Attention deficit hyperactivity disorder

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Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder with a prevalence of 1·4–3·0%. It is more common in boys than girls. Comorbidity with childhood-onset neurodevelopmental disorders and psychiatric disorders is substantial. ADHD is highly heritable and multifactorial; multiple genes and non-inherited factors contribute to the disorder. Prenatal and perinatal factors have been implicated as risks, but definite causes remain unknown. Most guidelines recommend a stepwise approach to treatment, beginning with non-drug interventions and then moving to pharmacological treatment in those most severely affected. Randomised controlled trials show short-term benefits of stimulant medication and atomoxetine. Meta-analyses of blinded trials of non-drug treatments have not yet proven the efficacy of such interventions. Longitudinal studies of ADHD show heightened risk of multiple mental health and social difficulties as well as premature mortality in adult life.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterised by developmentally inappropriate and impairing inattention, motor hyperactivity, and impulsivity, with difficulties often continuing into adulthood. In this Seminar, we aim to update and inform early career clinicians on issues relevant to clinical practice and discuss some controversies and misunderstandings.

Definitions of ADHD

ADHD is a diagnostic category in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV)[1] and the more recent DSM-5.[2] The broadly equivalent diagnosis used predominantly in Europe is hyperkinetic disorder, which is defined in WHO's International Classification of Diseases (10th edition; ICD-10).[3] This definition captures a more severely affected group of individuals, since reported prevalence of hyperkinetic disorder is lower than that of DSM-IV ADHD, even within the same population.[4] Key diagnostic criteria are listed in the panel. DSM-5 has longer symptom descriptors than those used in DSM-IV; these descriptors also capture how symptoms can manifest in older adolescents and adults. DSM-IV distinguished between inattentive, hyperactive–impulsive, and combined subtypes of ADHD; a diagnosis of the combined subtype required the presence of symptoms across the domains of inattention and hyperactivity–impulsivity. However, ADHD subtypes are not stable across time,[5] and DSM-5 has de-emphasised their distinctions. ICD-10 does not distinguish subtypes; symptoms need to be present from the three separate domains of inattention, hyperactivity, and impulsivity for a diagnosis of hyperkinetic disorder.

The diagnosis of ADHD or hyperkinetic disorder also requires the presence of symptoms across more than one setting (eg, home and school) and requires that the symptoms needed for diagnosis result in impairment, for example in academic, social, or occupational functioning. Onset must be early, although DSM-5 has changed the age of onset from before age 7 years (ICD-10 and DSM-IV) to before age 12 years.

Like all complex medical and psychiatric disorders, ADHD shows marked heterogeneity at clinical, aetiological, and pathophysiological levels. Individuals with a diagnosis of ADHD differ from each other in terms of their core symptom combinations, level of impairment and comorbidities, as well as on other background individual, family, and social factors.

For clinical purposes, defining ADHD categorically is useful given that clinical decisions tend to be categorical in nature—eg, whether to refer to specialist services or to treat. However, like many medical disorders (such as hypertension and diabetes), in terms of causes and outcomes, ADHD can be viewed as a continuously distributed risk dimension. In common with other continuously distributed phenotypes (eg, blood pressure), it could be argued that there is a lack of an objective cut-point that defines the diagnostic threshold. Indeed, individuals with subthreshold symptoms are at heightened risk of adverse outcomes[6] (as is seen in hypertension). However, ultimately, categorical decisions on resource allocation and treatment have to be made,

Search strategy and selection criteria

To identify studies for this Seminar, we searched PubMed for papers published between Jan 1, 2010, and March 31, 2015, using the search terms "ADHD", "aetiology", "epidemiology", "prevalence", "gender", "time trends", "prescribing", "genetic", "prenatal", "psychosocial", "toxins", "institutional rearing", "longitudinal", "prognosis", "animal model", "biological pathway", "cognition", "neuroimaging", "comorbidity", "neuropsychological", "medication", "stimulants", "behavioural interventions", "nonpharmacological interventions", "diet", and "outcomes". Only articles published in English were included. Key recent reviews and book chapters were also examined. To reduce the number of papers cited, the most up-to-date review papers and meta-analyses were used where possible. We selected papers according to our judgment of the quality of the study or review paper, the relevance to controversial or commonly misunderstood issues, and whether findings had clinical relevance. We included older papers that we judged to be important.

