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UPDATE ON ATTENTION DEFICIT HYPERACTIVITY DISORDER

- **Attention deficit hyperactivity disorder (ADHD) is a condition characterised by persistent symptoms of inattention, hyperactivity and impulsivity**
- **Patients with suspected ADHD should be referred for specialist assessment**
- **The management of ADHD usually involves both non-pharmacological and pharmacological interventions**
- **All patients with ADHD on pharmacological therapy should be monitored regularly**

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a complex, heterogeneous and multifactorial neurodevelopmental disorder **characterised by persistent symptoms of inattention, hyperactivity and impulsivity.**[1-3] The term hyperkinetic disorder (HKD) is also used to describe this condition.[1] ADHD is the most common childhood neurodevelopmental disorder.[1,2,4,5] It was previously considered to resolve during adolescence and young adulthood,[4] however it is now recognised that the symptoms and impairments associated with ADHD may persist into adulthood.[6,7] Studies have reported that **up to two-thirds of patients with childhood ADHD have symptomatic features continuing into adulthood.**[1,4,6,8-10]

The core symptoms of inattention, hyperactivity and impulsivity seen in ADHD can be considered to be an extreme of normal behaviour,[1,3] however **the distinction between ADHD and normal variation in the general population, is that in ADHD, these symptoms are persistent and pervasive and associated with significant levels of impairment.**[11] ADHD is a heterogeneous condition; individual patients differ in terms of the presentation of the core symptoms, the level of impairment and associated comorbidities.[1] **It is important to ensure optimal management as children and young people with ADHD often fail to achieve their academic potential.** Studies have shown an increased risk of antisocial behaviour, substance abuse and road traffic accidents in childhood and adolescence, and an increased risk of adverse occupational, economic, and social outcomes, antisocial personality, psychiatric hospital admissions, incarcerations and increased mortality in adulthood.[1,3-5,8,12] These outcomes are increased where the condition is not treated.[1,3,4] This bulletin outlines the current management of ADHD and updates the 2005 NMIC bulletin on ADHD.

EPIDEMIOLOGY

The prevalence of ADHD is dependent on 3 main factors 1) the population sampled 2) the method of assessment and 3) the diagnostic criteria used.[1,12] The prevalence varies in childhood from 1.4 to 9.5% and in adults from 1.0 to 4.4%[6,8,13]; the prevalence is lower in Europe than the US, which may reflect the different diagnostic criteria used to diagnose ADHD in the two areas.[1,9,12] **Males are more commonly affected than females; epidemiological studies report male:female ratios of 3-4:1.**[1,4,7]

ADHD is associated with other neurodevelopmental disorders such as autistic spectrum disorder, communication and specific learning motor disorders, intellectual disability and tic disorders (e.g. Tourette's syndrome).[1,9,12] **ADHD is also associated with comorbid psychiatric conditions such as oppositional defiant disorder (ODD) or conduct disorders (CD) in 25-50% of cases, anxiety disorders in 25% and mood disorders in 20%.**[1,9,12] Early comorbidity with CD and ODD is associated with the most adverse outcomes.[1,12]

AETIOLOGY

The aetiology of ADHD is unknown, however it is thought to be multifactorial and includes genetic and environmental factors.[3,5,9]

Genetic factors are thought to play an important role in the aetiology of ADHD, however it is unlikely that one single gene is responsible for ADHD.[1,14] Twin studies of ADHD have shown high rates of inheritance of up to 76%.[1] **The relative risk of ADHD is approximately 5 to 9 fold in first degree relatives of patients with ADHD;**[1,3] if a parent has ADHD, the risk to the offspring of having ADHD is up to 57%.[14]

Environmental factors such as exposure to a range of prenatal and perinatal factors, environmental toxins, dietary factors and psychosocial factors have been reported to be associated with ADHD in epidemiological studies.[1,14] **There is evidence to suggest that prematurity, low birth weight and maternal smoking in pregnancy have the highest association with ADHD.**[3] However, there is insufficient evidence to make definite conclusions with respect to other factors such as dietary factors, maternal use of illicit drugs, severe early childhood deprivation and psychosocial deprivation.[3] The relationship between parenting and ADHD may result from both the negative aspects of the child influencing the parents' behaviour and negative aspects of the parents influencing the child's behaviour.[14]

