shown by neuropsychological test results.<sup>36</sup> The animal model studies of hyperactivity developed by exposing them to nicotine<sup>37</sup> and 6-hydroxydopamine<sup>38</sup> support the notion that catecholaminergic pathways play a crucial role in the etiology of ADHD.<sup>39</sup> Converging evidence suggests that nicotine adversely influences the dopamine system in the brain of patients with ADHD.<sup>39</sup> Similarly, the efficacy of stimulants in ADHD children also suggests that both the central

dopaminergic system and 2-adrenergic activity are dysregulated in ADHD.<sup>40,41</sup> Furthermore, researchers have reported dysfunctions in the fronto-striatal dopaminergic and noradrenergic circuits with resultant deficits in cognitive-executive functioning.<sup>42</sup> Over the past decade, the researchers using neuroimaging<sup>43-45</sup> and neurophysiological techniques<sup>26</sup> have localized abnormalities in the striatum and the right midbrain with neurophysiological disturbances in ADHD children. The striatum mainly controls motor activity while the right midbrain controls attention. The level of <sup>18</sup>F Dihydroxy-L-Phenylalanine (DOPA) in the right midbrain of ADHD was 48% higher than the control group and was correlated with its symptom severity. Researchers also found abnormality in dopa decarboxylase enzyme activity that may be primary or secondary to deficits in other functional units of the dopamine pathways such as receptor, uptake transporter, vesicular transporter and degradation enzymes.<sup>45</sup> The origin of this abnormality is important to delineate mechanisms of midbrain control of attention, the most relevant in the pathophysiology of ADHD. This model may also guide the development of specific drugs for the treatment of ADHD. Teicher et al<sup>46</sup> also supported the notion that ADHD symptoms are closely tied to the functional abnormalities in the putamen that is involved in the regulation of motor behavior. Furthermore, researchers suggested that patients with ADHD use compensatory mental and neural strategies by activating occipital regions in response to a disrupted ability to inhibit attention to irrelevant stimuli. These patients also use internalized speech to guide the behavior.<sup>47</sup> The studies of large families, twins, adopted children and segregation analysis found that genetic factors are important in the pathophysiology of ADHD. Notably, genetic mechanisms have been identified to mediate familial transmission of ADHD.<sup>48</sup> One twin study found 51% of monozygotic co-twins of ADHD probands were suffering from ADHD.<sup>49</sup> However, other studies<sup>50,51</sup> have reported 92% concordance rate in monozygotic twins while 33% concordance rate in dizygotic twins. Further, some researchers have identified two dopamine [DA] candidate genes, which are DA transporter [DAT1] gene and DA receptor D4 [DRD4] gene.<sup>52</sup> The specific 10 and 7 repeat alleles of the aforesaid genes may alter dopamine transmission resulting into enhanced reuptake of DA and subsensitization of DA postsynaptic receptors in the neuronal networks implicated in ADHD.<sup>52</sup> In view of the nicotine-dopamine hypothesis, maternal smoking both by increasing nicotinic receptors in brain<sup>53,54</sup> and inducing fetal hypoxia<sup>55</sup> may cause ADHD in children.<sup>56</sup> Additionally, maternal smoking is also associated with low birth weight<sup>57</sup> that is etiologically related to ADHD.<sup>58,59</sup> Based on these grounds, nicotine dysregulation may be one of the

pathophysiological mechanisms underlying ADHD. Beside replication studies for confirming or refuting the role of maternal smoking during pregnancy in ADHD children, further research should be carried out to understand fully the underlying pathophysiological mechanisms including possible target genes of ADHD. More recently, essential fatty acids (EFA) are found to be deficient in persons with ADHD.<sup>60</sup> For more details on the neurobiology of ADHD, readers are referred to 2 comprehensive review articles.<sup>39,42</sup> Finally, we suggest that further genetic and advanced neuroimaging researches if carried out would reveal both the exact pathophysiology and also help develop drugs for the treatment of ADHD.

