

The management of attention-deficit hyperactivity disorder in children: Updated 2019

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder and involves the academic, social and family functioning of the child. It is the most commonly diagnosed behavioural disorder amongst children with a prevalence of approximately 7.2% worldwide, occurring mostly in boys. The consequences of ADHD may be substance abuse and other personality disorders, e.g. delinquency. Research has indicated that drug or behavioural interventions may decrease the rate of conduct and personality disorders. Diet therapy may include polyunsaturated fatty acids (fish oil) and iron supplements in children with low ferritin levels which may improve ADHD symptoms. Drug therapy that involves stimulants (methylphenidate) has been proven to be effective with a good safety profile. However, concerns have been raised about cardiac, psychiatric and growth side-effects. The non-stimulants (atomoxetine) have no abuse potential and reduce insomnia. They also have a better effect on growth in children. Other therapies include antidepressants and α 2-agonists. It is important to treat each patient using individualised therapy. The role of the pharmacist is important to monitor and minimise side-effects. New treatment options comprise modified formulations of currently available medicines.

Keywords: attention-deficit hyperactivity disorder, ADHD, children, methylphenidate, atomoxetine

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed chronic childhood disorders.^{1,2} It is a neurocognitive behavioural developmental disorder that is characterised by a persistent pattern of inattention or hyperactivity-impulsivity.^{1,3} Usually, the condition presents in childhood before the age of seven, but is also seen in adolescence and often extends to the adult years.³ Children with ADHD find it difficult to control their behaviour within their social and school environment. Normally, this interferes with their ability to live normal lives and often results in them not being able to achieve their full potential academically.^{2,3}

Epidemiology

Varying prevalence rates of ADHD have been reported over the years and across the world. These range from 1%–20%.⁴ Estimations differ for a number of reasons, including different diagnostic criteria for ADHD, different risk factors such as age, gender, chronic health problems, socio-economic status, family dysfunction and developmental impairment, as well as methodological differences across studies.^{5,6} The Diagnostic and Statistical Manual of Mental Disorders (DSM) fifth edition (DSM-5) cited a range of

3%–5%.^{3,5} On the other hand, a systematic review and meta-analysis of point prevalence estimates reported a higher overall prevalence of 7.2% (95% CI: 6.7–7.8).⁶ Data on prevalence rates in South Africa are limited and not officially presented, but approximately 8%–10% of children present with ADHD according to the Attention Deficit and Hyperactivity Support Group of Southern Africa (ADHASA).^{7,8}

The incidence of ADHD is greater in boys than in girls.^{3,6,9} The male:female ratio ranges from 2:1 to 9:1, depending on the presentation of the disorder (mainly inattentive or mainly hyperactive-impulsive).³ Evidence suggests that diagnosis could be influenced by gender, as well as non-adherence to diagnostic criteria, with subsequent over-diagnosis of ADHD.⁹ Boys might be seen as the more prototypical ADHD child and therefore diagnosed with ADHD more readily than girls.⁹

ADHD is no longer a condition that only presents in childhood. A South African study showed that ADHD persisted into adolescence in the majority of cases in which ADHD was diagnosed in childhood.⁸ The risk of psychiatric co-morbidities, learning difficulties and adjustment problems were also observed during adolescence.^{8,9}

Main causes and risk factors

The cause of ADHD is not clear. There are numerous possible risk factors for the development of ADHD or exacerbation of ADHD symptoms in individuals with the disorder.⁹ There is strong evidence of a genetic link.^{1,10,11} Children with a first-degree relative with ADHD will have a fourfold to eightfold increased risk of developing the disorder compared with the general population. A concordance rate of 90% for ADHD has been evident from studies of twins.^{12,13} A summary of other environmental risk factors for ADHD is shown in Table I and may require further research.⁹⁻¹⁴

Table I. Environmental risk factors for attention-deficit hyperactivity disorder^{11-13,15,16}

Dietary factors and nutritional deficiencies

- Hypersensitivity to foods and/or additives (preservatives and artificial flavouring and colouring)
- Essential fatty acid (omega-3 and omega-6) and phospholipid deficiencies
- Amino acid deficiencies, especially with low-protein diets
- Excessive consumption of refined carbohydrates and sugar
- Mineral deficiencies (zinc, iron, calcium, magnesium and selenium)
- Antioxidant deficiencies

Biological factors

- Prematurity with very low birth weight
- Foetal hypoxia
- Brain injury

Abnormal lighting

- Natural light ("green" outdoor) deficiency
- Exposure to cool-white fluorescent lighting

Exposure to environmental toxins

- Exposure to heavy metals (lead, cadmium, mercury and aluminium)
- Solvents, pesticides and polychlorinated biphenyls
- Neurotoxins
- Exposure to maternal smoking
- Exposure to maternal alcohol use
- Heroin use during pregnancy

Psychosocial factors

- Disrupted and discordant relationships
- Depriving institutional care
- Harsh parenting style
- Low social class
- Foster placement
- Maternal depression

