

# ADHD in Children and Adolescents: A Good Practice Guidance

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## 1. Introduction

The syndrome of restless, inattentive, and impulsive behaviour known as Attention Deficit Hyperactivity Disorder (ADHD) or Hyperkinetic Disorder (HKD) is a common neurodevelopmental problem in children and adolescents. Children affected with this disorder are at risk of academic failure, substance abuse, and criminality in adolescence and adulthood. ADHD is a reflection of an underlying deficit that may have several ultimate causes such as genetic predisposition, psycho-physiological factors and psychological dysfunction, but a common pathway at the behavioural level (Hill & Cameron, 1999). By labelling children with difficult behaviour as suffering from a disorder, we make it easier to treat and this carries with it the danger of over-diagnosis (Orford, 1998). On the other hand, under-diagnosis is also an issue (Dopheide, 2001).

## 2. Incidence

Prevalence of ADHD estimates that 3 to 7% children would meet the criteria of Diagnostic and Statistical Manual-IV (DSM-IV) of American Psychiatric Association's diagnostic criteria (APA, 1994). The ratio of boys to girls is between 3:1 and 9:1 but this may decrease with age (Swanson *et al.*, 1998). Part of the difference between sexes may be referral bias (Beiderman *et al.*, 1996). Follow-up studies of children with ADHD find that 15% still have the full diagnosis at 25 years, and another 50% are in partial remission, with some symptoms persisting (Faraone *et al.*, 2006).

## 3. Aetiology

No genetic marker has been identified in children with ADHD. Neuroimaging studies confirm abnormalities in those regions of the brain that are implicated in ADHD (Swanson *et al.*, 1998; Castellanos *et al.*, 2002). These studies report significantly smaller asymmetrical prefrontal and basal ganglia structures, in children with ADHD. Correlations of magnetic resonance imaging-based anatomical measures and specific-task performance in children suggest that the right prefrontal cortex is involved in inhibiting attentional and behavioural responses, whereas the basal ganglia seem to be involved in the execution of these responses (Konrad & Eickhoff, 2010). One third of affected individuals have at least one parent who

suffers from similar symptoms. ADHD is also associated with low birth weight (<1500g); tobacco and alcohol use during pregnancy (SIGN, 2001). Although ADHD is highly heritable, no specific susceptibility gene has been identified (Franke *et al.*, 2009).

#### 4. Symptoms

The symptoms of ADHD are excessive and impairing levels of activity, inattention, and impulsiveness. Children have great difficulty remaining seated when required in structured situations such as in the classroom or at the dinner table. They fail to pay attention to instructions in academic and social situations. The difference between ADHD and normal behaviour is the degree of impairment. The alarming signals may be a child who is academically under-achieving because of his/her behaviour, despite having a normal intellect or a child exhibiting behaviour problems both at home and in school, which are considerably worse than would be expected for the standard of parenting and home environment. The symptoms of ADHD change through out the lifecycle. Hyperactivity and impulsivity may decrease as patients get older but the demands on their attention may increase.

#### 5. Assessment

Concern about the future quality of life is heightened when parents observe their children struggling behaviourally at home, academically in school and socially on the playground. When told that a child has ADHD, parents are relieved by finding a reason for their child's difficulties. The diagnosis confirms that it is not their fault. Not all children and young people presenting with difficult behaviour will warrant a specialist referral. This depends on the severity of child's difficulties. ADHD can be provisionally diagnosed in preschool children but it should be confirmed after the child has started school. Some argue that problems with inattention, hyperactivity and impulsivity are the results of cultural phenomena (Block, 1977). Yet this point of view appears to be changing with the acceptance of ADHD as a cross-cultural disorder (Sandberg, 1996). Some children are inherently more inclined to be inattentive, impulsive and hyperactive than others. Such traits may run in families e.g. parents, siblings, and extended family members and there seems to be a genetic predisposition to them. Mental traits can be inherited just as height and weight. What we are dealing with are normal human variations that are only understood as being disorders when they are in conflict with cultural expectations and norms. The rating scales are an essential tool to obtain information but are not a substitute for a diagnosis. Reports from parents and teachers may not agree on the types of behaviours. This does not mean they are necessarily inaccurate; it may be attributed to the fact that the parents and the teachers are seeing the children in different settings. There are many rating scales available, most of which have been developed in the USA. The assessment should include information gathering. Apart from obtaining the completed rating scales, information should be obtained from the school about peer relationship and the child's academic progress. Information is gathered about child's current difficulties; family and social history; child's developmental and medical history and the educational progress. While interviewing parents, one needs to obtain a comprehensive knowledge of each parent's medical and psychiatric history. Family situations, such as a single working parent, separated or divorced parents, or reconstituted families where one or both parents have remarried, all affect the child.

