Attention Deficit Hyperactivity Disorder

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Summary

ADHD is a childhood-onset neurodevelopmental disorder with a prevalence of 1.4%-3%. It is more common in boys. Comorbidity with childhood-onset neurodevelopmental disorders and psychiatric disorders is substantial. ADHD is highly heritable and multifactorial; multiple genes and non-inherited factors contribute. Pre-/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 medication in those most severely affected. Randomised controlled trials show short term benefits of stimulant medication and atomoxetine. Meta-analyses of blinded non-drug treatment trials have not yet proven their efficacy. Longitudinal studies of ADHD show heightened risk of multiple mental health and social difficulties as well as premature mortality in adult life.

Second summary

ADHD is a common neurodevelopmental disorder characterised by developmentally inappropriate and impairing levels of inattention, hyperactivity and impulsivity across different settings. It presents in childhood and is more common in males than females. Its prevalence in the general population is 3.4%.

ADHD is diagnosed according to strictly defined criteria – despite extensive investigation into its pathophysiology there is as yet no diagnostic biological test. Although the ICD-10 and DSM-5 provide defined diagnostic thresholds, clinical features of ADHD behave as a continuously distributed risk dimension, meaning it is important to be mindful that sub-threshold ADHD symptoms, although not an indication for treatment, do carry risk.

The clinical presentation of ADHD varies considerably between individuals. Early comorbidity with developmental, learning and psychiatric problems is common. Whether ADHD itself persists into adulthood is variable – whilst many will continue to meet full diagnostic criteria or have sub-threshold symptoms, some will experience symptom remission but continue to have different types of difficulties. ADHD is a risk factor for later adverse outcomes such as poor educational attainment, social difficulties, substance misuse and criminality.

The causes of ADHD are complex and multifactorial, with genetics, early environment and gene-environment interplay all being involved. No single risk factor is either necessary or sufficient to explain its occurrence. ADHD is highly heritable, and multiple types of genetic variants appear to be involved. None are diagnostic. Early environmental factors (e.g. diet, pre- and perinatal factors, toxins and psychosocial risks) have also been extensively investigated but whilst correlations have been found between many environmental influences and ADHD, it is difficult to prove definite causes. Later, potentially modifiable factors might influence its course and outcomes and more research is needed on this.

Clinical assessment should be detailed and go beyond asking about diagnostic items. There are specific guidelines for the stepwise management of ADHD, and when following these, the severity of symptoms and an individual's circumstances and medical history should be taken into account. If ADHD medications are prescribed, it should be in conjunction with behavioural interventions. ADHD medication needs to be regularly reviewed.

ADHD in many respects behaves like a chronic medical disorder. For many individuals, multimodal interventions that are carefully adjusted over time will be important. A developmental approach to assessment and treatment is necessary, taking into account how presentation and risks change over time.

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.

Defining attention deficit hyperactivity disorder

ADHD is a diagnostic category in the American Psychiatric Association's Diagnostic and Statistical Manual (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 the World Health Organisation's International Classification of Diseases (ICD-10[3]). This definition captures a more severely affected group of individuals, as reported prevalence rates for hyperkinetic disorder are lower than for DSM-IV ADHD even within the same population.[4] Table 1 provides a description of the key diagnostic criteria. DSM-5 now has longer symptom descriptors which also capture how symptoms may manifest in older adolescents and adults. DSM-IV distinguished inattentive, hyperactive-impulsive and combined subtypes of ADHD, with the combined type requiring 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 are required in 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 (e.g. 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 (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 – e.g. whether to refer to specialist services or to treat. However, like many medical conditions (such as hypertension and diabetes), in terms of aetiology and outcomes as discussed later, ADHD may also be viewed as a continuously distributed risk dimension. In common with other continuously distributed phenotypes (e.g. blood pressure) it could be argued that there is a lack of objective cut-point that defines the diagnostic threshold. Indeed, those who have “sub-threshold” symptoms are also at heightened risk of adverse

outcomes[6] (as it is for hypertension). However, ultimately categorical decisions on resource allocation and treatment have to be made, and ICD- or DSM-defined diagnosis provides a reliable way of balancing the risks and benefits of giving someone a diagnostic label and providing treatments that are not free of adverse effects. A further challenge which is the case for all psychiatric disorders and some neurological conditions (e.g. migraine), comes from diagnosis being based on reported symptoms alone, there are no biological tests. This means that even with clear-cut diagnostic criteria, there is potential risk of over- and under-diagnosis and this underscores the importance of careful and rigorous expert assessment.[7] Concerns about under- and over-diagnosis are not restricted to ADHD or psychiatric conditions.[8]