**Comorbidity of ADHD.** Attention deficit hyperactivity disorder is reported to coexist with a variety of disorders. These conditions include 1. Oppositional defiant disorder 40%, 2. Developmental reading disorder, 3. Substance use disorder, 4. Anxiety disorder, 5. Mood disorder 10-20%, 6. Epilepsy, 7. Organic brain disorder, 8. Conduct disorder 20%-50%, 9. Antisocial behavior, 10. Tics or Tourette syndrome, 7%, 11. Obsessive compulsive disorder, 12. Subnormal intelligence, 13. Borderline personality disorder and 14. Multiple complex developmental disorder.<sup>17,61-64</sup> Moreover, the patients with ADHD also show other disabilities such as impaired social and academic functioning.<sup>59</sup> Overall, approximately 65% of patients with ADHD may have one or more co-morbid disorders. Alternatively, a myriad of disorders also mimic ADHD.<sup>65</sup> At the time of evaluation of patients with ADHD, these conditions should be screened as they reflect many competing hypotheses of co-morbidity,<sup>61,66</sup> and a variety of implications. Although the relationship is fuzzy,<sup>17</sup> ADHD is reported to contribute considerably to substance use problems and delinquency<sup>67-69</sup> in adolescents and adults. Comorbid conditions are reported to increase the magnitude of morbidity and disability associated with ADHD.<sup>70</sup>

**Diagnosis of ADHD.** Attention deficit hyperactivity disorder, formerly known as attention deficit disorder, hyperactivity reaction, minimal brain dysfunction, and minimal brain damage, is a chronic neuropsychiatric disorder of early onset with 3 salient clinical features.<sup>71</sup> It is a discrete disorder supported by well-defined diagnostic criteria with very good validity. Historically, the DSM-III diagnostic criteria, published in 1980, also emphasized that the three main symptoms in the form of hyperactivity, inattention, and impulsivity should be present for the diagnosis of ADHD. However, in DSM-III Revised,<sup>71</sup> 8 of the 14 symptoms related to 3 dimensions are essential for the diagnosis of ADHD. This change resulted in enhancing the diagnostic reliability but reducing its validity. However, for the first time the DSM-IV classification of ADHD allowed its 3 subtyping as predominantly inattentive, hyperactive, or

combined.<sup>72</sup> Earlier a cognitive form of ADHD was also described in the literature, which beside core features was characterized by severe academic underachievement.<sup>73</sup> The DSM-IV criteria for ADHD emphasized several important points, 1. The symptoms must be "maladaptive" and inconsistent with the developmental level, 2. Symptoms should be distressful and cause impairment, 3. Symptoms should be present across 2 settings, 4. Symptoms should not be explained by another disorder, and finally 5. Symptoms should have 6 months duration. Overall, these diagnostic criterias have a high inter-rater reliability of individual items. Accordingly, ADHD is not a transient disorder. Notably, the term ADHD is not retained in International Classification of Diseases, 10th version (ICD-10). However, 5 discrete conditions including hyperactivity disorder [F90], simple disturbance of activity and attention [F90.0], hyperkinetic conduct disorder [F90.1], other hyperkinetic disorders [F90.8], and hyperkinetic disorder not otherwise specified [F90.9] are well described in ICD-10.<sup>74</sup> In the absence of confirmatory laboratory or radiological tests,<sup>75</sup> the core clinical features are of greater help in the diagnosis of ADHD. Additionally, several neurocognitive tests and diverse assessment scales may further support the diagnosis of ADHD.<sup>75,76</sup> However, certain primary neuropsychiatric conditions may disturb the attention and motor activity and may lead to the diagnosis of secondary ADHD.<sup>17,76</sup> While evaluating patients with ADHD, an attempt should be made to identify primary/secondary disorder, as this dichotomy has etiological, diagnostic, treatment, prognostic and research implications. Notably, the symptom pattern of ADHD that varies with age may cause diagnostic difficulties. The concomitants of hyperactivity pervasive during childhood decline with age while impulsiveness and inattention is more common in older children and adolescents.<sup>77</sup> Additionally, adolescents and adults are also characterized by psychosocial disability, scholastic failures, lower socioeconomic status, and behaviors suggestive of antisocial personality and substance use disorders.<sup>78</sup> Like children with ADHD, adult patients also manifest symptoms such as stubbornness, low frustration tolerance, deficits in academics and occupation, and conflictual social relationships with peers and authorities.<sup>20</sup> Taken together, the evaluation of children, adolescents, and adults with ADHD must include, 1. A detailed interview with the patient's parents or adult caregivers, 2. A comprehensive mental status examination of the patient, 3. A medical evaluation of patient's general health, 4. A detailed neurological examination, 5. A cognitive assessment of abilities and achievements using several relevant scales, 6. Collection of useful information from parents and teachers using a variety of scales, 7. Comprehensive school reports, and