Pathophysiology

The exact pathological cause of ADHD is not known. It is a very complex neurobiological disorder that is associated with many regions of the brain and neurotransmitters.⁵ From a biological point of view, the neurotransmitters dopamine and noradrenalin, and from a neurological point of view, the prefrontal cortex, have been identified as key to the pathology of ADHD.^{5,12}

Noradrenalin is responsible for maintaining alertness and attention, and dopamine for regulating learning, motivation, goal setting and memory.¹²⁻¹⁴ Both noradrenalin and dopamine predominate in the frontal subcortical system of the brain which is responsible for maintaining attention and memory.¹⁴ Dopaminergic and noradrenergic neurotransmission in the prefrontal cortex are modulated by drugs that are effective in the treatment of ADHD.¹²⁻¹⁴

The prefrontal cortex plays a role in cognitive functions and has many connections with other brain regions.⁵ Evidence from imaging studies suggests that the prefrontal cortex, cerebral volume, basal ganglia and the caudate are smaller or have decreased activation in children with ADHD, than they are in those without the disorder.^{5,12,14}

One ADHD gene (dopamine receptor D4) allele may have conveyed advantage evolutionarily.¹⁷ Higher rates were found in migratory populations.¹⁷ Different thinking styles may assist with solving problems faced today, as this gene might encourage greater innovation or less fearfulness about the challenges of new environments.¹⁷ Risk-taking and innovation when harnessed correctly could offer valuable advantages, of which the process should be guided and assisted by healthcare professionals.¹⁷

Co-morbid conditions

Most children with ADHD (approximately 52%) also present with one or more other co-morbid conditions.^{16,18} Common co-morbidities that are associated with ADHD include learning disabilities, anxiety, depression, conduct disorder, oppositional defiant disorder, tics/Tourette's syndrome and substance abuse.^{15,19}

A thorough examination and screening for the presence of co-morbidities is of utmost importance in the newly diagnosed child with ADHD.¹⁹ Differentiation should be made between the presence of a concurrent condition and secondary symptoms as a result of the primary ADHD diagnosis. Similarly, the true presence of ADHD versus symptoms of inattention and/or hyperactivity that are caused by other psychiatric disorders should be established.^{19,20} Therefore, the child's treatment plan must consider the presence of co-morbidities, and primary treatment should target the disorder causing the most significant impairment.¹⁹

Diagnosis of attention-deficit hyperactivity disorder

The accurate diagnosis of ADHD is important in the effective management of the condition.^{1,21,22} Currently, there is no proven diagnostic test for ADHD. Therefore, a clinical diagnosis, based on specific criteria, is necessary. The diagnostic criteria for ADHD have changed many times over the years, although there is still controversy about accurate diagnosis of the condition.^{21,22} Generally, two sets of diagnostic criteria are used in the diagnosis of ADHD: the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5) criteria published by the American Psychiatric Association³ (5th edition), and the 11th edition of the International

Table II. Diagnostic and Statistical Manual of Mental Disorders³ criteria for attention-deficit hyperactivity disorder**A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterised by (1) and/or (2):**

1. Inattention: Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Inattention

- a. Often fails to give close attention to details, or makes careless mistakes in schoolwork, work or other activities.
- b. Often has difficulty sustaining attention in tasks or play activities.
- c. Often does not seem to listen when spoken to directly.
- d. Often does not follow through on instructions and fails to finish schoolwork, chores or workplace duties (not due to oppositional behaviour or failure to understand instructions).
- e. Often has difficulty organising tasks and activities.
- f. Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort, such as schoolwork or homework.
- g. Often loses things necessary for tasks or activities, for example, toys, school assignments, pencils, books or tools.
- h. Is often easily distracted by extraneous stimuli.
- i. Is often forgetful in daily activities.

2. Hyperactivity and impulsivity: Six (or more) of the following symptoms of hyperactivity/impulsivity have persisted for at least six months, to a degree that is maladaptive and inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

Hyperactivity

- a. Often fidgets with hands or feet or squirms in seat.
- b. Often leaves seat in classroom or in other situations in which remaining seated is expected.
- c. Often runs about or climbs excessively in situations in which it is inappropriate. (In adolescents or adults, this may be limited to subjective feelings of restlessness).
- d. Often has difficulty playing or engaging in leisure activities quietly.
- e. Is often "on the go" or often acts as if "driven by a motor".
- f. Often talks excessively.

Impulsivity

- a. Often blurts out answers before questions have been completed.
- b. Often has difficulty awaiting turn.
- c. Often interrupts or intrudes on others, for example, butts into conversations or games.

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.**C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. at home, school, or work; with friends or relatives; in other activities).****D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.****E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).****Specify whether:**

Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past six months.

Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past six months.

Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met but Criterion A1 (inattention) is not met over the past six months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past six months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in only minor functional impairments.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

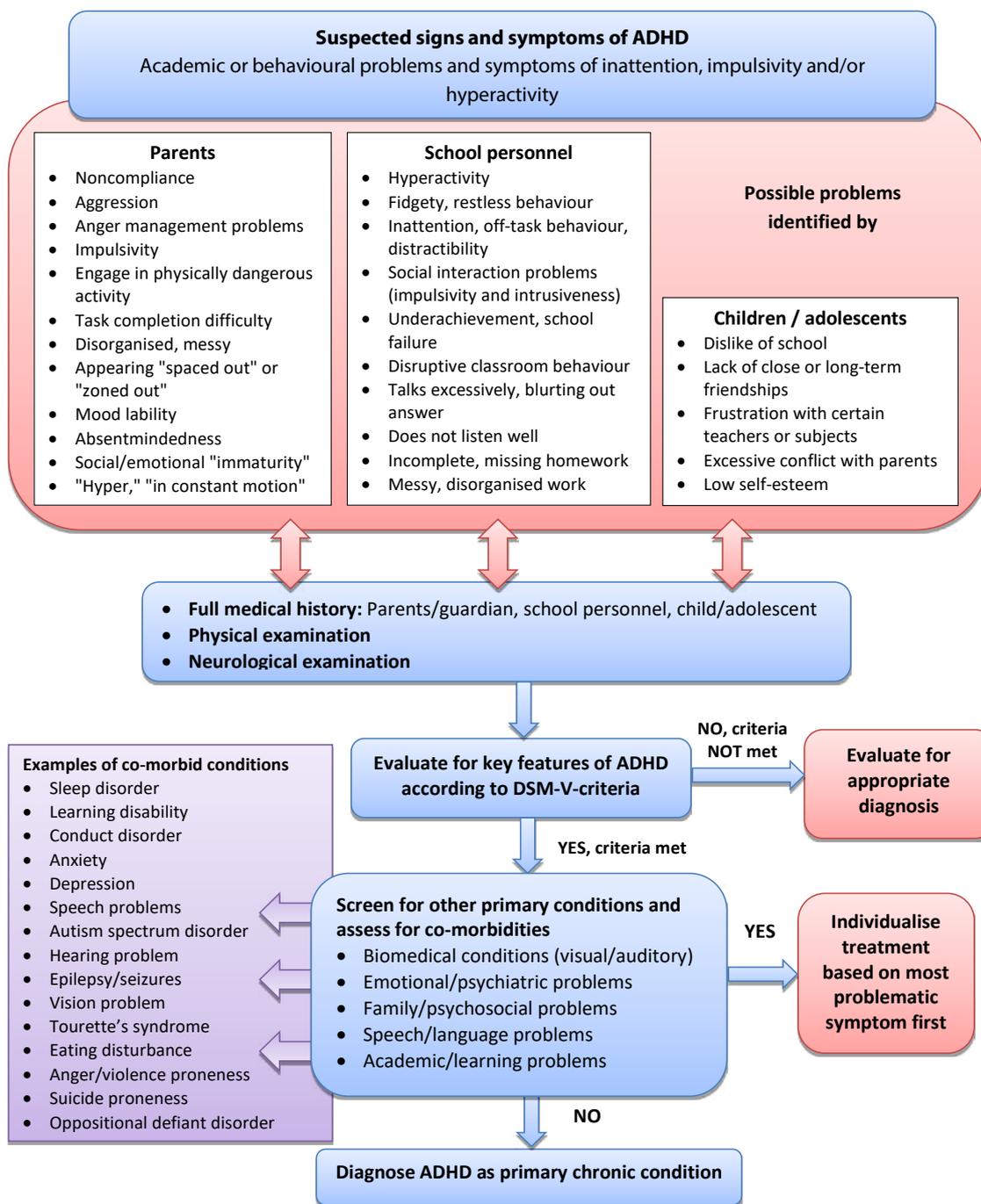


Figure 1. Evaluation and diagnosis of attention-deficit hyperactivity disorder^{1,22,23}

Table III. Three presentations of attention-deficit hyperactivity disorder according to the Diagnostic and Statistical Manual of Mental Disorders criteria^{2,3}

Predominantly inattentive	Combined inattentive hyperactive-impulsive	Predominantly hyperactive-impulsive
<ul style="list-style-type: none"> Approximately 30%–40% of children with ADHD Not overly active, thus symptoms may not be noticed Most common in girls with ADHD 	<ul style="list-style-type: none"> Most common type of ADHD Approximately 50%–60% of children with ADHD 	<ul style="list-style-type: none"> Small percentage (10%) of children with ADHD Characterised by hyperactive and impulsive behaviour Able to pay attention

Classification of Diseases (ICD-11) of the World Health Organization (WHO).^{3,23} The DSM-5³ is mainly used in the USA and South Africa, while the ICD-11²³ is used in the UK and Europe.