and ICD-defined or DSM-defined diagnosis provides a reliable way of balancing the risks and benefits of giving an individual a diagnostic label and providing treatments that are not free of adverse effects. A further challenge, which occurs in all psychiatric disorders and some neurological disorders (eg, migraine), comes from the diagnosis being based on reported symptoms alone; there are no biological tests. This difficulty means that even with clear-cut diagnostic criteria, there is potential risk of overdiagnosis and underdiagnosis, which underscores the importance of careful and rigorous expert assessment.[7] Concerns about underdiagnosis and overdiagnosis are not restricted to ADHD or psychiatric disorders.[8]

Epidemiology

In the general population, the estimated prevalence of ADHD in children is 3·4% (95% CI 2·6–4·5) according to the most recent meta-analysis,[9] with lower rates of around 1·4% reported for hyperkinetic disorder from European studies.[10] International comparisons show that prevalence does not vary by geographical location but is affected by heterogeneity in assessment methods (eg, use of an additional informant to the parent or carer) and diagnostic conventions (eg, ICD *vs* DSM).[11] Notably, there is a marked under-representation of studies on ADHD from low-income and middle-income countries.

One common assumption is that ADHD must be a modern occurrence. However, a case series of children presenting with the characteristic clinical features was published by the British paediatrician Sir George Still in *The Lancet* in 1902,[12] and there are descriptions that pre-date this publication by several centuries. Time trends studies of non-referred population cohorts in the late 20th and early 21st centuries show no evidence of a rise in rates of ADHD symptoms or diagnosis across time.[13,14] However, there has been a very marked rise in the number of prescriptions issued for ADHD pharmacological treatment across high-income countries in the past decade.[15–17] Rises in clinic incidence and treatment could simply indicate increased parent and teacher awareness of ADHD or changes in the impact of symptoms on children's functioning, or both.[18,19] Nevertheless, European studies have repeatedly reported that despite the rise in ADHD treatment, the administrative prevalence is lower than the population figure, highlighting that in these countries there is still underdiagnosis.[17,20,21] However, in the USA, similar types of studies show geographical variation in patterns of underdiagnosis and overdiagnosis or in ADHD medication prescribing.[22,23] Such findings highlight that there is the potential for misdiagnosis and inappropriate use of pharmacological interventions if safeguards are not in place. These safeguards include ensuring full, good-quality clinical assessments are undertaken, even though these require time, and adherence to national and international treatment guidelines. However, there is no evidence of rising population rates of ADHD explained by social change, contrary to the opinion of some people.

***Panel:* Key diagnostic symptoms of attention deficit hyperactivity disorder[2]**

Inattentive symptoms

- Does not give close attention to details or makes careless mistakes
- Has difficulty sustaining attention on tasks or play activities
- Does not seem to listen when directly spoken to
- Does not follow through on instructions and does not finish schoolwork, chores, or duties in the workplace
- Has trouble organising tasks or activities
- Avoids, dislikes, or is reluctant to do tasks that need sustained mental effort
- Loses things needed for tasks or activities
- Easily distracted
- Forgetful in daily activities

Hyperactivity or impulsivity symptoms

- Fidgets with or taps hands or feet, or squirms in seat
- Leaves seat in situations when staying seated is expected
- Runs about or climbs when not appropriate (may present as feelings of restlessness in adolescents or adults)
- Unable to play or undertake leisure activities quietly
- "On the go", acting as if "driven by a motor"
- Talks excessively
- Blurts out answers before a question has been finished
- Has difficulty waiting his or her turn
- Interrupts or intrudes on others

An excess of affected male individuals is a strongly consistent epidemiological finding, although the male:female ratio of 3–4:1 recorded in epidemiological samples is increased in clinic populations to around 7–8:1, suggesting referral bias in relation to female patients with ADHD.[24] The same male preponderance is seen for other neurodevelopmental disorders such as autism spectrum disorder, intellectual disability (intelligence quotient [IQ] <70), and communication disorders.[25]

The natural history of ADHD is best examined in prospective longitudinal studies. As is typical of neurodevelopmental disorders, the core defining features of ADHD tend to decline with age, although inattentive features are more likely to persist. However, in line with its heterogeneous clinical presentation, the developmental trajectories of ADHD are highly variable. Although around 65% of patients continue to meet full criteria or have achieved only partial remission by adulthood, some patients do achieve full remission.[26] Good-quality, large epidemiological studies of the prevalence of ADHD in adulthood are lacking, but one meta-analysis of adult ADHD yielded a pooled prevalence of 2·5% (95% CI 2·1–3·1).[27] However, there are still uncertainties as to what constitutes the best way of defining ADHD (or indeed any

neurodevelopmental disorder) in adulthood. DSM-5 explicitly allows for symptom decline and requires a reduced number of symptoms for diagnosis of adult ADHD.[2] In clinical settings, diagnosis of ADHD in adults who did not present in childhood requires some caution in the absence of documented information because of the difficulty for young adults and those who know them to date symptom onset retrospectively.[28] Objective records (eg, school reports) could help in this regard. Despite these caveats, there is certainly sufficient evidence to conclude that ADHD is not simply a problem that most children grow out of. However, transitioning from child to adult mental health clinics is difficult because of a scarcity of adult services.[29]

