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Primer

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Attention-deficit/hyperactivity disorder

Stephen V. Faraone[1] ✉, Mark A. Bellgrove[2], Isabell Brikell[3,4,5], Samuele Cortese[6,7,8,9,10], Catharina A. Hartman[11], Chris Hollis[12], Jeffrey H. Newcorn[13], Alexandra Philipsen[14], Guilherme V. Polanczyk[15], Katya Rubia[16,17], Margaret H. Sibley[18] & Jan K. Buitelaar[19,20]

Abstract

Attention-deficit/hyperactivity disorder (ADHD; also known as hyperkinetic disorder) is a common neurodevelopmental condition that affects children and adults worldwide. ADHD has a predominantly genetic aetiology that involves common and rare genetic variants. Some environmental correlates of the disorder have been discovered but causation has been difficult to establish. The heterogeneity of the condition is evident in the diverse presentation of symptoms and levels of impairment, the numerous co-occurring mental and physical conditions, the various domains of neurocognitive impairment, and extensive minor structural and functional brain differences. The diagnosis of ADHD is reliable and valid when evaluated with standard diagnostic criteria. Curative treatments for ADHD do not exist but evidence-based treatments substantially reduce symptoms and/or functional impairment. Medications are effective for core symptoms and are usually well tolerated. Some non-pharmacological treatments are valuable, especially for improving adaptive functioning. Clinical and neurobiological research is ongoing and could lead to the creation of personalized diagnostic and therapeutic approaches for this disorder.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: svfaraone@upstate.edu

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common condition characterized by inattention, hyperactivity and impulsivity. The first known description of the syndrome is from Hippocrates in 493 B.C. and the first description in medical textbooks by German and Scottish physicians is from the end of the eighteenth century (see ref. 1 and Supplementary Fig. 1). ADHD is often a seriously impairing and predominantly persistent condition. The disorder is primarily influenced by genetic factors, but environmental factors also have a role, many of which remain unknown. Moreover, from many large, well-designed, epidemiological, clinical and longitudinal studies, we know the disorder's core symptoms (inattention, hyperactivity and impulsivity), impairments (for example, school and occupational failure, poor socialization, and accidental injuries) and comorbidities (for example, anxiety and mood disorders).

The diagnosis of ADHD requires a clinical interview that queries about the core symptoms and associated impairments following the guidelines of either the Diagnostic and Statistical Manual of the American Psychiatric Association 5th edition (DSM-5)[2] or the International Classification of Diseases 11th edition (ICD-11)[3]. The evaluation of patients can be assisted with reliable and valid measurement tools for screening, diagnosis and monitoring treatment outcomes. Many rigorous clinical trials have documented the safety and efficacy of many ADHD treatments. We know which ADHD treatments work (and for which outcomes), which do not[3], and which require further study[4].

This Primer provides an overview of the epidemiology, mechanisms, diagnosis and treatment of ADHD. In the past 5 years, we have learned much about the aetiology of this disorder from breakthroughs in genetics. That work, along with further imaging studies, provides hints about mechanisms of disease onset. We know much more about clinical features and the course over the lifespan, emotional dysregulation, the association of ADHD with somatic disorders, variation in age at onset and fluctuations in severity. In addition, more management options are available due to the development of new pharmacological and non-pharmacological treatments.

Epidemiology

In school-aged children, the prevalence of ADHD based on epidemiological samples representative of the general population is 5.3% and does not differ markedly by geographical region[5,6]. In some individuals, symptom severity declines during adolescence[7] but two-thirds of children with ADHD retain impairing symptoms in adulthood at clinical or subthreshold levels[8]. In early adulthood, the prevalence of ADHD is ~2.5%[9,10] with a gradual decrease to 1% at older ages[10,11] (Fig. 1; onset in childhood required). Diagnosis is often delayed. Children who are primarily inattentive do not disrupt the classroom or aggravate parents and are typically referred later to treatment, which leads to lower rates of referral of girls who are typically more inattentive than boys. Referral for treatment is also delayed for children whose environments protect them with social, emotional and intellectual scaffolding. Due to diagnostic delays, the peak age at diagnosis is 9.5 years, with a median of 12 years. Only 56.8% of individuals with ADHD are diagnosed before 14 years of age; 73.0% are diagnosed by 18 years and 91.8% by 25 years[12].

ADHD is a heterogeneous disorder, and symptoms vary among individuals. In addition to this variability, the course of symptoms and impairment in ADHD fluctuate over time within individual patients[13–16]. ADHD symptoms and impairments tend to worsen under certain conditions, that include increased self-regulation challenges, weak support systems, intensification of comorbid conditions and poor fit between individuals and their environment. Recurrence of ADHD in those in remission is common, and can occur even in those in full remission[13–17]. Typically, severe ADHD has an earlier onset[18] and a less fluctuating course through adulthood than milder ADHD[13].

In youth, the male-to-female sex ratio of ADHD is 2.4:1 in the general population[5]. However, the ratio is much higher (4:1) in those seeking treatment[19] because boys are more disruptive than girls, which makes boys more likely to be referred[20,21]. The sex ratio drops to 2:1 in adolescents[22], and, in adults, ranges from 1.9:1 to 1.2:1 in registry and claims data[23–26] and 1.1:1 in population surveys[27]. The shifting ratios throughout the lifespan is attributed to several factors, such as later recognition of ADHD in females than in males, an increase in women seeking help in adulthood, and a decreased emphasis on hyperactivity in adult ADHD diagnoses, which aligns more closely with the presentation of ADHD in females[28–30]. In addition, parent referral for treatment in childhood is replaced by self-referral in adulthood, and women are more likely to seek professional help for mental health problems than men[31].

Little is known about ADHD in racial and ethnic minority populations, although health-care disparities have been documented[32,33]. Population studies suggest that ADHD is under-diagnosed in Black and Latin minority youth[34–39], even among children with many ADHD symptoms[34]. In Europe, ADHD is less likely to be diagnosed among immigrants than among non-immigrants[33]. The reasons for these differences are differences in access to care, or cultural factors that affect the diagnostic process. For example, in white-majority countries, Black patients with ADHD are significantly less likely to receive pharmacological treatment than white patients[40]. However, the diagnosis of ADHD in individuals of certain ethnicities may be improving[41].

ADHD often coexists with other psychiatric disorders[42,43]. The presence of these comorbid conditions is associated with higher ADHD symptom severity and poorer outcomes, including premature death[44–47]. Up to 70–80% of individuals with ADHD are estimated to have at least one comorbid mental condition across the lifespan[48]. In childhood, meta-analyses of general population studies have yielded pooled odds ratios of 10.7 (95% CI 7.7–14.8) for conduct disorder, 5.5 (95% CI 3.5–8.4) for major depressive disorder, and 3.0 (95% CI 2.1–4.3) for anxiety disorders[49]. Oppositional defiant disorder is also a common comorbidity of ADHD[50,51]. In adulthood, meta-analyses based on findings from large general population studies have yielded pooled odds ratios of 5.0 (95% CI 3.3–7.5) for anxiety disorders, 4.5 (95% CI 2.4–8.3) for major depressive disorder, 8.7 (95% CI 5.5–13.9) for bipolar disorder and 4.6 (95% CI 2.7–7.8) for substance use disorder[43].

ADHD is also often comorbid with somatic conditions[52,53]. Meta-analyses have found in children and adolescents pooled odds ratios of 1.4 (95% CI 1.3–1.5) for dermatitis, 1.3 (95% CI 1.2–1.5) for obesity, 1.6 (95% CI 1.2–2.1) for asthma and 1.6 (95% CI 1.3–1.9) for rhinitis[54], and in adults a pooled odds ratio of 2.3 (95% CI 1.5–3.6) for type 2 diabetes mellitus[55]. Moreover, a nationwide population-based study in adults found hazard ratios of 2.05 (95% CI 1.98–2.13) for onset of any cardiovascular disease[56]. ADHD is also associated with vision problems, but not with structural alterations of the eye[57]. Children with ADHD have many sleep difficulties, including bedtime resistance, late sleep onset, night awakenings, morning awakenings, sleep disordered breathing and daytime sleepiness[58].

Mechanisms/pathophysiology

Genetics

Meta-analyses of twin studies and family studies have shown that the heritability of ADHD is ~80%[59–61], meaning that genetic factors

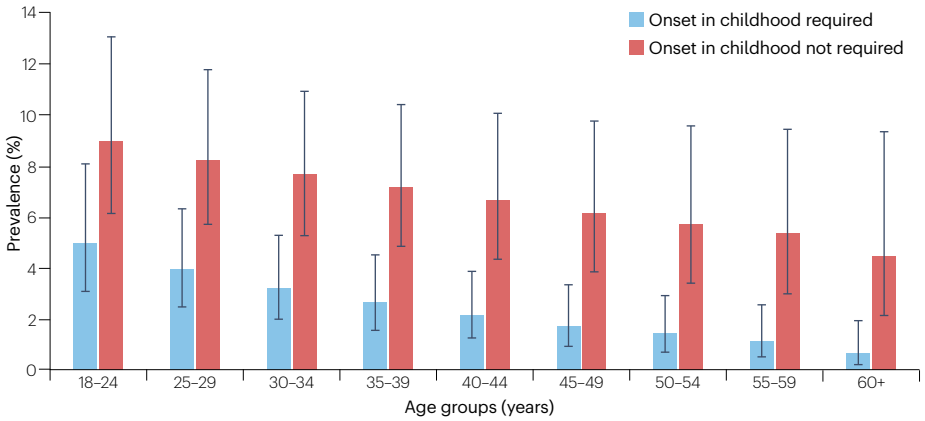

Fig. 1 | The age-dependent prevalence of ADHD in adulthood. Prevalence of attention-deficit/hyperactivity disorder (ADHD) declines during adulthood, although the disorder still occurs at older ages. Higher prevalence estimates are obtained when onset of ADHD during childhood is not required for diagnosis. The age-dependent decline in ADHD prevalence in adulthood has been found in several studies. Data from ref. 10.

contribute strongly to the development of ADHD. Heritability of ADHD is similar across sexes[60], childhood and adulthood[62], and symptom domains (inattentive or hyperactive–impulsive)[63]. Twin and family studies have found that the same genetic factors influence both the disorder of ADHD and lower levels of ADHD symptoms in the general population[61,64], and that shared genetic factors partly explain the co-occurrence of ADHD with other psychiatric disorders (including anxiety, major depressive, bipolar, conduct, autism spectrum and substance use disorders)[59,65–69] and some somatic conditions[70]. Twin studies also found that ADHD is genetically associated with measures of cognition, electroencephalographic (EEG) variability and subtle structural brain differences[65,66].

