The management of attention deficit-hyperactivity disorder in children

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Abstract
Attention deficit-hyperactivity disorder (ADHD) involves the academic, social and family functioning of the child. Prevalence of the disorder is approximately 5.3% worldwide and occurs 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 nonstimulants (atomoxetine) have no abuse potential and reduce insomnia. They also have a better effect on growth in children. Other therapies include antidepressants and α₂ agonists. It is important to treat each patient using individualised therapy. The role of the pharmacist is important to monitor and minimise side-effects.

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.4,5 A systematic review of prevalence studies estimated a worldwide pooled prevalence rate of 5.3%.4 Data on prevalence rates in South Africa are limited, but approximately 4-5% of children present with ADHD.6,7 The incidence of ADHD is greater in boys than in girls.3,8 The malefemale ratio ranges from 2:1-9:1, depending on the subtype of the disorder (mainly inattentive or mainly hyperactive-impulsive).1 Evidence suggests that diagnosis could be influenced by gender, as well as nonadherence to diagnostic criteria, with subsequent overdiagnosis of ADHD.8 Boys might be seen as the more prototypical ADHD child and therefore diagnosed with ADHD more readily than girls.8

ADHD is no longer a condition that only presents in childhood. A recent South African study showed that ADHD persisted into adolescence in the majority of cases in which ADHD was diagnosed in childhood.9 The risk of psychiatric co-morbidities, learning difficulties and adjustment problems were also observed during adolescence.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.10 There is strong evidence of a genetic link.1,10-12 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.10,14
Pathophysiology

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

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

The prefrontal cortex plays a role in cognitive functions and has many connections with other brain regions. Evidence from imaging studies suggests that the prefrontal cortex, cerebral volume, basal ganglia and the caudate nucleus are smaller or have decreased activation in children with ADHD.

Co-morbid conditions

Most children with ADHD also present with one or more other co-morbid conditions. 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.

A thorough examination and screening for the presence of co-morbidities is of utmost importance in the newly diagnosed child with ADHD. 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 vs. symptoms of inattention and/or hyperactivity that are caused by other psychiatric disorders should be established. Therefore, the child's treatment plan must consider co-morbidities. Primary treatment should target the disorder that causes the most significant impairment.

Diagnosis of ADHD

The accurate diagnosis of ADHD is important in the effective management of the condition. 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. There is still controversy about accurate diagnosis of the condition. Generally, two sets of diagnostic criteria are used in the diagnosis of ADHD: the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria published by the American Psychiatric Association (4th edition), and the 10th edition of the International Classification of Diseases (ICD-10) of the World Health Organization. The DSM-IV-TR is mainly used in the USA and South Africa, while the ICD-10 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-IV-TR criteria can be used to diagnose different subtypes of ADHD. The ICD-10 criteria is used to diagnose hyperkinetic disorder, which is a narrower definition than ADHD and requires a greater degree of symptom expression.

The essential diagnostic features of ADHD, according to the DSM-IV-TR criteria, are shown in Table II as criteria A to E. 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. The DSM-IV-TR criteria allows for the classification of three subtypes of ADHD (Table III).
Table II: DSM-IV-TR criteria for ADHD

A. Either (1) or (2)

1. 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:

   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. 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:

   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.
   g. Often blurts out answers before questions have been completed.
   h. Often has difficulty awaiting turn.
   i. Often interrupts or intrudes on others, for example, butts into conversations or games.

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before seven years of age.

C. Some impairment from the symptoms is present in two or more settings, for example, at school/work or at home.

D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder, and are not better accounted for by another mental disorder, e.g. mood disorder, anxiety disorder, dissociative disorder or personality disorder.

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 and the physician, to collaborate in documenting specific symptoms and their effects on the child’s daily functioning. 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.

Various tools and rating scales are available for physicians, parents and teachers to assist them in the process of making a diagnosis. 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. The American Academy of Child and Adolescent Psychiatry’s practice guideline recommends that ADHD be treated with a comprehensive treatment plan that should include psychoeducation for the family and initial psychopharmacological treatment. Pharmacological interventions seem to focus on the modifications in the dopaminergic and noradrenergic systems as the core of the symptoms. Figure 2 is a schematic representation of the practice guidelines which should be taken into consideration when initiating treatment.

Behavioural interventions

A broad set of specific interventions are designed to modify the physical and social environment, in order to alter or change the behaviour of the child in the management of ADHD. This is carried out, together with modifying the environment where the child is going to school, as well as the home environment. Environmental modifications have not been studied as an individual parameter for efficacy, but are included in most treatment plans. It is recommended that children with ADHD perform better in a structured environment and that psychoeducation should start with the parents.

