Attention-deficit hyperactivity disorder

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Attention-deficit hyperactivity disorder (ADHD) is a disorder of inattention, impulsivity, and hyperactivity that affects 8–12% of children worldwide. Although the rate of ADHD falls with age, at least half of children with the disorder will have impairing symptoms in adulthood. Twin, adoption, and molecular genetic studies show ADHD to be highly heritable, and other findings have recorded obstetric complications and psychosocial adversity as predisposing risk factors. Converging evidence from animal and human studies implicates the dysregulation of frontal-subcortical-cerebellar catecholaminergic circuits in the pathophysiology of ADHD, and molecular imaging studies suggest that abnormalities of the dopamine transporter lead to impaired neurotransmission. Studies during the past decade have shown the safety and effectiveness of new non-stimulant drugs and long-acting formulations of methylphenidate and amfetamine. Other investigations have also clarified the appropriate role of targeted psychosocial treatments in the context of ongoing pharmacotherapy.

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In the 20th century, attention-deficit hyperactivity disorder (ADHD; in the diagnostic guise of very minimal brain dysfunction and other related terms) emerged as the first psychiatric disorder to be diagnosed and treated in children, with studies of stimulant treatment since 1937 and regulatory approval of stimulant treatment for children beginning in the 1960s.[1] But despite the long research history and robust findings, divergent opinions about ADHD during the 20th century fuelled public controversy, clinical uncertainty, and scientific debate. Fortunately, as we enter the 21st century, fierce opinion has been replaced by data from empirical studies of epidemiology, cause, pathophysiology, and treatment.[2,3] We review controversies about ADHD in the context of this scientific work, emphasising new developments and focusing on pathways of discovery that could lead to improved treatments for patients with this disorder.

Epidemiology and diagnosis

ADHD affects 8–12% of children worldwide, and results in inattention, impulsivity, and hyperactivity.[4] The controversy about how to diagnose ADHD is seen in the differences between US diagnostic criteria for the disorder, as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition; DSM-IV), and the European diagnostic criteria for hyperkinetic disorder (HKD), as defined by the International Classification of Diseases (10th edition; ICD-10). Both classifications include children displaying developmentally inappropriate levels of inattention, hyperactivity, and impulsivity that begin in childhood and cause impairment to school performance, intellectual functioning, social skills, driving, and occupational functioning.[4] But HKD criteria are more restrictive (table 1) than the DSM-IV diagnosis of ADHD because they need a greater degree of symptom expression. Unlike the ICD-10, DSM-IV allows for three symptom-based subtypes of ADHD: mainly inattentive, mainly hyperactive-impulsive, or both combined. Evidence for the validity and clinical use of these subtypes is mixed,[5–7] and current work has not yet resolved the ongoing controversy about whether a purely inattentive disorder exists that could be causally different from either ADHD or HKD.[8,9]

DSM-IV ADHD is more prevalent than ICD HKD,[10] a finding which has sometimes been misinterpreted to mean that ADHD is more common in the USA than in countries using ICD criteria. That controversy was resolved by a review of 50 epidemiological studies, which reported the prevalence of DSM-defined ADHD to be similar worldwide (panel 1).[1] Epidemiological studies show that the prevalence of ADHD is overestimated if the diagnosis does not adequately incorporate functional impairment into the diagnosis. In a US study, Wolraich and colleagues[11] reported the prevalence of the disorder to be 16·1% if based on symptoms alone and 6·8% if functional impairment was needed. Similar results were reported from Australian[7] and German[12] studies.

Epidemiological studies have shown that the male sex, low socioeconomic status, and young age are associated with a raised prevalence of ADHD.[1,13] The male-to-female sex ratio for the disorder is greater in clinical studies than in community studies, which indicates that female individuals with the disorder are less likely to be referred for services than male individuals. This difference in

	DSM-IV ADHD	ICD-10 HKD
Symptoms	Either or both of following: At least six of nine inattentive symptoms At least six of nine hyperactive or impulsive symptoms	All of following: At least six of eight inattentive symptoms At least three of five hyperactive symptoms At least one of four impulsive symptoms
Pervasiveness	Some impairment from symptoms is present in more than one setting	Criteria are met for more than one setting

Table 1: **Differences between US and European criteria of ADHD or HKD**

Search strategy and selection criteria

To identify studies relevant to this Seminar, we searched MEDLINE citations (from January, 1966, to July, 2004) using PubMed. References cited in these works were also reviewed to identify additional works not indexed by MEDLINE. We refer readers to review articles or book chapters for comprehensive overviews that are beyond the scope of this Seminar.

