



A current treatment approach for attention deficit hyperactivity disorder

Alasdair Vance, Professor and Head, Academic Child Psychiatry, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Murdoch Children's Research Institute, Melbourne

Summary

Attention deficit hyperactivity disorder is a common neurodevelopmental disorder mainly affecting primary school aged children. There are usually one or more comorbid conditions that add to the child's functional impairment and affect their response to medication and psychosocial treatments. There is emerging evidence that children do better when medicines are given in conjunction with comprehensive behavioural interventions. The psychostimulants dexamphetamine and methylphenidate are the primary drug treatments for attention deficit hyperactivity disorder.

Key words: atomoxetine, dexamphetamine, methylphenidate, psychotropic drugs.

(Aust Prescr 2008;31:129–32)

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterised by developmentally inappropriate levels of inattention and hyperactivity/impulsiveness. It is associated with academic underachievement, social marginalisation, early school-leaving and occupational underachievement. ADHD can have deleterious effects on adult personality formation and is a risk factor for a range of adult psychiatric disorders, alcohol and substance abuse and dependence disorders.¹

The two most common subtypes of ADHD are the combined type, where impairment is due to inattention and hyperactivity/impulsiveness (also known as hyperkinetic disorder), and the inattentive type, where impairment is caused by inattention alone. About 3–5% of primary school aged children have ADHD at any one time, with approximately 1.5% having the combined type. The prevalence of ADHD reduces by approximately 50% every five years from childhood through adolescence into adulthood. Hence, there are a small group of adult ADHD patients who require ongoing comprehensive treatment.

Aetiology

The precise cause of ADHD remains unknown although there appear to be numerous risk factors that contribute to its onset.

Biological factors remain pivotal and include high familial heritability. Genes involved in the regulation of neurotransmitter catabolism and release have been implicated in ADHD.

Dysfunction of the dopamine and noradrenaline neurotransmitter systems are crucial for the onset, progression and treatment responsiveness of children with ADHD. Key regions of the human brain rich in these two neurotransmitters are structurally altered and functionally different in ADHD. These brain regions promote verbal and visuospatial attention, memory, working memory and impulse control. These abilities are known to be deficient in affected children.

Key psychosocial risk factors, such as the quality of relationships in the family unit, school classroom and playground, are now considered to be non-specific maintaining (risk) or protective (resilience) factors, depending on their nature.² Dietary factors such as artificial food colourings and additives are now known to be non-specific risk factors of small effect in primary school aged children. Similarly, other environmental factors such as maternal smoking, exposure to toxic levels of lead, reduced iodine levels and early physical abuse or neglect exert non-specific effects that have remained hard to define.

Comorbid disorders

ADHD is rarely encountered as a 'pure', discrete disorder. The majority of children present with one or more comorbid disorders that can make ADHD symptoms worse or affect treatment responsiveness. Up to 75% of children with tic disorders manifest ADHD. Oppositional defiant disorder (such as impairment due to excessive arguing back, wanting your own way, being negative) affects between a third and a half of children with ADHD, with 2–3% of these children then developing conduct disorder (impairment due to rule-breaking behaviour such as lying, thieving, destruction of property, cruelty). Anxiety disorders such as separation anxiety, social anxiety and obsessive compulsive disorder affect 20–30% of children with ADHD. Similar rates of comorbid depressive disorders such as dysthymic disorder (the most common depressive disorder in children) and major depressive disorder are reported in ADHD sufferers. Language learning disorders (reading, spelling, arithmetic and writing disorders) are present in 20–30% of children with ADHD. Developmental coordination disorder and speech and language disorders make up the list of key comorbid disorders most often associated with ADHD.

However, recent clinical research interest in comorbid autistic spectrum disorders and an early onset form of bipolar disorder may well extend this list.

Diagnosis

A comprehensive specialist clinical assessment is required to identify ADHD. This should include a patient history provided by multiple informants (parents, children, teachers and other responsible adults, siblings, peers with parental permission) and patient examination. Comorbid conditions such as learning disorders, hearing impairment, speech and language developmental delay and developmental coordination disorder need to be identified so they can be treated appropriately.