It is evident that there are differences between the two classification systems regarding the specific criteria that are

necessary to meet the diagnostic requirements for the diagnosis of ADHD. The main difference is that the DSM-5 criteria can be used to diagnose different subtypes of ADHD and include a description of symptoms for those 17 years and older.^{3,24} The ICD-11 criteria, updated in 2018, are similar to the DSM-5 criteria used to diagnose ADHD.^{22,23}

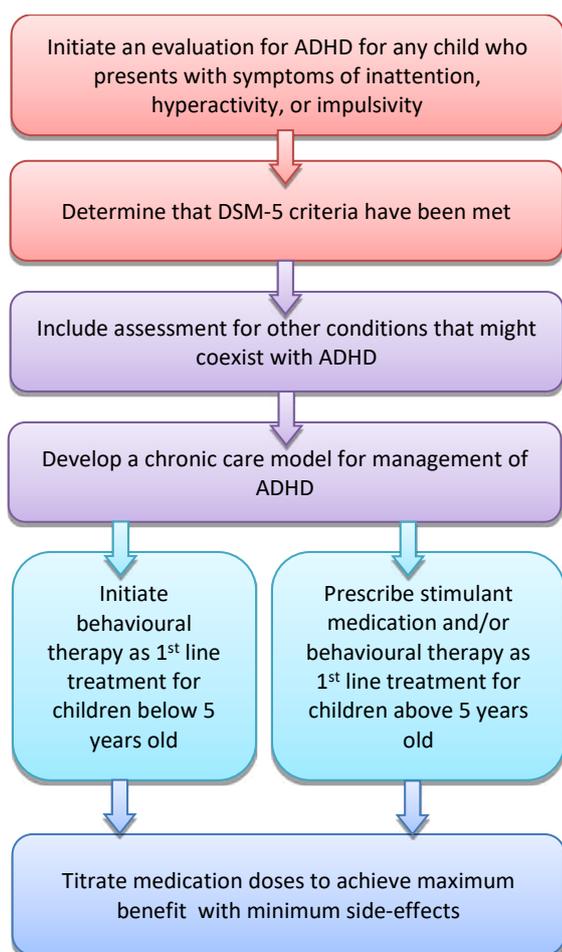


Figure 2. Practice guidelines for the treatment of attention-deficit hyperactivity disorder³¹

The essential diagnostic features of ADHD, according to the DSM-5 criteria, are shown in Table II as criteria A to E.³

The DSM-5 criteria allow for the classification of three presentations of ADHD (see Table III).^{2,3} In many cases individuals present with symptoms of inattention, as well as hyperactivity-impulsivity. There are individuals in whom either one of these patterns of behaviour is dominant.

Because the diagnosis of ADHD is based on the persistent presence of varying symptoms over a period of time, accurate diagnosis relies on the documentation of symptoms that are associated with functional impairment from multiple environments. Therefore, it is important for all role players, including family members, teachers at school and the physician, to collaborate in documenting specific

symptoms and their effects on the child’s daily functioning.^{1,2} An interview with the parent or guardian is essential when the child is assessed for ADHD symptoms, as the child might be unable or unwilling to report symptoms accurately.¹⁴

Various tools and rating scales are available for physicians, parents and teachers to assist them in the process of making a diagnosis.^{1,2} A management plan can only be developed once an accurate diagnosis has been made. The process of evaluation and diagnosis of ADHD is shown in Figure 1.

Treatment

Various strategies are proposed for the management of ADHD and most suggest that non-pharmacological therapy should be first-line treatment for children below five years of age.^{23,25-27} The American Academy of Child and Adolescent Psychiatry’s practice recommends for ADHD to be treated with a comprehensive treatment plan that should include psychoeducation for the family and initial psychopharmacological treatment as approved by the Change to SA Health Products Regulatory Authority.^{3,28} Similar to this, the South African government established guidelines and according to the Education White Paper, “all children and youth can learn and need support and that learners’ individual strengths need to be encouraged”.^{28,29}

Children diagnosed with ADHD require special education and understanding from their teachers, who should be trained on how to manage these children in the classroom.³⁰ Pharmacological interventions seem to focus on the modification in the dopaminergic and noradrenergic systems as the core of the symptoms.³¹ Figure 2 shows a schematic representation of the American Academy of Paediatrics’ practice guidelines, which should be taken into consideration when initiating treatment.³¹

Non-pharmacological therapy

Psychological interventions

Psychological interventions include behavioural techniques, cognitive behavioural therapy, parent training, cognitive training and social skills training.^{25,26}

Behavioural techniques

A broad set of specific interventions is designed to modify the physical and social environment in order to alter or change the behaviour of the child in the management of ADHD.³²⁻³⁴ This is

Table IV. Suggested effective behavioural techniques for children with attention-deficit hyperactivity disorder^{34,35}

	Positive reinforcement	Time-out	Response cost	Token economy
Behavioural technique	Providing rewards or privileges according to good behaviour	Remove any factors that could reinforce problem or unwanted behaviour	Withdrawing rewards or privileges after unwanted or problem behaviour	Combination of positive reinforcement and response cost
Practical example	After completing house duties and assignments, the child can watch TV or play on the computer	After displaying rude behaviour, e.g. hitting a brother, the child has to sit in the corner of the room for a period of time, e.g. five minutes	If homework was not completed, the child loses free time privileges	Child earns stars for completed assignments and loses stars for untoward behaviour, e.g. getting out of his or her seat

carried out, together with modifying the environment where the child is going to school, as well as the home environment.³⁴ Environmental modifications have not been studied as an individual parameter for efficacy, but are included in most treatment plans.³¹ It is recommended that children with ADHD perform better in a structured environment and that psychoeducation should start with the parents.²⁰

Behavioural therapy, involving intensive contingency management techniques, e.g. positive rewards for good behaviour, has been proven to be as highly effective and comparable to low-dose stimulants.²⁰