Panel 1: **Diagnosis and epidemiology of ADHD**

Prevalence: 6–12% worldwide
Sex ratio: Common in men
Social class: Common in lower economic strata
Ethnic origin: Under-identified and treated in minority groups
Age: Prevalence falls with age

referral rates by sex is probably because of ADHD being less disruptive in women than in men,[14] and the raised population prevalence in male individuals could be due to their increased exposure to environmental sources of cause, such as head injury.[15]

Although both DSM-IV and ICD-10 provide well-structured, criterion-based diagnoses for ADHD and HKD, they have several weaknesses. The diagnostic items, although well-described, do not have developmentally sensitive definitions to help doctors differentiate ADHD symptoms from developmentally healthy levels of inattention, hyperactivity, and impulsivity. Clinicians often receive diagnostic data from multiple informants (eg, parent and teacher; parent and teenage child; adult with ADHD and spouse), but the DSM-IV and ICD-10 provide no guidelines to integrate this information. The weaknesses of the diagnostic system have led to critics of ADHD describing the diagnosis as subjective and much less credible than objective laboratory tests used in other medical specialties. This criticism is at odds with developments in medical testing studies that emphasise that the quality of a diagnosis derives from its reliability and clinical use and not from the apparent objectivity of the method of diagnosis.[16] As reviewed elsewhere,[17] the diagnosis of ADHD is reliable—ie, well-trained raters agree on the presence or absence of the disorder.

ADHD diagnosis can predict clinically meaningful outcomes. Much work from both clinical[18–20] and epidemiological[21–23] studies shows that the disease puts children at risk for comorbidity with other psychiatric and substance use disorders. Some studies suggest that ADHD can put adults at risk for personality disorders,[24,25] and at all ages, ADHD is associated with functional impairments such as school dysfunction, peer problems, family conflict, poor occupational performance, injuries, antisocial behaviour, traffic violations, and traffic accidents.[26–31] Because ADHD typically starts in early childhood, clinicians can practise primary and secondary prevention by alerting parents to the potential adverse outcomes associated with the disorder and by routinely screening for these conditions so that, if they emerge, they can be treated at an early stage and, if warranted, the treatment can be adjusted.[32,33] More importantly, clinical errors will arise if clinicians routinely discount symptoms of comorbid disorders as associated features of ADHD.[34] In such cases, clinicians expose patients to the adverse effects of the untreated disorder and those problems could be further compounded if the choice of ADHD treatment exacerbates the untreated disorder (eg, stimulant treatment can worsen tics and mania).

For several decades, the idea that ADHD persisted into adulthood was met with scepticism. But, as reviewed by Faraone and colleagues,[35] follow-up studies of ADHD have shown that it persists into adulthood. There is clearly an age-dependent decline in symptoms, but even when symptoms are not prominent enough to prompt a diagnosis, they are frequently associated with clinically significant impairments.[36] As a result, by age 30–40 years, most individuals who had ADHD in childhood will no longer meet the full threshold criteria for the disorder, but about half will show continued impairing symptoms that are consistent with the DSM-IV diagnosis in partial remission. Yet, despite the partial remission of symptoms in adulthood, prospective follow-up studies show that when children with ADHD reach adolescence and adulthood, they are at high risk for such impairments.[14,37–39]

Temporal trends in the use of stimulant drugs for ADHD have raised questions about possible over-identification and over-treatment. Several studies have shown increases in the prescription of stimulant drugs in the USA,[40,41] Israel,[42] Canada,[43] and Europe,[44] particularly in very young children (eg, less than 5 years old) in whom differentiation of developmentally healthy levels of symptoms can be difficult and in whom more research is needed.[45] Although these studies show increased pharmacological treatment of ADHD, they present little evidence for systematic over-treatment. Zito and colleagues[40] showed that in preschoolers in the USA, the prevalence of stimulant treatment tripled from 1991 to 1995, although in 1995 this value was only 1%. The rate of outpatient treatment for ADHD has also risen from 0·9 per 100 children in 1987 to 3·4 per 100 children in 1997.[41] Treated prevalence of the disorder in German children also increased from 0·6% to 1·4% in 2000–01,[44] and similar results were reported from Israel,[42] Canada,[43] and Australia.[46] Although all these studies showed rises, the treated prevalence of ADHD remained far below the population prevalence.