## 5.1 Medical assessment

Since symptoms of ADHD can occur due to a wide variety of underlying conditions, a comprehensive approach to the evaluation of a child with ADHD is recommended (Reiff *et al.*, 1993, AACAP, 1997). Medical assessment should include a perinatal history, behavioural/developmental history, family history (SIGN, 2001) and a physical examination for any contraindications for possible medication use, such as some cardiac dysrhythmias. Perinatal history should include about pregnancy and birth, maternal exposure to drugs, alcohol and smoking cigarettes, cannabis etc and high-risk pregnancy (e. g. prematurity, LBW). Behavioural/developmental history should include developmental milestones, difficulty engaging in quiet play and problems with obeying commands. Family History should include history of ADHD, drug or alcohol abuse, psychiatric illnesses, problems with the law, specific precipitant where symptoms can be dated, events precipitating ADHD symptoms such as neglect, physical or sexual abuse, parenting issues and cardiac arrhythmias or sudden death especially in 35 years or younger age, home Environment (key caregivers, frequent moves or frequent change in foster care, frequent changes of school, home environment and family dynamics e. g. single family, same gender partners), interpersonal relationship/s in the family, Poor or crowded housing. History should be obtained about time spent on TV-watching, computer and video games. History should also be obtained about peer relationships, academic under-achievement, truancy, does the child enjoy school, ask the school age child if she/he thinks she/he has trouble concentrating, review current school report as well as those from earlier years and psychometric evaluation by education psychologists for cognitive abilities and academic achievement levels. History of sleep pattern needs to be obtained. Eating History should include appetite and eating habits and joining the other members for dinner. Physical examination is done to document a baseline growth parameters (height and weight) which should be plotted on a centile chart and at each follow-up visit if the child is prescribed medication, blood pressure and pulse rate are recorded and plotted on the centile chart, cardiac examination including auscultation for murmurs and femoral pulses, dysmorphic features suggestive of Fetal Alcohol Syndrome (FAS) or other genetic conditions, cutaneous stigmata, such as café au lait spots, bruising or other evidence of injury, tonsillar hypertrophy suggestive of mouth breathing, neurologic exam and age-appropriate mental status exam, tics, play skills (particularly problem solving), observing the child/parent interaction, co-ordination tasks and handwriting, menstrual/pubertal status in adolescents and if deemed necessary, psychological assessment. The assessment process should take account of the other conditions, which may better account for the challenging behaviour (AACAP, 1997). These might include medical disorders such as sleep apnoea, seizure disorders, developmental disorders (e. g. Intellectual disability (Learning disability, LD ), Specific Learning Difficulty (SpLD) formerly dyslexia and Developmental Coordination Disorder (DCP) formerly dyspraxia), brain injury, use of other medications (e. g. anti-epileptic drug) or sensory impairments; mental health disorders such as Oppositional Defiant Disorder (ODD)/Conduct disorder (CD), anxiety/depression, adjustment disorder, attachment disorder or substance abuse. Other conditions include Autism Spectrum Disorder (ASD) and the normal active preschool child. In addition to the history mentioned above, evaluation of an adolescent should also include eliciting history regarding use of alcohol and drugs, cigarette smoking, number of accidents and speeding tickets, sexual activity and spending history. The above assessments are not indicative of ADHD but may help to rule

out the possibility of other under-lying medical or developmental conditions mimicking ADHD symptoms.

## 6. Guidelines

The guidelines for assessment and treatment have been issued by American Academy of Child and Adolescent Psychiatry (AACAP, 2007), the American Academy of Pediatrics (AAP, 2001), the European Guidelines (Taylor *et al.*, 2004, Banaschewski *et al.*, 2006), National Institute for Health and Clinical Excellence (NICE, 2008) and the Scottish Intercollegiate Guideline Network (SIGN, 2004). While there is a degree of consensus among these publications, there seems to be some international difference such as NICE recommends drug treatment in severe ADHD, whereas the American guidelines advice to start medication and later other management strategy may be considered (CADDRA, 2010).

## 7. Diagnosis

ADHD is a clinical diagnosis for which there are no tests. It is important to gather the information from parents/carers and school. The diagnosis is made by using the diagnosis criteria either of DSM -IV (APA, 2000) or ICD -10 (WHO, 1992). Both major systems of classification identify identical 18 symptoms (table 1).

Inattention (IN)	Hyperactivity (H)	Impulsivity (IMP)
Fails to attend to details	Fidgets with hands or feet	
Difficulty sustaining attention	Leaves seat in classroom	
Does not seem to listen	Runs about or climbs	
Fails to finish	Difficulty playing quietly	
Difficulty organising tasks	Motor excess (on the go, in DSM-IV)	
Avoids sustained effort	Talks excessively (DSM-IV)	Talks excessively (ICD-10)
Loses things		Blurts out answers to questions
Distracted by extraneous stimuli		Difficulty waiting turn
Forgetful		Interrupts or intrudes on others

Table 1. Symptom domains for ADHD in DSM-IV and ICD-10

### 7.1 Differences between the two major diagnostic manuals (table 2)

**7.1.1** In the symptom domains of Inattention, Hyperactivity, and Impulsivity; an ICD-10 diagnosis of HKD needs some symptoms from all three groups whereas DSM-IV ADHD does not, but instead specifies subtypes if symptoms are from only one domain. HKD is broadly similar to severe type of ADHD.

**7.1.2** Because of the high rate of conduct disorder, ICD-10 uses the presence or absence of conduct disorder as the basis for the main subdivision of HKD. DSM-IV does allow the diagnosis of conduct disorder as a comorbid condition.

**7.1.3** Another difference between the two classifications is the use of other conditions as exclusion criteria. ICD-10 aims at a single diagnosis. DSM-IV aims to recognize, as many diagnoses as there are symptoms.

<b>HKD (ICD-10)</b>	Six or Six or more from IN domain, three or more from H domain and one or more from IMP domain.
<b>ADHD &amp; subtypes (DSM-IV)</b>	
Combined type	Six or Six or more from IN domain and six or more from the H / IMP domain.
Inattentive type	Six or Six or more from IN domain and less than six from H / IMP domain+/- H / IMP less than 6
Hyperactive/Impulsive	Six or Six or more from H / IMP domain and less than six from IN domain.

IN: Inattention; H: Hyperactivity; IMP: Impulsivity

Table 2. HKD diagnosis and ADHD diagnosis subtypes

## 7.2 Limitations of diagnosis criteria

Although the DSM-IV and ICD-10 are widely used as diagnostic tools, there are a number of limitations (AAP, 2000).

**7.2.1** The numbers of symptoms required to make the diagnosis of ADHD / HKD does not vary with the severity of the symptoms or with the age. Therefore an older child with a few severe symptoms may not meet the diagnostic criteria, whereas a younger child with many less severe symptoms may meet the criteria, even though the former may experience more functional impairment. For a child with few severe symptoms, the diagnosis of ADHD not otherwise specified that is included in DSM-IV may be used, but the manual provides no criteria for when to make this diagnosis.

**7.2.2** The requirements that symptoms occur in at least two settings can be problematic at times. It may hinder the diagnosis for children who may have significant difficulties with attention in school but do not have problems at home.

**7.2.3** Although the criteria include symptoms be present before 7 years is useful in highlighting that ADHD rarely is the correct diagnosis when inattention, hyperactivity, or impulsivity is occurring for the first time in adolescence or in adulthood; however, it may be problematic in excluding children whose limited attention spans becomes more noticeable when they start secondary school because of increased school and home work.