Techniques that can be used to eliminate inappropriate behaviour include point systems and token economy. Refer to Table IV for behavioural techniques.²⁰

Behavioural techniques are recommended as initial treatment in children with ADHD in the following instances¹⁹:

- ADHD symptoms are mild with minimal functional impairment
- The diagnosis of ADHD has not been confirmed or is uncertain
- The diagnosis of ADHD is disputed between the parents and/or the parents and the teacher
- The parents reject drug therapy

Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) focuses on the interaction between an individual's cognition, emotion and behaviour.²⁵ The aim of CBT is to enable children with ADHD to self-regulate their behaviour, adapt to set rules and routines, interpret information correctly, develop healthy social relationships, alleviate distress and develop a healthy self-esteem.^{36,37} Cognitive behavioural therapy reduces inattention, impulsivity-hyperactivity symptoms and improves concentration.³⁶ Therapy has several goals which include psychoeducation, parent training, organising and planning tasks, problem-solving, emotional regulation and improving social skills.³⁷

Complementary and alternative medicine

Although there is limited evidence to support the efficacy of complementary and alternative medicine (CAM), its use is widespread in the management of ADHD among children and adolescents.^{38,39} There are several types of CAM, namely, dietary modifications, mind-body therapy and natural health products.^{38,39}

Dietary modifications

Many patients are advised to follow diets such as oligoantigenic, elimination and additive-free diets, but these can be disruptive, complicated and very impractical for the family and the patient.³² Iron and zinc may be supplemented in patients with documented deficiencies and may enhance the efficacy of stimulant therapy.³² Omega-3 supplementation may warrant a trial in patients who fail to respond to therapy, or in cases where parents refuse pharmacotherapy.³² Studies have shown that a combination of methylphenidate and Omega-3/6 fatty acids is

beneficial in improving compliance as it increases tolerability of methylphenidate in children.⁴⁰

Mind-body therapy

Results from various studies demonstrated the positive effect of physical exercise and mind-body therapies on children and adolescents with ADHD, especially when combined with pharmacotherapy.^{38,39} Interventions such as martial arts, aerobics, walking, playground activities, relaxation, homeopathy, acupuncture, chiropractic manipulation, yoga and meditation have resulted in improved concentration, planning, academic performance, executive function and cognitive functioning.^{38,39,41-44} Regular physical exercise and mind therapy are especially beneficial when pharmacotherapy is either not the first treatment option or when it does not provide consistent positive outcomes for the child.^{35,43} Physical exercise is affordable, prevents conditions such as obesity and is non-invasive.⁴³

Natural health products

Herbal medicines, such as valerian and chamomile, have traditionally been used to alleviate some of the ADHD symptoms such as restlessness, poor concentration, and sleep difficulties.³⁹ Saffron (*Crocus sativus* L.) has been proven to possess antidepressant, memory enhancing and neuroprotective effects.⁴⁵ A recent double-blinded clinical trial comparing the efficacy and safety of saffron with methylphenidate in children with ADHD over a six-week period, found no significant difference between the two groups.⁴⁵ Further clinical research is required to validate the safety of herbal medicines when used alone or in combination with prescription medicines.^{39,45}

Pharmacotherapy

When initiating pharmacotherapy for the child with ADHD, it is important when counselling the parents or caregivers to stress that the treatment will not be curative, but will target the core symptoms.⁴⁶ Treatment that is discussed in this section will focus on primary ADHD, in other words, ADHD with no co-morbid conditions. This is labelled "multimodal treatment". The objectives of multimodal treatment are depicted in Figure 3.^{46,47}

Recent studies have indicated that treating children with ADHD has a better academic outcome than not treating such children with medicines.^{22,46,47} Some studies have demonstrated the superiority of stimulants over behavioural therapy in alleviating some of the symptoms of ADHD.⁴⁸ Some parents may be apprehensive about initiating stimulant therapy, and may be concerned that the child will be at increased risk of becoming involved in substance abuse later on.²² This is because ADHD itself is associated with a greater risk of developing a substance abuse disorder. Recent studies suggest that stimulant therapy for ADHD neither increases nor decreases the risk of subsequent substance abuse.²² In some instances it has been shown that early stimulant initiation had a protective effect against the emergence of conduct disorders.²²

The use of stimulants in preschool children (aged 3–5 years) should be carefully assessed in terms of the risk versus the benefit ratio.²⁰ These children take longer to clear the drugs from their system