A Canadian study reported that 1% of children who did not meet criteria for ADHD had been treated with stimulants;[47] this proportion was 5% in a US study.[48] However, there is also evidence from community and school studies that many cases of the disorder are not pharmacologically treated. Community studies of children with ADHD in the USA and Canada have reported the prevalence of pharmacological treatment to be 5·3–72%[47–51] and, in an ADHD survey of special education classes,[52] 63% were pharmacologically treated. Minority status, female sex, and low income predicted failures to diagnose and treat the disorder. Community studies[48] showed higher treatment rates for ADHD cases meeting full diagnostic criteria (72%) than for cases showing clinically significant symptoms in the absence

of full criteria (22%). Reduced rates of pharmacological treatment were also reported for minority ADHD children, but not for children with other psychiatric disorders.[53]

Cause

Genetics of ADHD

Is ADHD merely the extreme of a healthy variation exacerbated by adverse environmental circumstances rather than a medical disorder with biological causes (panel 2)? For many decades, studies have shown that ADHD is transmitted in families.[54,55] According to twin and adoption studies, genes have a substantial role in the familial transmission of ADHD. Figure 1[56] shows heritability data from twin studies of the disorder or quantitative measures of its symptoms from Australia, Sweden, the UK, and many sites in the USA. These data, which estimate the heritability of ADHD to be 0·76, show that genes are very important in initiating ADHD. Figure 1 also shows that estimates of heritability have not changed from 1973 to 2004, despite intervening changes in diagnostic systems. Adoption studies also implicate genetic causes. Adoptive relatives of children with ADHD are less likely than biological relatives to have the disorder or associated syndromes.[57]

Molecular genetic studies are beginning to unravel the complex genetics of ADHD. Genome scans of individuals with ADHD have used the method of linkage analysis to screen the genome for regions that might include disease-related susceptibility genes.[58–60] With the exception of chromosome 17p11, genomic regions implicated by these studies do not overlap (table 2). For ADHD, the absence of repeated results across studies so far suggests that genes with moderately large effects are unlikely to exist, and for this reason, further studies need to have increased power of available linkage data.

By contrast with the few linkage studies undertaken, many candidate-gene studies have used association methods to determine whether biologically relevant gene variants affect the susceptibility to ADHD by comparing cases and controls or by showing greater transmission with ADHD offspring in family studies. Faraone and colleagues[56] reviewed this published work and examined pooled odds ratios for candidate genes examined in at least three case-control or family-based association studies (table 3).

The dopamine D4 receptor (DRD4) is prevalent in the frontal-subcortical networks that are implicated in the pathophysiology of ADHD.[61] Most DRD4 studies have assayed a variant known as the exon III 7-repeat allele, which produces an in-vitro blunted response to dopamine. When data from analyses of this variant were pooled, the association with ADHD was significant in both case-control (odds ratio 1·45) and family studies (1·16). Studies of the dopamine 5 receptor (DRD5) have analysed a repeated sequence near the transcription start site.[62] A study that combined 14 independent family studies of this variant reported an association of the 148-bp allele with ADHD (odds ratio 1·2).[63]

Stimulant drugs that are effective against ADHD block the dopamine transporter[64] and imaging studies have shown reduced dopamine-transporter binding in adults with the disorder.[65–69] When pooled, studies of a ten-repeat sequence in the 3′ untranslated region of the dopamine transporter gene (*SLC6A3*) in ADHD estimate an odds ratio of 1·13. Dopamine β-hydroxylase is the main enzyme responsible for the conversion of dopamine to norepinephrine. Pooled family-based studies of this gene jointly suggest a significant association between ADHD and the 5′ Taq1 polymorphism (odds ratio 1·33).