**7.2.4** The terms "significant" and "some impairment" are subjective and unclear.

**7.2.5** The diagnosis is also environmentally dependent, which explains why clinicians will see differences in the child's behaviour between school and home settings.

**7.2.6** It is a challenge to make a diagnosis when there are no explicit criteria for defining what is typical for a particular age?

**7.2.7** Currently the major diagnosis criteria are only applicable to adolescents up to 18 years of age. There are no diagnosis criteria for adults.

## **8. Management**

Following diagnosis of ADHD, written information and available option of various management strategies, website addresses, and contact details of the local support groups should be given to the parents and the child's school regarding the condition and its management. Parents/carers should be informed that ADHD is a neuro-behavioural condition with a possible genetic aetiology which is the result of low or imbalanced levels of specific neurotransmitters in certain areas of the brain. Abnormally low levels of these neurotransmitters are associated with the impairments that are the hallmarks of ADHD. The need to rule out other possible diagnoses should be explained. Subsequently various treatment options need to be explored. Ensure that the patient and family have had an adequate opportunity to be educated about ADHD (CADDRA, 2010). Do ask the family to find out more about ADHD through reputable websites and recommended reading. They need to be informed of the symptoms that indicate a diagnosis and the aims and rationale for treatment (with an understanding that no medication eliminates all the symptoms of ADHD and that other strategies are also indicated as part of management). There needs to be a discussion of the risks and benefits of the advised therapy and the alternatives. There should also be discussion regarding the potential risks of no therapy. It is important to describe to the parents the findings obtained from the assessment, including a clear statement about the diagnosis and the basis on which the diagnosis is made. The family should be told that a copy of the clinic letter, with their consent, will be sent to the school.

The child's surroundings should support routines and decrease distractions. Consistent age-appropriate limit setting is important. Retaining a positive, enjoyable relationship with their child improves the child's self-esteem. Thus, doing things that the child enjoys is important. Parents/carers need to help the child to develop appropriate social behaviours with peers and adults. Whenever possible, an attempt should be made to work with both parents so that they are consistent with each other in their approaches. Family support should aim to improve relationships within the family, promote parental empowerment and develop strategies to manage behaviour, e.g. through a parenting group. In addition, families should be advised of ADHD parent support groups existing in their area. In many cases careful management of behaviour and advice to parents and teachers and working with the child to control impulsiveness and maintain concentration may be sufficient to manage the problems (AAP, 2001). Where these are not deemed to be sufficient, medication may be tried. Liaison with the school should help inform behaviour management strategies within the classroom. Further support from behaviour specialist teachers may be sought where necessary. The child's school and the school nurse should be notified at the start of medication. Any change of the dosage must be notified to school and school nurse by the prescribing doctor, rather than simply being relayed to them by the parents or the child. Individual counselling or group work may be offered to the child to address issues of low self-esteem as well as to promote social skills and the peer relationships and offer skills in the area of anger management. Time should be spent with the child/young person to help them understand

what ADHD is and if medication is to be used, how it works and its side effects. In the more severe cases, and usually following behavioural interventions, a trial of medication may be considered. ADHD is a chronic condition requiring access to long-term treatment and support, sometimes over many years. However, the level and type of support needed can vary. The principal aims of treatment are to promote the child's development and to reduce secondary difficulties.

### 8.1 Non psychopharmacological interventions

This treatment is a non-drug intervention and is recommended in mild and moderate degree of severity of ADHD (NICE, 2008). The therapist consults with parents and teachers to train them to change the learning environment for the child. It means to physically calming the child, to enable them to stay still, even in a group. The goal is to teach parents and teachers to use rewards and punishment consistently and effectively. Together with the therapist, the parents and teacher find rewards that will motivate the child to work. Group based parenting programmes can help parents/carers to develop their skills and boost confidence in managing challenging and difficult behaviour of their children. Some parenting programmes include Incredible Years, which use Webster Stratton programme for parents of children aged 2 - 8 years (Incredible years), Triple P for parents and the programme run by barnardo's (Barnardo's). Using effective communication skills to develop a loving, guiding, limit setting, consequence providing that rewards the desired behaviour and eliminates the undesired behaviour is the long term aim of non psychopharmacological intervention.

### 8.2 Medications

Advice and support about the child's self esteem, peer group progress, academic progress and family relationships will also be required even if medication is used. A positive response to medication is not diagnostic and a good response to drugs does not validate the diagnosis. The presently available medications are symptomatic therapies; they are not able to cure the condition. Medication aims to reduce the core symptoms and to improve the effectiveness of other interventions. Medication treatment should focus on behavioural improvement and not on getting better grades in school; grades may be the net result of a many factors, including learning disabilities, motivation and family attitudes.

Drugs used in the treatment of ADHD are grouped into two major categories: stimulants and non stimulants. Methylphenidate (MPH) and Atomoxetine (ATX) are not licensed for use in children less than six years of age or in adults. ATX is licensed after 6 years of age and may be continued in adulthood where they have been started in adolescence. Dexamfetamine (DEX) may be prescribed after 3 years of age. Stimulants (MPH and DEX) are not licensed for children with marked anxiety, agitation or tension, symptoms or family history of tics or Tourette's syndrome, hyperthyroidism, angina or cardiac arrhythmia, glaucoma or thyrotoxicosis. Stimulants are controlled by the Misuse of Drugs Act 1971 and are subject to the regulations for Controlled Drugs. For details the practitioners are advised to consult the European treatment guidelines (Taylor *et al.* 2004, Banaschewski *et al.* 2006). Parents should have been explained the advantages and disadvantages of various available drugs. Concerns and questions parents may have regarding both effects and side effects need to be addressed. An explanation of what medication can and cannot do, and what

other interventions are available should be given. Parents/carers should be told that not every medication is suitable for every patient. The guiding principle of drug intervention is to achieve the optimum response with the lowest dose possible that does not give side effects. Therefore, start with a low dose and gradually increased until the maximum recommended dose level is reached or target symptoms have improved or side effects appear. There are recommendations for dosing for different medications in accordance with their licenses. Where there are comorbidities, additional or multiple medications may be used. The summary of product characteristics (SPC) contains specific advice about a drug.