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

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

Behavioural techniques are recommended as initial treatment in children with ADHD in the following instances:
Suspected signs and symptoms of attention-deficit hyperactivity disorder

Academic or behavioural problems and symptoms of inattention, impulsivity and/or hyperactivity, identified by:

- Full medical history: Parents or guardian, school personnel, and the child/adolescent himself or herself
- Physical examination
- Neurological examination

Examples of co-morbid conditions:9,16

- Sleep disorder
- Learning disability
- Conduct disorder
- Anxiety
- Depression
- Speech problems
- Autism spectrum disorder
- Hearing problems
- Epilepsy and seizures
- Vision problems
- Tourette’s syndrome
- Eating disturbances
- Prone to anger and violence
- Prone to suicide
- Oppositional defiant disorder.

Evaluate for key features of ADHD according to the DSM-IV-TR criteria

No, criteria not met

Evaluate for appropriate diagnosis

Yes, criteria met

Screen for other primary conditions and assess for co-morbidities:

- Biomedical conditions (visual and auditory)
- Emotional and psychiatric problems
- Family and psychosocial problems
- Speech and language problems
- Academic or learning problems.

Yes

Individualise treatment based on most problematic symptom first

No

Diagnose ADHD as the primary chronic condition

Figure 1: Evaluation and diagnosis of ADHD1,18
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.

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. Iron and zinc may be supplemented in patients with documented deficiencies and may enhance the efficacy of stimulant therapy. Omega-3 supplementation may warrant a trial in patients who fail to respond to therapy, or in cases where parents refuse pharmacotherapy.

Pharmacotherapy

On initiating pharmacotherapy in 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. 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.

Recent studies have indicated that treating children with ADHD has a better academic outcome than not treating such children with medicines. Certain studies have demonstrated the superiority of stimulants over behavioural therapy in alleviating some of the symptoms of ADHD. Some parents may be apprehensive about initiating stimulant therapy. They may worry that the child will be at increased risk of becoming involved in substance abuse later on. This is because ADHD 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. In some instances, it has been shown that early stimulant initiation had a protective effect against the emergence of conduct disorders.

The use of stimulants in preschool children (aged three to five years) should be carefully assessed in terms of the risk vs. benefit ratio. These children take longer to clear the drugs from their system and have higher rates of adverse effects, e.g. reduced annual growth rates, emotional outbursts and irritability.

Principles of medication use

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

- 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, the following 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.
Initiating pharmacotherapy

Therapy in the management of primary ADHD will be discussed according to the algorithm depicted in Figure 4.25

Stimulant therapy

Stimulant therapy (methylphenidate and amphetamine) remains the first-line therapy in medication intervention for ADHD. It has the best evidence for safety and efficacy.19,24,27 Amphetamine is not available in South Africa. Methylphenidate (Ritalin®) 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, and also by competitively inhibiting monoamine oxidase.2

Table V: Checklist for therapeutic monitoring of ADHD24

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>The dose should be initiated at a low “test” dose (25% of target).</td>
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<tr>
<td>Dose, timing and preparation (long- or short-acting) must be titrated according to individual needs.</td>
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<tr>
<td>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.</td>
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<tr>
<td>The response of the patient to the test dose must be reviewed after a few weeks. This can be carried out telephonically. The response of the patient to the test dose must be monitored regularly.</td>
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<tr>
<td>The efficacy of the medicine should be monitored using a rating scale.</td>
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<tr>
<td>Before therapy is labelled as ineffective, the dose should be titrated to maximum.</td>
</tr>
<tr>
<td>Symptoms should be controlled all day, unless they are situation specific.</td>
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<tr>
<td>Adverse drug effects that are specific to the drug should be assessed.</td>
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</tbody>
</table>