The effects of genetics and environmental factors are not distinct; potentially important environmental risk factors for ADHD and its outcomes may be brought about as a consequence of genetic pre-disposition.[1]

Imaging studies have shown that **cortical brain development (especially in the pre-frontal cortex) appears to be delayed by 2 to 3 years in children with ADHD.**[3] There also appears to be abnormalities of structural and functional connectivity.[3] Dopaminergic pathways have also been implicated in ADHD, with studies finding reduced dopamine transporter availability in adults and children with ADHD.[3,5,9]

DIAGNOSIS

The initial presentation of a patient with ADHD is usually to a general practitioner (GP), or other healthcare professional (HCP) in primary care, or to education and social work professionals.[7,12] **Children typically present with ADHD symptoms during early school years**, however they may also present at later stages due to increased academic

demands or if subtle symptoms are unrecognised at an earlier age.[5] **Adults with ADHD usually present to GPs** with 1) a past childhood diagnosis of ADHD, or 2) the core symptoms of ADHD which began in childhood and persisted throughout life, which are not explained by other psychiatric conditions and have resulted in moderate/severe psychological, social and/or educational or occupational impairment.[15] Symptoms in adults may present differently compared with younger age groups, as inattention, hyperactivity and impulsivity are generally expressed in more subtle and diverse ways.[4]
Diagnostic criteria for ADHD differ between Europe and the US. The European diagnostic criteria for HKD are defined by the International Classification of Diseases (10th edition: ICD-10) and the US diagnostic criteria for ADHD are defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition; DSM-IV, which was updated in DSM-V in 2013), as shown in table 1.[1,16] **DSM-IV and DSM-V are generally similar except the age of onset increases from before 7 years (DSM-IV) to before 12 years (DSM-V).**[1]

Table 1: Diagnostic criteria for ADHD/HKD[1,16]

A. Attention symptoms	B. Hyperactivity symptoms	C. Impulsiveness symptoms
Poor attention to detail/careless errors	Often fidgets or squirms on seat	Often blurts out answers before the question is complete
Often fails to concentrate on tasks or play	Often leaves seat when expected to sit	Often fails to wait in turn in groups, games or queues
Often appears not to listen	Excessive inappropriate running or climbing	Often intrudes into games or conversations
Often fails to finish things	Often noisy/difficulty being quiet	Often talks excessively without response to social appropriateness
Poor task organisation	Persistent over-activity not modulated by request or context	
Often avoids task which require sustained mental effort		
Often loses things for tasks		
Often distracted by external stimuli		
Often forgetful		

ICD-10: onset before 6 yrs; at least 6 symptoms from A, 3 symptoms from B and 1 symptom from C
DSM-IV: onset before 7 yrs; at least 6 symptoms from A and 6 symptoms from B and C
DSM-V: onset before 12 yrs; at least 5 symptoms from A and 5 symptoms from B and C

The ICD-10 definition has more restrictive criteria than the DSM criteria, and is thought to capture the more severely affected group of individuals.[1] DSM-IV also distinguishes between 3 different subtypes of ADHD (inattentive, hyperactive-impulsive and combined) which is not included in the ICD-10 criteria.[1]
The evaluation of ADHD in patients requires a detailed clinical assessment including a medical history and physical examination, review of information across home and community settings and application of the diagnostic criteria (ICD-10 or DSM-IV/V).[5,12,15] In addition to the criteria in table 1, the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines advise that, **a diagnosis of ADHD requires that the patient's symptoms are persistent for more than 6 months, be pervasive (occurring in more than one setting) be out of keeping with developmental level, be maladaptive and significantly impair the patient's social, academic or occupational functioning.**[12,15]
There is no definitive biological diagnostic test for ADHD, however there are standardised ADHD questionnaires (e.g. the Conners' parent and teachers rating scales and the Strength and Difficulties Questionnaire),[17] which may be helpful in deciding which patients need referral to a specialist assessment service.[1,15] If on the basis of a preliminary assessment it is suspected that a child or young person has ADHD, **referral for specialist assessment by a child and adolescent mental health clinician (e.g Child and Adolescent Mental Health Services [CAMHS]) or paediatrician with a special interest in this field is recommended.**[12,15] A diagnosis of ADHD should be made only after a comprehensive assessment by a specialist.[10] **Adults who have previously been treated for ADHD as children and present with symptoms suggestive of continuing ADHD should be referred to general adult psychiatric services (e.g. Adult Mental Health Services [AMHS]) for assessment.**[15]