Epidemiology

In the general population, the estimated prevalence of ADHD in children is 3.4% (CI 95% 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 the prevalence does not vary by geographical location but is affected by heterogeneity in assessment methods (e.g. using an additional informant to parent) and diagnostic conventions (e.g. ICD vs. DSM).[11] It is worth highlighting that there is a marked under-representation of ADHD studies from low- and middle-income countries.

One common assumption is that ADHD must be a modern phenomenon. 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 predate this publication by several centuries. Time trends studies of non-referred population cohorts in the later 20th and early 21st centuries find 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 medications across high-income countries in the last decade.[15,16,17] Rises in clinic incidence and treatment could simply indicate increased parent and teacher awareness of ADHD and/or changes in impact.[18,19] Nevertheless, European studies have repeatedly found that despite the rise in ADHD treatment, the administrative prevalence is lower than the population figure, highlighting that in these countries there is still under-diagnosis.[17,20,21] However, in the United States, similar types of studies show geographical variation in patterns of under- and over-diagnosis/ADHD medication prescribing.[22,23] Such findings highlight there is the potential for misdiagnosis and inappropriate medication use if safeguards are not in place. These include ensuring full, good quality clinical assessments are undertaken although these require time and adhering to national and international treatment guidelines. However there is no evidence of rising population levels of ADHD explained by social change contrary to belief by some.

An excess of affected males is a strongly consistent epidemiological finding, although the male:female ratio of 3-4:1 found in epidemiological samples is increased in clinic populations to around 7-8:1 suggesting referral bias in relation to females with

ADHD.[24] The same male preponderance is observed for other neurodevelopmental disorders such as autism spectrum disorder, intellectual disability (IQ<70) and communication disorders.[25]

The natural history of ADHD is best observed in prospective longitudinal studies. As is typical of neurodevelopmental disorders, its core defining features 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 - whilst around 65% continue to meet full criteria or have only achieved partial remission by adulthood, some do experience full remission.[26] Although good quality, large epidemiological studies of the prevalence of ADHD in adulthood are lacking, one meta-analysis of adult ADHD yielded a pooled prevalence rate of 2.5% (95% CI 2.1-3.1).[27] However, there are still uncertainties as to what constitutes the optimal way of defining ADHD (or indeed any neurodevelopmental disorder) in adulthood. The recently published DSM-5[2] explicitly allows for symptom decline and requires a reduced symptom number for adult ADHD. In clinical settings, diagnosing ADHD in adults who did not present in childhood requires some caution as it is challenging for young adults and those who know them to retrospectively date symptom onset in the absence of documented information.[28] Objective records (e.g. school reports) could help in this regard. Despite these caveats, there is certainly sufficient evidence (see also prognosis) 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 a problem due to a lack 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 (e.g. reading disability, developmental co-ordination disorder), intellectual disability and tic disorders.[30,31,32] Unsurprisingly, rates of comorbidity are higher in those who are referred.[33] ADHD also shows high concurrent comorbidity with behaviour problems, namely oppositional defiant and conduct disorders.[31,34] Children with ADHD and conduct disorder show greater neurocognitive impairment and a worse prognosis[35,36] and this subgroup of children with hyperkinetic conduct disorder is distinguished in ICD-10 but not in DSM-5. Comorbidity with psychiatric disorders that typically have onset after puberty is discussed later.

Risk factors

As for all complex disorders, no single risk factor is either necessary or sufficient to explain ADHD – multiple genetic and non-genetic/environmental factors contribute to risk and the pattern of inheritance is multifactorial for the majority of affected individuals.