Molecular genetic studies of ADHD have largely corroborated findings from twin studies and family studies[65] and support a polygenic contribution to ADHD risk, with heritability from common genetic variants (single-nucleotide polymorphisms (SNPs)) estimated at 14–20%[59,71], and evidence of high (>0.80) common variant genetic correlations across sexes[72], and across children diagnosed with ADHD and adults diagnosed with ADHD[73,74]. Genetic correlations estimated from SNPs have also suggested a strong genetic link between clinically diagnosed ADHD and ADHD symptoms in the population, and broadly between ADHD genetic liability and many mental and somatic conditions, and other traits[71,75–80] (Fig. 2). Among these, educational attainment has one of the strongest associations, with higher ADHD polygenic scores linked to worse cognitive performance and educational outcomes[71,76,81,82]. Genetic variants implicated in ADHD have also been linked to smaller intracranial brain volume[83] and to the functional connectivity of subcortical brain regions[84].

The largest genome-wide association studies (GWAS) of ADHD found 27 genome-wide significant loci implicating 76 genes, many of which are upregulated during early brain development. ADHD genetic risk is enriched for genes associated with several brain-specific neuronal subtypes and midbrain dopaminergic neurons[71]. Notable implicated genes include *FOXP1* and *FOXP2*, in which rare variants are linked to speech disorders and intellectual disability, and *SORCS3*, *PTPRF* and *MEF2C*, which are involved in the formation of synaptic connections and encode integral components of the postsynaptic density membrane, implicating synaptic development and density in the pathology of ADHD.

Studies of rare genetic variants also found an increased burden of rare protein-truncating variants in evolutionarily constrained genes in ADHD[71,85], and showed replicated associations with several copy number variants (CNVs), many of which are also implicated in autism spectrum disorder and schizophrenia[86–88] (Box 1).

Studies of common and rare variants (Fig. 3) converge on the conclusion that many ADHD risk loci implicate neurodevelopmental processes, which is consistent with the idea of a link between ADHD and alterations in brain development, structure and function. However, a major limitation is that the majority of genetic studies of ADHD are largely based on samples of European ancestry[60,71].

Progress in understanding the genetic basis of ADHD has generated hope that these findings may be used for patient stratification and prediction of disease and treatment outcomes. However, the current polygenic score for ADHD is not sufficiently precise for use in diagnosis[75]. Likewise, polygenic scores or single genetic variants are not useful for choosing medications, despite some data showing significant effects of genetic variants on the pharmacokinetics and pharmacodynamics of medications used to treat ADHD[89,90].

Environmental correlates

Because genetic variation is fixed before the onset of ADHD, its effects are not confounded by third variables. By contrast, in most cases, environmental causes of ADHD are more difficult to measure and their associations with ADHD may reflect an unmeasured third variable. Although there is strong evidence that rare events (for example, traumatic brain injury[91,92] and extreme emotional and nutritional deprivation early in life[93]) can cause ADHD, many other environmental events are associated with ADHD[94]. Most are events or complications occurring during pregnancy, delivery or early after birth (for example, low birthweight, perinatal hypoxia and advanced paternal age), although all have low risk ratios for ADHD. Low risk ratios are difficult to interpret because low levels of risk could be due to confounding[95,96].

Socioeconomic status (SES) is a good example of the difficulties interpreting environmental correlates of ADHD. Children in families of low SES are twice as likely to have ADHD than their peers in families of high SES[97], and people with ADHD can have low educational and occupational under-attainment[4]. Studies have evaluated whether low SES causes ADHD or whether ADHD causes families to have a lower SES, and have found support for both mechanisms[98], although twin studies suggest that the environmental correlates of ADHD are mostly individual-specific rather than, like SES, shared within families[60,99]. Moreover, SES and ADHD each have a partly genetic basis and are genetically correlated with each another[71,100], such that parents from low SES households impart a higher-than-average genetic risk of ADHD

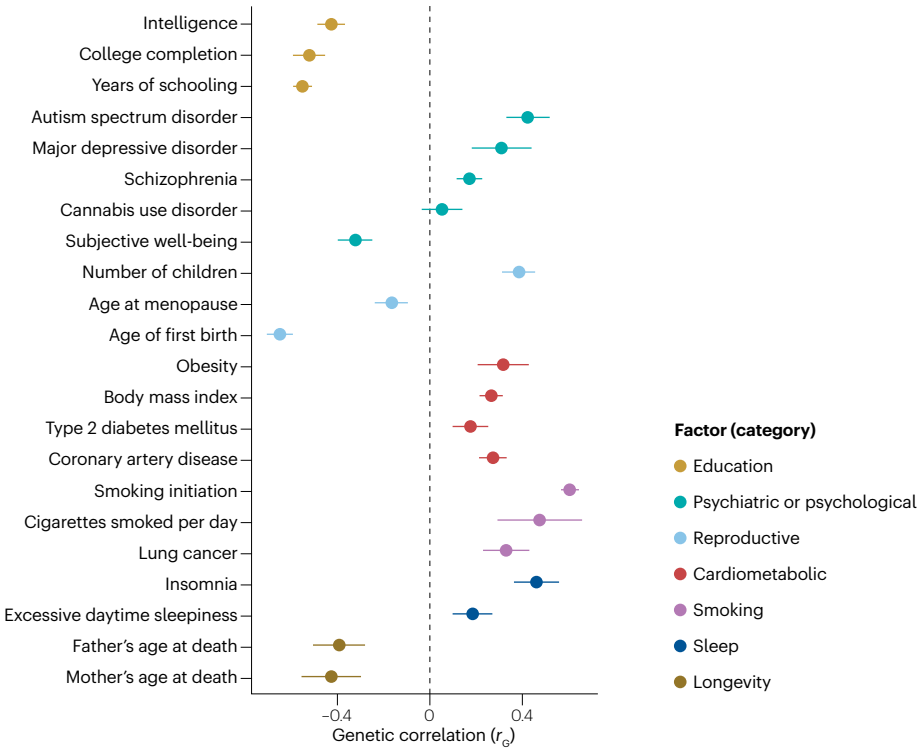

Fig. 2 | Genetic correlations of disorders and traits with ADHD. Genetic correlations show pronounced genetic overlap of attention-deficit/hyperactivity disorder (ADHD) with traits in the educational, psychiatric or psychological, reproductive, cardiometabolic, smoking-related, sleep-related and (parental) longevity domains. The horizontal bars indicate 95% confidence intervals. Data from ref. 71.

to their offspring. GWAS suggest that the SES–ADHD association is due to both direct genetic parent-to-offspring transmission and the effects of a low SES environment on the mental health of offspring[101,102].

Other studies have linked the polygenic liability for ADHD to negative health behaviours and psychosocial impairment[75–77,103–106]. Thus, some environmental correlates of ADHD may, in part, reflect the genetic risk for ADHD. When studies have adjusted for familial confounders, which include genetics, some apparent environmental correlates have attenuated or disappeared[107,108]. A good example of this effect is maternal smoking during pregnancy. Many epidemiological studies and meta-analyses of these studies[109–111] have concluded that maternal smoking during pregnancy is associated with ADHD. However, a meta-analysis of sibling-control studies found no association between ADHD and maternal smoking[112]. This meta-analysis also found that the mother's polygenic risk for ADHD significantly predicted whether she smoked during pregnancy. These data confirmed the findings of another study[113] showing that maternal smoking during pregnancy does not predict ADHD in offspring if the oocyte leading to pregnancy was donated.

Very little is known about which factors promote resilience in those susceptible to ADHD, although social, intellectual and emotional 'scaffolding' have been suggested to delay the onset of the disorder[114]. Scaffolding occurs when a compensating resource prevents the emergence of symptoms. Implicated mechanisms are social acceptance, positive parenting and self-perceptions of competence[115].

Electrophysiology and brain imaging

ADHD has a multifactorial aetiology and is clinically heterogeneous, suggesting that multiple pathophysiological pathways are involved in the development of this disorder (Fig. 4). Neurophysiology and neuroimaging studies have provided some clues to the pathophysiology.

Electrophysiology studies found a higher theta to beta ratio (which is related to inattention) and differences in event-related potentials (ERPs) of higher-order cognitive processing stages in people with ADHD compared with those without ADHD[116,117]. However, these findings are substantially heterogeneous, with only evidence of the theta to beta ratio in those with high levels of both inattentive and hyperactive–impulsive symptoms, and larger effect sizes for ERP differences in younger and non-medicated individuals with ADHD[118].