MANAGEMENT

Evidence shows that the appropriate management of ADHD is associated with improved symptoms and outcomes (e.g. in terms of antisocial behaviour and academic performance).[3,5,8,18,19] The management of patients with ADHD requires a multi-disciplinary approach, including communication between healthcare and education services where appropriate.[12,15] Management of ADHD involves both non-pharmacological and pharmacological interventions, however pharmacological management is not recommended for pre-school children.[12,15] Young people with ADHD receiving treatment from paediatric services (e.g. CAMHS) should be transferred to adult services (e.g. AMHS) if they continue to have significant symptoms of ADHD, when they reach 18 years.[15] However, a recent study found that many young people in Ireland with ADHD are not being referred or are refusing referral to AMHS in this transition period, therefore ongoing communication between CAMHS and GPs is important during this period.[20]

NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological interventions such as behavioural interventions form a core part of the management of ADHD, particularly in children.[1,8,15] Effective behavioural therapies include parent training, classroom management, peer interventions and combinations of these interventions for children.[5] Parent training in groups or as individuals provides education to improve their understanding of ADHD, behavioural problems and child development, and also helps them employ positive parenting strategies to help reduce disruptive child behaviours.[5] **Parent training/education programmes are recommended by UK guidelines as first-line treatment for parents or carers of pre-school children and for school-age children with mild ADHD.**[12,15] Contact should be made with the child's teacher (with the parent's consent) following a diagnosis of ADHD to explain the diagnosis and discuss the care plan including the requirement for any special educational needs.[15] Individual psychological interventions (such as cognitive behavioural therapy or social skills training) may be considered, for older adolescents and adults.[15] Patients (and their parents/carers where appropriate) should be provided with age-appropriate information on ADHD.[15] **HCPs should stress the value of a balanced diet, good nutrition and regular exercise for patients with ADHD.**[15] Evidence does not support the elimination of artificial colouring and additives from the diet as a general treatment for children and young people with ADHD.[1,14,15] Parents/

carers should be asked to keep a food diary, if clinical assessment suggests that food or drinks may appear to influence hyperactive behaviour; subsequent referral to a dietician and paediatrician if the diary supports a possible relationship is recommended.[15] Parents/carers should also be given information on local and national support groups;[15] HADD Ireland has a support group website at **http://www.hadd.ie/**, which may be useful.

PHARMACOLOGICAL MANAGEMENT

The use of medication for treating ADHD has increased over recent years in many countries including Ireland;[21] a study from the UK found that the use of pharmacological treatment over the last 20 years had increased eightfold.[22] This rise was most pronounced in younger males, however there was an increase in every age group including adults.[22] The increase in use is thought to have occurred due to both an increase in the number of patients diagnosed with ADHD and a higher percentage of patients with ADHD receiving treatment.[22] **Pharmacological treatment should only be initiated by an appropriately qualified physician with expertise in ADHD and should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.**[10,15,23-28] Table 2 identifies those patients where pharmacological treatment may be considered. Pharmacological treatment may not be indicated for all patients e.g. current EU guidelines do not recommend pharmacological treatment for pre-school children with ADHD or as first-line treatment unless severe for all school-age children and young people.[15]

Table 2: Indications for pharmacological treatment of ADHD [4,15]

Pharmacological treatment may be considered for:

- School-age children (>6 yrs) and adolescents with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent training/education programmes or group psychological treatment
- School-age children (>6 yrs) and adolescents with severe ADHD as first-line treatment
- Adults with either moderate or severe levels of impairment as first-line treatment

The pharmacological management of ADHD includes the use of stimulants (methylphenidate, dexamfetamine and lisdexamfetamine) and non-stimulants (atomoxetine and guanfacine).[1,3,12,15] These medications increase the availability of the neurotransmitters (noradrenaline and/or dopamine), which appear to be critical to their therapeutic efficacy.[3,5] **The choice of medication depends on various factors including the presence of comorbid conditions (e.g tic disorders and epilepsy), potential adverse effects of the drugs, issues such as adherence, the potential for drug diversion and/or misuse and patient preference.**[15] Adverse effects of medications are more commonly experienced in patients with ADHD and concomitant autism spectrum disorder or intellectual disability.[1] All patients should have a pre-drug assessment as outlined in table 3.