Early comorbidity

ADHD shows high concurrent comorbidity with other neurodevelopmental disorders—namely, autism spectrum disorder, communication and specific learning or motor disorders (eg, reading disability, developmental coordination disorder), intellectual disability, and tic disorders.[30–32] Unsurprisingly, rates of comorbidity are higher in individuals who are clinically referred than in those who are not referred.[33] ADHD also shows high concurrent comorbidity with behavioural problems—namely, oppositional defiant and conduct disorders.[31,34] Conduct disorder is a risk marker for greater neurocognitive impairment and worse prognosis in children with ADHD.[35,36] This subgroup of children with hyperkinetic conduct disorder is distinguished in ICD-10 but not in DSM-5.

Risk factors

Overview

As for all complex disorders, no single risk factor is either necessary or sufficient to explain ADHD—many genetic and non-genetic (or environmental) factors contribute to risk, and the pattern of inheritance is multifactorial for most affected individuals.

Genetics

ADHD is a familial disorder. Its relative risk is about 5–9 in first-degree relatives of probands with ADHD.[37] Many twin studies of ADHD from different countries have consistently yielded very high heritability estimates of about 76%, a magnitude similar to that reported for schizophrenia and autism.[38]

The genetic architecture of ADHD is similar to other neuropsychiatric disorders such as schizophrenia. Several different classes of genomic variants have been identified to be associated with ADHD risk.[39] These variants include common (defined as >5% population frequency) DNA sequence variants called single nucleotide polymorphisms (SNPs), but associations have only been reported when thousands of SNPs are combined into a composite genetic risk score.[40] Subtle chromosomal mutations, such as rare (defined as <1% frequency) deletions and duplications called copy number variants (CNVs), are also associated with ADHD risk.[41] These have larger effect sizes but are uncommon.

Before whole-genome investigations, specific single dopaminergic, serotonergic, and noradrenergic candidate genes were significantly associated with ADHD status in meta-analyses.[42,43] However, in the present era of whole-genome investigation, psychiatric candidate gene studies of DNA variants in single genes are viewed with caution because of the potential for false positives.[44]

ADHD-associated genomic variants are non-specific; composite genetic risk scores show significant overlap with those contributing to schizophrenia and mood disorders.[45,46] ADHD-associated CNVs also show overlap with ones associated with schizophrenia, autism, and intellectual disability.[41,47] Although testing for rare CNVs is now recommended for individuals with intellectual disability, this is not the case for ADHD. Ascertaining causality requires further and different types of investigation, as reviewed elsewhere.[39]

Although most cases of ADHD are multifactorial in origin, there are several known, rare genetic syndromes (such as fragile X syndrome, tuberous sclerosis, 22q11 microdeletion, and Williams syndrome) characterised by high rates of ADHD and ADHD-like features. These syndromes are also associated with high risk of other disorders, such as autism (especially in fragile X syndrome and tuberous sclerosis) and schizophrenia (22q11 microdeletion syndrome). In typical clinic populations with ADHD, there is no evidence that routine screening for these genetic syndromes is warranted in the absence of intellectual disability.[48]

Environment and gene–environment interplay

Environmental factors are also known to be important in ADHD. Because evidence for modifiable causes can affect clinical decision making, public health priorities, and clinician and patient behaviour,[49] we will discuss whether findings on individual environmental risks meet accepted standards for inferring causation.[50]

Observational case-control and epidemiological studies show that exposures to a range of prenatal and perinatal factors, environmental toxins, dietary factors, and psychosocial factors are all associated with ADHD.[38] If these associations are causal, it means manipulation of the risk factor can alter the outcome. However, association does not mean causation, because exposures to risks are not randomly allocated and can be affected by unmeasured confounders, selection factors, and reverse causation, whereby the phenotype influences the environmental exposure. Evidence for environmental causation must be interpreted with these caveats in mind.