Table VI: Stimulant side-effects and their management23

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Management strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td></td>
</tr>
<tr>
<td>Reduced appetite and weight loss</td>
<td>Food should be given when the stimulant effects are at their lowest (at breakfast or at dinner). These meals should be high in calories.</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>A stimulant should be administered with food.</td>
</tr>
<tr>
<td>Insomnia</td>
<td>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.</td>
</tr>
<tr>
<td>Headache</td>
<td>The dose should be given with food, or the dose can be divided. An analgesic may be administered for the headache, e.g. paracetamol.</td>
</tr>
<tr>
<td>Irritability and jitteriness</td>
<td>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.</td>
</tr>
<tr>
<td>Rebound symptoms*</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Psychiatric (mood changes)</strong></td>
<td>All of these should be reported immediately to the physician. A dose reduction, or even cessation of the stimulant, will be required.</td>
</tr>
<tr>
<td>Three broad categories have been identified:</td>
<td></td>
</tr>
<tr>
<td>• Psychosis and mania</td>
<td></td>
</tr>
<tr>
<td>• Anxiety and panic attacks</td>
<td></td>
</tr>
<tr>
<td>• Aggression and violent behaviour.</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>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.</td>
</tr>
<tr>
<td>Children on stimulants have a higher heart rate, by about five beats per minute, and blood pressure is increased by 2-7 mmHg.</td>
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</tr>
<tr>
<td><strong>Growth</strong></td>
<td>Provide a drug-free trial every year. Drug dosages should also be evaluated yearly.</td>
</tr>
<tr>
<td>• Decrease of 1 cm per year in height</td>
<td></td>
</tr>
<tr>
<td>• Weight decrease of 3 kg in the first year of treatment and 1.2 kg in the second year of treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon to rare</strong></td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.</td>
</tr>
<tr>
<td>&quot;Zombie-like&quot; state</td>
<td>Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.</td>
</tr>
<tr>
<td>Tic (motor) or abnormal movements</td>
<td>Reduce dosage and consider alternative therapy, e.g. atomoxetine or an antidepressant.</td>
</tr>
<tr>
<td>Hypertension or pulse fluctuations</td>
<td>Reduce dosage and consider alternative therapy, e.g. an antidepressant.</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Discontinue treatment and refer to the physician.</td>
</tr>
</tbody>
</table>

* Rebound symptoms are the symptoms that are experienced by the child when the stimulant medication starts to wear off, often later in the afternoon.
Methylphenidate is also available as longer-acting formulations, e.g. Concerta®, Ritalin SR® and Ritalin LA®. The longer-acting formulations allow for treatment persistence with reduced switching and increased adherence, and eliminate the need for in-school dosing. Immediate dose-release formulations are useful as they have lower associated costs, cause less insomnia and have the potential to reduce the effects on growth.

Methylphenidate transdermal systems (MTS) are a novel way to provide a new strategy for drug delivery in children who have difficulty swallowing tablets or capsules. 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. 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.

The side-effects of the stimulants should be carefully monitored once the treatment regimen has been stabilised. Baseline
information regarding the patients’ physical parameters (weight, height and blood pressure) and emotional status should be noted in the patient’s file. These parameters should be regularly recorded by the physician and/or pharmacist. They may be 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 drug in this category is atomoxetine (Strattera®). It is a nonselective noradrenaline reuptake inhibitor that results in increased synaptic noradrenaline. 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).

Atomoxetine is used in children who have 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. Dosage in children is weight based. A gradual increase in the twice-daily dose is recommended over two weeks. The side-effects of atomoxetine are comparable to those of the stimulants, with a few differences. Clearly, atomoxetine carries a higher risk of suicide. This should be monitored. Other side-effects are gastrointestinal. These can be minimised by taking atomoxetine with a meal. The growth suppression that is associated with atomoxetine is less than that noted with the stimulants. However, compared to the stimulants, it has been associated with a moderately increased heart rate. Hepatotoxicity was noted in two patients: a boy and a man. The liver function should be monitored and therapy should cease if there is any evidence of liver dysfunction, without rechallenge being attempted. 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.

**Antidepressant treatment**

This includes either bupropion or a tricyclic antidepressant (imipramine or amitriptyline). Bupropion is involved in the reuptake inhibition of dopamine and noradrenaline and potentiates dopaminergic neurotransmission. Bupropion causes less appetite suppression, but has a greater risk for seizures. During overdose, the tricyclic antidepressants have the highest risk of cardiovascular side-effects. Therefore, they should be the last line of therapy. They inhibit the reuptake of both noradrenaline and serotonin, and also act as antagonists on the muscarinic receptors (with untoward anticholinergic side-effects), α₂-adrenergic receptors and H₁ receptors.

**Alpha agonists**

Clonidine acts as a central α₂-adrenergic agonist presynaptically, to inhibit noradrenaline release, and postsynaptically, to increase the blood flow in the prefrontal cortex. The increased blood flow to the prefrontal cortex has been shown to improve working memory and executive functioning. Serious cardiovascular side-effects and sudden death in children have been published. Pulse and blood pressure should be monitored periodically. Alpha agonists may be used as adjunct therapy to reduce aggressive behaviour and to improve sleep.

**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 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.

**References**


News

Looking for a stocking filler?

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Dawn Garisch is unusual. She is both a doctor and an award-winning author. Her latest book, Eloquent Body, is her first non-fiction publication and is largely autobiographical.

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