Genetics

ADHD is a familial disorder. Its relative risk is around 5-9 in first degree relatives of probands with ADHD.[37] Numerous twin studies of ADHD from different countries

consistently yield very high heritability estimates of around 76%, a magnitude similar to that observed 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[39] have been found to be associated with ADHD risk. These include common (defined as >5% population frequency) DNA sequence variants called single nucleotide polymorphisms (SNPs), but associations have only been observed when thousands are combined into a composite genetic risk score.[40] Subtle chromosomal mutations involving 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.

Prior to whole genome investigations, certain single dopaminergic, serotonergic and noradrenergic candidate genes stood up to 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 recommended now for those with intellectual disability, this is not the case for

ADHD. Ascertaining causality requires further and different types of investigation (see [39] for details).

Whilst the majority of ADHD is multi-factorial in origin, there are a number of known, rare genetic syndromes (such as fragile X syndrome, tuberous sclerosis, 22q11 microdeletion and Williams syndrome) characterised by higher rates of ADHD and ADHD-like features. These syndromes are also associated with higher 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 to suggest that routine screening for these genetic syndromes is warranted in the absence of intellectual disability.[48]

Environment and gene-environment interplay

Environmental factors also are known to be important in ADHD. As evidence on modifiable causes impacts on 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 variety of pre-and perinatal factors, environmental toxins, dietary factors and psychosocial factors are all associated with ADHD.[38] If causal, that would mean manipulating the risk factor alters the outcome. However, association does not mean causation because exposures to risks are not randomly allocated and can be influenced by unmeasured confounders, selection factors and reverse causation

whereby the phenotype influences the environmental exposure. It is with these caveats in mind that evidence for environmental causation must be interpreted.

Pre-and perinatal factors observed to be associated with ADHD include low birth weight and prematurity[51] and *in utero* exposure to maternal stress, cigarette smoking, alcohol, prescribed drugs (e.g. acetaminophen/paracetamol) and illicit substances.[38,52,53] In relation to prenatal smoking and stress, quasi-experimental designs suggest most or all of the association with offspring ADHD, unlike with offspring birth weight, is explained by unmeasured confounds.[54,55,56,57,58]

Environmental toxins, specifically *in utero* or early childhood exposure to lead, organophosphate pesticides and polychlorinated biphenyls are risk factors (see detailed review in[38]). Nutritional deficiencies (e.g. zinc, magnesium and polyunsaturated fatty acids), nutritional surpluses (e.g. sugar and artificial food colourings) and low/high IgG food have not been found to convincingly 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 (see later).

Psychosocial risks, such as low income, family adversity and harsh/hostile parenting, whilst robustly causal for certain 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 appears to be different and causal. After being adopted away in the UK, Romanian orphans reared in institutions and exposed to extreme early privation in the first year of life showed elevated rates of ADHD-like features, cognitive difficulties and quasi-autistic features that persisted to adolescence.[62,63] Psychosocial context may well shape ADHD presentations and alter developmental trajectories, outcomes and impairments - but surprisingly this has been not been investigated widely (see Figure 1 on origins vs. trajectories).

Regardless of what causes ADHD, treatment is based on clinical features not assumed aetiology.

As a final word on risk factors, many mistakenly assume that the action of genes (or biology) and environment are distinct, which is incorrect. Potentially important environmental risks for ADHD and its outcomes may be brought about as a consequence of genetic propensities (gene-environmental correlation; e.g.[61]). Their effects on clinical phenotype may also depend on genetic liability. For example, animal studies have robustly shown experimentally that environment can alter behaviour in different ways depending on the variant of gene carried (gene-environment interaction[39]). Gene-environment interplay effects 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). This highlights that genes, environment and biology work together. However in humans, these issues are

complex - they will not be discussed in detail here, but have been reviewed elsewhere.[38,39,49]

Pathophysiology

Biology

The biological mechanisms through which genetic and environmental influences 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 currently limited by our incomplete understanding of its pathophysiology in humans and the extent to how well inattention, motor over-activity, and impulsive responses on behavioural tasks in non-human species represent ADHD.[64] However they have suggested involvement of dopaminergic and noradrenergic neurotransmission (in line with the neurochemical effects of ADHD medications) as well as of serotonergic neurotransmission. [65]

Cognition

Whilst there is no cognitive profile which 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 considerable

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 of its effect finding improvements in executive and non-executive memory, reaction time, reaction time variability and response inhibition.[74]

