Evidence-based Pharmacy Practice (EBPP):

Attention deficit hyperactivity disorder (ADHD)

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric conditions.¹ The core symptoms of ADHD are hyperactivity, impulsivity and/or inattention. These symptoms can lead to problems in academic achievement, behaviour, personal relationships with family and peers and low self-esteem. Symptoms first present in childhood and can continue through adolescence into adulthood. Co-morbid disorders include oppositional defiant disorder, conduct disorder, anxiety, depression, tics and Tourette's syndrome, and epilepsy. Stimulants are first-line in the pharmacological treatment of ADHD. Methylphenidate is the most common drug prescribed in this condition. Pharmacological treatment should form part of a comprehensive treatment plan which should include psychological, educational and social measures assessed on an individual basis.

Definitions

ADD stands for Attention Deficit Disorder and ADHD stands for Attention Deficit Hyperactivity Disorder. Internationally ADHD is the term that includes both ADD and ADHD.

ADHD is a behavioural syndrome characterised by the core symptoms of inattention, hyperactivity and impulsivity.^{2,3} ADHD can be diagnosed using either DSM-IV or ICD-10 criteria.

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders 4th Edition.⁴

Under this classification ADHD is divided into three types namely: predominantly inattentive, predominantly hyperactive-impulsive or a combination of the two.²

ICD-10 – International Classification of Mental and Behavioural Disorders 10th revision.⁵

Under this classification the signs of ADHD are given the name "Hyperkinetic disorder".5

Epidemiology

ADHD is a common disorder which affects 4% to 5% of South African children.⁶ ADHD is more common in boys than girls (male to female ratio 4:1 for predominantly hyperactive type and 2:1 for predominantly inattentive type).⁷ Girls display more inattention and less hyperactive and impulsive symptomology.^{8,9}

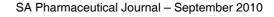
Children and adolescents with ADHD frequently have comorbid psychiatric disorders. These can be oppositional defi-

ant disorder, conduct disorder, depression, anxiety disorder, and with many developmental disorders such as speech and language delays and learning disabilities. The co-morbid conditions can be primary or secondary (exacerbated by the ADHD). Other conditions such as tics and Tourette's syndrome and epilepsy can also co-exist with ADHD. These conditions must be treated independently of the ADHD.

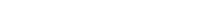
ADHD was thought to resolve around puberty as most hyperactive children become less hyperactive around this time.6 The symptoms of inattention and impulsiveness, however, can persist into adulthood.11 Recent studies have shown that 30% to 70% of children experience problems related to ADHD in adulthood.6 It is estimated that 4% of the adult population in South Africa has ADHD.11 While ADHD is more common in boys in children and adolescents, adult ADHD occurs equally in men and women.11 The prevalence of ADHD appears to decrease with age.11 An overlap of characteristics and symptoms with other psychopathological conditions can often lead to underdiagnosis or non-treatment of ADHD in adults.6 There are currently no officially recognised adult ADHD diagnostic criteria but the DSM-V (due in May 2013) is expected to include criteria for adult ADHD.6 Other conditions that may look like ADHD include some medical causes of tiredness (anaemia, hypothyroidism) and the more severe anxiety and mood disorders.⁶ If an adult has ADHD they will have always had ADHD.6 Those affected are likely to develop coping mechanisms as they mature which helps them to compensate for some or all their impairments.12











Aetiology/Pathophysiology

A specific cause of ADHD is not known. Genetic components as well as developmental and psychosocial factors are implicated in the pathophysiology of ADHD.7 There is strong evidence for a genetic basis to ADHD.7 The child of a parent with ADHD has up to a 50% chance of developing ADHD.8 Monozygotic twins have up to a 92% concordance rate for ADHD13 and dizygotic twins 33%.7 A number of genes have been identified to play a role in the development of ADHD.7 Psychosocial factors such as being institutionalised, prolonged emotional deprivation and adverse parent child relationships have also been implicated in the development of ADHD.7 Prenatal exposure to tobacco is associated with the development of ADHD.7 Other factors that have been associated with ADHD but are inconsistent include: prematurity and low birth weight, prenatal exposure to alcohol and head trauma in young children.7 Diet has also been suggested to play a secondary role in the pathogenesis of ADHD but the significance is controversial.7