Prenatal and perinatal factors reported to be associated with ADHD are low birthweight and prematurity,[51] and in-utero exposure to maternal stress, cigarette smoking, alcohol, prescribed drugs (eg, paracetamol), and illicit substances.[38,52,53] In relation to prenatal smoking and

stress, quasi-experimental designs suggest that most or all of the association with offspring ADHD, unlike with offspring birthweight, is explained by unmeasured confounding factors.[54–58]

Environmental toxins, specifically in-utero or early childhood exposure to lead, organophosphate pesticides, and polychlorinated biphenyls, are risk factors for ADHD, as reviewed elsewhere.[38] Nutritional deficiencies (eg, zinc, magnesium, and polyunsaturated fatty acids), nutritional surpluses (eg, sugar and artificial food colourings), and low or high IgG food have not been shown convincingly to precede ADHD and at present should be regarded as correlates. Effective treatments for any disorder, unlike prevention, do not necessarily have to deal with its causes or origins.

Psychosocial risks, such as low income, family adversity, and harsh or hostile parenting, although robustly causal for some psychiatric disorders, are also correlates rather than proven causes of ADHD. Longitudinal studies,[59] treatment trials,[60] and a study of children adopted away at birth[61] suggest that observed negative mother–child relationships (even in unrelated mothers) arise as a consequence of early child ADHD symptoms (reverse causation) and improve with treatment. However, exposure to very severe, early social deprivation seems to be different and causal. After being adopted away in the UK, Romanian orphans raised in institutions and exposed to extreme early privation in the first year of life showed increased rates of ADHD-like features, cognitive difficulties, and quasi-autistic features that persisted into adolescence.[62,63] Psychosocial context may well shape ADHD presentations and alter developmental trajectories, outcomes, and impairments, but surprisingly this has not been investigated widely (figure 1). Irrespective of the cause of ADHD, treatment is based on clinical features and not assumed aetiology.

As a final word on risk factors, many individuals mistakenly assume that the actions of genes (or biology) and environment are distinct. Potentially important environmental risks for ADHD and its outcomes may be brought about as a consequence of genetic propensities (gene–environmental correlation[61]). The effect of environmental factors on clinical phenotype may also depend on genetic liability. For example, animal studies have robustly shown that environment can alter behaviour in different ways depending on the variant of gene carried (gene–environment interaction[39]). Effects of gene–environment interplay are subsumed in twin heritability estimates. Finally, there is very good evidence that environmental exposures result in biological changes,[49] including ones involving brain structure, function, and altered DNA methylation (epigenetics). These findings highlight that genes, environment, and biology work together. However, in man, these issues are complex; they will not be discussed in detail here, but have been reviewed elsewhere.[38,39,49]

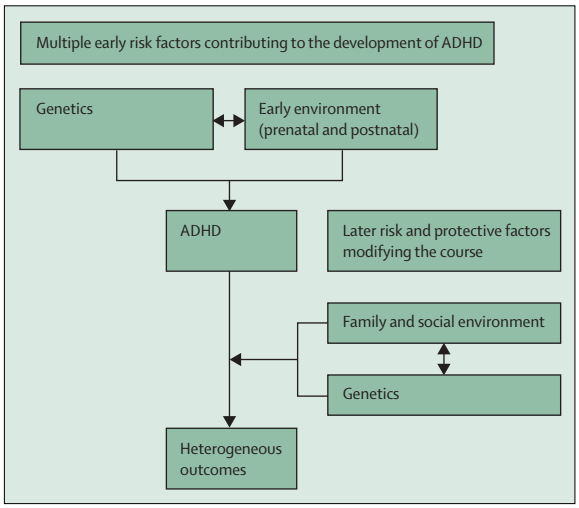

Figure 1: **Origins and trajectories of attention deficit hyperactivity disorder (ADHD)**

Pathophysiology

Biology

The biological mechanisms through which genetic and environmental factors act and interact to alter neurodevelopment in ADHD are not yet understood and there remains no diagnostic neurobiological marker. The validity of animal models of ADHD are limited by our incomplete understanding of its pathophysiology in man and the extent to how well inattention, motor overactivity, and impulsive responses on behavioural tasks in non-human species represent ADHD.[64] However, findings in animal models have suggested involvement of dopaminergic and noradrenergic neurotransmission (in line with the neurochemical effects of ADHD medications) as well as involvement of serotonergic neurotransmission.[65]

