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MANAGEMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

- ➡ ADHD is a disorder of inattention, impulsivity and hyperactivity
- ➡ Diagnosis is based on clinical evaluation using internationally validated systems
- ➡ Early diagnosis and appropriate management are important to reduce adverse consequences for the ADHD patient and his/her family
- ➡ Methylphenidate should only be prescribed as part of a comprehensive treatment programme and its continued use re-evaluated at regular intervals

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is an early-onset clinically heterogeneous disorder of **inattention, impulsivity and hyperactivity** [1]. It is estimated to affect 3-5% of children [2]. ADHD can have serious consequences for the child, his/her family and society, therefore early diagnosis and appropriate treatment are vital. This bulletin will outline the current approaches to diagnosis and management of ADHD in children.

CLINICAL FEATURES

The abilities to focus attention, regulate activity and control impulses emerge for all children as part of normal development. Therefore a history of ADHD-type behaviour (i.e. the core symptoms of inattention, impulsivity and hyperactivity) must be viewed in the context in which it occurs, especially with respect to its appropriateness for the age and developmental status of the child [3]. **A diagnosis of ADHD should only be considered if the child's behaviour is inappropriate for his/her developmental state and is reported to interfere with social functioning, learning or development** [4].

ADHD has been reported to be associated with **functional impairments** such as school problems (disruptive behaviour, academic impairment) and social problems such as family and peer-related conflict [5]. Although the prevalence falls with age, some studies have suggested that up to 35% of ADHD childhood cases may persist into adulthood, albeit frequently in an attenuated form; this can put the adult at risk for personality disorders resulting in criminality, unemployment, traffic accidents and substance misuse [6]. Predictors for persistent ADHD include family history of ADHD (or other conduct or bipolar disorders), family disadvantage, maternal depression, marital discord and negative parent-child interaction [7]. Epidemiological studies have shown that ADHD is commoner in males [3]. However, the male-to-female ratio is greater in clinical studies than in community studies, which indicates that in practice, female sufferers are less likely to be referred for services than male individuals; this may reflect the fact that in females, ADHD may be less overtly disruptive (i.e. Attention Deficit Disorder, ADD) [8]. However, they still display the same level of social and academic impairment.

ADHD frequently **co-exists with other mental health conditions**. At least 35% of sufferers will also have **oppositional defiant disorder** (defined as negativistic, defiant, disobedient and hostile behaviour toward authority figures) or the more serious **conduct disorder** (defined as a repetitive and persistent pattern of behaviour in which the basic rights of others, or major age-appropriate social norms or rules are violated) [9]. Follow-up studies indicate that ADHD patients with these disorders fare less well than those with ADHD alone [7]. Other co-morbidities include **anxiety** (in up to 18% of ADHD patients), **depression**, including bipolar disorder [10,11], and **tic disorders**. Various degrees of **learning disabilities / speech or language delays** and **Tourette's syndrome** have also been reported [9]. It is important that all co-morbidities and/or other diagnoses be identified and treated appropriately, rather than being considered part of ADHD as, if left untreated, they may have a negative bearing on the outcome of ADHD treatment [12].

DIAGNOSIS

There are 2 diagnostic systems (based on **clinical assessment**) currently used to classify behavioral disorders in children [13]. The DSM-IV classification for ADHD (Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, from the American Psychiatric Association) is used primarily in the US, while the ICD-10 (WHO International Classification of Diseases, Tenth Edition) defines Hyperkinetic Disorder (HKD) and is used in many other areas. Both classifications are in use in Europe. Each system includes the 3 main “core” symptoms but they differ in how these symptoms are expressed in the individual (**see table 1**). However, there is agreement that (1) symptoms should be “**pervasive**”, i.e. present in two or more settings e.g. school and home, (2) symptoms must have appeared **before the age of 7 years (ADHD) / 6 years (HKD)** and be **present for at least 6 months continuously**, (3) the child’s **behaviour** should be out of keeping with his/her development level, be **maladaptive** and result in **significant impairment in function**, either at a social, academic or occupational level [14]. In the DSM-IV classification, 3 subtypes of ADHD are described: “combined type” with signs of inattention and hyperactivity / impulsivity, “predominantly inattentive type” with inattention but not hyperactivity / impulsivity and “predominantly hyperactive-impulsive type” with hyperactivity / impulsivity but not inattention [6]. The HKD criteria are more restrictive as they require a greater degree of symptom expression (Table 1) - HKD is broadly similar to severe combined-type ADHD [6]. The differences between the classification systems may explain why the US appears to have a greater prevalence of ADHD [7,13].