Imaging

Functional magnetic resonance imaging (fMRI) studies have found abnormalities in the function of many neural networks in response to cognitive tasks. A meta-analysis of task-based fMRI studies has 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 highlights alterations in the basal ganglia and limbic areas.[76] A meta-analysis of diffusion MRI studies, which investigate white matter microstructure, finds alterations to be widespread, but mostly 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 appear to index familial risk for ADHD.[78] The 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 due to 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

yet known whether this phenomenon can be extrapolated to other metrics of structure, microstructure and function. The effect of medication is also a consideration as there is some evidence to suggest it appears to normalise 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 ADHD assessment process requires careful clinical history taking that goes beyond asking yes/no type questions in relation to core ADHD symptoms: a missed diagnosis has potential to jeopardise an individuals' learning/occupational and social relationships, whereas a misdiagnosis could lead to the use of medication which is not indicated. History taking should not be reductionist and focus exclusively 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. The key steps for assessing children are summarised in Figure 1.

It is important to consider whether endorsed symptoms are better explained by other difficulties which are amenable to intervention, for example hearing difficulties presenting as inattention. However diagnosis is based on clinical phenotype and not generally excluded by presumed aetiology. Information should be obtained from more than one informant including those who know the individual best at home and

at school (or college or work). For deciding who requires referral to a specialist assessment service or for monitoring treatment response, it can be helpful to use standardised ADHD questionnaires (e.g. Strength and Difficulties Questionnaire,[84] Conners' Parent and Teacher Rating Scales[85]) but these are not a substitute for detailed history taking prior to diagnosis. Structured interviews are more likely to be encountered in a research setting but might be valuable in a clinical context, especially ones that do not require extensive, expensive training (e.g. the Developmental and Wellbeing Assessment).[86] This requires further investigation. ADHD symptoms are commonly associated with a range of neurobehavioural difficulties. These could be comorbid features of ADHD but should also be considered as differential diagnoses as treatments for these disorders 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 reading disorders, developmental co-ordination disorder and tic disorders are also common.[87,88,89] Importantly, as ADHD and autism spectrum disorder co-occur so frequently,[90] autistic symptomatology should be considered. ADHD is also associated with lower IQ/intellectual disability[91] and emotion dysregulation symptoms e.g. 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 "uncomplicated" ADHD, even if full diagnostic criteria for other comorbid disorders are not met. This makes formalising differential diagnoses conceptually difficult, as 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 being experienced, even if some of these need to be described in terms of sub-threshold problems.

Neuropsychological testing does not have role in diagnosis as cognitive processes are not a defining characteristic.[66] However, it is important to consider cognitive comorbidities such as learning disability and dyslexia, which may require specialist assessment from education services.

Treatment

There are specific guidelines for the stepwise management of ADHD, including 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 them is that US guidance does not preclude the use of medication for pre-school children or for those with mild ADHD, practice that is not recommended in Europe where a step-wise approach is recommended. If medication 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 extensively investigated over the years. The only one of these which currently forms a core part of treatment guidelines are behavioural interventions. Initial results from the largest trial to date, the multimodal treatment study of children with ADHD (MTA),[97] suggested that the combination of intensive behavioural treatment plus medication did not offer additional benefit over medication alone for core ADHD symptoms, but that the combination may have provided some benefit in terms of associated symptoms and levels of functioning as well as a lower medication dose being required. A more recent series of meta-analyses investigating randomised controlled trials of non-pharmacological interventions including behavioural interventions concluded that they, along with neurofeedback, cognitive training and restricted elimination diets, cannot be recommended as interventions for core ADHD symptoms until there is better evidence of their effectiveness from blinded assessments.[98] Elimination of artificial food colouring[98] may be beneficial, but to what extent and for whom it may be so is unclear.[99] A recent meta-analysis has concluded that children with ADHD have overall reduced levels of omega-3 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 that it is not understood as to whether sub-normal blood levels should be the indication to treat.[100] However, there is blinded

evidence 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 medication.[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. Both increase catecholamine availability. There is meta-analytic 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 those with autism spectrum disorder and/or intellectual disability, medication side effects are more common.[106,107] There is also meta-analytic evidence for a beneficial effect 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.