Cognition

Although there is no cognitive profile that defines ADHD, deficits in various neuropsychological domains have been reliably identified. In terms of executive functioning, the most consistent and strong associations are seen for response inhibition, vigilance, working memory, and planning.[66] In terms of non-executive deficits, associations are seen with timing,[67] storage aspects of memory,[68] reaction time variability,[69] and decision making.[70] However, there is substantial heterogeneity in cognitive functioning even within single samples,[71] and there is not a straightforward association between cognitive performance and the trajectory of clinical symptoms.[72,73] There is evidence, though, that some cognitive deficits are improved by methylphenidate, with a meta-analysis showing improvements in executive and non-executive memory, reaction time, reaction time variability, and response inhibition.[74]

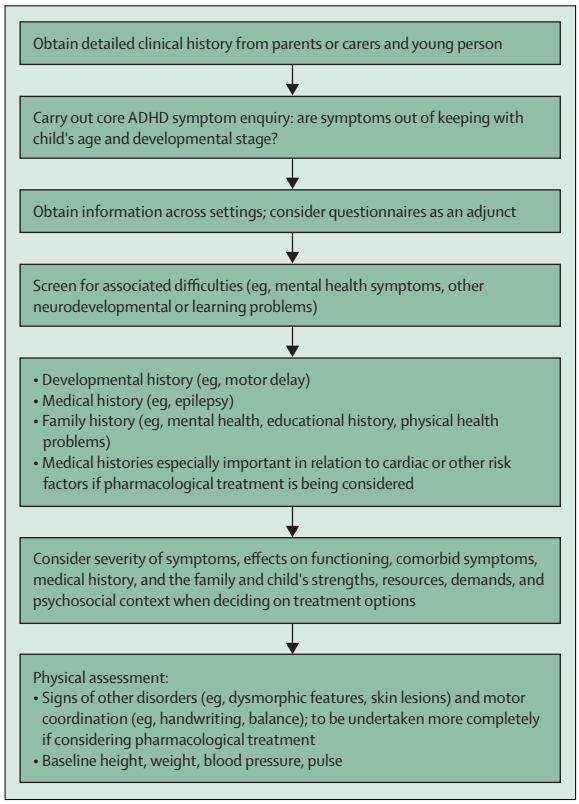

Figure 2: **Summary of the clinical assessment process for children**
ADHD=attention deficit hyperactivity disorder.

Imaging

Functional MRI (fMRI) studies in patients with ADHD have found abnormalities in the function of many neural networks in response to cognitive tasks. A meta-analysis of task-based fMRI studies identified alterations in several networks, including those related to attention and executive function.[75] In terms of brain structure, a meta-analysis of structural MRI studies highlighted alterations in the basal ganglia and limbic areas.[76] In a meta-analysis of diffusion MRI studies investigating white matter microstructure, alterations were reported to be widespread, but most reliably seen in the right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum.[77] Reduced total grey matter and altered basal ganglia volumes seem to index familial risk for ADHD.[78]

The scientific literature is increasingly suggesting that the pathophysiology of ADHD involves abnormal interactions between large-scale brain networks; however, current imaging studies do not yet have relevance to clinical practice.[79] Interpretation is complex because of many factors, including the cross-sectional nature of most studies. Longitudinal data regarding the trajectory of cortical development suggest that the brain may show maturational delay, with persistence of ADHD indexed by progressive divergence from the normal trajectory,[80] but it is not known whether this phenomenon can be extrapolated to other metrics of structure, microstructure, and function. The effect of pharmacological treatment is also a consideration because there is some evidence to suggest that it normalises macrostructure and function.[81] Nonetheless, there is some evidence from longitudinal studies of adults with childhood ADHD that grey and white matter abnormalities persist well into adulthood.[82,83]

Clinical assessment

The assessment process for ADHD requires careful clinical history taking that goes beyond asking yes or no questions in relation to core ADHD symptoms. A missed diagnosis has potential to jeopardise an individual's learning or occupational and social relationships, whereas a misdiagnosis could lead to the use of pharmacological treatment that is not needed. History taking should not be reductionist—ie, exclusively focused on asking about diagnostic items. A detailed developmental as well as medical history and an assessment of family processes and social circumstances (strengths as well as weaknesses) are also required. Figure 2 summarises the key steps in the assessment of children.

It is important to consider whether endorsed symptoms are better explained by other difficulties that are amenable to intervention—eg, hearing difficulties presenting as inattention. However, diagnosis is based on clinical phenotype and not generally excluded by presumed cause. Information should be obtained from more than one informant, including those who know the affected individual best at home and at school (or college or work). To decide which individuals need referral to a specialist assessment service or to monitor treatment response, use of standardised ADHD questionnaires (eg, Strength and Difficulties Questionnaire,[84] Conners' Parent and Teacher Rating Scales[85]) are helpful, but these are not a substitute for detailed history taking before diagnosis. Structured interviews are more likely to be encountered in a research setting, but might be valuable in a clinical context, especially interviews that do not require extensive, expensive training (eg, the Development and Wellbeing Assessment).[86] The use of structured interviews in a clinical setting requires further investigation. ADHD symptoms are commonly associated with a range of neurobehavioural difficulties, which could be comorbid features of the disorder but should also be considered as differential diagnoses because their treatments are very different.