In terms of structural brain alterations, MRI mega-analyses have found small to moderate structural brain differences in children but not adolescents or adults with ADHD compared with controls. Affected regions include a smaller total cortical surface area in late developing cortical association areas important for executive functions (such as the frontal, cingulate, parietal and temporal regions) and reductions in cortical thickness in areas important for emotion processing (such as the fusiform gyrus and temporal pole)[119]. In addition, studies have demonstrated smaller intracranial, basal ganglia and limbic volumes[120]. Moreover, the smaller cortical surface area and ventromedial orbitofrontal cortical thickness have also been shown to be associated with ADHD traits in population studies[121] and have been observed in siblings of people with ADHD[119], suggesting that they may reflect an underlying genetic vulnerability to ADHD[122–124]. Analyses of white matter tracts have most consistently shown smaller fractional anisotropy in tracts mediating visual attention, including the posterior corpus callosum connecting temporo-parieto-occipital regions and the sagittal striatum, which also connects to subcortical regions[119,125]. The most recent mega-analysis included five cohorts with almost 7,000 participants, and found reduced fractional anisotropy in inferior longitudinal and left uncinate fasciculi[126].

The most replicated finding in meta-analyses of functional MRI (fMRI) studies of cognitive control in ADHD, is under-activation of the

inferior frontal cortex (IFC) and the insula in people with ADHD relative to controls[127–130]. Meta-analyses have also shown under-activation in the right or bilateral dorsolateral prefrontal cortex (DLPFC) during attention and working memory tasks, respectively[127,131]. Regarding functional connectivity, attentional lapses in ADHD have been suggested to be due to inappropriate interference of the default mode network (DMN), that is involved in self-referential thoughts and mind-wandering, in the activity of networks involved in attention and cognitive control[132]. Two meta-analyses have provided evidence supporting this DMN interference hypothesis. These meta-analyses included resting-state fMRI studies restricted to a priori-specified brain regions[133,134], and found dysfunctional intrinsic connectivity involving the DMN and attention and cognitive control networks. Moreover, a large mega-analysis including 1,301 subjects with ADHD and 1,301 controls found decreased anticorrelation between the DMN and dorsal and ventral attention and somatoform networks[135]. However, a whole-brain meta-analysis[136] using a different analytical approach did not find any convergence across studies on multiple intrinsic connectivity metrics.

Longitudinal MRI studies provide evidence of a maturational delay in children with ADHD, finding a delay in cortical thickness and surface area development, especially in frontal and temporal regions, and in cerebellar white matter[137–139]. Other studies have found a delay in functional brain maturation in resting-state DMN, and cognitive control and ventral attention networks and in the anti-correlation between the DMN and these networks[140], with reduced connectivity with the right inferior prefrontal cortex associated with worse inattention later in life[141]. Collectively, these findings support the view that ADHD is due to immature brain structure and atypical functional development.

Many of the brain regions and network patterns of activity implicated by imaging studies are modulated by dopamine and noradrenaline, which are also the neurotransmitters that are affected by

Box 1

Selected genes implicated in ADHD

Genes identified through GWAS

PTPRF

PTPRF has, along with other attention-deficit/hyperactivity disorder (ADHD)-associated genes (*MEF2C*, *FOXP2* and CHRNA7), been suggested to contribute to ADHD pathology via its role in synaptogenesis, with a reduced synaptic density potentially linked to the reported smaller cortical volumes in individuals with ADHD[293]. *PTPRF* has also been associated with schizophrenia, autism spectrum disorder (ASD), educational attainment and smoking phenotypes in genome-wide association studies (GWAS).

FOXP1 and FOXP2

FOXP1 and *FOXP2* regulate synapse formation and neural mechanisms mediating speech, learning and cognition. Highly penetrant rare variants in these genes have been implicated in speech disorders and intellectual disability[294]. Common variants in *FOXP1* and *FOXP2* have also been associated with ASD, educational attainment, and cortical measures in GWAS.

MEF2C

MEF2C was mapped to one of the most strongly associated loci in the GWAS of ADHD[71]. *MEF2C* regulates neuronal proliferation, differentiation, survival and synapse development. *MEF2C* is highly expressed in developing cortical excitatory neurons[71] and mutations in *MEF2C* may lead to imbalances in excitatory and inhibitory synaptic transmission, which may contribute to risk of several psychiatric disorders, including ADHD, ASD, intellectual disorder and schizophrenia[295]. Prior GWAS have associated *MEF2C* with schizophrenia, educational attainment, intelligence quotient and BMI.

SORCS3

SORCS3 has been linked to attention-deficit/hyperactivity disorder (ADHD) both via common variants in GWAS[71] and in whole-exome-sequencing analyses showing enrichment of rare protein-truncating variants[71]. Rare copy number variants (CNVs) overlapping the *SORCS3* region have also been associated with ADHD[296]. *SORCS3* regulates functions important for neuronal development and migration, as well as synapse formation and plasticity. Common variants in *SORCS3* have been associated with several major psychiatric disorders in cross-disorder GWAS[297].

DUSP6

DUSP6 regulates mitogen-activated protein kinases, which are involved in embryogenesis, cellular proliferation and differentiation. *DUSP6* is thought to alter neurotransmitter homeostasis by affecting dopamine levels in synapses, which is likley to be of biological relevance to ADHD. *DUSP6* has also been associated with BMI, educational attainment, insomnia and smoking initiation in GWAS.

Genes identified through CNV analyses

CNV associations

CNVs in the 1q21.1, 6q26, 15q11–13, 16p11.2, 17q12 and 22q11.21 regions show well-replicated associations with ADHD. Most have also been implicated in ASD, schizophrenia and intellectual disabilities, or genetic syndromes[86–88]. Some CNVs implicate genes with potentially relevant biological function for ADHD. For example, *POLR3C* and *PRKN* are involved in dopamine regulation[86]; CNVs in the 15q11–13 region implicate genes involved in nicotinic signalling (for example, *CHRNA7*, which may be linked to ADHD through modulation of dopaminergic neurons).

Note: Box 1 highlights some genes associated with ADHD with biological functions of potential relevance to ADHD. We include genes associated via GWAS, which aim to identify common genetic variants or via studies of rare (prevalence <1%) CNVs, which are large structural deletions or duplications of DNA with a large impact on gene functioning. ADHD GWAS associations are from Demontis et al.[71]. CNV associations were identified in at least four independent samples and prioritized by bioinformatics[86] and/or replicated across the two largest CNV studies to date[87,88]. Gene function descriptions are based on information from Gene (National Center for Biotechnology Information) and prior GWAS associations with ADHD-related phenotypes on information from the GWAS Catalog.

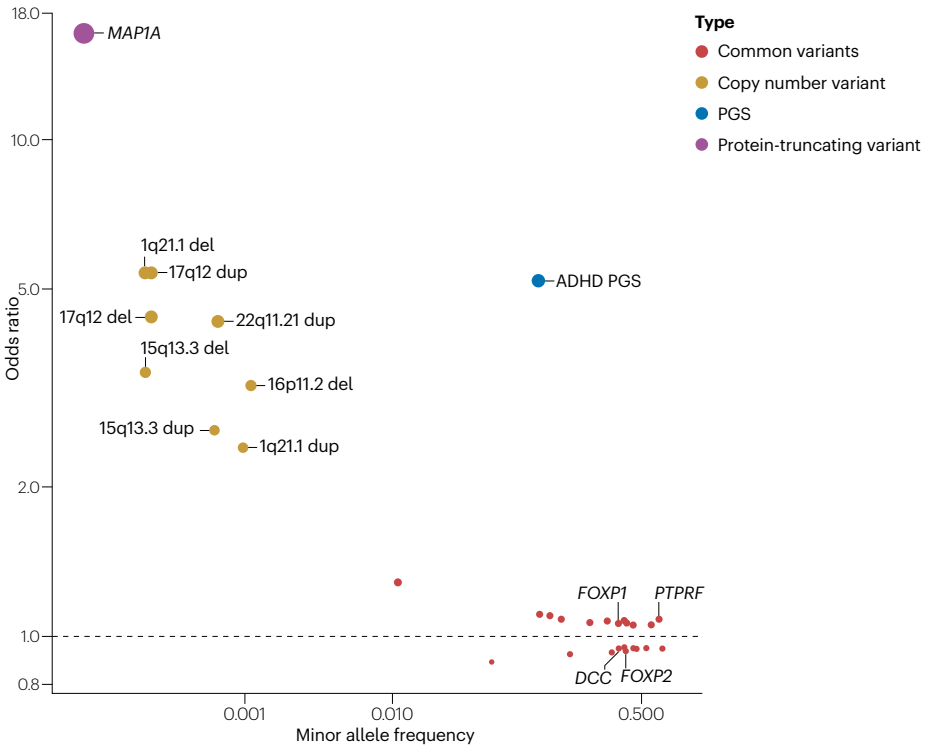

Fig. 3 | Genetic architecture of ADHD. Odds ratio and frequencies of attention-deficit/hyperactivity disorder (ADHD)-associated variants from the largest (to date) genome-wide association study (GWAS)[71], whole-exome sequencing (WES) study[85] and copy number variant (CNV) study of ADHD[88]. GWAS linked 27 genomic loci with ADHD, with each variant conferring a small increase in risk of the disorder[71]. Summing common risk variants for ADHD into a polygenic score (PGS) shows that individuals with a score in the highest decile have a roughly fivefold increased risk of ADHD, compared to individuals with a score in the lowest decile[291]. WES of ADHD are still too small to determine robust associations; however, *MAP1A* was identified as a possible risk gene for both ADHD and autism spectrum disorder in the largest WES of ADHD to date[85]. Several CNVs have shown replicated associations with ADHD, implicating various genes involved in glutamatergic neurotransmission, *PRKN*, and the 15q11–15q13 region, which contains genes involved in neuronal and nicotinic signalling pathways[61,86,292]. CNV associations shown in the figure come from the largest single-site CNV study carried out, which focused only on CNVs previously implicated in neuropsychiatric disorders[88]. Of note, odds ratios for common variants are plotted against the minor allele frequency in the European population, whereas odds ratios for protein-truncating variants and CNVs are plotted against the in-sample frequency (the proportion of carriers among controls) due to the uncertainty of the frequency in the general population for such rare variants[88]. Odds ratios for common single-nucleotide polymorphisms show the effect of the reference allele as reported by Demontis et al.[71], which for all but five associated variants was the major allele. Odds ratios <1 do not necessarily indicate a protective effect, but rather show a risk decrease associated with the reference allele of the top associated single-nucleotide polymorphism of the locus after covariate adjustment in the GWAS. Data from refs. 71,85,88.

medications for ADHD[142,143]. Whether stimulants affect brain structure and function is not fully known owing to a lack of prospective longitudinal imaging studies. The few prospective studies that have been carried out showed that methylphenidate normalizes left putamen volume loss in adults with ADHD[144], and is associated with less cortical thinning in the right medial frontal cortex[145], and with a more rapid increase in white matter integrity in several left hemispheric association tracts and the lateral corpus callosum in children, but not adults, with ADHD[146]. However, other studies testing the effects of cumulative exposure to stimulants found no effects on brain volumes[147], cortical thickness[148,149] or surface area[149], but did find an association with reduced volumes in two subregions of the hippocampus[149]. Meta-regression analyses, however, showed that long-term medication use is not associated with ADHD-related brain structural differences[119,120,128]. Other meta-analyses and meta-regressions of fMRI studies found that stimulants are associated with improved function in the IFC and insula during cognitive tasks[128,129,150].