finally 8. Adjunctive evaluations for speech and language and other developmental neurobehavioral faculties.<sup>79,80</sup> For more details, readers are referred to the most comprehensive American Academy of Pediatric clinical practice guidelines for the diagnosis and evaluation of the child with ADHD.<sup>81</sup>

**Treatment and outcome of ADHD.** The patients with ADHD need a combination of treatment approaches including psychosocial, behavioral, educational, and psychopharmacological.<sup>82</sup> In contrast to behavioral, psychological and social therapies, there is a relative lack of preventive strategies meant for patients with ADHD.<sup>24</sup> Also there is overall decline in the use of psychotherapy among patients with ADHD.<sup>83</sup> Although behavioral therapies alone or in combination with drugs are effective in the management of ADHD,<sup>84</sup> we will focus mainly on the pharmacotherapy of ADHD.

**Stimulants.** Methylphenidate, the drug of choice, is prescribed to approximately 90% of patients with ADHD. Other stimulants used in ADHD patients are a racemic mixture of amphetamines, d-amphetamine sulfate, and magnesium pemoline. These drugs act both on the central and the peripheral nervous system. They prevent the reuptake of catecholamines into presynaptic vesicles, hence enhancing the availability of catecholamines in the synaptic clefts. These are short acting compounds but their slow-release preparations are also available in the market. Unlike other drugs, pemoline has a long acting effect and can be administered once or twice daily. Amphetamines are twice more potent than methylphenidate while pemoline is 3 times less potent than amphetamines. These stimulants are administered orally and require slow titration so that the adverse effects can be avoided. The typical initial daily doses are; methylphenidate, 10mg, amphetamines, 5mg, and pemoline, 37.5mg. The results of many studies indicated that the response rate for any single stimulant drug in ADHD was approximately 70%. Furthermore, under careful titration and supervision, approximately 90% of children with ADHD respond to a stimulant drug without developing any major adverse effect.<sup>17</sup> The efficacy of stimulants has also been reported in adolescents with ADHD.<sup>85</sup> These drugs not only improve the salient symptoms of patients with ADHD but also improve their scholastic performance, aggressive spells, irritability, oppositional behavior, interactive relationships, associated anxiety and neurotic traits.<sup>86,87</sup> Methylphenidate reinforces some classroom behavioral manipulations. Several authors have suggested the assessment of behavioral treatments for individual ADHD patients on methylphenidate.<sup>88,89</sup> These stimulants have neither specific nor paradoxical effects and are devoid of any diagnostic value. In a preliminary study of patients with ADHD,

Loo et al have reported that the methylphenidate responders and non responders have differential electrophysiological correlates.<sup>90</sup>

**Adverse effect of stimulants.** Usually the adverse effects of stimulant drugs are mild and short-lived, which can be prevented by slow doses titration and proper timings. The common side effects are appetite suppression, insomnia, abdominal aches, headache, jitteriness, raciness, and anxiety-mood disturbances. Other uncommon side effects include motor tics, cognitive impairment and psychosis, which are reported rarely in children as compared to adults. Some researchers found no tics in ADHD children treated with methylphenidate.<sup>91</sup> Pemoline is infrequently associated with hepatic injury. Patients receiving this drug need monitoring of liver enzymes, in particular aspartate aminotransferase and alanine aminotransferase.<sup>92</sup> Mild increases both in blood pressure and pulse rate of not clinical significance have been reported among patients receiving stimulants.<sup>20,93</sup> Whether or not stimulant use in children is associated with growth retardation is equivocal. Another concern regarding stimulant use in children, adolescents and adults is abuse and dependence. The reported excessive production of stimulants raises some questions including diversion of these drugs to normal persons for the purpose of abuse.<sup>17</sup> These drugs are commonly polyabused resulting in death<sup>94</sup> and talc granulomatosis.<sup>95</sup> However, patients with ADHD and their family members infrequently abuse methylphenidate.<sup>96</sup>