Two genes involved in serotonergic transmission have been implicated in ADHD. A functional variant of the serotonin transporter gene (*SLC6A4*) has been examined

Panel 2: Causes of ADHD

Heritability: 75%
Genes with small effect: *DRD4, DRD5, SLC6A3, DBH, SNAP25, SLC6A4, HTR1B*
Genes with large effect: None
Environmental risk factors: Obstetric complications, family conflict

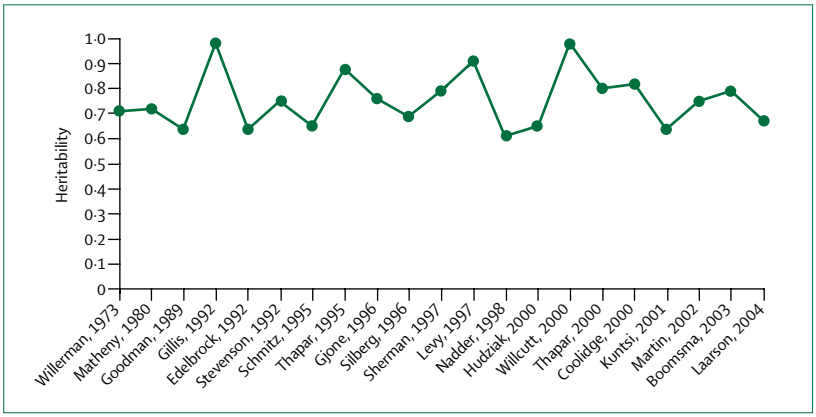

Figure 1: **Heritability of ADHD**

	Chromosome region	LOD
Study 1	5p13	2·6
	6q12	3·3
	16p13	3·7
	17p11	3·6
Study 2	15q15	3·5
	7p13	3·0
	9q33	2·1
Study 3	17p11	2·8
	11q22	2·5
	5q33.3	2·4

*LOD= logarithm of the odds (to the base 10). Study 1=US study of 270 sib-pairs.[57] Study 2=Dutch study of 164 sib-pairs.[58] Study 3=Colombian study of 14 three-generation pedigrees.[59]

Table 2: **Maximum LOD scores* from previous genome scans of ADHD**

in several studies, leading to a meta-analysis odds ratio of 1·31. Several studies of the serotonin 1B receptor gene (*HTR1B*) have also been positive, with a non-functional marker showing a pooled odds ratio of 1·44.

Synaptosomal-associated protein of 25 kDa (SNAP25) is a neuron-specific protein involved in synaptic-vesicle transport and release. Mice that do not have the *SNAP25* gene show spontaneous hyperactivity (reversible by stimulants) and delays in the achievement of complex neonatal motor abilities.[70] Insertion of a healthy *SNAP25* gene reduces their hyperactivity.[71] Several studies assessed the association between the gene and ADHD in people and a meta-analysis of these studies recorded an odds ratio of 1·19.[60]

By contrast with these positive findings (table 3), studies of other genes have produced equivocal or negative results,[56] which include catechol-O-methyl-transferase (COMT); monoamine oxidase (MAO); the norepinephrine transporter SLC6A2; and the 2A, 2C, and 1C norepinephrine receptors.

Environmental risk factors for ADHD

Biological adversity

Although the idea that particular foods or food additives might cause ADHD received much attention in the media, systematic studies have shown that this theory is wrong.[72,73] By contrast with the mostly negative studies of dietary factors, lead exposure has been implicated in the pathophysiology of the disorder,[74] although most affected children do not show lead contamination and many children with high lead exposure do not become affected with the disorder.

Several studies indicate that pregnancy and delivery complications raise the risk for ADHD. Specific complications implicated include toxaemia or eclampsia, poor maternal health, maternal age, fetal post-maturity, long duration of labour, fetal distress, and antepartum haemorrhage.[75–78] Complications associated with ADHD frequently lead to hypoxia and tend to include chronic exposures to the fetus (such as toxaemia) rather than acute, traumatic events (such as delivery complications). Notably, the basal ganglia, which are commonly implicated in ADHD, are also one of the most metabolically active structures in the brain, and are particularly sensitive to hypoxic insults, which have shown to cause enduring effects on dopaminergic functioning in animals.[79]

	Number of studies	Odds ratio	95% CI
FB: *DRD4*	17	1·16	1·03–1·31
CC: *DRD4*	13	1·45	1·27–1·65
FB: *DRD5*	14	1·24	1·12–1·38
FB: *SLC6A3*	14	1·13	1·03–1·24
FB: *DBH*	3	1·33	1·11–1·59
FB: *SNAP25*	5	1·19	1·03–1·38
CC: *SLC6A4*	3	1·31	1·09–1·59
FB: *HTR1B*	2	1·44	1·14–1·83

CC=case-control studies. FB=family-based studies.