The most important development in ADHD occurred in 1937 with the discovery of the beneficial effect of DEX on attention and behaviour among children (Bradley, 1937). The main breakthrough came in 1957 with the introduction of MPH and subsequently numerous trials confirmed safety and efficacy of stimulants (Laufer, 1971; Eisenberg, 1972). The mechanism of action of both the stimulants; DEX and MPH is similar; they act principally as inhibitors of the dopamine-uptake mechanism in the brain. DEX, in addition, promotes the release of this neurotransmitter, thus stimulating dopaminergic mechanisms. The stimulants also act on norepinephrine-containing neurones to promote an increased release of this monoamine. The most extensively used and researched stimulant is MPH, a derivative of DEX which has a rapid onset of action, short half-life. Dosage and frequency requirements vary with each individual child and are independent of the weight or the age. Stimulants are rapidly absorbed and easily cross the blood- brain barrier. If there is a lack of improvement or substantial side effects, another ADHD drug may be considered another (e.g., MPH vs. DEX). If a patient is responding well to one medication, it is advised that another medication should not be tried to see if there is a better response. Table 3 describes the properties of the ADHD drugs.

Agent	Onset	Max effect	Duration	Half-life	Dosage/day
<b>Short-acting MPH<sup>1</sup></b>					
MPH-IR <sup>2</sup>	20-30 min	1-2 hrs	3- 5 hrs	2-3 hrs	2.5-60 mg
DEX <sup>3</sup>	20-60 min	1-2 hrs	6 hrs	4-6hrs	1.25-40 mg
<b>Long-acting MPH</b>					
Concerta XL <sup>4</sup>	20-30 min	2 hrs	12 hrs	3.5 hrs	18-54 mg
Equasym XL	20-30 min	1-2 hrs	8 hrs	2 hrs	10-60mg
Medikinet XL	20-30 min	1-2 hrs	8 hrs	2 hrs	10-60mg
MPH-SR <sup>5</sup>	1-3 hrs	2 hrs	5-6 hrs	2-6 hrs	20-60mg
<b>Non stimulant</b>					
ATX <sup>6</sup>	1 wk	1- 2 hrs	24 hrs	3.6 hrs in rapid metabolisers	0.5mg/kg x 7 days; then 1.2mg/kg; max 100mg/day

MPH<sup>1</sup>= methylphenidate, MPH-IR<sup>2</sup>= methylphenidate-immediate release, DEX<sup>3</sup>= dexamfetamine, Concerta XL<sup>4</sup>= licensed up to 54 mg per day, MPH-SR<sup>5</sup> = methylphenidate slow release, ATX<sup>6</sup>=atomoxetine

Table 3. Properties of ADHD drugs.

## 8.2.1 Medications

The license status of ADHD medications varies in the different European countries. On average the drugs licensed and available in different European countries are: Methylphenidate immediate release (IR) available as 5, 10 and 20mg tablets (5 and 20mg only available as Medikinet and methylphenidate tablets).

Medikinet® XL (methylphenidate SR) available as 5, 10, 20, 30, and 40mg capsules.

Equasym® XL (methylphenidate SR) available as 10, 20 and 30 mg capsules.

Concerta® XL (methylphenidate SR) available as 18, 27 and 36 mg tablets.

Dexedrine® (Dexamfetamine) available as: 5 mg tablets.

Strattera® (atomoxetine) available as 10, 18, 25, 40, 60 and 80mg capsules.

### 8.2.1.1 Methylphenidate Immediate Release (MPH IR)

MPH is a central nervous system stimulant. The maximum recommended dosage is 0.7 mg per Kg per dose or 2.1 mg per Kg daily in divided doses. It is licensed from six years to eighteen years of age. MPH IR is active for about four hours after the last dose taken.

### 8.2.1.2 Methylphenidate sustained release (MPH SR)

Recently, there is an influx of sustained release stimulants. The first one that came in the market is OROS MPH, or Concerta XL (Tri-layer capsule-shaped tablets). This tablet has an osmotic membrane and overcoat of MPH, has two compartments for MPH, and a push compartment. It also has a laser-drilled hole that allows the release of medication at a pre-specified pace. This medication was developed to replace 3 doses of immediate-release MPH given 4 hours apart; therefore, this drug is active for about 12 hours. The tablet shell may appear in the faeces 20% MPH is excreted due to an osmotic pump action and therefore 18 mg tablet gives 15 mg IR The second MPH reformulation that came to market is marketed as Equasym XL which has a 30% short-acting bead, 70% long-acting bead. It is a Biphasic Release Bead-Delivery System drug. This medication was designed to replace 2 doses of MPH. It is advised to swallow whole or empty capsule contents onto one spoonful of apple sauce or similar soft food such as yoghurt The third MPH compound that came to UK market is called Medikinet XL. It has Bimodal Release for Once-Daily Dosing and has a 50% short-acting bead, 50% long-acting bead, so this medication is designed also to work for 6 to 8 hours to cover the school day. This capsule is either swallowed whole or capsule content can be emptied onto one spoonful of apple sauce or similar soft food Table 4 describes the immediate and extended release proportions of MPH. Ritalin slow Release (Ritalin SR) is not licensed in UK, but sometimes used. It is available as 20 mg tablets.

Concerta XL®			Equasym XL®			Medikinet XL®		
Tablet	IR 22%	ER 78%	Capsule	IR 30%	ER 70%	Capsule	IR 50%	ER 50%
-	-	-	10 mg	3 mg	7 mg	10 mg	5 mg	5 mg
18 mg	4 mg	14 mg	20 mg	6 mg	14 mg	20 mg	10 mg	10 mg
27 mg	6 mg	21 mg	30 mg	9 mg	21 mg	30 mg	15 mg	15 mg
36 mg	8mg	28 mg	40 mg	12mg	28 mg	40 mg	20 mg	20 mg
45 mg	10 mg	35 mg	50 mg	15 mg	35 mg	50 mg	25 mg	25 mg
54 mg	12 mg	42 mg	60 mg	18 mg	42 mg	60 mg	30 mg	30 mg

Table 4. Relative proportions of Immediate-Release (IR) and Extended-Release (ER) methylphenidate

### 8.2.1.3 Dexamfetamine (DEX)

DEX is also a central nervous system stimulant. Its effect and adverse event profile are similar to MPH. The initial dose may be 2.5mg once or twice daily and increased if necessary by weekly increments of 5-10mg in the daily dose. The maximum licensed dose is 40mg daily in divided dosage.