Pre-treatment checks, including in relation to medical and family medical history (in particular cardiac conditions) which are especially important if medication is to be initiated, are summarised in Figure 1. Height, weight, blood pressure and pulse should be checked at baseline prior to starting medication, and compared to normative data. It is reasonable to consider but not mandatory to routinely obtain an ECG prior to commencing ADHD medication, 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 are shown in Table 2. There is no evidence that ADHD medication is associated with changes in QT interval, sudden cardiac death, acute myocardial infarction and stroke.[110] Readers are referred to a comprehensive recent review regarding current best practice in managing adverse events associated with ADHD medications.[110] Once an optimal response is achieved, height, weight and growth will require regular monitoring. NICE guidance recommends that height be measured every six months in children and young people, weight be measured three and six months after initiation of treatment and every six months thereafter in children, young people and adults, and that 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 dose change and routinely every 3 months.[7] The adverse side effects of stimulant medication include appetite suppression and growth retardation which can be offset to a degree by stimulant "holidays" on days when symptom control is considered less critical such as weekends and holidays, and by adjusting the timing of doses. Other side effects of both 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 abuse, 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, individuals with childhood ADHD are also at significant risk of adverse outcomes into 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 those with sub-threshold symptoms.[111] ADHD also predicts serious antisocial behaviour, involvement with the police and substance misuse in adolescence.[36]

Until relatively recently, data on broad outcomes beyond the third decade of life were lacking. However, one long term follow up has shown that it is also associated with adverse occupational, economic and social outcomes, antisocial personality disorder, and risk of substance use disorders, psychiatric hospitalisations, incarcerations and mortality.[112] A recent Danish registry-based investigation of ADHD[113] showed significantly elevated rates of mortality in adult life, mainly as a result of accidents, which was especially increased in those with comorbid oppositional defiant disorder, conduct disorder and substance misuse.

A recent meta-analysis of ADHD in prison inmates showed on average the prevalence of ADHD to be 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

males.[114] Psychiatric comorbidity is high in prisoners with ADHD, especially so for adults.[115] Although randomised controlled trials of ADHD treatment have reported immediate but not as yet longer term benefits, there is epidemiological evidence which suggests that medication may reduce criminal behaviour[116] and trauma-related visits to emergency departments.[117]

Most with ADHD do not develop psychosis or a mood disorder. The largest studies only find a small sub-group who additionally develop later schizophrenia or bipolar disorder.[118,119] Evidence on links with later unipolar depression are mixed[112,120] and this might be because depression is more common in females 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 its inclusion 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 critical 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 (i.e. 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 (for example, use of medication where not indicated) and applying evidence-based treatments would become impossible (for example, 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. However, at present, we do not know what sorts of dimensions best capture ADHD and at what level they should be measured, for example reported symptoms, cognitive tests, brain imaging markers or other biological signatures.

Genetic research is progressing now via large scale collaboration but there is a need to understand the clinical as well as biological meaning of findings, if they are to impact on our understanding and treatment of ADHD. Currently, there is no rationale for routine genetic testing in ADHD because of limited predictive power. However, as ADHD is heritable, rates of ADHD in parents of those with ADHD are elevated. A pertinent future research question is how might treatment of parent ADHD impact on child ADHD features and comorbidity? There is, for example, evidence that treating parent depression appears to improve offspring mental health.[121,122] Another issue for future consideration is that genetic and environmental risk factors which "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 (e.g. social and other potentially modifiable risk factors) contribute to and modify the

longitudinal course of ADHD across time including better prognosis, using designs that can control for unmeasured confounders and genetic contributions from the affected person (e.g. twin studies) and related parents (e.g. adoption studies). This could inform interventions aimed at optimising outcomes.

So far, medication 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 appear 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 may change with age and development. It creates risks of its own and secondary mental health problems commonly arise in mid-childhood and after puberty. Almost certainly, for many individuals, multi-modal interventions that are carefully adjusted over time to prevent complications will be required, in the way perhaps that is undertaken for optimising diabetes control. How ADHD is best managed across the lifespan and across key transition periods, e.g. school entry, comprehensive/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 and that is not very satisfactory for a prevalent, impairing condition.