Diagnosis and screening

Clinicians should follow the latest DSM (DSM-5-TR) or ICD (ICD-11) criteria for the diagnosis of ADHD[2,3]. DSM-5 requires at least six impairing symptoms of inattention or hyperactivity–impulsivity in children (five impairing symptoms for diagnosis in those aged 17 years or older), which occur across multiple settings (for example at home, the workplace and school). Some impairing symptoms must be present for 6 months and have an onset before the age of 12 years. Initial diagnosis of ADHD in adults is possible if some impairing symptoms emerged before the age of 12 years. For diagnosis in both adults and children, symptoms must cause clinically meaningful impairment and not be better explained by another condition[2]. Symptoms must also be more severe than expected given the child's developmental level. Although not part of the core symptoms, deficient emotional self-regulation is common in ADHD and causes clinically meaningful impairments[151].

The requirement that symptoms cannot be better explained by another condition is meant to rule out cases where the symptoms

of ADHD covary with symptoms of another disorder (for example, if the ADHD symptoms only occur during episodes of depression). However, because comorbidity with other psychiatric disorders is common in individuals with ADHD, making two or more diagnoses is routine. Indeed, assessing patients with ADHD for comorbid disorders is essential during diagnostic work-up. Broadband rating scales (see below)

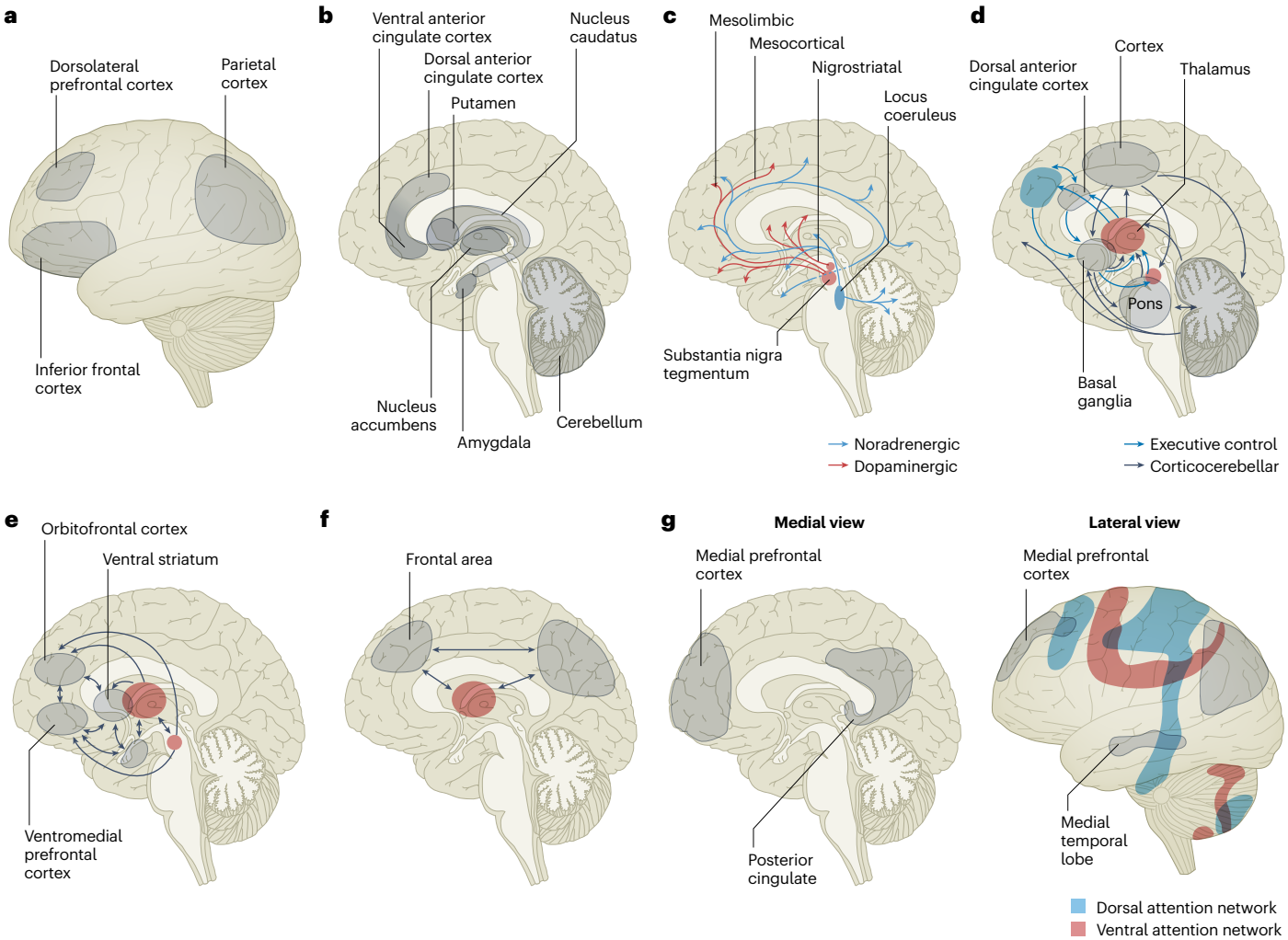

Fig. 4 | Neurobiological pathways involved in ADHD. a, Several cortical regions (lateral view) of the brain are particularly implicated in attention-deficit/hyperactivity disorder (ADHD). The dorsolateral prefrontal cortex is responsible for many executive functions including processing speed, working memory, (motor) planning, temporal foresight, selective attention and switching; the inferior frontal cortex is important for inhibition, timing and sustained attention, and the parietal cortex for attention and cognitive flexibility. **b**, ADHD also involves subcortical structures of the brain. The ventral and the dorsal anterior cingulate cortex mediate the affective and cognitive components of executive control, respectively. Together with the frontal lobes, the basal ganglia (that is, the nucleus accumbens, caudate nucleus and putamen) and the thalamus, they form the frontostriatal circuits. Frontocerebellar circuits have also been implicated in ADHD, in particular in the context of timing and motor control. Other subcortical regions involved are the amygdala and hippocampus, which mediate emotion and reward processing. **c**, Several neurotransmitter circuits are also involved in ADHD. The dopaminergic system plays an important part in the regulation of movement, mood regulation, attention, learning and memory, novelty and reward processing. The noradrenergic system is important for attention and arousal, signal-to-noise processing, mood regulation and stress response. Both neurotransmitters interact but also have independent effects. **d**, Networks that mediate executive functions are implicated in ADHD. The executive control and corticocerebellar networks mediate executive functions including planning, goal-directed behaviour, attention, inhibition, working memory, timing and cognitive flexibility. These networks are under-activated and have reduced functional inter-regional connectivity in people with ADHD compared with people without ADHD. **e**, Neuroimaging has also implicated the reward system in ADHD. The ventromedial prefrontal cortex, orbitofrontal cortex and ventral striatum together with the thalamus, amygdala and the cell bodies of dopaminergic neurons in the substantia nigra all form part of the reward processing network. **f**, The frontal and parietal cortical areas and the thalamus form part of the alerting network (indicated by the arrows), which supports arousal and attention, and is under-activated in individuals with ADHD compared with those without ADHD. **g**, There is evidence for abnormally enhanced activation and reduced development in ADHD in the default-mode network (DMN), which has been associated with mind-wandering. The DMN comprises the medial prefrontal and the posterior cingulate cortices (medial view) as well as the inferior parietal and medial temporal regions (lateral view). There is evidence for a reduced anti-correlation between the DMN and task-positive dorsal and ventral attention networks in people with ADHD compared with controls. Adapted from ref. 1, Springer Nature Limited.

are useful to identify patients who would benefit from a clinician interview to assess psychiatric comorbidity. Administering these rating scales on a yearly basis can discover emerging problems.

Of note, diagnostic criteria for ADHD in ICD-11 differ slightly from those in DSM-5-TR, as ICD-11 omits numbered symptom lists and instead requires several meaningful symptoms from one of three clusters (inattention, hyperactivity and impulsivity). Criteria in ICD-11 also consider intellectual functioning and environmental demands when judging whether symptoms and impairment are outside normal limits[3]. Both systems highlight that symptoms may be less evident when the individual is engaged in activities that provide intense stimulation or frequent rewards.