Table 3: **Pooled odds ratios for genes examined in three or more studies**

Many studies confirm that prematurity, as indexed by low birthweight, is a risk factor for ADHD,[76–78,80] with one study showing that such effects could not be accounted for by potential confounders such as prenatal exposure to alcohol and cigarettes, parental ADHD, social class, and comorbid disruptive behaviour disorders in parents and offspring.[75] Prospective studies of infants show that fetal exposure to maternal alcohol use leads to behavioural, cognitive, and learning problems that could present as ADHD.[81–83] And studies of children with the disorder show an increased likelihood of having been exposed to alcohol as a fetus.[84]

A chronic exposure that has been extensively studied is maternal smoking during pregnancy.[85–87] With exposure of the fetus to nicotine, maternal smoking can damage the brain at critical points in the developmental process. Animal studies in pregnant mice and rats have shown a correlation between chronic exposure to nicotine and hyperactive offspring.[88–90] Because nicotinic receptors modulate dopaminergic activity and dopaminergic dysregulation could cause ADHD, maternal smoking could theoretically be regarded as a risk factor for the disorder. Furthermore, a review of 24 studies recorded an increased risk for the disorder in children whose mothers smoked during pregnancy.[87]

Psychosocial adversity

Rutter's studies of the Isle of Wight and the inner borough of London[91] revealed six risk factors in the family environment that correlated significantly with childhood mental disturbances: severe marital discord; low social class; large family size; paternal criminality; maternal mental disorder; and foster placement. The aggregate of such adverse factors impaired development, rather than the presence of any one factor. Biederman and colleagues[92,93] identified a positive association between Rutter's index of adversity and ADHD, measures of ADHD-associated psychopathology, impaired cognition, and psychosocial dysfunction.

Other cross-sectional and longitudinal studies have identified variables such as marital distress, family dysfunction, and low social class as risk factors for psychopathology and dysfunction in children. For example, the Ontario Child Health Study[94] showed that family dysfunction and low income predicted the persistence and onset of one or more psychiatric disorders over a 4-year follow-up. Other published work has indicated that low maternal education, low social class, and single parenthood are important adverse factors for ADHD.[95–97] Biederman and co-workers[93,98] showed that chronic conflict, reduced family cohesion, and exposure to parental psychopathology (especially maternal psychopathology) were more common in ADHD families compared with control families. The differences between children with or without ADHD

were not accounted for by social class or by parental history of major psychopathology. Many studies have shown maternal depression as a risk factor for psychological maladjustment and psychiatric disorder in children,[99] and some data have suggested that depressed moods could lead mothers to perceive their children as more deviant than would be warranted by the child's behaviour. However, Richters[100] reviewed 22 studies of this issue and concluded that there was no empirical foundation for this claim.

Pathophysiology

The idea that dysregulation of dopamine and norepinephrine circuits underlies ADHD was initially suggested by the action of drugs for the disorder, which increase the synaptic availability of these neurotransmitters, and by animals showing that lesions in dopamine pathways create animal models of ADHD, as shown in developing rats[101] and monkeys.[102] As one of the most compelling animal models of ADHD, the spontaneously hypertensive rat (SHR)[103] shows dopamine release abnormalities in subcortical structures.[104]

Because executive dysfunction is common, although far from universal[105,106] in ADHD, it has driven much neuropsychological theory about the disorder.[107–112] Executive functions, which are controlled by frontal-subcortical circuits, include inhibition, working memory, set-shifting, interference control, planning, and sustained attention.[108,113–116] This pattern of dysfunction has led to much debate about what core neuropsychological deficit might cause both ADHD symptoms and neuropsychological impairments. Candidates for core deficits include failure of inhibitory control;[117] dysregulation of brain systems mediating reward and response cost;[118,119] and deficits in arousal, activation, and effortful control.[112,120,121] Deficits in arousal and effort lead to state-dependent cognitive deficits and a view of ADHD that emphasises problems in regulating cognitive functions rather than core deficits in any single function. But, because no single neuropsychological theory can explain all ADHD features, neuropsychological impairments of the disorder could be heterogeneous and this heterogeneity probably corresponds to causal heterogeneity.[122,123]