Treatment strategies

There is insufficient evidence to identify which child with ADHD will respond to psychosocial or drug treatments. All cases of ADHD should be initially treated with psychosocial interventions alone. This is usually sufficient for milder cases, while moderate to severe cases of ADHD need medication in conjunction with psychosocial interventions. Often psychiatric referral is indicated to optimise the complex mix of medication, targeted psychosocial and specific specialist services that are needed to maximise learning and development.^{3,4} These services include speech therapy for speech and language disorders, educational remediation for learning disorders, and occupational therapy for developmental coordination disorder.

At present, there is insufficient evidence to support targeted dietary adjustments or free fatty acid supplementation (for example, fish oils).^{2,4}

Psychosocial interventions

Appropriate psychosocial interventions include positive reinforcement of desired behaviours (including token systems), penalties for undesired behaviours, and contingency contracts for older children and adolescents. Learning techniques to self-manage stress and group social skills training have also proven helpful. In contrast, other psychosocial treatment approaches such as psychodynamic therapies are ineffective, aside from improving a given child's or parents' level of satisfaction that something is being done.²

Dexamphetamine and methylphenidate

The psychostimulants dexamphetamine and methylphenidate remain the primary effective drug treatments for ADHD.^{2,4} They do not differ in effectiveness or adverse effects, although individual patients may appear to respond better to one than to the other.

These drugs decrease ADHD symptoms, improve cognitive deficits (for example, attention, memory and working memory), decrease academic and social impairments due to

ADHD, improve quality of life for children and their families, and increase adherence and learning from psychosocial interventions. These effects were evident in short-term (4–6 weeks) and long-term (1–2 years) controlled trials.

Psychostimulant medications are thought to work by increasing the functional activity of dopamine and noradrenaline through inhibiting their presynaptic uptake. These actions appear to facilitate compensatory brain neural networks that promote more situation-appropriate cognitions, emotions and behaviour in a child with ADHD.⁵ The effects are dose-dependent for hyperactivity/impulsiveness, while, in a subgroup of children, attention and working memory improve at low doses but can become impaired at high doses.

The clinical effects of dexamphetamine and methylphenidate last for 3–4 hours on average, necessitating 2–3 times daily dosing. Modified-release formulations of methylphenidate are available in Australia with the primary advantage of once-daily dosing which aids adherence. The medication can be taken every day during the week with a break on weekends. This is an option that some families may prefer because of mild adverse effects (for example mild initial insomnia) or for ideological reasons (they want their child to use the least amount of medication possible).

Initiating and monitoring drug therapy

Paediatricians, psychiatrists and neurologists are approved prescribers of psychostimulant medication in Australia and should initiate and optimise the dosage in children with ADHD. General practitioners can be approved (through their state drug regulatory authority) to provide maintenance doses when working with a paediatrician or child psychiatrist. They can monitor for specific beneficial and adverse effects of psychostimulant medication and seek a second opinion if unsure of either.

Before starting psychostimulant drug therapy, children with pre-existing heart disease, a strong family history of heart disease or current symptoms and signs suggesting heart disease, require ECG monitoring.⁶

To assess for therapeutic and adverse effects in the early phase of treatment, children should be carefully monitored by their parent(s) for the first five days with weekly consultations by phone or in person. Dosing is usually optimised after 1–2 weeks, and then weekly to monthly face-to-face monitoring is recommended. Each child should be thoroughly reassessed every six months and their requirement for psychostimulant medication re-evaluated. This involves a comprehensive diagnostic reassessment (including risk and resilience factors) and re-targeting of medication or psychosocial treatments to minimise impairment and maximise adaptation. Withdrawal of psychostimulant medication should be considered to evaluate whether ADHD symptoms re-emerge.

Stopping treatment

Psychostimulant treatment should be ceased if there is no beneficial effect at home or at school, unacceptable adverse effects emerge in the short- or long-term, or the legal guardian of the child requests a trial of an alternative treatment.