### 8.2.1.4 Safety of stimulant medications

Although some parents express concern that stimulants may cause drug abuse or dependence, a review of long-term studies of stimulants and substance abuse showed that drug abuse was less likely in children with ADHD who were treated with stimulants compared with those who were not (Wilens *et al.*, 2003). Patients or parents/carers, who are at risk for substance abuse/drug-diversion, should not be prescribed short-acting stimulants until precautionary measures have been put. One of the most common reasons for non-compliance is related to a lack of awareness or understanding of the side effects and lack of liaison between the clinician and parents. The common side-effects reported with MPH are insomnia, decreased appetite, pain in abdomen and headache. They are often mild and transient, and may be alleviated by reducing or adjusting the dosage. Many parents complain that their children are 'picky eaters'. In addition, both stimulant and non-stimulant ADHD medication can further suppresses appetite. Moreover children with ADHD may not sit still long enough to finish their meals. Common sense dictates that while balanced diet is not likely to cure ADHD, nutritious food would improve overall health, and thus indirectly benefit behaviour and attention. Unwanted effects of appetite suppression can be avoided by advising the drug to be taken after breakfast and lunch. Problems with sleep are a common complaint among ADHD patients. A decrease in sleep quality and/or quantity may lead to worsening of behaviour. It is therefore important to screen for sleep difficulties. The acronym BEARS (Owens & Dalzell, 2008) is useful for this purpose: **B**edtime resistance and delayed sleep onset, **E**xcessive day time sleepiness, **A**wakenings during night, **R**egularity, pattern and duration of sleep and **S**nororing and other symptoms of sleep-disordered breathing. The causes of sleep problems include anxiety, ODD, sleep disorders (Obstructive Sleep Apnoea, Delayed Sleep Phase Syndrome (DSPS) and Restless Leg Syndrome). Stimulants may increase the difficulty of falling asleep. In DSPS, teenager falls asleep later than the expected time, has a normal sleep at night but wakes up late the next day. Sleep is optimized by maintaining a quiet and comfortable sleep environment. Exposures to TV, computer games or internet chat lines disrupt the initiation of sleep. The bed is not for watching TV, eating, or doing homework. No vigorous exercise within two hours of bedtime is recommended. Avoid drinks containing caffeine such as chocolate, coffee, tea and cola in the late afternoon and evening and advice a bath before bed to help relax. Melatonin is a natural hormone produced by the pineal gland in the brain. It is a sleep inducer and helps to fall asleep at night. Certain foods are rich in melatonin such as oats, rice, sweet corn, barley and tomatoes. Melatonin 2-10 mg may be administered 30-60 minutes before the bedtime for children with significant difficulty getting to sleep. There is evidence that melatonin is safe with short term use, but additional studies are needed to determine its long term safety (Buscemi *et al.* 2006). A very rare but important adverse reaction is bone marrow suppression. A routine full blood count is not warranted unless there is a clinical indication. The most commonly reported adverse effects with ATX are appetite decrease, headache, somnolence, nausea, vomiting and abdominal pain. Hostility

(predominantly aggression, oppositional behaviour and anger) is an uncommon adverse effect with ATX. Aggression is a common side-effect of stimulants. Stimulants are advised to avoid in those with suicidal tendency and suicidal ideation, although suicidal attempt (including completed suicide) is very rare. Patients with emergent suicidal ideation or behaviour during treatment should be evaluated immediately by their physician. Patients on ATX should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability. A full list of potential adverse effects is listed in the summary of product characteristic (SPC) of individual drugs. They are also available online on the Electronic Medicines Compendium website (<http://www.medicines.org.uk/emc/>). Side effects which may warrant dose omission until discussed with an ADHD specialist include raised blood pressure, increase in seizure frequency in patients with epilepsy, heart rhythm changes, blurred eyesight or evidence of rare blood disorders. Anxiety is a commonly occurring adverse event with MPH. Clinical evaluation for anxiety or agitation should precede use of MPH and patients should be regularly monitored for the emergence or worsening of these symptoms regularly. A caution is needed to use ADHD drugs in women of childbearing age as effects of ADHD medications on the foetus and on breast-feeding are unknown. As per the SPC, ATX or MPH should not be used during pregnancy unless the benefit outweighs the risk and DEX is contra-indicated in pregnancy and during lactation. Full list of precautions / contra-indications are included in the SPC. ATX should be discontinued in patients with jaundice or laboratory evidence of liver injury. Very rarely, liver toxicity with elevated hepatic enzymes and bilirubin has been reported. Uses of all ADHD medications with MAOIs are contraindicated. It is good practice to explain to a teenager about the condition and the option of various drugs to gain her/his confidence. The use of medications may protect them from poor social skills. Combining medications for ADHD with illicit drugs or alcohol could be dangerous as the effects may be exaggerated.

#### **8.2.1.5 Is there any tolerance to stimulants?**

Acute tolerance, or tachyphylaxis means in order to maintain the response in the neuron, we need to increase the concentration of medication to maintain the response. In fact, two of the available stimulants, Concerta XL and Equasym XL, use the principle of what's called an ascending curve, meaning that the concentration of MPH goes up across the day to counteract acute tolerance. So the concentration rises across the day. Thus the issue of acute tachyphylaxis has been considered in the development of some of the compounds available today.