The pattern of neuropsychological deficit in ADHD patients has been interpreted as being caused by dysregulation of frontal-subcortical circuits. That hypothesis has now been confirmed by structural and functional neuroimaging studies showing patients to have small volume reductions in these regions.[124] But other findings suggest that aberrant frontal-subcortical circuitry is not sufficient enough to explain the pathophysiology of the disorder. One study[125] has reported widespread, albeit small (eg, 4%) volume reductions throughout the brain, another has shown widespread cortical abnormalities,[126] and others have implicated structures such as cerebellum and corpus callosum, which are outside the frontal-subcortical circuits.[127]

Functional neuroimaging studies have assessed the degree of brain activation associated with neuropsychological tasks of attention and disinhibition. Because tasks are constructed so that ADHD and control individuals do equally well, activation differences indicate group differences in the neural systems used to accomplish the tasks. These studies are consistent with the structural studies locating abnormalities of brain activation in patients with ADHD in fronto-subcortical-cerebellar circuits. For example, when completing a go or no go task, children with the disorder did not activate frontostriatal regions as efficiently as children without. Instead, affected children activated a diffuse network of regions, including more posterior and dorsolateral prefrontal regions than those of controls.[128]

In the subcortical structures associated with ADHD, the striatum has been of particular interest because it is rich in dopaminergic synapses,[129] is vulnerable to the perinatal hypoxic complications implicated in the disorder, and if not intact, it produces hyperactivity and poor inhibitory control in animals.[130] In-vivo neuroimaging studies in people showed that methylphenidate, which is used to treat ADHD, exerts its effects by binding to dopamine transporters, most of which are located in the striatum,[131,132] and, as reviewed above, genetic studies have implicated the dopamine transporter gene in ADHD pathophysiology.

Dougherty and colleagues[65] measured dopamine transporter binding in the striatum by single photon-emission CT (SPECT) using the radiolabelled ligand [^{123}I]Altropane. They found dopamine-transporter binding to be raised by 70% in adults with ADHD. Similar findings were reported by studies using radiolabelled ligands [^{99m}Tc]TRODAT-1,[66–68] [^{123}I]IPT,[133] and [^{123}I]loflupane.[69] Despite these positive findings, van Dyck and colleagues[134] did not find altered dopamine-transporter binding in ADHD, which could have been due to the use of a different radioligand ([^{123}I]β-CIT). In view of the disagreement of data between studies and the inability of SPECT scans to accurately differentiate children with or without ADHD, the use of SPECT for diagnosis is not warranted.

Treatment

For 40 years, the main treatments for ADHD (panel 3) have been the stimulant drugs, methylphenidate and amfetamine, which are believed to enhance neurotransmission of dopamine and norepinephrine.[135] The stimulant pemoline is less commonly used because of its hepatotoxic effects. Non-stimulant treatment has also been used, but for many years reduced efficacy and occurrence of side-effects had restricted their use. The average effect size for stimulants (0·91 for immediate release and 0·95 for long-acting versions) is greater than

Panel 3: Drug treatment for ADHD

Stimulants
Methylphenidate
Amfetamine
Pemoline

Tricyclic antidepressants
Amitriptyline
Desipramine
Imipramine
Clomipramine
Nortriptyline

MAO inhibitors
Phenelzine
Selegiline

α2 agonists
Clonidine
Guanfacine

Others
Atomoxetine
Modafinil
Bupropion

the average effect for non-stimulants (0·62), although much variability exists within classes (figure 2).[136]

Two clinically important developments in ADHD treatment have been the use of long-acting stimulant formulations and the non-stimulant, atomoxetine. Because the immediate-release stimulants were effective for 3–6 h, multiple doses were needed to maintain their effectiveness during the day. Additional doses created embarrassment and stigma for school-age children who typically had to take a dose at the nurse's office during the school day, although at what age the children begin to experience such problems is unknown. The dosage also created problems for adults who would forget to take midday doses. As table 4 shows, clinicians now have many choices of stimulant drugs that allow them to choose the best regimen based on patients' needs for coverage throughout the day. The long-acting stimulants show effectiveness and side-effects similar to that seen for the immediate-release drugs.[136–141]

Despite many decades of clinical use, stimulant drugs have been controversial because of concerns that they might cause tics, kindle substance abuse, and delay growth. Although early reports showed stimulants to raise the risk for tics in patients with a personal or family history of tic disorders,[142] work in the past decade has challenged that view.[143–145] Although these new data are reassuring, more information is needed in large studies for extended periods, to show that non-stimulants be considered for patients at risk for tic disorders.