If psychostimulant medication is ceased, it should be withdrawn gradually decreasing by one tablet per day until finished for short-acting preparations, and by switching from a long-acting to an equivalent short-acting form and then decreasing gradually until finished. Children should be monitored carefully over the following 1–2 weeks for re-emerging ADHD symptoms.

Adult use

Occasionally, psychostimulant medication will need to be continued into adult life. The abuse potential of such drugs has been repeatedly noted in the media. Interestingly, the pharmacodynamic and pharmacokinetic properties of psychostimulant medication and methamphetamine (the illegal form of amphetamine) differ to the extent that psychostimulant medication has a much lower potential for abuse.

Adverse effects

Key adverse effects are all dose-dependent and can be managed through subtle dose reduction. Appetite suppression and initial insomnia are the most common adverse effects, along with nervousness, dysphoria, nausea and headache early in treatment. Motor or vocal tics and growth retardation (of small effect) can occur. Rarer adverse effects are vomiting, rash, dizziness, weight loss and irritability.

Other medications

When psychostimulant medication is ineffective, has adverse effects such as emotional disturbance or worsening of tics, or is not a treatment option that a patient will use, alternative options can be considered.^{2,4} These involve additional types of medication or specific psychosocial interventions known to ameliorate ADHD symptoms when mastered and put into practice by children with ADHD and their families.

Atomoxetine

Atomoxetine is the current second-line treatment for ADHD. It is a potent reuptake inhibitor of noradrenaline at the presynaptic terminal and is of some benefit for children with ADHD in the short and long terms. It has a longer duration of action than psychostimulant medication and can be helpful during the evening and sleep as well as during the day. Its adverse effects profile is similar to psychostimulant medication. Initial insomnia, appetite suppression, irritability and nervousness are the most common adverse effects along with nausea and headache. There is a precaution in the product information that atomoxetine may increase the risk of suicidal ideation.

Imipramine

Imipramine, a tricyclic antidepressant, is a current third-line treatment for ADHD, although it is being virtually phased out of routine clinical practice. It is similar to atomoxetine although it has significant potential for cardiac adverse effects, mainly cardiac arrhythmias and/or conduction defects.

Clonidine

Clonidine, a central adrenergic agonist that reduces the presynaptic release of noradrenaline, is an alternative to imipramine. It can be used when other options are ineffective or contraindicated. Clonidine decreases the hyperactivity/impulsiveness symptoms more than inattention at low doses, while there is some evidence of improved attention at higher doses.

Neuroleptic drugs

Atypical antipsychotics (for example, risperidone) and the sedative antipsychotics (for example, pericyazine) have limited benefit on core ADHD symptoms and unreliably improve cognition. However, they can be of benefit when there is severe co-occurring aggression or irritability/affective instability. Specialist assessment is required before these medications are prescribed, given the potential for drug interactions and effects on the psychosocial treatments being applied.

Drug combinations

Every attempt should be made to use a single medication that maximises benefits and minimises adverse effects. However, combinations of medication are frequently required that target specific key symptoms associated with impairment, for example psychostimulants and clonidine to aid initial insomnia. Specialist advice is always recommended when drug combinations are used.

Conclusion

Developing an effective treatment plan for a child with ADHD involves careful and comprehensive assessment of information from the parents, child and teacher (with permission). Key comorbid conditions need to be identified and specific approved treatments applied for them. These treatments may require the management of ADHD to be modified.

The general practitioner has a central role in reviewing an agreed treatment plan and liaising with the paediatrician or psychiatrist to ensure adjustments are being made as each child with ADHD develops through adolescence into adulthood.

References

1. Sandberg S. Hyperactivity and attention disorders of childhood. Cambridge: Cambridge University Press; 2002.
2. Taylor E, Dopfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, et al. European clinical guidelines for hyperkinetic disorder – first upgrade. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):i7-i30.