Mental health symptoms, which should also be screened for, include those of oppositional defiant disorder, conduct disorder, anxiety, and mood disturbance. Developmental and learning problems such as reading disorders, developmental coordination disorder, and tic disorders are also common.[87–89] Because ADHD and autism spectrum disorder co-occur so frequently,[90] autistic symptomatology should be considered. ADHD is also associated with lower IQ or intellectual disability[91] and emotion dysregulation

symptoms (eg, irritability),[92] both of which can further complicate the presentation and interpretation of symptoms. In practice, it will be rare to find an individual who presents with so-called uncomplicated ADHD, even if full diagnostic criteria for other comorbid disorders are not met. This situation makes formalising differential diagnoses conceptually difficult, because in reality an individual with neurodevelopmental problems is unlikely to have a pure presentation of any one condition as a unifying explanation for their difficulties. A formulation should capture the full range of developmental, behavioural, and psychiatric difficulties, even if some of these need to be described in terms of subthreshold problems.

Neuropsychological testing does not have a role in diagnosis of ADHD because cognitive processes are not a defining characteristic.[66] However, cognitive comorbidities such as learning disability and dyslexia should be considered, which may require specialist assessment from education services.

Treatment

There are specific guidelines for the stepwise management of ADHD, such as those developed by the National Institute for Health and Care Excellence (NICE)[7] and the Scottish Intercollegiate Guidelines Network (SIGN)[93] in the UK, by the Eunethydis European ADHD Guidelines Group (EAGG)[94] in Europe, and by the American Academy of Pediatrics (AAP)[95] and the American Academy of Child and Adolescent Psychiatry (AACAP)[96] in the USA. The main difference between these guidelines is that US guidance does not preclude the use of pharmacological treatment for preschool children or for those with mild ADHD; practice that is not recommended in Europe where a stepwise approach is recommended. If pharmacological treatment is prescribed, it should be in conjunction with behavioural interventions—namely, optimised classroom management strategies, parental psychoeducation, and behavioural management techniques. However, there is no one-size-fits-all solution to management. Individual circumstances such as current academic or employment demands and medical history should be taken into account, and appropriate evidence-based treatments for comorbidities should also be initiated.

Non-pharmacological interventions have been investigated extensively over the years. The only non-pharmacological interventions that currently form a core part of treatment guidelines are behavioural interventions. Initial results from the largest trial of ADHD interventions so far, the multimodal treatment study of children with ADHD (MTA),[97] suggested that the combination of intensive behavioural treatment plus pharmacological treatment did not offer additional benefit over pharmacological treatment alone for core ADHD symptoms, but that the combination might have provided some benefit in terms of associated symptoms and levels of functioning as well as the need for a lower drug dose. In a more recent series of meta-analyses investigating randomised controlled trials of non-pharmacological interventions, the investigators concluded that, along with neurofeedback, cognitive training, and restricted elimination diets, behavioural interventions cannot be recommended as interventions for core ADHD symptoms until better evidence of their effectiveness is reported by blinded assessments.[98] Elimination of artificial food colouring[98] might be beneficial, but to what extent and for which population of patients is unclear.[99] A meta-analysis has shown that children with ADHD have lower concentrations of omega-3 fatty acids than controls and that supplementation improves ADHD symptoms to a modest degree (an effect size about a quarter as large of that seen for pharmacological treatment); but whether subnormal blood concentrations should be the indication for treatment is not understood.[100] However, there is evidence from blinded randomised controlled trials of a beneficial effect of behavioural interventions on parenting and child conduct problems,[101] and there is evidence that cognitive behaviour therapy may be useful for adults with ADHD when used in conjunction with pharmacological treatment.[102]

Stimulants such as methylphenidate and dexamfetamine are the first-line pharmacological treatments for ADHD, and the noradrenaline reuptake inhibitor atomoxetine is the second-line treatment. Each of these treatments increases catecholamine availability. Meta-analyses have provided evidence for the efficacy of stimulants for ADHD in children,[103] in children with co-occurring autism spectrum disorder,[104] and in adults.[105] Although it is recommended that ADHD is treated in individuals with autism spectrum disorder or intellectual disability, or both, side-effects of pharmacological treatment in these individuals are more common than in those with ADHD alone.[106,107] Meta-analyses have shown beneficial effects of atomoxetine in children[108] and in adults.[109] Extended-release guanfacine and extended-release clonidine are licensed for use in the USA. Atypical antipsychotics are not indicated for treatment of core ADHD symptoms.