Diagnosis of ADHD must be based on an interview of the parent and/or patient. No biological measure of ADHD shows sufficient sensitivity and specificity to serve as a standalone diagnostic test[90,152]. When used alongside a clinical assessment, some tests can streamline the assessment process and shorten the time to diagnosis[153,154]. Measures of neurocognitive functioning can assist with treatment planning and assist measurement-based care[155]. Symptom checklists are useful for screening but lead to many false-positive diagnoses when used alone[156] because they do not assess impairment, age at onset and pervasiveness[156,157]. Accordingly, these checklists should never be used as standalone tools for diagnosis of ADHD[158].

Assessment of children and adolescents

Parent-administered structured or semi-structured interviews are cornerstone diagnostic tools for ADHD[159]. These interviews determine symptom and impairment severity with questions about the settings in which symptoms occur, onset, duration, and any periods of remission, as well as comorbid disorders that may mimic ADHD. Broadband psychopathology and narrowband ADHD symptom or impairment scales supplement, but do not replace interviews[158]. These scales are quick and cost-effective, and permit gathering data from teachers and other care-givers. They are useful for assessing treatment response and fluctuations over time. Narrowband scales assess the severity of ADHD, whereas broadband scales provide valuable information about the presence and severity of comorbidity and signal which additional assessments might be fruitful. A comprehensive list of free ADHD assessment tools is provided in Supplementary Box 1. Several rating scales are also available for a fee; these scales cover the same symptom domains but have the added value of normative data.

Assessment modifications for children who have not yet entered elementary school include structured behavioural observations (clinic-based or classroom-based) and more emphasis on teacher ratings than ratings from other individuals. Other individuals may struggle to perceive inattentive symptoms or differentiate normative and non-normative hyperactivity or impulsivity in pre-elementary school children[1], whereas preschool teachers and clinicians are typically better than parents at differentiating normative versus non-normative behaviours owing to their interaction with many young children.

Modifications for adolescents include using self-reports, which promotes rapport and improves the detection of symptoms and impairments unknown to their parents. Speaking with the affected individual often yields information about the individual's self-awareness and motivation for treatment. However, as adolescents with ADHD often struggle with self-awareness, parent and teacher reports remain central to diagnosis[160]. Obtaining a report from every secondary school teacher is not necessary and, if feasible, the class where the student struggles most is a useful starting point for assessment. Clinicians can also obtain additional teacher ratings to better understand variability in the adolescent's symptoms across settings[161]. Comorbidities such as depression, anxiety and substance use commonly first appear during adolescence, necessitating thorough screening and assessment[162].

Assessment of adults

Because adults with persistent childhood ADHD tend to not recognize their past and current symptoms of ADHD[163,164], they are more likely to seek help for a new-onset disorder that commonly co-occurs with ADHD such as substance use, mood, anxiety, sleep or co-occurring somatic disorders. Screening patients with these disorders for ADHD is useful, particularly in those not responding to standard therapies for the comorbid condition. Treating ADHD in these patients often improves management of the comorbidity[165,166]. Some rating scales are available for screening for ADHD in adults (see Supplementary Box 1). The sensitivity of diagnosing ADHD in adults is improved when spouses, parents or close friends supply information[29].

Although some studies have suggested that the onset of ADHD in adulthood is common, limitations of these studies[114] and subsequent research[157] indicate that, although ADHD is often first identified late in life, its onset is mostly in childhood or adolescence. As mentioned above, the onset of ADHD often precedes its identification by many years[29,167]. Many patients with ADHD detected in adulthood were protected from an earlier onset of ADHD by high intelligence, supportive parents or other protective scaffolding[168]. Although DSM and ICD criteria permit diagnosis of apparent adult-onset ADHD, it should be made cautiously[169].

When a patient's status supports a clear diagnosis of ADHD but onset prior to the age 12 years cannot be documented, alternative explanations should be considered, such as emergent health conditions or normal cognitive or behavioural fluctuations (for example, stress-related strains on cognition, effects of ageing or menopause). Of note, some patients, especially young adults, will fake ADHD symptoms in the hope of acquiring a stimulant prescription for diversion or abuse[170]. Individuals with a history of substance abuse or antisocial behaviour are at greatest risk. Online health misinformation about ADHD is increasing[171], and some adults may confuse ADHD with another disorder or misinterpret normal cognitive fluctuations. The misinformation circulated via social media worsens this problem[171]. Accordingly, clinicians might consider asking adults who self-refer to share how they came to believe they have ADHD. Documenting that symptoms of ADHD cause impairment is even more essential when ADHD is first diagnosed in adulthood, keeping in mind that impairment should be gauged in comparison with potential (for example, as measured by intelligence quotient (IQ))[172].

Diagnostic challenges

Supplementary Table 1 lists common diagnostic challenges and recommendations for ADHD. After standard information gathering, tailored assessment must refine details of the presentation, particularly in complex cases (for example, individuals with multiple comorbidities, mitigating psychosocial factors such as supportive family members or low academic demands that may mask impairment). Assessing simplex ADHD is relatively straightforward and efficient, whereas complex cases require careful attention because mental comorbidity is common, and some symptoms of ADHD are present in other disorders. Referral to a clinician specializing in ADHD may be called for to ensure proper assessment of a complex case.

Management

Pharmacological treatments

In most clinical guidelines (for example, those of the National Institute for Health and Care Excellence (NICE))[173] pharmacotherapy is considered the first-line treatment for ADHD (after implementation of environmental modifications), although the American Academy of Pediatrics[174] recommends using pharmacotherapy in combination with behavioural therapy. Behavioural therapy could be tried first in preschool children, but medication[175] may be needed if behavioural therapy is unsuccessful or in those with severe ADHD[176] (Fig. 5).

Medications approved for use in ADHD by the FDA and other regulatory agencies are stimulants (methylphenidate and amphetamine formulations) and non-stimulants. Non-stimulants comprise noradrenaline reuptake inhibitors (atomoxetine, viloxazine extended release (ER)) and α_2-adrenergic agonists (clonidine ER and guanfacine ER) (Table 1). Some medications in each stimulant class are approved for use in both children and adults. Atomoxetine and viloxazine ER are approved for use in children and adults. Clonidine ER and guanfacine ER are approved in the USA for use in children only, even though studies support the efficacy of guanfacine ER in adults[177,178]. Randomized controlled trials (RCTs) have demonstrated the efficacy of these medications in reducing symptoms of ADHD[143,179,180]. Outside North America, methylphenidate is often the only licensed stimulant medication for the treatment of ADHD.

Clinical guidelines recommend stimulants as the first-choice medication for ADHD owing to their high efficacy. The NICE guidelines specify that methylphenidate should be tried first in youths, followed by lisdexamfetamine or other amphetamines, and then non-stimulants[173]. Amphetamines or methylphenidate can be considered as first-line in adults, followed by non-stimulants[173]. These recommendations are consistent with results from a network meta-analysis[179] of RCTs of ADHD medications. Other guidelines[159] do not prioritize between methylphenidate and amphetamine, which are both highly effective in youths. Importantly, clinical recommendations and meta-analyses refer to the group level; at the individual level, many patients respond equally well to methylphenidate and to amphetamines, whereas others have a more selective response or tolerability to one of the two stimulant classes.

Some patients have an excellent response to non-stimulant monotherapy[143], whereas others are optimally treated with combinations of stimulants and non-stimulants, or combinations of longer-acting and shorter-acting stimulants. Managing the duration of response to the different medications is often a focus of clinical treatment. Response to medication should be assessed in relation to the pharmacokinetics and duration of action of the selected formulation. Symptoms and level of function are best addressed when the blood levels are adequate relative to the time of greatest need and the specific tasks to be addressed. However, there is significant individual variability in pharmacokinetic characteristics and duration of action of specific formulations. The duration of action of non-stimulants may be longer than that of stimulants because the long-acting α_2 agonists and selective noradrenaline reuptake inhibitors have long half-lives[181,182]. The α_2 agonists can be dosed once daily; atomoxetine has a relatively short half-life in the large majority of patients and is approved for both once-daily and twice-daily administration. Moreover, although clinical guidelines recommend starting pharmacological therapy with stimulants, starting with a non-stimulant could be considered in some patients, including those with comorbid anxiety, tics, sleep problems, mood dysregulation or substance abuse. However, of note, none of these conditions are exclusionary for the use of stimulants, and data indicate that stimulants can be used effectively in the presence of these comorbid conditions[166].

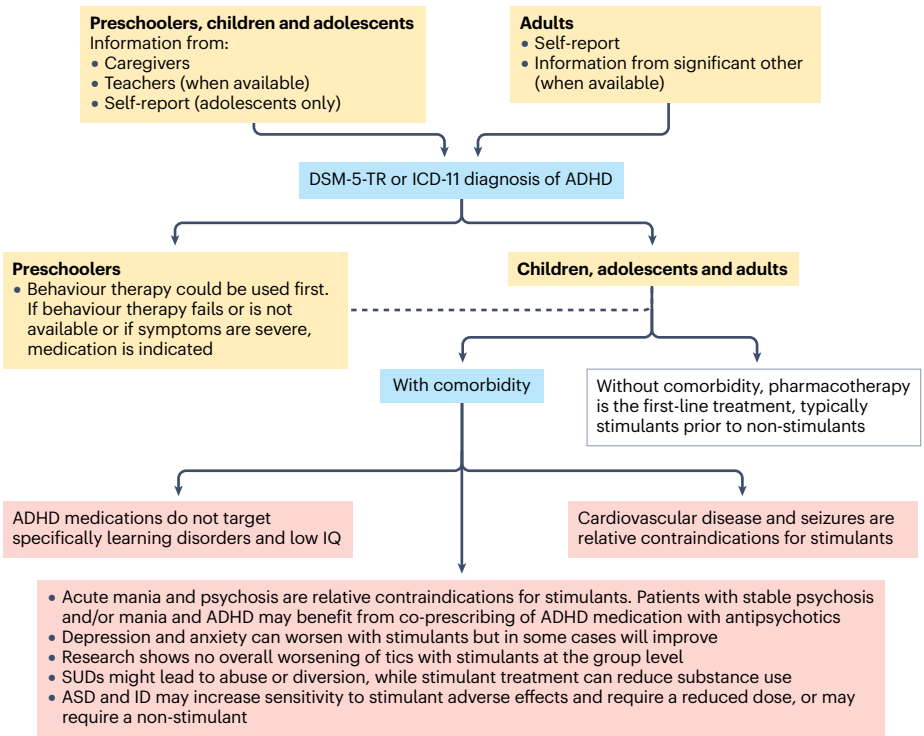

Fig. 5 | Diagnosis guides treatment. The management of attention-deficit/hyperactivity disorder (ADHD) takes into account the patient's age and psychiatric, psychological, and medical comorbidities. The patient's history of other conditions and a variety of other clinical and contextual factors may determine whether a stimulant or non-stimulant is selected. ASD, autism spectrum disorder; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; ICD-11, International Statistical Classification of Diseases and Related Health Problems, 11th edition; ID, intellectual disability; IQ, intelligence quotient; SUD, substance use disorder. Adapted from ref. 1, Springer Nature Limited.