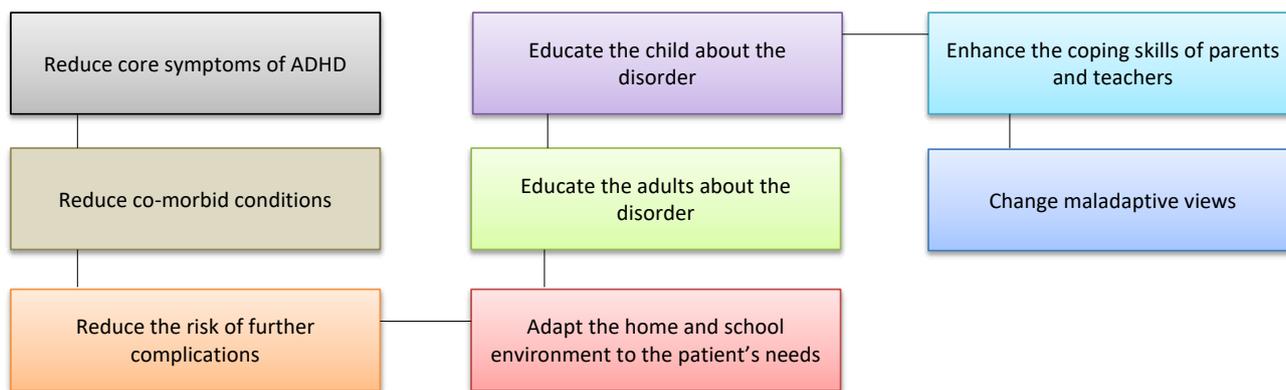


Figure 3. Objectives of multimodal treatment in attention-deficit hyperactivity disorder^{46,47}

and have higher rates of adverse effects, e.g. annual growth rates may be less than expected for height, emotional outbursts and irritability.²²

Principles of medication use

There are a few principles that are important for the pharmacist when counselling the parents⁴⁷:

- All drugs have side-effects. Highlight the ones that may be frightening to the parents.
- It may not be possible to predict which drug will work the best, so advise that each treatment should be regarded as a trial of therapy.
- Prepare the parents for a possible second- or third-line trial.

When therapy is initiated, a number of factors should be considered when evaluating a patient for ADHD or when assessing a prescription. Table V can be used as a checklist by the pharmacist when appraising prescribed therapy for ADHD.

Table V. Checklist for therapeutic monitoring of attention-deficit hyperactivity disorder in children⁴⁶

Key points	Checklist ✓
The dose should be initiated at a low "test" dose (25% of target).	
Dose, timing and preparation (long- or short-acting) must be titrated according to individual needs.	
A drug information leaflet should be provided to the parents and caregivers that contains either the pharmacist's or physician's contact details for urgent advice.	
The response of the patient to the test dose must be monitored regularly, and reviewed after a few weeks. This can be carried out telephonically.	
The efficacy of the medicine should be monitored using a rating scale.	
Before therapy is labelled as ineffective, the dose should be titrated to maximum.	
Symptoms should be controlled all day, unless they are situation-specific.	
Adverse drug effects that are specific to the drug should be assessed.	

Initiating pharmacotherapy

Therapy in the management of primary ADHD will be discussed according to the algorithm as depicted in Figure 4.⁴⁷

Stimulant therapy

Stimulant therapy (methylphenidate and amphetamine) remains the first-line therapy in medication intervention for ADHD, and has the best evidence for safety and efficacy.^{19,46,48} Amphetamine is not available in South Africa. Methylphenidate is an amphetamine derivative that causes an increase in the synaptic concentration of noradrenaline and dopamine via the release of these neurotransmitters by causing a calcium-independent release from the nerve terminal, but also by competitively inhibiting monoamine oxidase.²

Methylphenidate (Ritalin[®], Adaphen[®], Methylphenidate HCl-Douglas[®]) is also available as longer-acting formulations, e.g. Concerta[®], Neocon[®], Ritalin SR[®], Ritalin LA[®], Contramyl XR[®] and Adaphen XL[®]. The longer-acting formulations allow for treatment persistence with reduced switching, increased adherence and eliminate the need for in-school dosing.⁴⁷ Immediate dose-release formulations are useful as they have lower associated costs, provide less insomnia and have the potential to reduce the effects on growth.^{47,48}

Methylphenidate transdermal systems (MTS), not available in South Africa, is an alternative route for drug delivery in children who have difficulty swallowing tablets or capsules.⁴⁹ The once-daily MTS also has the advantage of providing a 12-hourly, weight-based dosing. This does not necessarily result in an improved response. However, weight can be used to determine the amount that the child should receive.^{47,48} Each patient has his or her own individual dose-response curve. The full range of doses should be employed before therapy is said to be ineffective.⁴⁷

The side-effects of the stimulants should be carefully monitored once the treatment regimen has been stabilised.⁴⁸ Baseline information regarding the patient's physical parameters (weight, height and blood pressure) and emotional status should be noted in the patient's file.³¹ These parameters should be regularly recorded by the physician and/or pharmacist. They may be