#### **8.2.1.6 Non-stimulant**

Atomoxetine hydrochloride (ATX) is a non stimulant drug with no abuse potential and is effective for 24 hours. It is a selective inhibitor of noradrenaline reuptake licensed for the treatment of ADHD in children aged 6 years and older, adolescents and adults. It may be useful in children who do not respond or develop severe side effects to stimulants. Certain situations such as comorbidity with tics, Tourette's syndrome or substance abuse would support ATX as a first line option. It is available as Strattera® 10, 18, 25, 40, 60 & 80 mg capsules. The recommended starting dose in six years or older and adolescents with body weight up to 70kg is 0.5 mg/kg/day (the dosing is weight based). The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The dose is usually administered as a single daily dose but can

also be given in two divided doses. The maintenance dose is 1.2mg/kg/day (depending on the available dosage strengths). No additional benefit has been demonstrated for doses higher than 1.2mg/kg/day. The plasma half-life is 3.6 hours in extensive metabolizers and 21 hours in poor metabolizers. It is not a schedule II drug. Strattera has been studied in trials involving over 4000 children and adolescents with ADHD. Peak efficacy occurs between 2 and 6 weeks after initiation, in contrast to the stimulants, which provide a response within hours. It is safe, well tolerated, and effective in 6 published trials in children and adolescents (Corman *et al.*, 2004). Labelling for ATX includes "Black Box" warning for severe liver injury since February 2005, and for suicidality since November 2005, both of which reflect a pooled analysis of short-term placebo-controlled clinical trials found an average risk of suicidal ideation of 0.4% of children and adolescents (Wooltorton, 2005). Although uncommon, suicidal ideation is reported to be significantly more frequent in paediatric ADHD patients treated with ATX compared to those treated with placebo (Bangs *et al.*, 2008).

### 8.2.1.7 Choosing between stimulant and nonstimulant drug

Tasks that require mental effort change over the years. In childhood there may only be a need to treat during daytime while in adolescents, the need to cover the evenings may be necessary. This may be critical for tasks such as driving. When selecting stimulants Vs non-stimulants, it is helpful to assess and compare the different side effect profiles. Another consideration when choosing a drug category is the onset of action. When patients require rapid response, stimulants are the treatments of choice. Non stimulant may require two to six weeks to show a treatment response. MPH/ DEX/ATX dependence is not a problem in the drug therapy of ADHD.

### 8.2.2 Monitoring

Heart rate, blood pressure, height and weight should be checked regularly and recorded on a growth chart. Drug related side effects should be checked at each clinic visit. Blood tests should not be viewed as routine. Patients and their families/carers need to be educated about ADHD and prescribed drug. Biases against the use of ADHD medications are often due to misinformation regarding side effects. Alternatively, parents/carers may have excessive expectation from the drug therapy which may lead to disappointment. It is important to inform parents/carers that medication is a part of the holistic approach to the management of ADHD. Obtain the completed rating scales to monitor treatment response. Advise the parents to stop the medication during weekends and during school holidays if growth appears to be adversely affected. A telephone call may be beneficial to follow up the prescribed ADHD medication. Once a stable optimal dose has been determined, the ideal medication follow-up is six months. Non-compliance to treatment may be related to lack of frequency of follow-up. A monitoring form such as in appendix 1 may be used in the clinics.

### 8.2.3 Polypharmacy

When a clinician feels that a second medication is needed, it is advised to begin with an ADHD medication that is known to combine safely with the second medication. For example, in the selection of an ADHD medication for a patient with severe conduct disorder and aggressive behaviour, a psychostimulant could be combined with an atypical antipsychotic (Turgay, 2005). MPH SPC has a caution around this combination. Some of the

side effects related to drug interaction occur because of competition for liver enzymes that metabolise the drug. MPH increases plasma concentrations of phenytoin and delays intestinal absorption of phenytoin, phenobarbitone and ethosuximide. MPH inhibits metabolism of tricyclic antidepressants and warfarin. ATX can be combined with stimulants to augment the effect in the case that the clinician feels the patient has not achieved an adequate response (Wilens *et al.*, 2009). Such a combination should be initiated by a clinician with specialization in ADHD. The combinations of ADHD drugs are used sometimes in clinical practice although it is not recommended. Results from the handful of studies suggest that combining stimulant therapy with nonstimulant alternatives may result in more significant symptom reductions in patients for whom monotherapy is less than optimal. There are no studies to suggest that combining stimulant with a non-stimulant increases the risk of cardiac side-effects. Combination usage of stimulant and non-stimulant is not included in the SPCs and hence appropriate safety and efficacy have not been determined.

### **8.2.4 Length of treatment**

Many children will need to be on medication for years, hence the need to be clear about the diagnosis and review the diagnosis if required.

### **8.2.5 Compliance**

Between a third and a half of medicines that are prescribed for long-term conditions are not used as recommended (NICE, 2009). Psychoeducation is the most useful means of ensuring compliance. The aim should be to get the adolescent to take responsibility for his/her own medications. Parents involvement may be necessary to ensure that medication is taken as scheduled. Once-daily dosing improves compliance.

## **8.3 Non psychopharmacological interventions**

ADHD patients may take longer time to integrate socially acceptable habits into their lives. They are at significant risk of being involved with bullying as a bully, as a victim or both. The key factor is to create a positive environment that motivates the individual. When families are reluctant to use medications or there are side-effects behavioural treatments alone can be a viable alternative, provided that both parents and teachers are willing to undertake the effort required. National Institute for Health and Clinical excellence (NICE) recommends group parent training for ADHD with moderate levels of impairment (NICE, 2008). Parents/carers should be informed that children with ADHD may have additional social, academic, and emotional problems. Interventions such as additional help in academic work, social skills training, individual psychotherapy, parent training, family therapy or explaining to the child about ADHD, removing guilt, low self-esteem may be needed for the child and family.

### **8.4 Practice point**

Make sure to review the child's strengths, not just his/her areas of weaknesses. This establishes a rapport with the child and family that makes future visits easier and can aid intervention planning. If there are any signs or symptoms of a physical illness that may be a factor in explaining the clinical symptoms, this takes precedence in the evaluation. Begin the

interview by talking about the child's strengths. Ask the child to draw a picture of themselves and then their family on the same page. This helps to determine the child's perspective of the family. Note any unusual perceptual differences like drawing themselves bigger than the parents. Make appropriate referral if one or both of the parents need an assessment for ADHD or other psychiatric disturbance if it appears evident.