Table 1 | Medications approved by the FDA for the treatment of ADHD

Preparation	Duration of response (h)
Amphetamines[a]	
Mixed amphetamine salts	4–6
Racemic amphetamine sulfate	4–6
D-amphetamine sulfate	4–6
Racemic amphetamine sulfate oral disintegrating tablets	10
D-amphetamine transdermal system	Depends on wear time (max 9)
Mixed amphetamine salts extended-release	12
Amphetamine extended-release (oral suspension or oral disintegrating tablets)	12
Lisdexamfetamine (prodrug)	13
Extended-release oral suspension and chewable tablet	13
Tripled bead mixed amphetamine salts extended-release	16
Methamphetamine	Not reported
D-amphetamine sulfate extended-release	Not reported
Methylphenidate[a]	
Methylphenidate immediate release tablet, chewable tablet, or solution	4
D-Methylphenidate	6–7
Methylphenidate controlled delivery	7.5–12
Methylphenidate long-acting	8
Methylphenidate extended-release chewable tablets, tablet, capsule	8
Methylphenidate delayed-release and extended-release	11
Methylphenidate osmotic-release oral system	12
D-Methylphenidate extended-release	12
Methylphenidate extended-release oral disintegrating tablets	12
Methylphenidate multilayer release	12
Methylphenidate extended-release oral suspension	12
Serdexmethylphenidate/dexmethylphenidate	12
Methylphenidate multilayer release extended release	16
Methylphenidate transdermal system	Depends on wear time (max 9)
Selective noradrenaline reuptake inhibitors[b]	
Atomoxetine	Not specified[c]
Viloxazine extended-release	Not specified[c]
α_2 Agonists[b]	
Clonidine extended-release (approved for use only in children and adolescents)[d,e]	Not specified[c]
Guanfacine extended-release (approved for use only in children and adolescents)[e]	Not specified[c]

ADHD, attention-deficit/hyperactivity disorder. [a]Stimulants. [b]Non-stimulants. [c]May be considered particularly in individuals with comorbid anxiety or tics, even though in some cases stimulants may be more effective and equally well tolerated. [d]Due to sedative effects, may be considered in individuals with sleep onset delay. [e]May be effective in decreasing temper outbursts.

No clinical or biological predictors of response are available for ADHD[183]. Finding the optimal medication relies on educated trial-and-error. Identifying the optimal dose of stimulants may require several weeks, with weekly titration. The full effects of atomoxetine and viloxazine may not be evident before 6–8 weeks of use, but good responders show substantial improvement after 2–4 weeks[184–186]. Titration to the maximum tolerated dose is often recommended to maximize treatment efficacy.

Managing stimulant-refractory ADHD requires an assessment of the reasons underlying non-response (Box 2). Although several guidelines recommend using doses beyond the maximum approved doses, such doses should be considered in selected cases only (for example, individuals who have a partial response to and tolerate the maximum dose). Before titrating stimulants above the upper recommended dose threshold, clinicians could consider switching to the other stimulant class, which may make it possible to use a dose within guidelines. However, our understanding of the best maximum dose, and of the relationship between dose and blood level, brain level or drug metabolism is limited.

The most common adverse events are appetite reduction, delayed sleep onset (stimulants) and other sleep issues (non-stimulants), although patients can also experience improvement in sleep owing to decreased hyperactivity in the evening. Insomnia generally can be managed and does not require stopping an effective ADHD treatment. Headaches and stomach aches are also common adverse effects. Some individuals experience dysphoria and irritability, though irritability often improves with treatment. Moreover, when initiating treatment, a slight increase in heart rate and blood pressure is common, although it is not clinically significant in most patients. With long-term treatment at higher doses, there is a small but significant risk of hypertension and arterial disease in adults[187], but more studies are needed[188]. Data from meta-analyses suggest that, at the group level, stimulants are not significantly associated with the onset or worsening of tics[189]; however, this may not be the case in some individuals.

There are no guidelines as to how long a treatment should be continued and how or when it should be stopped in individuals with ADHD. Although discontinuation trials support the persistence of beneficial effects beyond the first 2 years of treatment, reassessing the effectiveness of treatment at least once each year is recommended[190]. Whether it is possible or even desirable to pause stimulant use at weekends is debated[173]. Against this recommendation is that ADHD occurs in multiple settings (not just in school) and causes impairments in family and social function that can equally occur on weekends and on weekdays. Moreover, some academic activity is often required on weekends. In favour of pausing stimulants on weekends is that, in some patients, academic function is the primary focus of treatment, and tolerability may be an issue. Frequently occurring adverse events that may necessitate weekend pauses in treatment are decreased appetite and sleep problems. Others advise medication-free weekends and/or pauses in treatment at various times during the year to address concerns about growth delays, which are typically small and reversible[191,192].

No specific guidelines are available on the use of ADHD medications in pregnant or breastfeeding women. Accordingly, the choice of continuing treatment in this population should be discussed on a case-by-case basis. However, of note, there is no evidence suggesting that the use of ADHD medication during pregnancy results in significant adverse consequences for mother or offspring[193,194].

Non-pharmacological treatments

Management of patients with ADHD should be comprehensive and holistic, including psychoeducation for the patient and the patient's family. Treatment should consider the severity of ADHD, comorbid conditions, resources and environmental factors. Non-pharmacological treatments address symptoms of ADHD that do not respond to medication and other impairments (for example, defiance, disruptive behaviour and low self-esteem)[195,196]. They are also used in those with contraindications or preferences against medication (Fig. 6). However, non-pharmacological treatments are usually not first-line for ADHD due to their lower efficacy compared with stimulants (Fig. 7). In some patients, assessment of neurocognitive functions may detect cognitive strengths and weaknesses that are helpful for planning educational or vocational strategies.

Psychosocial interventions in children and adolescents. Behavioural therapy and cognitive–behavioural therapy (CBT) delivered in clinics or schools are the primary psychosocial treatments for children with ADHD. These therapies are typically multicomponent, engage parents and modify behaviours based on social learning principles and cognitive–behavioural strategies (organization skills, problem solving, metacognitive strategies and social skills)[197]. These therapies seek to temper the effect of ADHD on the individual's daily life by modifying environmental factors (for example, parenting and educational context) and psychological factors (for example, psychological beliefs and coping mechanisms). Young children may not be direct recipients of treatment; however, behavioural therapy collaboratively engages adolescents and parents, incorporating engagement strategies such as motivational interviewing[198,199]. Motivational interviewing provides clinicians with a toolbox of technical and relational communication strategies that increase the patient's interest in behavioural change.

An individual participant mega-analysis showed small to medium sized improvements in ADHD symptoms with behavioural therapies, with manipulation of antecedents of behaviour and reinforcement techniques being effective components[200,201]. Furthermore, dozens of well-designed RCTs have established the substantial efficacy of behavioural therapy in reducing disruptive behaviours and improving the impairments in children, and improving parenting skills of their parents[197]. Compared with medication, behavioural therapy puts higher demands on parents, patients and clinicians. Moreover, behavioural therapy takes longer to show initial efficacy than pharmacological therapy, because many weeks of therapy are needed. Behavioural therapy is well-liked by patients and consistently shows maintenance effects for months and sometimes years after treatment, particularly in adolescents[197]. However, behavioural therapy may not be appropriate in those who require immediate symptom relief or if no adult is positioned to consistently participate in the treatment. The effects of behavioural therapy on comorbidity show mixed results with both positive and null effects reported for externalizing comorbidities, internalizing comorbidities and emotional dysregulation. The effect on comorbidities probably depends on the specific focus of the behavioural therapy and the underlying comorbidity[197].

Psychosocial interventions in adults. In adults with ADHD, CBT in individual or group settings as well as skills training have the greatest evidence for efficacy[202]. CBT aims to change dysfunctional thoughts and behaviours[203,204]. Skills training addresses problem solving, distraction delay techniques, time management, behavioural control instructions, emotion regulation, mindfulness and social communication.

Box 2

Management of stimulant-refractory ADHD[298]

Prior to changing to non-stimulants or adding medications consider the following:

- Has the dose been titrated correctly to the maximum tolerated dose?
- Should the dose or preparation be changed for a more balanced effect?
- Are the right symptoms and time of day being targeted?
- Has the patient become tolerant to the medication?
- Does the patient have any life circumstances contributing to the poor response?
- Have any comorbidities been missed?
- Is the diagnosis correct?

Use of second-line medications (atomoxetine, guanfacine extended-release (ER), clonidine ER, viloxazine ER).

Augmenting agents (combine stimulants with other immediate release or ER stimulants, guanfacine ER or clonidine ER).