There are **no validated laboratory or radiological tests** for ADHD. Magnetic resonance imaging (MRI) studies have shown that some regions of the frontal lobes, cerebellum and basal ganglia are smaller in ADHD/HKD patients compared with control groups [15,16]. Functional MRI studies suggest hypofrontality in ADHD [17]. However, these findings are not reliable enough to discriminate between children with and without ADHD and their routine use for diagnostic purposes is not recommended [9]. Therefore at present, the diagnosis of ADHD / HKD is based on clinical evaluation.

TABLE 1: Criteria for ADHD / HKD [14]

Inattention (A)	Hyperactivity (B)	Impulsivity (C)
*poor attention to detail/careless errors	*often fidgets / squirms on seat	*often blurts out answers before question is complete
*often fails to concentrate on tasks of play	*often leaves seat when expected to sit	*often fails to wait turn in groups/games/queues
*often appears not to listen	*excessive inappropriate running or climbing	*often intrudes into games or conversations
*often fails to finish things	*often noisy / has difficulty being quiet	*often talks excessively without response to social appropriateness
*poor task organization	*persistent overactivity not modulated by request or context	
*often avoids tasks which require sustained mental effort		
*often loses things for tasks		
*often distracted by external stimuli		
*often forgetful		

ADHD requires at least 6 symptoms from A and 6 from a combination of B and C, present for at least 6 months

HKD requires at least 6 symptoms from A, 3 from B and 1 from C, present for at least 6 months

CAUSES

Heredity: Many studies support a genetic involvement in the aetiology of ADHD. It is known that parents and siblings of ADHD children have an increase in the risk for ADHD [1,18,19]. Twin studies have shown a high correlation with inheritance suggesting a **heritability of 75-80%** [20, 13]. However as yet, no one gene with a large effect has been identified, therefore it is postulated that there are several genes, each with a modest effect, potentially involved in the development of ADHD.

Biology: Dopamine is known to play a central role in psychomotor activity and reward-seeking behaviour [21]. Molecular genetic studies suggest that one or more genes associated with dopaminergic function may be implicated in ADHD [22]. Such abnormalities would fit in with the putative sites of damage within the brain, seen with MRI imaging. However, not all studies have found these abnormalities in their ADHD patients; a study carried out in Irish children diagnosed with ADHD failed to show this association [23]. Moreover, some workers have suggested a role for **other neurotransmitter systems**, e.g. serotonergic or noradrenergic [15,24, 25].

Environment: Pregnancy and delivery complications have been reported to predispose children to ADHD. These include toxemia, maternal smoking or drug abuse, poor maternal health, maternal age, low body weight and duration of labour. It is postulated that it is the chronic exposure to hypoxia, associated with some of these complications (rather than acute hypoxia as seen with a traumatic labour), that may be the relevant factor; this needs to be confirmed by further research [1]. In terms of psychosocial factors, **low socioeconomic status, maternal depression, paternal criminality and severe family conflicts** have been reported from various studies to be associated with various childhood psychiatric disturbances, including ADHD [13]. Although much has been written about the association of certain foods with ADHD, the bulk of systematic controlled studies do not support this theory [7].

In summary, it is postulated that several genes, each of modest effect, combine with each other and with environmental risk factors to alter the function of one or more neurotransmitter systems in the brain, triggering ADHD [26].

PRINCIPLES OF TREATMENT

The aims of treatment are to control symptoms, improve academic and social functioning in all spheres and aid transition to adult life [3]. Treatment is tailored to suit the needs of the individual ADHD patient. It usually includes a range of non-pharmacological modalities with pharmacological treatment as appropriate, usually for cases with significant levels of hyperactivity (so-called multimodal treatment).