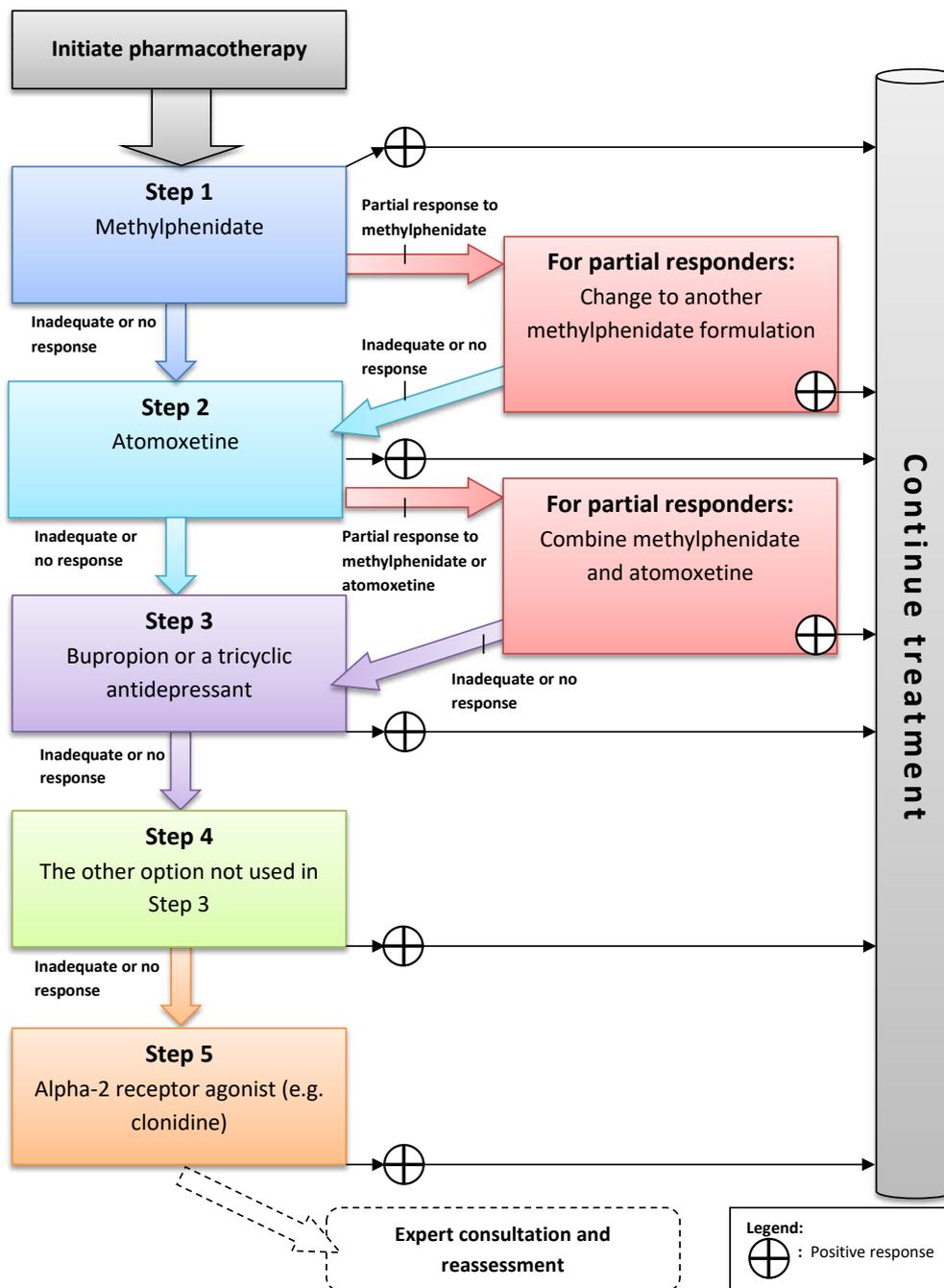


Figure 4. Adapted treatment algorithm for primary attention-deficit hyperactivity disorder⁴⁷

useful for the pharmacist when counselling parents on the use of stimulant medication. Refer to Table VI for the most common side-effects and their management.

Non-stimulant therapy

The only approved drugs in this category include atomoxetine (Strattera®, Iniv®) and guanfacine extended release (Intuniv®), of which only atomoxetine is available in South Africa.^{19,51} Atomoxetine is a nonselective noradrenaline reuptake inhibitor that results in increased synaptic noradrenaline.^{19,34} The difference between atomoxetine and the stimulants, e.g. methylphenidate, is that atomoxetine does not increase the availability of dopamine

in the nucleus accumbens (a decrease in the feeling of euphoria or the abuse potential) and the striatum (the absence of tic and motor activity).³⁴

Atomoxetine is used in children with a failed stimulant trial as first-line therapy due to untoward side-effects, e.g. mood fluctuations or tic disorders, or those with a history of substance abuse.⁵⁰ Dosage in children is weight-based. A gradual increase in the twice-daily dose is recommended over two weeks.¹⁹

The side-effects of atomoxetine are comparable to those of the stimulants, with a few differences. Atomoxetine has a higher risk of suicide, which should be monitored.^{19,34,47} Other side-effects are