Table 3: Pre-drug treatment assessment[15]

Assessment should include:

- Full mental health and social assessment
- Full history and physical examination including:
  - Assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
  - Heart rate and blood pressure (plotted on a centile chart)
  - Height and weight (plotted on a growth chart)
  - Family history of cardiac disease and examination of the cardiovascular system
  - An ECG if there is a past medical history or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination
  - Risk assessment for substance misuse and drug diversion

All patients commenced on medication need to be monitored regularly;[3,15] the initial dose should be titrated against symptoms and adverse effects over 4 to 6 weeks.[15] Medication in children and adolescents should be reviewed regularly and the need for continued treatment assessed, if possible using validated scales.[3] If no response to treatment is obtained after a completed trial of medication, both the diagnosis and possible comorbidity should be reviewed.[3] In addition other aspects such as adherence to medication and adverse effects must be considered.[3] The Summary of Product Characteristics (SmPC) for each medicine has complete prescribing information including dose titration, contraindications, special precautions, potential drug interactions and adverse effects (available on www.hpra.ie or www.medicines.ie). Not all medications that are licensed for use in children with ADHD are also licensed in adults. Moreover the licensed indication may vary between countries; therefore the SmPC should be consulted.

There have been few studies which address the impact of **drug holidays**, however it is generally accepted that stopping the medication during, for example, school holidays can minimise the impact of adverse effects on appetite, allow catch-up growth and enable assessment of persistence of symptoms and impairment.[3] In adults, drug treatment should be continued for as long as it is clinically effective; it should be reviewed at least annually.[3]

Stimulants

Stimulants have been the standard pharmacological treatment for ADHD for >50 years; they have been found to be significantly more effective than non-stimulants,[1,3,4,29] although concerns of abuse, dependence, tolerability, adverse effects and slowing of growth may limit their use in some patients.[4,29] **Stimulants are generally recommended as first-line pharmacological treatment for ADHD in children and adults.**[4,5,15] Approximately 70% of patients respond to their first stimulant medication and 90-95% of patients respond to a second stimulant.[5] Of note, stimulants have been shown to exacerbate tics and Tourette's syndrome.[26] The use of stimulants are contraindicated in patients being treated with monoamine oxidase inhibitors (MAOIs) or within 14 days after MAOI treatment due to concerns of possible hypertensive crisis.[23-26]

Methylphenidate hydrochloride improves the symptoms of children >6 years, adolescents and adults with ADHD. It is **usually considered first-line pharmacological treatment for children and adults unless there are contraindications,**[10,15] such as pre-existing cardiovascular disease, pre-existing cerebrovascular disease, history of severe depression, suicidal tendencies or hyperthyroidism.[24] Methylphenidate is available in immediate or modified-release forms.[12] **Modified-release preparations** of methylphenidate should be considered for reasons including convenience, improving adherence, reducing school issues and for those at risk of substance abuse.[3,15] **Immediate-release preparations** may be more appropriate if more flexible dosing regimens are required or in the initial titration to determine correct dosing levels.[15] **Adverse effects**

include decreased appetite, growth retardation with prolonged use, insomnia, depression, worsening of tics, headache, cardiac arrhythmias, palpitations and hypertension.[23,24] **Regular monitoring is required for adverse effects including cardiovascular effects, exacerbation or emergence of psychiatric disorders, growth retardation, seizures (due to lowering of seizure threshold) and substance abuse.**[23,24]

Dexamfetamine shows similar efficacy to methylphenidate.[1,3,30] It is not authorised for use in adults (and is currently not marketed in Ireland).[25] It has a similar adverse effect profile to methylphenidate.[25]