Non-pharmacological treatment: Many psychosocial interventions have been used for children with ADHD. **Behavioural modification techniques** (e.g. using reward and response cost) have been shown to be the most useful against symptoms and associated features of ADHD, especially non-compliant or oppositional behaviour [7,13]. However, evidence from controlled trials has shown such interventions are not more effective than medication [27]. Moreover, they may not be adequate for children with significant levels of hyperactivity, who will usually need the addition of a pharmacotherapeutic agent [28]. Results on the effectiveness of other techniques such as **cognitive training** or **educational interventions** have been conflicting [29] and appear to depend on the individual child and the available resources [7]. ADHD causes management problems in the home and community, and children with ADHD have been reported to evoke negative parenting; therefore it is important that the treatment programme includes **parental training** and **school involvement** as appropriate [7]. Such interventions require regular supervision by healthcare professionals specifically trained in this area. There are conflicting recommendations regarding **dietary modifications**; although systematic review of the currently available literature does not support a role for supplementation with certain minerals (such as iron, magnesium or zinc), some experts recommend their use in individuals suspected of having a deficiency [7]. In addition, although the evidence regarding the role of refined sugar in ADHD is conflicting, restrictions may be recommended especially if parents or teachers report that symptoms appear to be aggravated by such use in the individual child [6]. Although there is increasing evidence for the beneficial effects of fatty acid supplements, it remains unclear as to which type of patient benefits most, which supplement to use and for how long [30].

In summary, psychosocial interventions, tailored to meet the needs of the individual ADHD sufferer and his/her family (and school if appropriate) have been shown to be a valuable part of the overall management programme. Dietary modifications may be considered useful on an individual basis.

Pharmacological treatment: The principal drugs used to treat ADHD are the CNS stimulants **methylphenidate** and dexamfetamine (the latter is not authorised in Ireland). Both are structurally similar to amphetamine and are thought to act by enhancing neurotransmission of dopamine and noradrenaline [13]. Several short-term placebo-controlled randomized controlled trials (of up to 12 weeks' treatment), predominantly from the US, have shown that methylphenidate demonstrates a 70% response in reducing the 3 core symptoms of inattention, impulsivity and hyperactivity in children who continue to take the drug, highlighting the importance of treatment adherence [27]. Side effects include insomnia and nervousness (occurring in up to 10% at the start of treatment and usually remedied by altering dosage schedule), reduced appetite and weight loss [6]. CNS stimulants have also been reported to cause cardiovascular symptoms including tachycardia, hypertension and rarely chest pain [31-34]. Psychiatric symptoms such as tics or aggressive behaviour may also occur with CNS stimulant use and are a cause for discontinuing treatment [7]. Controlled trial data **evaluating long-term usage of methylphenidate** are sparse. Two controlled studies have evaluated stimulant treatment, as part of a **multimodal treatment programme** for periods of up to 2 years in 679 children [35,36]. Results showed that methylphenidate was effective for managing ADHD symptoms with a satisfactory safety profile and without significant tolerance. Moreover, in ADHD children with co-morbid disorders such as anxiety, methylphenidate in combination with behavioural therapy produced greater improvements in social, academic and family functioning compared with either modality alone [37]. In contrast, observational studies have shown that ADHD cases receiving stimulant treatment in childhood continue to function less well academically and socially compared with healthy controls in adolescence and/or adulthood. However, as these studies followed ADHD sufferers who received drug treatment in childhood, it is likely that they represented the more seriously affected ADHD cases, causing study bias [35]. Comparison of their outcome with non-treated ADHD cases of the same age has shown that while academic and working achievements are similarly impaired, treated ADHD cases have better social skills and self-esteem, fewer road traffic accidents and less substance abuse in adolescence and adulthood. **Other drugs** such as tricyclic antidepressants, alpha 2-adrenergic agonists (e.g. clonidine), MAO inhibitors and bupropion have been used to treat children with ADHD who cannot take methylphenidate or who have co-morbid conditions [13]. None of these treatments are authorised for such use and adequate data on their efficacy are lacking. **Atomoxetine**, a highly selective noradrenaline reuptake inhibitor is the first non-stimulant drug to be developed for ADHD. This is not authorised in Ireland [38]; recently new safety warnings relating to the risk of suicidal thoughts and hepatotoxicity with its use in children with ADHD have been added to its prescribing information in other countries [13,39].