Diagnosis

The diagnosis of ADHD is clinical and based on comprehensive medical, developmental, educational and psychological evaluations.² In North America, the DSM-IV criteria are used as a basis for diagnosis while countries in Europe usually use the ICD-10. In South Africa, the DSM-IV is most commonly used. (Refer to Table I.) If the DSM-IV criteria are used rather than ICD-10, a diagnosis of ADHD is three to four times more likely.¹⁴ ADHD-specific behaviour scales can be used to gather information from parents and teachers regarding behaviour.¹⁵ These scales are not recommended to be used in isolation to diagnose ADHD but can definitely aid in the diagnosis.^{9,15}

Differential diagnosis

Other conditions which may have similar symptoms to ADHD include¹⁶:

- Allergies/Asthma difficulty with breathing can interrupt a child's concentration.
- Diabetes/hypoglycaemia can have an affect on concentration and energy levels.
- Hearing or visual problems can lead to behaviour outbursts, incompletion of work and disturbance of classmates and hyperactivity.
- Lead intoxication can lead to hyperactivity.
- Learning difficulties can lead to frustration and ADHD-like behaviour.
- Emotional difficulties: could be due to divorce, bereavement, or a traumatic event which may lead to hyperactivity.

Clinical approaches to ADHD for the pharmacist

Pharmacists can play an important role in ADHD by creating an awareness of the condition by educating patients and carers and referring when necessary and also by giving advice on how best to take medications.⁸ The pharmacist can explain the importance of not chewing, crushing or dividing extended release preparations and can give advice on how to make it easier to administer these preparations. The following aids can be suggested to aid swallowing:

- Take a couple of swallows of milk or juice before taking the capsule, to make the throat and tongue more slippery.⁸
- Try swallowing the capsule with a teaspoon of soft food, e.g. yoghurt or mousse.⁸
- Try putting the capsule on the back of the tongue, taking a sip of a favourite drink and tilting the head back before swallowing.⁸

Pharmacists can also advise on how to manage side effects associated with stimulant use (Refer to Table II). They can also educate patients and their families about the possible adverse effects of atomoxetine especially the warning signs of hepatotoxicity (such as abdominal pain, unexplained nausea, malaise, and darkening of the urine or jaundice) and suicidal ideation. Pharmacists can also help to improve treatment adherence in patients with ADHD by³:

- Recommending the use of simple drug regimens (e.g. once-daily modified-release doses).
- Offering clear instructions (pictures or written) about how to take the drug.
- Advising patients and carers; providing reminders to take medication regularly (e.g. alarms, clocks, pill boxes or notes on calendars or fridges); helping to incorporate medication into daily routines; and helping them develop a positive attitude about taking medication, including praise and positive reinforcement.

Pharmacists can also refer teenagers, adults and parents of children who have ADHD to information and support services such as ADHDSA (www.adhdsupport.co.za).¹⁶

Available treatment options Non pharmacological management

- Behaviour therapy
- Psychological therapy
- · Complementary and alternative medicines (CAMs)
- Dietary modifications

Pharmacological treatment

- Stimulants
- Non-stimulants
- Other medications e.g. antidepressants, clonidine, antipsychotics

Therapeutic objectives

The aims of treating ADHD include both remission of symptoms and normalisation of functioning, including school (and work performance) and social interactions.¹⁷ Desired results include¹⁸:

- Improvements in relationships with parents, siblings, teachers and peers.
- Decreased disruptive behaviours.
- Improved academic performance, particularly in volume of work, efficiency, completion and accuracy.
- Increased independence in self-care or homework.
- Improved self-esteem.
- Enhance safety in the community e.g. such as crossing the road and riding bicycles.