Table VI. Stimulant side-effects and their management^{34,50}

Adverse effect	Management strategy
Common	
Reduced appetite and weight loss	Food should be given when the stimulant effects are at their lowest (at breakfast or at dinner). These meals should be high in calories.
Stomach ache	A stimulant should be administered with food.
Insomnia	The dose should be given earlier in the day. The dose that is administered last should be the lowest dose. Sedating medicines can be given at bedtime, e.g. clonidine or melatonin.
Headache	The dose should be given with food, or the dose can be divided. An analgesic may be administered for the headache, e.g. paracetamol.
Irritability and jitteriness	It should be established if there is a co-morbid condition, e.g. bipolar disorder. The co-morbid condition should be treated. The dose of the stimulant can be reduced.
Rebound symptoms*	A longer-lasting stimulant should be considered on a trial basis, or the fast-acting stimulant later in the day at a low dose. Atomoxetine or an antidepressant may also be contemplated as an alternative.
Serious	
<i>Psychiatric (mood changes)</i> Three broad categories have been identified: • Psychosis and mania • Anxiety and panic attacks • Aggression and violent behaviour	All of these should be reported immediately to the physician. A dose reduction, or even cessation of the stimulant, will be required.
<i>Cardiac</i> Children on stimulants have a higher rate of about five beats per minute and an increased blood pressure of 2–7 mmHg.	Stimulants should not be used in children with known cardiac abnormalities. Before initiation of stimulants, all children should be screened for existing cardiac conditions. Ideally, an electrocardiogram should be carried out.
<i>Growth</i> • Decrease of 1 cm per year in height • Weight decrease of 3 kg in the first year of treatment and 1.2 kg in the second year of treatment	Provide a drug-free trial every year. Drug dosages should be evaluated yearly.
Uncommon to rare	
Dysphoria	Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.
Zombie-like state	Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.
Tic (motor) or abnormal movements	Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.
Hypertension or pulse fluctuations	Reduce dosage and consider alternative therapy, e.g. an antidepressant.
Hallucinations	Discontinue treatment and refer to the physician.

*Rebound symptoms are the symptoms that are experienced by the child when the stimulant medication starts to wear off, e.g. later in the afternoon.

gastrointestinal, which can be minimised by taking atomoxetine with a meal.^{33,46} The growth suppression that is associated with atomoxetine is less than that noted with the stimulants. They have been associated with a moderately increased heart rate as compared to the stimulants.¹⁵ Hepatotoxicity and cases of severe liver injury are rare.^{15,52} Liver function should be monitored and therapy should cease if there is any evidence of liver dysfunction, without rechallenge being attempted.⁵³ Compared to the stimulants, atomoxetine can cause sedation and dizziness. It is sometimes used in combination with a stimulant in patients who are only partially responsive.^{35,50}

Antidepressant treatment

This includes either bupropion or a tricyclic antidepressant (imipramine or amitriptyline).³⁸ Bupropion is involved in the reuptake inhibition of dopamine and noradrenaline and potentiates dopaminergic neurotransmission.³⁸ Bupropion causes less appetite suppression, but has a greater risk for seizures.⁴⁷ During overdose, the tricyclic antidepressants have the highest risk of cardiovascular side-effects. Therefore, they should be

the last line of therapy.^{34,47} They inhibit the reuptake of both noradrenaline and serotonin, and also act as antagonists on the muscarinic receptors (with untoward anticholinergic side-effects), α_1 -adrenergic receptors and H_1 receptors.³⁴

α -agonists

Clonidine acts as a central α_2 -adrenergic agonist pre-synaptically to inhibit noradrenaline release, and post-synaptically to increase the blood flow in the prefrontal cortex.^{35,42} The increased blood flow to the prefrontal cortex has been shown to improve working memory and executive functioning.^{46,48} Cardiovascular adverse events have raised some concern over the years, however there is little evidence thereof, including no significant corrected QT abnormalities.⁵⁴ Pulse and blood pressure should be monitored periodically.^{34,47} α -agonists may be used as adjunct therapy to reduce aggressive behaviour and to improve sleep.^{40,42}

New advances in the management of ADHD

New formulations to increase compliance and reduce stigmatisation have become a focus area of treatment in ADHD.

To this effect, in 2015, the Food and Drug Administration (FDA) approved a once-daily extended-release oral liquid for the treatment of ADHD in children aged six years and older.⁵⁵⁻⁵⁷ Another paediatric dosage formulation, a chewable tablet form of extended-release methylphenidate, to be sold as QuilliChew ER[®], for treatment of ADHD in patients aged six years or older has also been approved by the FDA. The chewable tablet will also be sold in strengths of 20, 30, and 40 mg and are scored so they can be split easily. Like the other products the tablet should be taken once daily in the morning.⁵⁵⁻⁵⁷ A novel formulation of amphetamine (Adzenys XR-ODT[®]) was recently approved for ADHD treatment in patients from six years of age and older. It is the first approved extended release orally disintegrating tablet and does not require chewing or water to disintegrate thus making it a suitable option for children with swallowing difficulties.⁵⁸ The formulation is not available in South Africa.

New molecules are currently undergoing clinical trials. It seems as though some of these molecules currently being developed are modified versions of already available medicines or have similar mechanisms of action.

Conclusion

ADHD is a complex condition with multiple aetiologies and an intricate pathophysiology that may not yet be well understood. The treatment involves a multimodal approach and active discussion with parents, the child and the pharmacist. The pharmacist has an important role to play in monitoring the drug therapy to prevent serious side-effects. This is true for all the drug classes. It is important that the pharmacist has knowledge of each of the drugs, their place in therapy and their side-effect profile. To improve adherence to treatment it is imperative for the pharmacist to seek out the drug, dose and dosage form that will be best suited to the needs of the patient.

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