Because stimulant drugs are controlled substances with addictive potential, concerns had been raised about children with ADHD being prone to abuse and addiction when used for many years. Because long-term, placebo-controlled trials are not ethical, this issue can only be addressed by longitudinal, naturalistic studies. Meta-analyses of such studies have shown that rather than causing subsequent substance-use disorders, the pharmacotherapy of ADHD has a significant protective effect, reducing the risk for substance-use disorder by 50%.[146,147]

Stimulants routinely result in appetite and weight loss,[148] and most studies show that children with ADHD continue to grow while medicated, although the growth in height is less than expected. These deficits in expected height could be transient maturational delays that are associated with ADHD rather than with the stunting of growth in children with the disorder.[149] Overall height seems to be unaffected if treatment is discontinued in adolescence[150] and several long-term studies suggest that deficits in expected height are reversible even with continued treatment for 2–3 years,[151–154] although no attenuation was recorded over 2 years in one study.[155] Clinicians should continue to monitor growth in children treated with stimulant drugs.

Tricyclic antidepressants had been the best established non-stimulant treatments, until their use was curtailed because of reports of sudden unexplained death in four ADHD children treated with desipramine, although the causal link between desipramine and these deaths remains uncertain.[156] Anticholinergic side-effects have also restricted clinical use of these drugs. Similar to the tricyclics, atomoxetine blocks the norepinephrine transporter, which is believed to attenuate ADHD symptoms by increasing norepinephrine in the synapse. However, unlike tricyclics, this compound does not have anticholinergic side-effects and has a safe cardiovascular profile.[157,158]

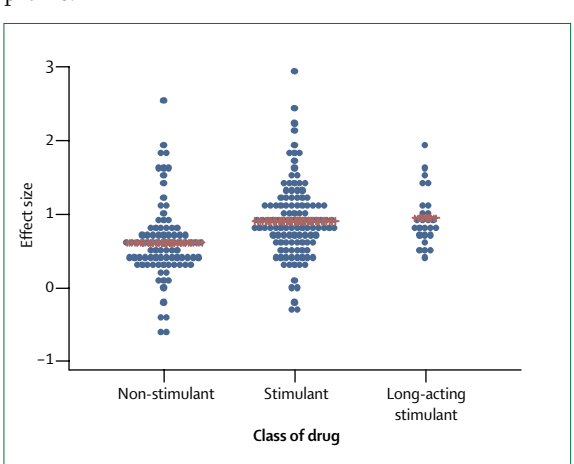

Figure 2: **Effect sizes grouped by drug class**
Effect sizes for every drug-versus-placebo comparison in 55 manuscripts reviewed in reference 136 are plotted.

	Duration of action
Methylphenidate	
Ritalin, methylin, focalin	3 h
Concerta	10–12 h
Ritalin LA	8–9 h
Metadate CD	8–9 h
Amfetamine	
Dexedrine	3 h
Adderall	6 h
Adderall XR	10–12 h

Table 4: **Duration of action of stimulant drugs**

After a request from the US Food and Drug Administration, the manufacturer of atomoxetine recently updated the drug's labelling with a bolded warning about the potential for severe liver injury. The warning followed two reports about pronounced hepatoxic effects in patients taking atomoxetine (of 2 million patients exposed to the drug). Both patients recovered on discontinuation of atomoxetine. The bolded warning indicates atomoxetine should be discontinued in patients with jaundice and that patients should contact their doctors if they develop pruritis, jaundice, dark urine, right upper quadrant tenderness, or unexplained flu-like symptoms.

Bupropion has shown modest efficacy in ADHD treatment in open-label and controlled trials.[159,160] However, these studies have been small. Despite this uncertainty, bupropion is clearly efficacious for controlling cigarette smoking,[161] which is increased in ADHD patients,[162] and some studies suggest bupropion could be especially helpful for patients with comorbid depression, bipolar disorder, or substance abuse.[163–165] Although bupropion is well tolerated by most patients,[159–161,163–165] in rare cases it induces seizures.[166] Thus, the drug should not be given to patients with a history of seizure disorders.

