

Unravelling the mystery of ADHD

Samixa Shah gives an overview of attention deficit hyperactivity disorder and its current drug treatment

Is attention deficit hyperactivity disorder (ADHD) a real illness? This question is often asked because of a belief that ADHD is caused by environment or upbringing and, therefore, should not be treated with medicines. This belief is reinforced by media reports about “drugging” children who behave badly. However, a lot of work has been done to show that differences in brain development, structure and function can give rise to behavioural and learning problems.

The term “ADHD” has been used since 1987. The principal characteristics of ADHD are inattention, hyperactivity and impulsiveness. These appear over many months, with impulsiveness and hyperactivity often preceding those of inattention by a year or more. Different symptoms can appear in different settings, depending on the demands a situation imposes on the child’s self-control but, generally, children with ADHD:

- Are restless, fidgety and overactive
- Continuously chatter and interrupt others
- Are easily distracted and do not finish tasks
- Are inattentive and cannot concentrate
- Are impulsive, suddenly doing things without thinking first
- Have difficulty waiting their turn in games, in conversation or in queues

In 1992, the World Health Organization coined a second term, “hyperkinetic disorder”, which comprises the more serious cases. ADHD is thought to affect around 3 per cent of children, although some studies give figures as high as 19 per cent. It has been found in four times as many males as females but this may be because males tend to show hyperactive and rebellious behaviour more than females. The condition occurs in all ethnic groups. Other conditions, such as anxiety, depression, tics, Tourette’s syndrome and epilepsy can often co-exist with ADHD.

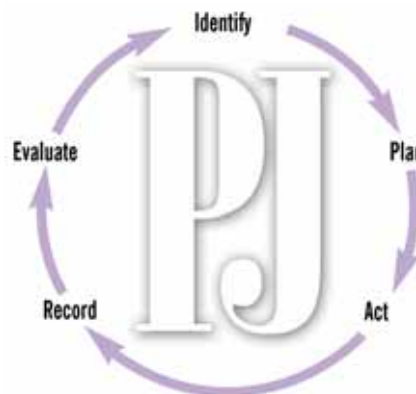
Diagnosis

When hyperactivity, distractibility, poor concentration or impulsivity begin to affect performance at school, social relationships with other children, or behaviour at home, ADHD may be suspected. However, the condition is not easy to diagnose, especially when inattentiveness is the primary symptom. The most commonly used diagnostic guide is the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). This splits symptoms into two categories, inattention and hyperactivity-impulsivity, and the doctor will look at how many symptoms a child has in each category. The WHO International Classification of Diseases, 10th Revision (ICD-10), has a similar list of symptoms for hyperkinetic dis-



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ADHD is thought to affect around 3 per cent of children



Identify knowledge gaps

1. Can you list three signs of ADHD?
2. What is the evidence that ADHD is not simply bad behaviour?
3. Which drugs are used to treat ADHD?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “common disease states” and (see appendix 4 of “Plan and record”).

order. For a diagnosis of ADHD under either ICD-10 or DSM-IV, symptoms must:

- Have been present for at least six months
- Have developed before the child is seven years old
- Be greater than expected for the child’s age and intelligence (ie, more than just being a busy toddler)
- Have a significant negative impact in at least two areas of a child’s life (eg, at home, at school, in the playground, in the community or in social settings)

In addition, the child must not have another disorder that could cause the same symptoms (eg, mood, anxiety or a personality disorder).

The symptoms of ADHD can manifest in children as young as 18 months but, because diagnosis requires observation in at least two different settings, most children are usually of school age before ADHD is confirmed. In addition, sometimes parents do not notice a problem at home because they have no other children to compare with or because they have adjusted to the child’s behaviour. Some people might not be diagnosed until adulthood and others may never be diagnosed. In adults, symptoms are similar but the hyperactivity tends to become a feeling of restlessness or being on edge, fidgeting and a difficulty in relaxing.

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Panel 1: Executive functions affected in ADHD

Executive functions	Features of ADHD
Sustained attention	Poor concentration
Reflection	Impulsivity
Temporary immobilisation	Overactivity
Self-organisation	Lack of planning
Self-regulation	Inflexibility
Self-appraisal	Poor self-esteem
Social cognition	Gaucheness
Compliance	Defiant behaviour
Working memory	Forgetfulness
Co-ordination of movement	Clumsiness

Panel 2: Genes involved in ADHD

Gene	Effect of the ADHD variant gene
Dopamine transporter (DAT1)	Excessive reabsorption of dopamine
Dopamine receptor D4 (DRD4)	Blunted response to dopamine by receptor
Dopamine beta-hydroxylase	Decreased dopamine synthesis
DOPA decarboxylase	Reduced amount of dopamine stored in vesicles
Adrenergic 2A receptor	Blunted response to noradrenaline by receptor

The US has a higher rate of diagnosis of ADHD and prescribing for it than the UK. This is because the definition of ADHD used in the US is wider than hyperkinetic disorder, (which has been used in the UK) and prescription guidelines are more flexible (eg, stimulant drugs are prescribed for children under the age of six years). Some US schools even insist that children with ADHD take medicine or they will be excluded. However, more UK specialists are now using the DSM-IV definition, so rates of diagnosis are rising.