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Table I: Diagnostic criteria for ADHD, DSM-IV-TR4

Attention-deficit/hyperactivity disorder

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:

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

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

Impulsivity:

- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (e.g. 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 (e.g. at school [or work] and at home)
- D. There must be clear evidence of clinically significant impairment that affects 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 a personality disorder)

Code based on type

ADHD combined type

Both criteria A1 and A2 are met for the past 6 months

ADHD predominantly inattentive type

Criterion A1 is met, but criterion A2 is not met for the past 6 months

ADHD predominantly hyperactive-impulsive type

Criterion A2 is met but criterion A1 is not met for the past 6 months









Targeted outcomes need to be developed on an individual basis for each patient and they require input from the children themselves as well and parents and teachers.¹⁸

Non pharmacological management Behaviour therapy

Behaviour therapy includes a broad range of interventions that have a common goal of modifying the physical and social environment to alter or change behaviour. ¹⁸ It has not been demonstrated to significantly reduce the core symptoms of ADHD but it can improve behaviour problems often seen in children with ADHD. ¹⁹ It

Table II: Stimulant adverse effects and management®				
Common	Recommendation/management strategy			
Reduced appetite/ weight loss	Give high-calorie meal when stimulant effects are low (at breakfast or at bedtime)			
Stomach ache	Administer stimulants on a full stomach			
Insomnia	Give dose earlier in the day; lower the last dose of the day or give it earlier; consider a sedating medication at bedtime (clonidine)			
Headache	Divide dose; give with food; or give an analgesic (e.g. paracetamol or ibuprofen)			
Rebound symptoms	Consider long-acting stimulant trial or antidepressant trial			
Irritability/jitteriness	Assess for co-morbid condition (e.g. bipolar disorder); reduce dosage; consider mood stabiliser or atypical antipsychotic			
Uncommon to rare				
Dysphoria	Reduce dosage; reassess diagnosis; consider alternative therapy			
Zombie-like state	Reduce dosage or change stimulant medication			
Tics or abnormal movements	Reduce dosage; consider alternative medication			
Hypertension	Reduce dosage; change medication			
Hallucinations	Discontinue stimulant; reassess diagnosis; mood stabiliser and/or antipsychotic may be needed			

may be recommended as an initial treatment if ADHD symptoms are mild with minimal impairment, diagnosis is uncertain, parents reject medication treatment or there is marked disagreement concerning the diagnosis between parents or parents and teachers.¹ Behaviour therapy is usually implemented by training parents and teachers in specific techniques of improving behaviour.¹⁹ Parents can help support better behaviour in a child with ADHD by¹⁹:

- · Maintaining a daily schedule.
- · Keeping distractions to a minimum.
- Providing specific and logical places for the child to keep his schoolwork, toys, and clothes.
- · Setting small, reachable goals.
- · Rewarding positive behaviour.
- Using charts and checklists to help the child stay "on task".
- · Limiting choices.
- Finding activities in which the child can be successful (e.g. hobbies and sports)
- Using calm discipline (e.g. time out, distraction, removing the child from the situation)

Other effective behavioural techniques recommended by the American Academy of Pediatrics are included in Table III.

Psychological therapy

Psychological interventions designed to change the child's emotional status (e.g. play therapy) or thought patterns (e.g. cognitive behaviour therapy) have little documented efficacy in the treatment of children with ADHD.¹⁸ Gains achieved in the treatment setting are not usually transferred into the classroom or home.¹⁸

CAMs

There are many CAMs that are promoted for ADHD but their use is controversial. Consumers of these therapies are often not knowledgeable about their usefulness and effectiveness.²⁰ The most often used of these therapies are dietary modifications, dietary supplements, herbal treatments, biofeedback, sound therapy, exercise and chiropractice.²⁰ In a study conducted in the Eastern Cape in which a questionnaire survey was conducted, it was seen that natural products such as Eye q[®], Biostrath[®], and evening primrose oil had been used most often, followed by diet modifications.²⁰ Other alternative treatments used included occupational therapy, the playing of more sport,

Table III: Effective behavioural techniques for children with ADHD ¹⁸							
Technique	Description	Example					
Positive reinforcement	Providing rewards or privileges contingent on the child's performance.	Child completes an assignment and is permitted to play on the computer.					
Time-out	Removing access to positive reinforcement contingent on performance of unwanted or problem behaviour.	Child hits sibling impulsively and is required to sit for 5 minutes in the corner of the room.					
Response cost	Withdrawing rewards or privileges contingent on the performance of unwanted or problem behaviour.	Child loses free time privileges for not completing homework.					
Token economy	Combining positive reinforcement and response cost. The child earns rewards and privileges contingent on performing desired behaviours and loses the rewards and privileges based on undesirable behaviour.	Child earns stars for completing assignments and loses stars for getting out of seat. The child cashes in the sum of stars at the end of the week for a prize.					