## **9. Treatment consideration in common comorbidities**

It is estimated that at least 65% of children with ADHD have one or more comorbid conditions (Biederman *et al.*, 1991). When there is a comorbid psychiatric disorder, it is generally advised that the ADHD should be treated first. However, if comorbidity puts the patient at risk for harm to others or to himself/herself, then this comorbidity takes precedence for treatment.

### **9.1 Oppositional Defiant Disorder (ODD)**

In childhood, the most common comorbid disorder is ODD in as many as 40% of ADHD children (Taylor *et al.*, 2004). ODD is characterized by the child's inability to accept parental authority and the strong need to be in control. Distinguishing between normal adolescent self-assertion and ODD may not always be easy. Treatment of the ADHD may not resolve all ODD symptomatology. Strategies leading to positive reinforcement and targeting positive goals are often useful. Use of time-out and appropriate strategies that are applied with consistency also help to deal with the oppositional defiance. Behavioural interventions are effective, but they need to be consistent and ongoing.

### **9.2 Conduct Disorder (CD)**

The risk for the development of CD in children with both ADHD and ODD is two to three times greater (Barkley, 2004). Behavioural interventions are necessary for this disorder. Comorbid CD also puts children at risk for gravitating towards other children with similar problems. Strategies that promote positive peer relationships and effective empathy development are indicated. A medication trial may be advised in conjunction with comprehensive psychosocial treatment.

### **9.3 Intellectual Disability (Learning Disability, LD)**

Children with ADHD frequently fall below control groups on standardised achievement tests (Barkley *et al.*, 1990). Children with ADHD often have weaknesses in the cognitive areas of executive functioning, working memory and processing speed. If LD is documented, it may need more one to one support for the age-appropriate educational progress. Children and adolescents with an IQ less than 50 should not ordinarily be prescribed stimulants as they are usually sensitive to the side effects.

### **9.4 Aggression**

Verbal and physical aggression is not uncommon in ADHD. The most common reason why children with ADHD would act aggressively is a combination of ADHD with either ODD or CD. Treating the ADHD is usually the first step. However, aggression might be part of

another diagnosis. Behavioural interventions and all ADHD medications may decrease aggressive behaviour. If needed, new generation antipsychotic medications can be tried. A study has shown that risperidone is effective in controlling ADHD, ODD and CD (Aman *et al.*, 2004). Monitoring of metabolic changes, weight gain, and extra-pyramidal side effects are necessary if an antipsychotic is used.

### **9.5 Bipolar Disorder (BD)**

This is an uncommon disorder in childhood. BD should be considered as the primary diagnosis if there are prominent, episodic, cycling mood symptoms. BD may be suggested by a strong family history of BD or depression and paradoxical response to stimulants (worsening of mood or rage symptoms). If BD is suspected, referral to a Child and Adolescent Psychiatrist is recommended (CADDRA, 2010).

### **9.6 Pervasive Developmental Disorder (PDD)**

PDD presents with difficulties in social communication, social interaction and stereotyped, repetitive behaviour. Clinical symptoms of PDD supersede that of ADHD and should be the primary diagnosis and can co-exist. The FDA recently approved the use of risperidone in controlling aggressive and self-injurious behaviour and irritability (Taylor *et al.*, 2004).

### **9.7 Depression**

Many patients with depression may present with transitional inattention, short-term memory problems, irritability and impulsivity (Voeller, 2004). When the depression is associated with problem in the social environment, treatment strategies include individual and family therapy. Stimulants may produce a mild antidepressant effect in some patients, while they may worsen mood in others. All of the drugs used to treat ADHD have the potential to unmask a mood disorder or to cause mood symptoms.

### **9.8 Anxiety**

Anxiety in ADHD can manifest as Generalized Anxiety Disorder, Social Phobia, Separation Anxiety Disorder, Post Traumatic Stress Disorder (PTSD) or Obsessive-Compulsive Disorder (OCD). PTSD may be a misdiagnosed as ADHD as there are similar symptom complex. PTSD is likely if there is no clear family history of ADHD or pre-morbid symptoms of ADHD prior to the traumatic situation.

### **9.9 Tic disorders**

Stimulant medications can be used to treat ADHD with tic disorders, but caution should be exercised as tics may be exacerbated in some children. If tics appear with stimulants, consider lowering amount/discontinue or change to a non stimulant. The MPH SPC has warnings for tics and anxiety. There are currently no warnings relating to the use of atomoxetine in tics or anxiety. If OCD exists then the combination with ADHD may be part of a Tic Disorder (e.g., Tourette's syndrome) so it is important to look for motor and phonic tics.

### 9.10 Epilepsy

Seizure control is first priority as numbers of seizures are directly related to processing and attention difficulties. Structural abnormality in brain is probably a risk factor for epilepsy with comorbid ADHD. Moreover uncontrolled seizures cause disturbed sleep, which in turn may result in attention difficulties during the day. Side effects of some anti epileptic drugs such as topiramate, vigabatrin, gabapentine are known to increase aggression in LD and many children with epilepsy are likely to have LD. Stimulants seem to be safe in children with well controlled seizures. ADHD children are more prone for unprovoked seizures than the normal population (Hersdorffern *et al.*, 2004). The SPC for MPH state it may lower the convulsive threshold in patients with prior history of seizures and in patients with prior EEG abnormalities.

### 9.11 Substance Use/Abuse Disorder (SUD)

ADHD patients are at increased risk of using illicit substances. It is essential that a history for substance abuse is explored with the individual alone. Ask whether their friends use drugs or alcohol. A positive response suggests they are likely to be at high risk for substance use. By treating ADHD, there is better outcome in comorbid SUD.

## 10. Cardiac risks of drugs

Sudden death with ADHD medications is very similar to those with sudden death in the general population. Structural heart diseases, history of syncope, family history of sudden death/exercise induced sudden death are clues, which can help to suspect a higher risk. The usefulness of ECG screening in patients being treated with drugs is unknown. The small but unproven potential contribution of ADHD drugs to the rare incidence of sudden death in children must be weighed against the clinical benefit of the medication. In a child or adolescent with ADHD, who has no cardiac symptoms, the risk of cardiac adverse events from ADHD medications is very low. The American Heart Association Recommends (Vetter *et al.*, 2008) that before therapy with psychotherapeutic agents is initiated, a careful history should be obtained with special attention to fainting or dizziness particularly with exercise, complaint of chest pain or shortness of breath with exercise and about seizures. The family history should focus on the long QT syndrome, sudden cardiac death or heart attack in members below 35 years of age and history of Marfan syndrome. Presence of these symptoms/risk factors warrants a cardiovascular evaluation by a cardiologist before initiation of drug. Patients should be asked the occurrence of any of the cardiac symptoms during the follow up visits. The physical examination should include checking heart rate and blood pressure.