Use of other agents (off-label) under specialist advice and/or supervision.

The available evidence is most robust for CBT[195]; other psychosocial interventions have insufficient evidence for a clear recommendation for their use in adults[205]. Data from RCTs show that combined treatment with medication and CBT is superior to medication alone for ADHD symptoms[206]. CBT alone also improves anxiety, depression, self-esteem[207] and emotional regulation[208]. Behavioural therapies can have long-lasting effects in adults[206,209]. Indeed, participants and their significant others rate these interventions as very helpful[210,211]. However, multicentre RCTs have shown that CBT does not reduce core ADHD symptoms to the same extent as first-line stimulant medication[212], particularly in studies using appropriate control groups[213–215].

Nutrition and exercise. ADHD is associated with unhealthy diets, with high intake of ultra-processed foods with high proportions of refined sugar and saturated fat[216,217], and nutritional deficiencies, such as of vitamins B_2 and B_6 and polyunsaturated fatty acids[218]. Importantly, however, these findings are observational rather than causal, because ADHD symptoms and the genetic risk of ADHD may influence dietary choices[219]. Three types of dietary interventions for ADHD have been studied: supplements, exclusions and complex dietary approaches. Significant although small to moderate reductions in ADHD symptoms based on properly blinded and controlled RCTs have been reported for ω3 fatty acid supplements[195,220], broad-spectrum micronutrient supplements[221], and exclusion of food colour additives and preservatives[195]. The effects of diets limited to only a few hypo-allergenic foods vary widely, depending on sample selection and study design[195,222]. Complex interventions with healthy diets, a Mediterranean diet and the Dietary Approach to Stop Hypertension offer promise but await rigorous testing[223–225]. Similarly, physical exercise may briefly relieve ADHD symptoms but has limited efficacy[205].

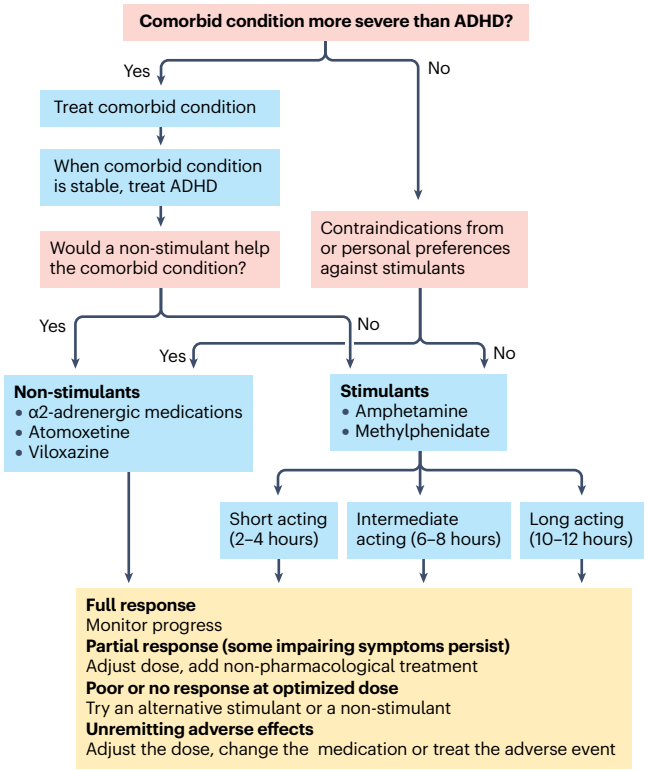

Fig. 6 | Treatment algorithm for ADHD with and without comorbid psychiatric disorders. The pharmacological algorithm for attention-deficit/hyperactivity disorder (ADHD) considers comorbid conditions, such as anxiety or depression, contraindications for medications, patient or parent preferences, and the required duration of effect throughout the day. Strategies for addressing partial or non-response include dose adjustments, changing medications or adding pharmacological and/or non-pharmacological treatment. Regular monitoring and follow-up promote effective management of efficacy and adverse effects. Adapted from ref. 1, Springer Nature Limited.

Neurotherapeutic interventions. EEG neurofeedback trains corrective brain activity by providing patients with real-time feedback on their brainwave patterns through visual or auditory cues. Meta-analyses have shown small to medium effects of EEG neurofeedback in individuals with ADHD, that are inferior to the effects of pharmacotherapy[226–228]. The effects of EEG neurofeedback are non-significant when analyses are limited to high-quality studies[229,230] and long follow-up periods[231]. The only two RCTs of fMRI neurofeedback (of the right IFC) showed no clinical or cognitive improvements relative to active[232] or sham conditions[233], despite promising changes in functional brain activity[232,234] and connectivity[235].

There is no meta-analytical evidence of clinical improvements with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) in individuals with ADHD[226,236,237] and a meta-analysis of cognitive effects showed no improvements[236]. However, a large multi-session RCT of TMS of the right IFC and the DLPFC combined with cognitive training showed clinical improvement[238] and one out of two larger parallel, sham-controlled multi-session RCTs of tDCS[239,240] showed improved attention in adults with ADHD after 28 sessions over the right DLPFC[240]. Trigeminal nerve stimulation (TNS) is an FDA-approved treatment for ADHD, based on an RCT in 62 children with ADHD that showed improvement in symptoms, with a medium effect size, after 4 weeks of nightly TNS applications[241].

Digital and virtual tools. Digital health interventions (DHIs) for ADHD leverage consumer technology platforms (for example, computers, smartphones and wearable devices) providing therapeutic game-based products that deliver neurocognitive and behavioural interventions along with tracking and remote measurement technologies[242]. Digital interventions offer important opportunities to transform clinical care. First, they are highly scalable and can overcome many barriers to accessing treatment as they can be accessed any time and anywhere, and do not require highly trained therapists, even if adjunctive human support is offered. Second, therapy can be offered with high fidelity as the active intervention components are contained within the software. Third, DHIs can be used to collect important information to augment assessment and treatment response (for example, symptom ratings, medication adherence, psychoeducation and timing of doses).

Although the evidence base for digital interventions in ADHD is growing, the quality of many studies is low, and studies have shown inconsistent benefits on ADHD outcomes[243]. However, digital therapies targeting broader cognitive functions may have greater effects. A large RCT of a video game-like intervention targeting divided attention and cognitive control, played at home by children with ADHD for 25 min per day, 5 days per week, for 4 weeks, demonstrated a small, but significant, improvement on a neuropsychological measure of attention but a non-significant improvement in ADHD symptoms[244]. Central executive functioning training, another gamified treatment, has shown promise in an RCT for reducing symptoms of ADHD and improving academic achievement[245,246]. The most recent meta-analysis of computer-based cognitive training confirmed previous meta-analytical findings of no significant effects on ADHD symptoms when considering probably blinded raters[247].

Quality of life

ADHD negatively affects various functional areas throughout development, which can often lead to a negative self-perception in relation to a person's place in life, considering the cultural and value systems to which that individual belongs. The accumulation of impairments leads to a low quality of life (QoL)[248].

In youths, ADHD can lead to educational and occupational failure, peer conflicts and social exclusion, family conflict, teenage pregnancy and sexually transmitted diseases[4]. Psychosocial, school and emotional functioning are the QoL domains most frequently affected in youths with ADHD[249]. These impairments accumulate over time, reducing self-esteem and wellbeing and increasing the risks of suicidality[249]. The comorbidities of ADHD aggravate these outcomes[43]. In adults, ADHD impairs work functioning, relationship quality, financial stability and parenting skills[250,251]. These issues can affect QoL, which is further reduced with the continued risk of accidents and the emergence of adverse medical outcomes such as cardiometabolic disease[53,56,70,252] and premature death[44]. In adults, psychosocial domains of QoL and dysfunctional cognitive beliefs are common[253–255].

Measures to evaluate QoL or functional impairment in individuals with ADHD differ between children and adults. In children, a standard set of measures can be used to evaluate QoL, namely, the clinician-reported Developmental Disability–Children's Global Assessment Scale (for overall functioning), the KIDSCREEN-10 (for family-related QoL and activities of daily living) and the Family Strain Index (for care-giver burden). Other commonly used measures are

the Columbia Impairment Scale, the Barkley Functional Impairment Scale, and the Impairment Rating Scale. General QoL measures for adults are the 36-item Short Form Health Survey[256] or the Quality of Life Enjoyment and Satisfaction Questionnaire[257]. Other measures are the Adult ADHD Quality of Life survey, which focuses on ADHD-specific problems in daily life[258], and the Weiss Functional Impairment Rating Scale, which is a measure of ADHD-related functional impairment[259].

Pharmacological treatments improve QoL in children and adolescents with ADHD[260]. Naturalistic studies have shown that medications improve many functional outcomes[89,261], reduce motor vehicle crashes[262], lower the risk of substance use[263], lead to higher educational achievement[264] and reduce mortality[265]. Prospective pharmacological studies in adults have shown concurrent short-term improvements in QoL[266] mediated by reductions in ADHD symptoms[259,267–272]. Naturalistic studies using linked prescription databases from Europe, North America and Asia, and frequently adopting a within-individual design, have shown that medication use is associated with lower levels of accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage pregnancy[4,89,261]. Moreover, one RCT demonstrated stable and long-term QoL benefits following multimodal treatment with methylphenidate combined with CBT group treatment or supportive counselling[273], and a meta-analysis found that discontinuing medication reduce the QoL of youths with ADHD[274]. These findings could be explained by the additional substantial effect of CBT on QoL[275] documented in a meta-analysis[208].