physiotherapy, speech therapy and remedial therapy.²⁰ It was found in this study that symptom control was insufficient when pharmacological treatment for ADHD was stopped and only non-pharmacological treatments were used.²⁰ It was recommended that if alternative therapies were to be used in ADHD they should be combined with pharmacological treatment.²⁰

Dietary modifications

The influence of diet on attention, hyperactivity and behaviour is controversial. The following areas of diet have been implicated 7,16:

- Food additives (artificial colours and flavours, preserva-
- Refined sugar intake (may be due to allergy or a functional reactive hypoglycaemia which triggers stress hormones like adrenaline)
- Fruits and vegetables containing high levels of salicylates
- Food sensitivity (allergy and intolerance)
- Essential fatty acid deficiency
- Iron and zinc deficiency

These areas of diet generally do not impact to a clinically significant level on ADHD and do not account for the majority of cases of ADHD.⁷ However, there is a small subset of children who may demonstrate mild adverse behavioural effects in response to certain dietary influences.⁷ Major practice guidelines for the treatment of ADHD do not routinely recommend elimination of food additives in the management of children with ADHD.^{3,7,18}

Pharmacological treatment

Pharmacological treatment aims to increase the amount of dopamine or noradrenaline available. Only methylphenidate and atomoxetine are licensed for use in ADHD in South Africa. (Refer to Table IV.) It seems to be established that pharmacological treatment is more effective than behavioural treatment alone.

When choosing a drug prescribers should consider¹⁰:

- Co-morbidities e.g. tics (can be worsened by methylphenidate), Tourette's syndrome, epilepsy.
- Side effects.
- Potential for drug misuse (can change with circumstances and age e.g. going into puberty).
- Preferences of patients and carers (e.g. extended release preparations so no medication needs to be taken at school).

Treatment should be continued for as long as it is effective.³ Treatment should be reviewed at least annually in children and adolescents and annually in adults.³ The following points should be covered in the review³:

- Clinical need, benefits and side effects of treatment.
- The views of the person with ADHD as well as the parents, carers and teachers, or spouse close friend in adults.
- The effect of missed doses, planned dose reductions and brief periods of no treatment.
- The preferred pattern of drug use (with or without periods without treatment e.g. weekdays only).

- Any coexisting conditions which should be treated or referred if necessary.
- The need for psychological, social and occupational support for the person and their parents.

Dosing schedules of methylphenidate can be adjusted to cover specific days and times e.g. during school hours and while doing homework especially in patients who suffer from the predominantly inattentive type of ADHD. ^{2,19} Drug holidays are not routinely recommended according to the NICE guidelines. ³ If they are to be employed, consideration must be given to the risks of negative effects on learning, socialisation and self-image while off therapy when determining the frequency and duration of drug holidays. ⁸ Drug holidays can be tried on weekends or holidays and placebo periods may also be tried for five to 10 school days to ensure reliability of observations to determine whether the drugs are still needed. ² Drug holidays are not an option for patients taking atomoxetine as it needs to be taken on a continual basis. ²²

Monitoring

Careful documentation of baseline symptoms and complaints over a one month pre-drug period is beneficial in being able to assess therapeutic and adverse outcomes.8 Depending on which medication a patient is taking, side effects need to be monitored. Routine blood tests and ECGs are not recommended unless there is a clinical indication.3 The child's height, weight, blood pressure and pulse should be monitored for patients taking either methylphenidate or atomoxetine.^{3,22} Any occurrence of seizures would result in termination of therapy.3 In patients taking methylphenidate, the occurrence of tics, psychotic symptoms such as delusions or hallucinations, anxiety symptoms and drug misuse and diversion need to be monitored and if they occur acted upon.3 In patients taking atomoxetine side effects concerning the reproductive system and sexual function need to be monitored and the warning signs of hepatotoxicity and agitation, irritability and suicidal thinking and self-harm need to be identified and treatment terminated if necessary.3 Routine liver function tests are not necessary so long as patients and carers are warned of the rare potential for liver damage and the warning signs.3