Research

Proof that ADHD is a brain disorder, and not simply a matter of inappropriate child rearing or unrealistic expectations of learning and behaviour, comes from research into executive function deficits, frontal lobe under-activity, neurotransmitter depletion and gene defects.

Executive function deficits The brain carries out tasks in an orderly manner. Lower order functions include talking, moving and seeing, and higher functions, also known as the executive functions, include self-organisation, self-regulation and self-appraisal. Panel 1 lists executive functions and how they are affected in ADHD. Executive functioning can become impaired during brain development (as in ADHD), by trauma (eg, injury) and by neurological disorders (eg, epilepsy).

Frontal lobe underactivity Positron emission tomography can show which part of the brain is active (ie, using glucose and oxygen) at any one time. When normal individuals carry out executive functions, activity in the frontal lobes increases. The frontal lobes communicate with every functional unit of the brain via a rich network of nerve pathways. In most people with ADHD the connecting pathways to and from the frontal

lobes function inadequately. The commonest pathway affected is the fronto-striatal connection, linking the prefrontal cortex to the caudate nucleus, which forms part of the striatum. The striatum works with the frontal lobes. Together, these are referred to as the greater frontal lobes and contain pleasure centres that depend on dopamine for stimulation. Without enough dopamine, individuals cannot experience the pleasure of anticipation and tend to live for the moment. (Drugs of dependence raise dopamine levels in this area, which might explain the high rates of substance abuse in untreated individuals with ADHD.) The nerves in the fronto-striatal connection produce dopamine and noradrenaline. Both these neurotransmitters are significant in ADHD. Serotonin may also play a part in ADHD but its role is less significant.

Neurotransmitter depletion Neurotransmitters transmit electrical impulses from one nerve cell to another. The amount of neurotransmitter present in a synaptic cleft depends on the amount released and how quickly it is metabolised (and thus inactivated). A re-uptake mechanism allows the neurotransmitter to be used again and feedback mechanisms enable the cell to gauge whether there is sufficient neurotransmitter in the synapse or not. In ADHD, dopamine or noradrenaline, or both, are not released or re-loaded effectively, leading to poor transmission of nerve impulses.

Gene defects ADHD is primarily a genetic disorder with a heritability factor of 95 per cent (ie, if a parent has ADHD, there is a 95 per cent chance that his or her child will inherit it). A number of defective genes associated with ADHD have been identified and all of these influence the amount of dopamine and noradrenaline available in nerves connected to the frontal lobes. The most studied are the dopamine D4 receptor (DRD4) and the dopamine transporter (DAT1) genes. Children with impulsive-type ADHD probably have a variant DRD4 gene, which explains their risk-taking behaviour. Examples of genes and the effect of their ADHD variant are given in Panel 2.

Treatment

A comprehensive treatment programme for ADHD should include psychological, educational and social measures and not medication alone. Examples include family therapy focusing on management strategies, individual therapy focusing on changing behaviours, school-based interventions, such as help with reading, social skills training and co-ordination training. Pharmacological treatments aim to increase the amount of dopamine or noradrenaline available. See Panel 3 for details of recent research.

Current prescribing guidelines Drug treatment should be initiated by a specialist but may be continued by GPs under a shared-care arrangement. Treatment is often contin-

A common concern with all these drugs is their potential to retard growth and development

ued into adolescence and may need to be carried on in adulthood. Guidance from the National Institute of Health and Clinical Excellence issued in March 2006 states that methylphenidate, atomoxetine and dexamfetamine are options for the treatment of ADHD in children and adolescents as part of a comprehensive treatment programme. When choosing a drug, prescribers should consider:

- Co-morbidities (eg, methylphenidate can worsen tic disorders)
- Side effects
- Potential for drug misuse (this can change with circumstances and age)
- Preferences of patients and carers

A common concern with all these drugs is their potential to retard growth and development and this should be monitored during therapy.

New clinical guidance from NICE is expected in August and a draft for consultation was launched last month. This includes the statement that drug treatment is not recommended as first line in children under the age of five and the proviso that sometimes doses higher than those in the BNF should be considered.