Pretreatment checks, including in relation to medical and family medical history (in particular cardiac disorders), are especially important if medication is to be initiated (figure 2). Height, weight, blood pressure, and pulse should be checked at baseline before starting treatment, and compared with normative data. It is reasonable but not mandatory to consider the routine performance of an ECG before starting pharmacological treatment, and the need to do so should be at the treating clinician's discretion, taking into account factors such as medical history, family medical history, and physical examination findings.[7,110]

It is best practice to start with a low dose, titrate up according to response, and monitor side-effects carefully.[7] The most common side-effects of medications for ADHD are shown in the table. There is no evidence that

	Methylphenidate (MPH)	Atomoxetine (ATX)
Loss of appetite	+	+
Growth restriction	++	+
Other gastrointestinal symptoms: abdominal pain, nausea, vomiting, diarrhoea (MPH), constipation (ATX), dyspepsia, dry mouth	+	+
Increase in blood pressure and heart rate	+	+
Cough, nasopharyngitis	+	..
Sleep disturbances	++	+
Tics	+	..
Irritability, mood changes	+	+
Drowsiness	+	++
Dizziness	+	+
Headache	++	+

+=common side-effect. ++=if the side-effect is common for both drugs, the effect is more pronounced for this drug compared with the other. ..=side-effect not common.

Table: **Some of the more common side-effects associated with pharmacological treatment**

pharmacological treatment for ADHD is associated with changes in QT interval, sudden cardiac death, acute myocardial infarction, or stroke.[110] A comprehensive review of best practice in managing adverse events associated with pharmacological treatment for ADHD has been published elsewhere.[110] Once an optimum response is achieved, height, weight, and growth will need regular monitoring. NICE guidance recommends that height is measured every 6 months in children and young people; weight is measured 3 months and 6 months after initiation of treatment and every 6 months thereafter in children, young people, and adults; and height and weight in children and young people should be plotted on a centile chart.[7] Blood pressure and pulse should also be plotted on a centile chart before and after each change in dose and routinely every 3 months.[7] Adverse side-effects of stimulant medication for ADHD include appetite suppression and growth retardation, which can be offset to a degree by so-called stimulant holidays on days when symptom control is deemed less crucial, such as weekends and holidays, and by adjusting the timing of doses. Other side-effects of stimulants and atomoxetine include gastrointestinal symptoms, cardiac problems, insomnia, and tics (although tics are less common with atomoxetine). Stimulants are controlled drugs with potential for diversion for misuse, and if there is a concern in this regard then an alternative drug may be preferable.

Prognosis

Not only do core ADHD symptoms themselves persist, but individuals with childhood ADHD are also at substantial risk of adverse outcomes in adolescence and adulthood. In this regard, ADHD behaves dimensionally: there is no distinct threshold at which adverse outcomes appear. A diagnosis of ADHD is associated with low academic attainment and premature cessation of education, and poor educational outcomes also extend to individuals with subthreshold symptoms.[111] ADHD also predicts serious antisocial behaviour, involvement with the police, and substance misuse in adolescence.[36]

Until recently, few data for broad outcomes beyond the third decade of life were available. However, one long-term follow-up study has shown that childhood ADHD (participants aged 6–12 years) is also associated with adverse occupational, economic, and social outcomes, antisocial personality disorder, and risk of substance use disorders, psychiatric hospital admissions, incarcerations, and mortality.[112] A Danish registry-based investigation showed substantially increased mortality in adult life in individuals with ADHD compared with individuals without the disorder. This increase in mortality was mainly a result of accidents, and was especially increased in those with comorbid oppositional defiant disorder, conduct disorder, and substance misuse.[113]

A meta-analysis of ADHD in prison inmates showed an estimated prevalence of 30·1% in youth prison populations and 26·2% in adult populations, with the risk for female prisoners being nearly as high as that for male prisoners.[114] Psychiatric comorbidity is high in prisoners with ADHD, especially in adults.[115] Although randomised controlled trials of ADHD treatment have reported immediate but not as yet longer term benefits, there is epidemiological evidence that pharmacological treatment might reduce criminal behaviour[116] and trauma-related visits to emergency departments.[117]

Most people with ADHD do not develop psychosis or a mood disorder. The largest studies only find a small subgroup of individuals who additionally develop schizophrenia or bipolar disorder.[118,119] Evidence about associations between ADHD and later unipolar depression is inconsistent;[112,120] this might be because depression is more common in female patients who are under-represented in ADHD samples.