**Antidepressants.** It is reported that a proportion of children do not respond to stimulants, or develop sensitive reactions.<sup>17,97</sup> Therefore, psychotropic drugs like desipramine and imipramine<sup>97,98</sup>, bupropion,<sup>99,100</sup> fluoxetine,<sup>101</sup> clonidine and guanfacine,<sup>102,103</sup> lithium carbonate,<sup>104</sup> neuroleptics, monoamine oxidase inhibitors, and diet<sup>105</sup> are recommended in the patients with ADHD with variable results. Among them serotonin reuptake and monoamine oxidase inhibitors and Feingold diet are not of much therapeutic value. However, tricyclic compounds and bupropion have proven efficacy in ADHD patients. The other advantages of tricyclics over stimulants are flexible dosing and longer duration of action. Tricyclic compounds also have adverse effects that include anti-cholinergic effects, narrow therapeutic margin and potential lethality in case of overdose. Doses higher than 450mg/day of bupropion are associated with seizures in vulnerable children. P300 is a cognitive evoked potential that evaluates attention and information processing and has some relevance in children with ADHD.<sup>106</sup> Prolonged P300 latency in ADHD is reported to predict poor response to imipramine and pemoline. Normal P300 topography predicted good response to pemoline. Small right frontocentral auditory P300 amplitudes predicted poor response to pemoline but good response to imipramine. Clonidine and other  $\alpha$ -blocking drugs have limited efficacy in ADHD.

However, clonidine alone or in combination with methylphenidate is effective among patients with ADHD comorbid with oppositional defiant or conduct disorder.<sup>107</sup> Lithium and neuroleptics have some clinical efficacy in ADHD but their long-term use is associated with changes in kidney functions and tardive dyskinesia. The newer cholinergic drugs such as ABT-418 are reported to be effective among patients with ADHD.<sup>108</sup> Neurotherapy, a new modality is found to improve symptoms of ADHD. Improvement in ADHD is reflected in EEG signature that is declining theta/beta ratios over frontal/central cortex and reduction in theta/alpha band amplitude.<sup>109</sup> Overall, the treatment of ADHD should be tailored according to the individual need. Many patients with ADHD have comorbid disorders and, therefore, may benefit from polydrug therapy such as stimulants combined with antidepressants for the treatment of ADHD with depression. Attention deficit hyperactivity disorder persists into adolescents and adults with adverse consequences. Therefore, proper preventive strategies should be devised. Alternatively, ADHD symptoms diminish by approximately 50% every 5 years between the ages of 10 and 25 years. Attention deficit hyperactivity disorder without comorbid disorders and its negative family history predict good prognosis and outcome. For more details regarding pharmacotherapy of ADHD, readers are referred to a comprehensive review.<sup>70</sup>

In conclusion this review article describes critically different aspects of ADHD reported variably among children, adolescents and adults. This syndrome is characterized by unique symptomatology. Although tremendous progress is made in understanding the pathophysiology of ADHD, advanced genetic, neuroimaging and neurophysiological researches may further reveal the exact mechanisms underlying ADHD. The DSM-IV and ICD-10 diagnostic criteria plus a detailed evaluation and cognitive assessment of the child might collectively help in the diagnosis of ADHD. Attention deficit hyperactivity disorder usually coexists with other neuropsychiatric disorders, which should be identified and treated appropriately for achieving good results. Notably, a variety of psychotropic drugs are recommended in the treatment of ADHD. However, a multi-modal integrated approach combining appropriate drugs with psychosocial and behavioral therapies bring maximum improvement in children with ADHD. We feel that in addition to primary preventive and rehabilitative strategies, new drugs with better clinical profiles should be developed for the treatment of ADHD.

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