Methylphenidate Methylphenidate and dexamfetamine increase the amount of dopamine in synapses. Methylphenidate blocks the dopamine transporter thus reducing dopamine reuptake. The dose must be titrated (eg, over four weeks with weekly increments). The appropriate dose is determined by the age and weight of the patient, but the desired outcomes (eg, improved academic functioning, fewer co-morbid symptoms and better behaviour) have significant influence.

Stimulants only alleviate symptoms while each dose is active. Methylphenidate is available in immediate and modified release forms. The immediate release product (eg, Ritalin, Equasym, Medikinet) takes effect an hour after administration and effects last for between three and six hours. Modified release preparations are designed to carry the child through the school day without the need for a midday dose (which also removes the problems of schools having to store a Controlled Drug). In the UK, three modified release preparations are available (Medikinet XL, Concerta XL and Equasym XL). Most are given once a day although some adults take Concerta XL in the morning, followed by a dose at lunch time. These products have two release phases, immediate and prolonged. Each product has a different release profile (see Panel 4) so, if switching between formulations, the total daily dose must be adjusted according to guidelines. The exception is if changing from Medikinet to the once daily product — the total daily dose of methylphenidate remains the same.

Methylphenidate is not licensed for use in children under six years, but the BNF for Children quotes a maximum dose of

Panel 3: The Multimodal Treatment Study¹

The Multimodal Treatment Study of Children with ADHD has followed 579 American children with ADHD and aged seven to nine years, since the 1990s and compared the effects of "intensive medication management" (medicine provided by the study and which included special care in optimising doses — which were generally higher than those used in routine care — and monthly follow-ups), behavioural therapy, a combination of the two and routine community care (which also usually included medication). Results published in 1999 indicated that medication management alone or in combination with behavioural therapy produced better outcomes (reduced symptoms) than behavioural therapy alone or community care at 14 months. This was the first major randomised trial comparing different treatments for ADHD.

An analysis of new data (follow up at three years), published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2007, reveals that by 36 months, the earlier advantage of 14 months of managed medication is no longer apparent. The researchers suggest that possible explanations include age-related decline in ADHD symptoms, changes in medication management intensity and starting or stopping medication altogether. So it appears that medication only may not be a long-term solution.

According to the US National Institute of Mental Health, most children treated in a variety of ways showed "sustained improvement" after three years but the increased risk of behavioural problems, including delinquency and substance abuse, remained higher than normal. Researchers said that it would be incorrect to conclude that treatment makes no difference or is not worth pursuing and that results emphasise that medication can make a long-term difference for some children if it is continued with optimal intensity and not started too late.

The new data also confirmed an earlier finding that decreased growth rate is related to stimulant use. Sixty-five children who had never taken ADHD medicines grew, on average, 2cm taller and 3kg heavier than those who had taken medicines for three years. By the third year, growth rates normalised but there was no rebound growth to make up for the earlier decrease. The MTA study is continuing, following the children through adolescence. Key points for pharmacists to bear in mind include:

- No single treatment is the answer for every child — a number of factors are involved in determining the best treatment
- Manufacturers recommend that drug treatment is suspended every one or two years so that the child's condition can be reassessed
- Appropriate withdrawal strategies are required for patients not continuing with therapy
- New clinical guidance from NICE is expected in August

Panel 4: Modified release methylphenidate

Preparation	Duration of action	IR/ER*
Concerta XL	12 hours	22/78
Equasym XL	8 hours	30/70
Medikinet XL	8 hours	50/50

*IR = percentage of drug released immediately; ER = percentage of drug released gradually

Panel 5: Advice on taking the medicines

It is important to take Medikinet XL and Equasym XL with or after breakfast to achieve an action that lasts and to avoid high plasma peaks. If taken on an empty stomach, the drug is absorbed too quickly. On the other hand, if taken with food that is high in fat, absorption of the drug can be delayed by about 1.5 hours although, according to the manufacturer, advice on types of food is unnecessary. For those who find swallowing the capsules difficult, the contents can be sprinkled in a tablespoon of apple sauce. This should be taken followed by some water. Concerta XL can be taken with or without food. The tablet shell is non-absorbable so some patients may be concerned if they notice what looks like a tablet in their stool. Strattera can also be taken with or without food. The contents of the capsules can be irritant so, ideally, they should not be opened and mixed with food. Instead, the manufacturer suggests the following tips to aid swallowing:

- Take a couple of swallows of milk or juice before the capsule, to make the tongue and throat more slippery
- Try swallowing the capsule with a teaspoon of soft food, such as yoghurt or mousse
- Try putting the capsule on the back of the tongue, taking a sip of a favourite drink and tilting the head back before swallowing

1.4mg/kg daily in divided doses for children between four and six years of age.