Conclusions

ADHD is an extremely important condition due to its high prevalence, persistence into adult life and adverse outcomes which extend beyond the affected individual. Whilst ADHD is still viewed with scepticism by some and often remains stigmatised by the media, the evidence on 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 require many adjustments over time. Consideration of impairments beyond core diagnostic criteria, developmental change and an individual's psychosocial strengths, weaknesses and resources are all important aspects to consider.

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Author contributions

AT was invited to contribute this review and used the headings recommended for Lancet Seminars to draft the initial outline/structure. AT wrote the first draft of the summary and sections on introduction, defining ADHD, epidemiology, comorbidity, genetics, environment and gene-environment interplay, future research and clinical directions. MC wrote the first draft of the sections on pathophysiology, clinical

assessment, treatment and prognosis, and prepared the tables and figures. Both authors undertook literature searches and edited the manuscript. All figures and tables were produced for this review.

Table 1. Key diagnostic symptoms of ADHD

Inattentive symptoms	Hyperactivity / impulsivity symptoms
Does not give close attention to details or makes careless mistakes	Fidgets with / taps hands or feet, or squirms in seat
Has difficulty sustaining attention on tasks or play activities	Leaves seat in situations when staying seated is expected
Does not seem to listen when directly spoken to	Runs about or climbs when not appropriate (may present as feelings of restlessness in adolescents / adults)
Does not follow through on instructions and does not finish schoolwork, chores, or duties in the workplace	Unable to play or undertake leisure activities quietly
Has trouble organising tasks / activities	"On the go", acting as if "driven by a motor"
Avoids, dislikes, or is reluctant to do tasks that need sustained mental effort	Talks excessively
Loses things needed for tasks / activities	Blurts out answers before a question has been finished
Easily distracted	Has difficulty waiting his/her turn
Forgetful in daily activities	Interrupts or intrudes on others

Table 2. Some of the more common side effects associated with ADHD medication

Side effect	MPH	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	✓✓	✓

MPH, methylphenidate. ATX, atomoxetine.

✓= common side effect

✓✓ = if a common side effect of both drugs, effect is more pronounced for one compared to the other