Lisdexamfetamine dimesylate is a prodrug which is administered once daily and metabolised to its active metabolite dexamfetamine.[3,4] It is not authorised for use in adults.[26] The adverse effect profile is similar to dexamfetamine and methylphenidate; there is some evidence that its potential for recreational abuse is lower.[3,4]

Non-stimulants

Atomoxetine (a noradrenaline reuptake blocker) and guanfacine (a preferential α_{2A}- adrenoceptor agonist) are highly selective noradrenergic drugs that have proven efficacy in treating ADHD and are usually used as second-line therapy.[3,4,30-32] Reasons for starting a second-line drug include strong family preference for a non-stimulant medication, concern about drug diversion or comorbid conditions (e.g. an anxiety or tic disorder).[5]

Atomoxetine is effective in children >6 years, adolescents and adults with ADHD.[9,27] It is the preferred first-line pharmacological treatment if there are contraindications to use of stimulants.[1,3,15] Patients who have an inadequate response or tolerability issues with stimulants may benefit from a switch to atomoxetine and it may be particularly useful when ADHD is associated with comorbidities, or in patients at risk of substance abuse.[3,4,15,29,30] Atomoxetine is metabolised by the cytochrome P-450 (CYP) CYP2D6 pathway and therefore the **potential for drug interactions should be considered**.[29,30] It should not be used with MAOIs.[27]

Adverse effects include nausea, decreased appetite, headache, palpitations, QT prolongation, depression, psychiatric disorders (including suicide related events) and abnormal liver function.[4,27,30] Patients should be monitored closely for agitation, suicidal thinking, self-harming behaviour and liver toxicity (parents/carers should be warned).[15,30]

Guanfacine has been shown to be effective in children >6 years and adolescents.[3,4] It is not indicated for adults and is reserved for patients when stimulants are not suitable, not tolerated or shown to be ineffective.[28] It may be beneficial for patients with specific comorbidities such as tics disorders or ODD that have failed to respond to first-line treatment options.[32] Guanfacine is metabolised by CYP3A4/5 pathways; its plasma concentration is affected by CYP3A4/5 inhibitors and inducers; therefore the **potential for drug interactions should be considered.**[28]

Adverse effects include decreased appetite, depression, anxiety, insomnia, somnolence, dizziness, bradycardia, hypotension and gastrointestinal effects.[28]

Other drugs

Other medications which have been used as third-line pharmacological treatment (off-label usage) of ADHD include bupropion (an atypical antidepressant with mixed catecholaminergic effects), clonidine (an alpha agonist) and modafinil.[3] Guidelines advise that these should only be considered in the context of specialist services.[15] Antipsychotics are not recommended for the treatment of ADHD.[15]

MANAGEMENT OF ADHD IN CLINICAL PRACTICE

Table 4 summarises the diagnosis and management of a patient with ADHD.

Table 4: Steps in the management of ADHD[1,5,15]

Take a detailed clinical history from parents and the young person/patient to include:

- **Assess for core ADHD symptoms**
  - Are symptoms out of keeping with child's age and development stage?
  - Obtain information across settings e.g. home, school
  - Consider questionnaire as an adjunct (e.g. the Conners' parent and teachers rating scales)
- **Review history**
  - Medical - birth history and early developmental progression, medical and mental health evaluation and treatment, past and current medications
  - Social – family, social and financial support, family stressors
  - Family – history of ADHD, other mental health concerns
- **Physical assessment** – include cardiac and neurological examinations, vision and hearing screening

Refer patients with suspected ADHD to specialist service for assessment (e.g. CAMHS or AMHS)

Patient with confirmed diagnosis of ADHD: management steps (specialist supervision)

- General advice to all patients/carers on ADHD
- Non-pharmacological therapy – consider for all patients
  - Parent training /education programme (where appropriate)
  - Involvement with education (where appropriate)
  - Psychological interventions for older children and adults
- Pharmacological therapy (when indicated)
  - Pre-drug assessment (see table 3)
  - Choose drug treatment for the individual patient
    - ◊ Advise patient/carer of potential adverse effects
  - Monitor patient on therapy regularly to:
    - ◊ Assess efficacy of therapy
    - ◊ Assess for adverse effects
    - ◊ Assess adherence
    - ◊ Assess need to continue with therapy

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