Future research and clinical directions

The early age of onset, male preponderance, and strong comorbidity with other childhood-onset neurodevelopmental disorders support the inclusion of ADHD in the DSM-5 grouping of neurodevelopmental disorders. The previous practice of not diagnosing ADHD in the presence of autism spectrum disorder or intellectual disability has been a crucial barrier to research on aetiological and clinical overlaps and distinctions as well as to clinical and educational practice. Unfortunately, referral and treatment pathways and service provision in health and education tend to be diagnostically focused (ie, autism only or intellectual disability only), although some clinics and services are focusing more broadly on childhood neurodevelopmental disorders, a change which is welcomed and supported by research.

We accept that for clinical practice, there is a need for strict categories, otherwise diagnostic spread would become at best unhelpful and at worst risky and unethical (eg, use of pharmacological treatment where not indicated) and application of evidence-based treatments would become impossible (eg, interpreting the severity of difficulties of individuals included in a trial). However, for aetiological and outcome research purposes, there is strong evidence in favour of viewing ADHD dimensionally. At present, we do not know what sorts of dimensions best capture ADHD and at what level they should be measured—eg, reported symptoms, cognitive tests, brain imaging markers, or other biological signatures.

Genetic research is progressing via large-scale collaboration, but there is a need to understand the clinical as well as biological meaning of findings, if they are to affect our understanding and treatment of ADHD. Currently, there is no rationale for routine genetic testing in ADHD because of limited predictive power. However, because the disorder is heritable, rates of ADHD in parents of those with ADHD are increased. A pertinent future research question is how might treatment of parent ADHD affect child ADHD features and comorbidity? There is, for example, evidence that treating parent depression seems to improve offspring mental health.[121,122] Another issue for future consideration is that genetic and environmental risk factors that cause ADHD are not necessarily the same as those that alter the later course of the disorder or contribute to adverse outcomes. What is greatly needed is research that tests which environmental risks (eg, social and other potentially modifiable risk factors) contribute to and modify the longitudinal course of ADHD across time, including better prognosis, with designs that can control for unmeasured confounders and genetic contributions from the affected person (eg, twin studies) and related parents (eg, adoption studies). This could inform interventions aimed at optimising outcomes.

So far, pharmacological and behavioural treatments for ADHD have focused on symptomatic relief of the core symptoms of inattention, overactivity, and impulsivity. However, according to trial-based data, benefits seem to be short-lived. Another issue is that treatment typically begins after a child has already begun to fail across multiple domains. ADHD in many respects behaves like a chronic medical disorder. Many features remain problematic long term, although the most prominent or presenting features can change with age and development. ADHD creates risks of its own and secondary mental health problems commonly arise in mid-childhood and after puberty. Almost certainly, for many individuals, multimodal interventions that are carefully adjusted over time to prevent complications will be needed, perhaps in the way that is undertaken for optimising diabetes control. How ADHD is best managed across the lifespan and across key transition periods (eg, school entry, comprehensive or high-school entry, transition to adult services, and transition to parenthood) needs much more investigation. Until now, guidelines have been based on evidence, but unless research keeps pace, guidance will have to be based on professional consensus, which is not very satisfactory for a prevalent, impairing disorder.

Conclusions

ADHD is a very important condition because of its high prevalence, persistence into adult life, and adverse outcomes that extend beyond the affected individual. Although ADHD is still viewed with scepticism by some and often remains stigmatised by the media, the evidence for it being a clinically and biologically meaningful entity is robust and consistent across design type and sample. There are established assessment methods and good treatment evidence. However, as is true for any chronic disorder, repeated assessment is likely to be needed and treatment will typically need many adjustments over time. Impairments beyond core diagnostic criteria, developmental change, and an individual's psychosocial strengths, weaknesses, and resources are all important aspects for consideration.

Contributors

AT drafted the initial outline and structure and wrote the first draft of the summary and sections on introduction, definitions of ADHD, epidemiology, early comorbidity, genetics, environment and gene–environment interplay, and future research and clinical directions. MC wrote the first draft of the sections on pathophysiology, clinical assessment, treatment, and prognosis, and prepared the table, panel, and figures. Both authors undertook scientific literature searches and edited the manuscript.

Declaration of interests

We declare no competing interests.

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