Stimulants

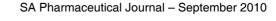
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Methylphenidate

Methylphenidate blocks the dopamine transporter thus reducing dopamine reuptake and increasing dopamine in synapses. ¹⁰ The dose needs to be titrated over four weeks with weekly increments. ¹⁰ Dosing should be titrated for maximum individual efficacy and minimum side effects. ⁸ The appropriate dose is determined by the age and weight of the patient but the desired outcomes such as improved academic functioning and better behaviour also have an influence on the optimal dose. ¹⁰ Learning is often enhanced at low doses but improvement in behaviour often requires larger doses. ² Methylphenidate only alleviates symptoms while each dose is active. ¹⁰ Methylphenidate is available in immediate and modified release forms. ¹⁰ The immediate release product takes effect an hour after adminis-









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	Table IV: Pharmacological preparations indicated for ADHD in South Africa ^{1,27}					
Drug	Brand [®]	Strength	Dosage instructions	Additional information		
Methylphenidate HCI	Concerta® ER tablets	18 mg 36 mg	New patients 18 mg once daily. Adjust in 18 mg increments at weekly intervals to max 54 mg/d for children 6–12 yrs.	Not for children under 6 years. Administer once daily in the mornings. Effects shown to be present 12 hours after		
		54 mg	72 mg/d for adolescents 13–18 yrs. Patients currently taking methylphenidate: 18 mg od for pts taking 5 mg tds, 36 mg od for pts taking 10 mg bd-tds, 54 mg od for pts taking 15 mg bd-tds, 72 mg od for pts taking 20 mg bd-tds.	dose. Swallow whole and never crush, chew or divide. Non-absorbable tablet shell may be seen in stool. Longer acting stimulants offer greater convenience, confidentiality, and adherence with single daily dosing but may have greater problematic effects on evening appetite and sleep.		
Methylphenidate HCI	Methylphenidate HCI-Douglas	10 mg	Initially 5 mg before breakfast and 5 mg before lunch with gradual weekly increments of 5–10 mg to max 60 mg/d. Admin to a total daily dose in divided doses. Dose in terms of body wt: usual 0.25 mg/kg/d, double each week to 2 mg/kg. Consider short-act trial dose at bedtime if rebound effects experienced.	Short-acting stimulants often used as initial treatment in small children (< 16 kg) but have disadvantage of bd-tds dosing to control symptoms throughout the day.		
Methylphenidate HCI	Ritalin [®] tablets	10 mg	Initiate in small doses with gradual weekly increments. Daily dose over 60 mg not recommended. Discontinue if no improvement observed after appropriate dose adjustment over one month.	Short-acting stimulants often used as initial treatment in small children (< 16 kg) but have disadvantage of bd-tds dosing to control symptoms throughout the day.		
	Ritalin®LA capsules	20 mg	Recommended start dose 20 mg. Dose to	Administer once daily in the morning. Do not crush or chew or divide. Contents may be sprinkled on a small amount of soft cold food and swallowed immediately. Longer acting stimulants offer greater convenience, confidentiality, and adherence with single daily dosing but may have greater problematic effects on evening appetite and sleep.		
		30 mg	replace standard formula: 20 mg LA od to replace 10 mg bd, 30 mg LA od to replace 15			
		40 mg	mg bd, 40 mg od to replace 20 mg bd. In case of other regimens use clinical judgement.			
Atomoxetine HCI	Straterra® capsules	10 mg	Child and adolescent < 70 kg: Initial total	If dose missed take ASAP but prescribed		
Audinoxeune 1101	Circle Ta Capoules	18 mg	daily dose 0.5 mg/kg. Maintenance dose: initial dose for 7 days before upward titration according to clinical response. Recommended maintenance dose: 1.2 mg/kg/day. No add benefits seen with higher dose. Child and adolescent > 70 kg: Initial total daily dose 40 mg.	total daily dose not to be exceeded in any 24 hours. Consider if active substance abuse or severe side effects of stimulants (mood lability or tics) give every morning or bd (effects on late evening behaviour). Monitor closely for suicidal thinking or behaviour, clinical worsening, or unusual changes in behaviour.		
		25 mg				
		40 mg				
		60 mg				
			No additional benefits seen with higher dose.			