Modafinil, which has been used to promote wakefulness for narcolepsy, has also shown some efficacy against ADHD, initially in an open-label study in children.[167] In a double-blind, placebo-controlled study[168] of 223 children with the disorder, one 300 mg dose of modafinil per day greatly improved disease symptoms that were rated by teachers, clinicians, and parents. Modafinil doses of 400 mg per day had much better results than placebo, but did not add great beneficial effect to doses of 300 mg per day. All modafinil dosing regimens were well tolerated. The most common adverse events were insomnia, abdominal pain, anorexia, cough, fever, and rhinitis. Two small studies also suggest the drug could be effective against adult ADHD.[169,170]

Two α2-adrenergic agonists, clonidine and guanfacine, are also used in the treatment of ADHD but because of scarce efficacy and side-effect data, they are not routinely prescribed. Connor and colleagues[171] did a meta-analysis of 11 studies and concluded that clonidine was significantly but only moderately effective against ADHD. Some work suggests that clonidine could be useful as an adjunct to stimulant treatment when symptoms of hyperactivity, impulsivity, and aggression are not well controlled, or if tics or sleep difficulties are present.[172] The scarce data for guanfacine suggests that it could be moderately efficacious against ADHD and might also alleviate tics in children with ADHD and tic disorders.[173] The most common side-effects of α2 agonists are sedation, drowsiness, and depression.

Many psychosocial interventions are used for children with ADHD both alone and in combination with drug treatment. Behavioural modification, which uses reward and response cost to change behaviour, has been useful against symptoms and associated features of ADHD,[174] and cognitive-behaviour therapy has shown positive results in adults with the disorder.[175] But what is the relative value of pharmacological and psychosocial interventions for children with ADHD? This issue was recently resolved by a multisite study comparing drug management, intensive behavioural treatment, combined drug and behavioural treatment, and standard community care.[174] For most ADHD symptoms, combined treatment and drug management groups showed greater efficacy than behavioural treatment and community-care groups. This pattern of effect continued to the 2-year follow-up.[176] These analyses suggest that for children with ADHD, drugs should be the first-line treatment for the disorder. Nonetheless, other data from the MTA study (Multimodal Treatment of ADHD)[174] indicate that behavioural treatment can be valuable for some patients.[32,177] For clinicians, these findings suggest that, after drug treatment is successfully titrated, assessments of residual disabilities should guide subsequent decisions regarding psychosocial interventions.

See http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01335.html

Conclusions

ADHD has emerged from the 20th century with a large amount of scientific work investigating its validity and clarifying clinical controversies. The disorder is highly prevalent worldwide, is associated with substantial life impairments, and frequently persists into adulthood. Hypotheses about the cause of ADHD have evolved from simple one-cause theories to the view that it is a complex, multifactoral disorder caused by the confluence of many different types of risk factors (ie, genetic, biological, environmental, psychosocial), with every type having a small effect on the increasing vulnerability to the disorder through their additive and interactive effects. If an individual's cumulative vulnerability exceeds a threshold, he or she will manifest the signs and symptoms of ADHD. According to this multifactorial model of ADHD, no one causal factor is necessary or sufficient to initiate the disorder and all these factors are interchangeable (ie, only the total number is important). This multifactorial view of ADHD is consistent with the recorded heterogeneity in its pathophysiology and clinical expression.

Although brain-imaging studies have documented both structural and functional pathological changes in frontal-subcortical-cerebellar circuits, imaging methods cannot be used as diagnostic methods. The same approach is true of the genetic variants associated with ADHD. These neurobiological data provide insights into cause and pathophysiology, but more work is needed before they can be considered diagnostically useful. We can expect genetic studies to provide more insights into how molecular pathophysiology leads to ADHD symptoms and to endophenotypes, which are subclinical manifestations of ADHD caused by one or more of the same genes that lead to the disorder.[178,179] Emerging knowledge about the cause and pathophysiology of ADHD should lead to an improved understanding of the neural mechanisms underlying the disorder, which should improve diagnostic and treatment strategies.

Conflict of interest statement

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