The main side effects of the stimulants are loss of appetite and insomnia, and parents have reported children often being awake at 2am. If more than one dose is needed, the second dose should be given early in the evening to avoid any sleep problems. Although methylphenidate is contraindicated in those with tics or a family history of them, some parents may prefer tics to ADHD symptoms. Clonidine has been used alongside methylphenidate to reduce the incidence of tics.

Atomoxetine Atomoxetine is not a stimulant but acts like one, blocking the recycling of noradrenaline. It is active mainly in the frontal lobe and it is less likely to cause or to worsen tics or to cause insomnia than methylphenidate. Strattera, the only product available, is a modified release preparation that can be given once or twice a day but the second dose must be taken no later than early evening. Although Lilly recommends stopping treatment after the first three weeks if there is no significant response some specialists have reported that, in some patients, an improvement is not seen until eight weeks of treatment.

Side effects include anorexia, abdominal pain, dry mouth, nausea and vomiting, palpitations and tachycardia (atomoxetine should not usually be prescribed for children who use salbutamol nebuliser solution). Some specialists suggest that gastric side effects can be reduced by taking the dose with food.

The Committee on Safety of Medicines recommends that patients and carers should be advised of the risk of hepatic disorders and be told to seek help in the event of dark urine, jaundice, abdominal tenderness, nausea and lethargy. Patients and carers should also be advised of the risk of suicidal ideation. Atomoxetine is less likely to be addictive and, therefore, to be abused. As a "black triangle" drug, all possible adverse reactions should be reported. In the case of significant side effects, medication can be stopped abruptly.

Dexamfetamine and other drugs Dexamfetamine is an alternative for patients who do not respond to other drugs. It is licensed for use in children aged over three years. In specialist centres treatment can include the use of bupropion and imipramine (unlicensed).

Adolescents and adults Shortly before puberty, the frontal cortex matures and the nerve cells already present become more powerful. There is also synaptic pruning whereby any newly formed synapses that are not used are discarded.

Frontal lobe synapses formed during late childhood and early adolescence will survive if the child is exercising his or her executive functions. Thus children who are prescribed stimulants at a younger age will be able to cope better during adolescence because they will already be exercising their executive functions. In some people, the first signs of ADHD

Resources

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References

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3. Durham Research. Using fatty acids for learning conditions. Available at www.durhamtrial.org (accessed on 1 February 2008).

present between the ages of 12 and 20 years. These children often drop out of school because they do not receive appropriate intervention in time and are unable to cope — ADHD is not a question of low intelligence, but of being able to cope with normal systems.

Children who have not been treated for ADHD tend to turn to illicit drugs, smoking and alcohol during adolescence and substance misuse often continues into adult life. Studies have shown that a number of adolescents are diagnosed with ADHD while in detention centres and prison officers are now being trained how to deal with them.

Between 50 and 80 per cent of children with ADHD will still have it as teenagers, and up to 60 per cent will still have it as adults. There are few NHS adult ADHD centres in the UK. The two main ones are at the Maudsley Hospital, London, and Addenbrookes Hospital, Cambridge. No drugs are licensed for the treatment of newly diagnosed ADHD in adults and evidence of efficacy is limited.

Foods and supplements

A link between diet and ADHD has been suggested. For example, it is thought that high carbohydrate low protein diets lead to catecholamine (neurotransmitter) depletion. In addition, a study carried out at Southampton University, found that some common food colourings (eg, sunset yellow E110, carmoisine E122, ponceau 4R E124, tartrazine E102 quinoline yellow E104) and sodium benzoate preservative (found in Coca-Cola, Pepsi Max and many fruit drinks) appear to increase the risk of hyperactive behaviour among children.²

Several trials suggests that omega-3 fish oil supplementation might benefit children with ADHD symptoms. In March 2006, Durham Local Educational Authority released the results of its latest study in which teenagers with ADHD-related problems were given fatty acid supplements. At the beginning of the trial, 94 per cent were rated as moderate to severe on inattention scale ratings, but after three months, this had fallen to 17 per cent.³

Role of the pharmacist

ADHD is recognised as a disability under the Disability Discrimination Act and it is important for health professionals to understand the condition and its effects on daily life. Pharmacists can play a specific role in ADHD by giving advice on how best to take medicines, particularly modified release products (prolonged release tablets and capsules and their contents should not be crushed or chewed), and especially when children have problems swallowing capsules (see Panel 5, p193).

Pharmacists can also signpost teenagers, adults and parents of children who have ADHD to information and support services, such as ADDISS (www.addiss.co.uk), and support drug and alcohol service user clients by making them aware of ADHD where appropriate.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Identify any adult drug and alcohol service clients who may have ADHD. Signpost and advise as necessary.
2. Keep an eye out for the new NICE ADHD guidelines. Consider what will they mean for your patients.
3. Find out about your local child and adolescent mental health service.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?