Prescribing information: CNS stimulants are not suitable for all ADHD sufferers, therefore **methylphenidate should only be used under the supervision of a specialist in childhood behavioural disorders, as part of a comprehensive programme for ADHD** [31-34]. It is licensed for use in children aged 6 years and older, and prescribing information recommends that the dosage be carefully titrated to suit the individual child's needs. Typically methylphenidate treatment should start at 5mg once or twice daily, increasing the dose and frequency of administration by weekly increments (as appropriate according to the weight of the child) to a maximum of 40-60mg/day (typically < 45mg/day) or until adverse reactions occur. During this titration period there should be regular contact between the family and prescribing physician to enable rapid dosage adjustments as necessary [7]. Methylphenidate is available in both immediate release and long-acting formulations; studies have not shown a difference in the efficacy of the two formulations [40]. Long acting formulations may increase patient compliance because the child will not need to have treatment administered during school hours. Of importance, **methylphenidate should be discontinued if there is no response after one month's treatment** [31-34]. There are no drugs licensed for use in children < 6 years; dexamfetamine has been used in children aged 3-6 years of age under specialist supervision on a named patient basis.

In summary, CNS stimulants such as methylphenidate have been shown to reduce the symptoms of ADHD in the short-term. Long-term data are inadequate but studies of up to 2 years suggest continued effect. The effect of methylphenidate use in childhood in later life, in particular adolescence and adulthood is uncertain; from the data available, it does not appear to have an effect on persistence of ADHD symptoms but childhood users appear to have better social skills and a reduced rate of substance abuse compared with unmedicated ADHD children.

MANAGEMENT OF ADHD IN PRACTICE

Table 2 outlines recommendations for the diagnosis of ADHD. Because of the complexity of diagnosis, **it is recommended that suspected cases of childhood ADHD / HKD at primary care level should be referred to appropriately qualified healthcare professionals as early as possible.**

Table 2: Recommended Steps in the Diagnosis of ADHD /HKD [9]

- **Suspect the diagnosis if a child presents with behavioural problems inappropriate for age/development**
- **Determine if child's symptoms fulfill the criteria for ADHD / HKD**
- **Full details about degree and duration of behavioural symptoms should be elicited from both parent / caregiver and teacher / school professional and from direct observation of the child**
- **Child should also be evaluated for co-morbid psychiatric conditions**

Once the diagnosis is made, the child's **treatment programme** should set out **long-term goals for therapy** [12] and the child's family and school personnel should be involved in the programme. If the child is receiving medication, the treatment team should keep in close contact with the family, especially in the early weeks of treatment, in order to ensure correct individualised titration of the dose and to monitor emergence of adverse drug effects [7]. The child should be followed up on a systematic basis (by collecting data from family and school personnel) to check for adherence and efficacy; **failure to meet targets might be due to previously undiagnosed co-morbidity, lack of adherence, lack of response of symptoms to the programme or incorrect initial diagnosis.** Such follow-up will ensure that the treatment programme remains appropriate to the individual child's needs. As there are inadequate data regarding the optimal duration of use of medication, it is recommended that for those children in whom stimulant therapy is beneficial, the need for continuing medication should be re-evaluated on a regular basis, at least annually [6]. **Blood pressure should be monitored regularly** and methylphenidate should not be used in children with co-existing cardiovascular disease [31-34]. Because of problems with reduced weight gain and the **potential for slight growth retardation, discontinuation of medication at regular intervals (under careful supervision) is recommended** in stabilised patients, in order to assess both the child's progress and need for continued medication [6,7].

SUMMARY

ADHD in childhood is a troublesome psychiatric condition that impacts on the child, his/her family and social contacts. It requires careful clinical diagnosis and monitoring by healthcare professionals with specific expertise in the area. Treatment needs to be determined on an individual basis and should consist of psychosocial interventions with medication as appropriate. The treatment programme should be reviewed and the need for continuing medication re-evaluated at intervals on a regular basis.

References available on request. Date prepared: October 2005

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC) for specific information on drug use.

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