Figure 1. Origins and trajectories of ADHD

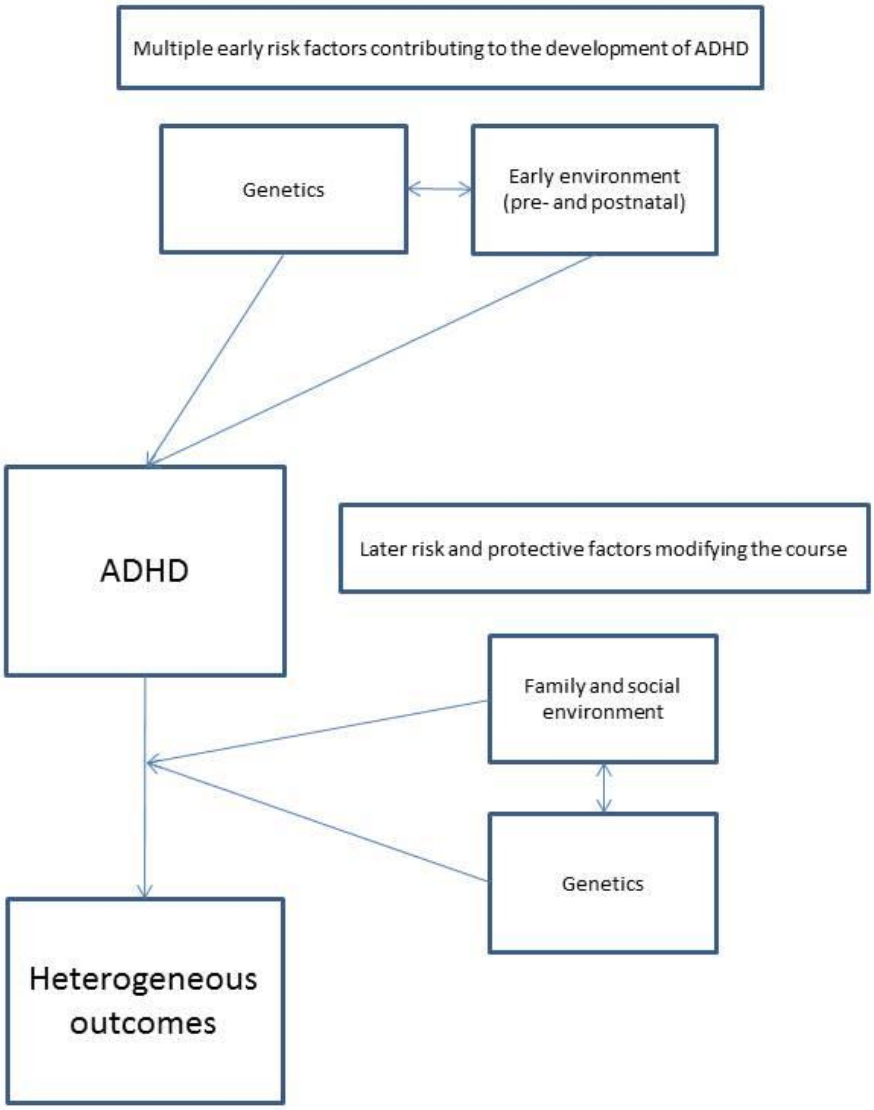
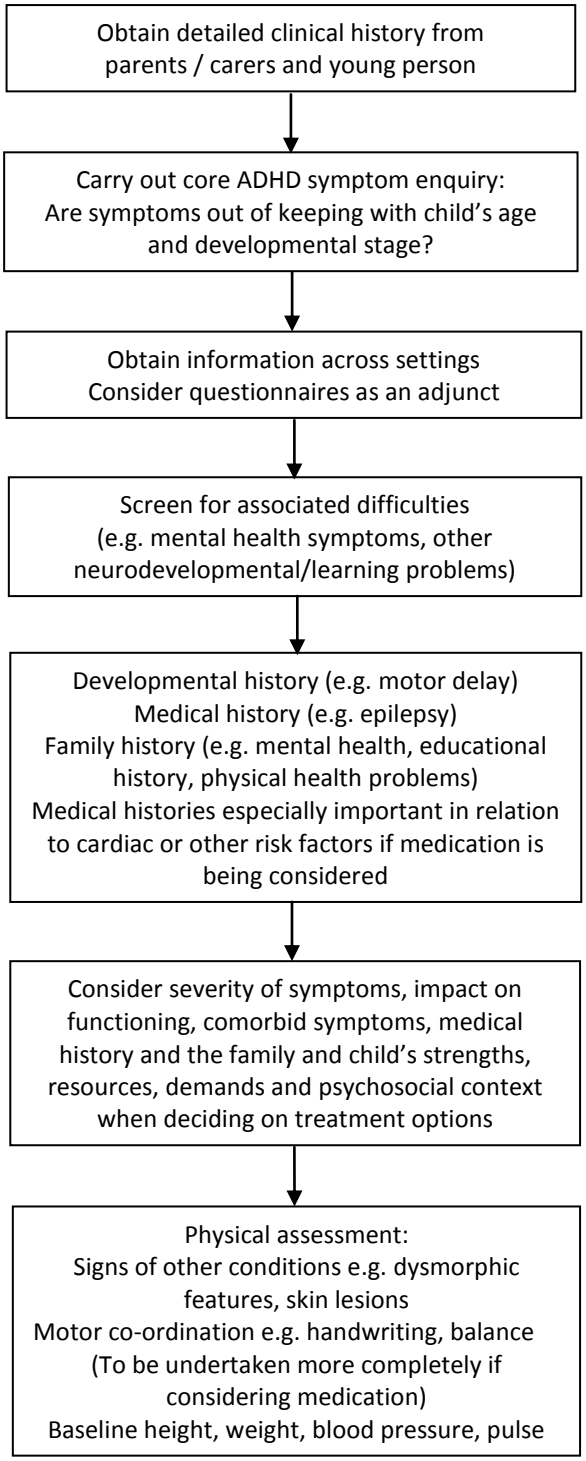


Figure 2. Summary of the ADHD clinical assessment process for children



Box 1. Search strategy and selection criteria

Papers published were first identified by searches of PubMed from 1st January 2010 to 31st March 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”, “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. The authors further selected papers according to their judgement of the quality of the study or review paper, of the relevance to controversial or commonly misunderstood issues and whether findings had clinical relevance. Older papers were included when judged to be important.

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