Outlook

Although the knowledge base on ADHD provides a firm foundation for clinical practice, future research should also improve both knowledge and clinical practice (Table 2). We need to learn more about the extent and effect of stigma on people with ADHD, and to improve strategies to avoid stigma. Epidemiological studies, in particular prospective studies, will further our understanding of the aetiological links between ADHD and its mental and somatic comorbidities, which may lead to better treatments for those with multiple diagnoses. Such studies will also improve our understanding of treatment discontinuity, longitudinal trajectories, key transitions and long-term outcomes, especially the impact of ADHD in older adults and the risks for mild cognitive impairment and dementia. More work is needed in under-represented groups to reduce health-care disparities, improve health-care accessibility and better understand how culture moderates symptom expression and response to treatment.

Studies of mechanisms and pathophysiology have reached a turning point. Large collaborative studies have yielded clear evidence about the effect of genetic variants on ADHD and we are beginning to understand the subtle brain differences between individuals with and those without ADHD. Moreover, deep sequencing studies should find genetic variants that regulate the function of other genes or affect proteins that are involved in the development or function of the brain. By better understanding the functional consequences of genetic variants, researchers aim to discover novel targets for ADHD medications[276,277].

Although we know much about the impairments in ADHD, much less is known about potential assets and strengths associated with the disorder (although see ref. 278). Likewise, little is known about protective and resilience factors, both environmental and genomic[279,280], that might improve outcomes in patients with ADHD.

Studies of environmental correlates of ADHD have lagged behind those of genetics due to the limits of epidemiology to prove causal links. Fruitful directions for environmental studies will be to use high-risk infant, sibling-control and in vitro fertilization designs[108], test hypotheses about gene–environment interplay, and invest in the detection of resilience mechanisms. Epigenetics may clarify how putative environmental causes are relevant to ADHD. Studies that track changes in brain structure and function throughout development will yield insights into developmental trajectories and reasons for the persistence of the disorder[281].

Moreover, there is growing interest in developing objective methods for diagnosing ADHD and predicting treatment response[282]. Machine learning algorithms will be used to analyse multidomain data from medical records, objective behavioural measures, physiology, brain imaging and genomics, to find patterns that predict the onset and outcomes of ADHD. The use of polygenic risk scores as a predictor will increase as more data become available and methods are improved[78,80]. Given that the onset of ADHD is typically prior to the onset of its psychiatric and somatic comorbidities, more work should be done to predict which patients should be targeted for preventive efforts to eliminate or reduce the impact of these co-occurring conditions.

Future research will also continue to investigate personalized treatment approaches based on studies seeking a better understanding of the heterogeneity of ADHD in terms of its aetiology, pathophysiology and clinical expression. More stimulant and non-stimulant medications will be developed, and learning how to best select and sequence treatments will be essential. Although response to ADHD medications is robust, there is considerable variability in response and tolerability, especially for non-stimulants, which have distinct profiles of responders and non-responders. Learning how to best match patients to treatments will become a research prioirty[183] and methods to improve adherence to medication, which is poor[283–285], will greatly improve outcomes.

Skills training and CBT will be improved by studies that investigate which skills are particularly effective and which elements should be

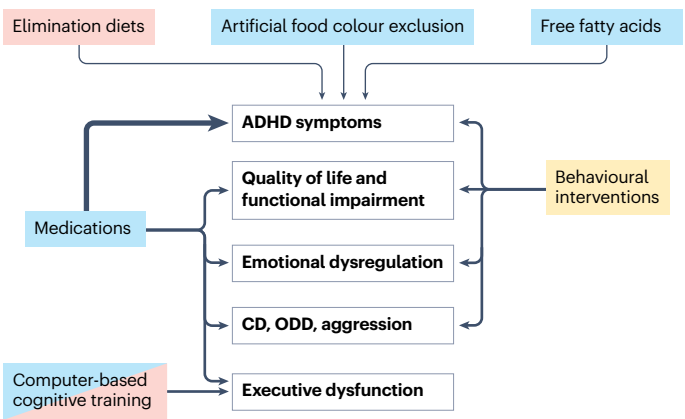

Fig. 7 | Efficacy of treatments. Treatments with a blue box have the highest level of supporting evidence (from probably blinded raters), and treatments with a red box have supporting data from non-blinded raters (where blindness is difficult to achieve). The yellow box signifies inconsistent evidence for behavioural interventions, which improve anxiety, depression, self-esteem and emotion regulation, but for core attention-deficit/hyperactivity disorder (ADHD) symptoms the evidence is less robust. Arrow thickness indicates the magnitude of the treatment effect. This figure is based on results from meta-analyses only. At the group level, stimulants have a greater efficacy than non-stimulants. CD, conduct disorder; ODD, oppositional defiant disorder.

Table 2 | Selected resources for clinicians, parents and patients

Organization	Website[a]	Content
National Institute of Mental Health	www.nimh.nih.gov	Information for patients and families
National Institute for Health and Care Excellence (NICE)	www.nice.org.uk/guidance/ng87	NICE ADHD guideline NG87
European Network for Hyperkinetic Disorders (EUNETHYDIS)	www.eunethydis.eu/	Network of researchers with annual meeting
American Professional Society of ADHD and Related Disorders (APSARD)	www.apsard.org	Meetings for health professionals and researchers
World Federation of ADHD	www.adhd-federation.org	Meetings for health professionals and researchers
Children and Adults with Attention-Deficit/ Hyperactivity Disorder (CHADD)	www.chadd.org	Information for patients and families
ADHD in Adults	www.adhdinadults.com	Continuing education for health professionals
ADHD Evidence Project	www.adhdevidence.org	Blogs, videos and the International Consensus Statement on ADHD
Canadian ADHD Resource Alliance (CADDRA)	www.caddra.ca	Meetings for health professionals and researchers
Australian ADHD Professionals Association (Australia)	https://adhdguideline.aadpa.com.au/	Information for Health professionals, patients and families
ADHD Europe	www.adhdeurope.eu/	Information for patients and families
European Network Adult ADHD	www.eunetworkadultadhd.com/	Meetings for health professionals and researchers
International Collaboration on ADHD and Substance Abuse (ICASA)	www.adhdandsubstanceabuse.org/	Meetings for health professionals and researchers
UK Adult ADHD Network (UKAAN)	www.ukaan.org	Meetings for health professionals and researchers
China ADHD Alliance	www.adhdchina.com/	Information for patients and families (in Mandarin)
Zentrales adhs-netz	www.zentrales-adhs-netz.de	Information for patients and families (in German)
American Academy of Family Physicians (AAFP)	www.aafp.org/family-physician/patient-care/prevention-wellness/emotional-wellbeing/adhd-toolkit.html	Adult ADHD toolkit
Saudi ADHD Society	https://adhd.org.sa/en/	Information for patients, families and practitioners (in Arabic)
American Academy of Pediatrics (AAP)	https://www.aap.org/en/patient-care/attention-deficit-hyperactivity-disorder-adhd/	A practical resource toolkit providing information for health professionals

ADHD, attention-deficit/hyperactivity disorder. [a]Websites are in English unless otherwise indicated.

added to enhance effectiveness (for example, mindfulness and positive aspects of ADHD)[214,215]. Currently, the group setting is recommended for cost-effectiveness reasons. However, the best setting and duration for the sustained therapeutic success of CBT is still an open question.

Studies on neurotherapeutic treatments for ADHD have shown varied results due to the limited size and diversity of the trials. To gain a clearer understanding, it is essential to conduct larger RCTs that specifically focus on identifying the most effective treatment protocols for various age groups and clinical or cognitive subgroups within the ADHD population.

Lifestyle recommendations will become a component of multimodal treatment programmes for ADHD along with medication and behavioural interventions. We will see studies of neurotherapies, applications, wearables, gaming platforms and other digital tools aiming to reduce symptoms of ADHD and monitor symptoms during treatment. Future work on ADHD will be influenced by the neurodiversity framework that considers ADHD to be associated with differences in brain development and cognitive style rather than being a disorder per se[286].

Well-designed studies will assess if changes in brain activity or structure following interventions could be used as objective measures of treatment response. Measurement-based care[287,288] and the use of quality care metrics[289,290] hold much promise but require standards for implementation. More research is needed to develop combination therapies that better address the range of impairments in ADHD and its comorbidities. Predictive modelling[184,185] may help personalize treatments and optimize outcomes. More research is needed to find effective food interventions for ADHD and on the biological pathways involved (immune system, oxidative biology, brain plasticity and the microbiome–gut–brain axis).

All these innovative directions will benefit from the international and interdisciplinary resources and collaborations (see Supplementary Table 2) that have, during the past decade, clarified the aetiology of ADHD, generated hypotheses about mechanisms, refined its diagnosis, optimized treatment outcomes, and improved the QoL of patients with ADHD across the lifespan.

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Competing interests

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Additional information

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[1]Departments of Psychiatry and of Neuroscience and Physiology, Norton College of Medicine at SUNY Upstate Medical University, Syracuse, NY, USA. [2]School of Psychological Sciences, Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia. [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [4]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway. [5]Department of Biomedicine, Aarhus University, Aarhus, Denmark. [6]Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK. [7]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK. [8]Solent NHS Trust, Southampton, UK. [9]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, NY, USA. [10]DiMePRe-J-Department of Precision and Rigenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy. [11]Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, Netherlands. [12]National Institute for Health and Care Research

(NIHR) MindTech MedTech Co-operative and NIHR Nottingham Biomedical Research Centre, Institute of Mental Health, Mental Health and Clinical Neurosciences, School of Medicine, University of Nottingham, Nottingham, UK. [13]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [14]Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany. [15]Department of Psychiatry, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil. [16]Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neurosciences, King's College London, London, UK. [17]Department of Child & Adolescent Psychiatry, Transcampus Professor KCL-Dresden, Technical University, Dresden, Germany. [18]University of Washington School of Medicine, Seattle, WA, USA. [19]Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, Netherlands. [20]Karakter Child and Adolescent Psychiatry University Center, Nijmegen, Netherlands.