- Halasz G, Vance AL. Attention deficit hyperactivity disorder in children: moving forward with divergent perspectives. *Med J Aust* 2002;177:554-7.
- Pliszka S; AACAP work group on quality issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:894-921.
- Vance A, Silk TJ, Casey M, Rinehart NJ, Bradshaw JL, Bellgrove MA, et al. Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Mol Psychiatry* 2007;12:826-32.
- Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. *Circulation* 2008;117:2407-23.

Further reading

Hazell P. Stimulant treatment of attention deficit hyperactivity disorder. *Aust Prescr* 1995;18:60-3.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 139)

- Atomoxetine is the most effective drug for children with ADHD.
- Psychosocial therapy is the initial intervention in ADHD.

Subsidised palliative care medicines

The Pharmaceutical Benefits Scheme (PBS) website contains a new consolidated list of palliative care medications (see www.pbs.gov.au/html/healthpro/browseby/palliative-care). This list is for use in conjunction with the general PBS listings section, which also contains many drugs used in palliative care.

For the purposes of prescribing these medicines, a patient receiving palliative care is defined as 'a patient with an active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life'.

All of the drugs on this list (see box) are 'Authority required'. Prescribers can request an **initial** authority for up to four months of treatment. When **continuing** treatment is required, the prescriber must confirm that a palliative care physician or palliative care service has been consulted about the care of the patient.

Authority approvals can be obtained by phoning 1800 888 333 for general benefits and 1800 552 580 for repatriation benefits.

Prescribers must heed state and territory laws when prescribing narcotic drugs and must notify, or receive approval from, the appropriate health authority.

When a palliative care authority application is for a drug of addiction, the following guidelines apply:

- the maximum quantity authorised is generally for 1 month
- where supply for a longer period is warranted, quantities are for up to 3 months
- telephone approvals are limited to 1 month's therapy.

Doctors should also state (on the prescription) the interval of repeat where repeats are called for, and ensure state and territory health authorities are notified about ongoing treatment.

PBS listings as at 1 September 2008

Analgesics

morphine sulfate tablets (10 mg, 20 mg, 200 mg)
fentanyl lozenges (200, 400, 600, 800, 1200, 1600 microgram)
methadone hydrochloride oral liquid (25 mg/5 mL)
paracetamol suppositories (500 mg) and tablets (665 mg)

Antiemetics and antinauseants

promethazine hydrochloride oral liquid (5 mg/5 mL)
and tablets (10 mg and 25 mg)

Antiepileptics

clonazepam oral liquid (2.5 mg/mL) and tablets
(500 microgram, 2 mg)

Anti-inflammatory and antirheumatic products

diclofenac sodium suppositories (100 mg) and
tablets (25 mg, 50 mg)
indomethacin suppositories (100 mg) and capsules (25 mg)
sulindac tablets (100 mg, 200 mg)
ibuprofen tablets (200 mg, 400 mg)
naproxen tablets (250 mg, 500 mg, 750 mg, 1 g)
naproxen oral suspension (125 mg/5 mL)
naproxen sodium tablets (550 mg)

Drugs for functional gastrointestinal disorders

hyoscine butylbromide injection (20 mg/mL)

Laxatives

bisacodyl suppositories (10 mg) and tablets (5 mg)
sterculia with frangula bark granules (62% / 8%)
lactulose mixture (3.34 g/5 mL)
macrogol 3350 powder (13.125 g sachets)
bisacodyl enemas (10 mg/5 mL)
sorbitol with sodium citrate and sodium lauryl
sulfoacetate enemas (3.125 g/450 mg/45 mg in 5 mL)
glycerol suppositories (700 mg, 1.4 g, 2.8 g)

Psycholeptics

diazepam tablets (2 mg, 5 mg)
oxazepam tablets (15 mg, 30 mg)
nitrazepam tablets (5 mg)
temazepam tablets (10 mg)

Stomatological preparations

benzylamine hydrochloride mouth and throat rinse
(22.5 mg/15 mL)
carmellose sodium mouth spray (10 mg/mL)