## 11. Complimentary and Alternative Medicine (CAM) in ADHD

Over the years, a great deal of media attention has focused on diets for treatment of ADHD. Some suggested a "few foods" approach elimination diet if psychological interventions are not effective (Carter *et al.*, 1993; Hill & Taylor, 2001). Most of these dietary manipulations involve eliminating additives (Feingold diet) and foods incriminated to increase hyperactivity, such as sugar, chocolate and caffeine or common food allergens such as wheat, milk and eggs. Several double-blind placebo-controlled studies have failed to

support beneficial effect of dietary manipulation on the behaviour, except possibly in a very small percentage of children (Egger *et al.*, 1992; Wolraich *et al.*, 1995). Few studies have reported behavioural improvement with hypoallergenic diets (Kaplan *et al.*, 1989; Egger *et al.*, 1992; Boris *et al.*, 1994). The results of these studies require further replication before dietary intervention can be considered efficacious. A working group of the American Academy of Child and Adolescent Psychiatry has stated "Given the minimal evidence of efficacy and extreme difficulty of inducing children and adolescents to comply with restricted diet, they should not be recommended (AACAP, 1997). Current evidence suggest that diets are arduous to implement and some may be nutritionally deficient (DTB, 1995) and a restriction or elimination of diet in children with ADHD is not recommended (SIGN, 2001). The available best evidence practice is that a response to food may show change in mood state (irritability) rather than ADHD symptoms per se. An additive-free diet, low in sugar, and avoiding foods that are suspected of exacerbating symptoms is often tried by families to help improve ADHD symptoms. As long as needs for essential nutrients are met, these diets are safe, although their effectiveness in individual children is difficult to predict.

## 12. Long term outcomes

It was thought that hyperactivity simply goes away by adolescence. Although hyperactivity lessens with time but it is often replaced by problems of antisocial behaviour. There appears to be three different patterns of outcomes- resolution of symptoms in young adulthood in about 30%, persistence of some symptoms in about 40% and severe dysfunction associated with persistent symptoms, substance abuse and antisocial behaviour in 30% (Cantwell, 1996). A prospective study in London community survey found that hyperactive behaviour was a strong risk factor for later psychiatric diagnosis, antisocial behaviour, and social and peer problems, even after allowing for a coexistent CD (Taylor *et al.* 1996).

## 13. Summary

ADHD is a persistent and impairing disorder. Although its origin is uncertain, biological, psychological, and social factors are implicated. The first step in the management is accurate diagnosis. Behavioural modification and educational approaches are strategies of first choice. Medication can provide respite from the symptoms during which time other essential aspects of therapy can be implemented. Advice and support about behaviour management and attention to the child's self esteem, peer group interaction, academic progress and family relationships are required even if medication is used. Children with ADHD are cared for at home. Parents are both part of the team and carer for the child and the family needs care themselves. As their child's primary carers, they must be included in the decision of any treatment plans. Some parents collect endless opinions. Sometimes the initial counselling or diagnosis was inadequate and questions that could have been answered were ignored or sidestepped. There are many parents who want specific advice on what more they themselves can do to help the child. For parents of an ADHD child, the number of possible interventions can be extremely confusing. They are likely to hear about a host of treatment options that lack scientific support.

## 14. Key points

- ADHD is a common behavioural disorder with clear diagnosis criteria.
- ADHD co-exists with other conditions in a high proportion.
- Treatment options for ADHD include behaviour management, medications and educational modification.
- Early recognition and treatment of ADHD may result in less antisocial behaviour, criminality and substance abuse in later life.

## 15. Appendix 1.

### Side-effects Questionnaire (parents/carers)

Child's Name: \_\_\_\_\_ D O B: \_\_\_\_\_ Date: \_\_\_\_\_

All medication has side-effects; some are more troublesome than others. We want to make sure that children who are taking medication do not suffer.

For each item, please tick on each line how much that statement applies to your child over the last seven days according to your own observations

- 0 is not at all  
 1 is a few occasions only  
 2 is about half the time  
 3 is most of the time  
 4 is all the time

Symptom	0	1	2	3	4
Talks less than usual					
Poor appetite					
Irritable					
Complains of stomach ache					
Complains of headache					
Drowsy					
Looks sad, miserable					
Looks anxious					
Seems unsteady					
Excited					
Angry					
Has nightmares					
Displays twitches (tics)					

Is there anything else you would like to add?

\_\_\_\_\_

Thank you very much

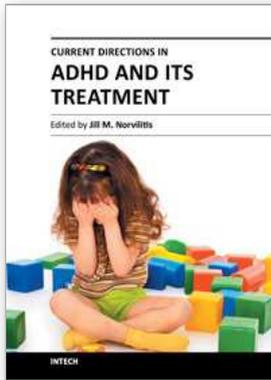
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## **Current Directions in ADHD and Its Treatment**

Edited by Dr. Jill M. Norvilitis

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The treatment of Attention Deficit Hyperactivity Disorder is a matter of ongoing research and debate, with considerable data supporting both psychopharmacological and behavioral approaches. Researchers continue to search for new interventions to be used in conjunction with or in place of the more traditional approaches. These interventions run the gamut from social skills training to cognitive behavioral interventions to meditation to neuropsychologically-based techniques. The goal of this volume is to explore the state-of-the-art in considerations in the treatment of ADHD around the world. This broad survey covers issues related to comorbidity that affect the treatment choices that are made, the effects of psychopharmacology, and non-medication treatments, with a special section devoted to the controversial new treatment, neurofeedback. There is something in this volume for everyone interested in the treatment of ADHD, from students examining the topic for the first time to researchers and practitioners looking for inspiration for new research questions or potential interventions.

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