tration and effects last from three to six hours. 10 Most patients require a two to three times daily dosing schedule.8 Modifiedrelease preparations provide eight to twelve hour symptom control.8 These preparations are taken once a day although some adults take Concerta XL® in the morning followed by a dose at lunchtime. 10 Concerta XL® uses an oral osmotic (OROS) controlled-release delivery system.8 It has two release phases, immediate (22% of drug released) and prolonged (78% of drug released). 10 Concerta XL® is a nondeformable tablet so it should not be given to children with gastrointestinal narrowing due to the risk of obstruction.8 Ritalin SR® uses a wax-matrix sustained release system.8 The most common side effects of methylphenidate (and other stimulants) are appetite decrease, weight loss,

insomnia and headache.1 Less common side effects include tics and emotional lability/irritability.1 Strategies for dealing with side effects include monitoring, dose adjustment and adjunctive pharmacotherapy to treat the side effects.1 Refer to Table II for the management of side effects of stimulants.

Other stimulants such as dextroamphetamine and mixed amphetamine salts (Adderall®) are not available in South Africa.

Non-stimulants

Atomoxetine

Atomoxetine (Strattera®) is a noradrenaline reuptake inhibitor. Atomoxetine can be dosed once or twice daily with the second

SA Pharmaceutical Journal - September 2010



16





EVIDENCE-BASED PHARMACY PRACTICE

dose given in the evening. 1,17 Atomoxetine may have less pronounced effects on appetite and sleep than methylphenidate but may produce relatively more nausea or sedation.1 Peak efficacy occurs between two to six weeks after initiation but can take up to eight weeks which is in contrast to the stimulants, which give a rapid response.¹⁷ Side effects include constipation, dry mouth, nausea, decreased appetite, dizziness, insomnia, sexual side effects, menstrual cramps and difficulty in passing urine.23 Gastric side effects may be reduced by taking with food. 10 It can also cause hepatotoxicity and increase the risk of suicidal ideation.²³ It should not be taken in patients with glaucoma or in patients who have received a monoamine oxidase inhibitor in the past fourteen days.23 It has also shown to be effective in co-morbid anxiety and it is a good alternative to methylphenidate (which has the potential for abuse and diversion) in adolescents and adults with a substance abuse disorder.¹⁷ Atomoxetine has not been found to be effective for the treatment of co-morbid depression.¹⁷ It does not worsen tics in patients with ADHD and concomitant Tourette's syndrome.²³

Other medications

Other medications may be effective in reducing the symptoms

of ADHD although data from controlled studies is limited.²² These medications are usually used when patients respond poorly to a trial of methylphenidate or atomoxetine, or have unacceptable side effects, or have significant co-morbid conditions that warrant their use.²² (Refer to Table V)

Antidepressants

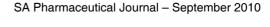
Antidepressants that have been used in the treatment of ADHD include tricyclic antidepressants (TCAs), such as imipramine, desipramine and nortriptyline and dopamine reuptake inhibitors such as bupropion.²²

Tricyclic antidepressants (TCAs) inhibit the reuptake of noradrenaline and serotonin.²² They are considered to be secondline after stimulants and atomoxetine.²² TCAs have been associated with cardiovascular adverse events so a review of the patient's history and family history is essential before initiating therapy.²² They also have anticholinergic side effects such as dry mouth and constipation which may limit their use and they also lower the seizure threshold.²² Desipramine should be used with extreme caution in children and adolescents (if at all) because there have been reports of sudden death.¹

	Table V: Other agents used for ADHD and associated symptoms ^{8,17}					
	Drug	Dosing	Adverse effects	Comments		
	Bupropion	50–300 mg/d; 3 mg/kg/d by end of week one may increase to 6 mg/kg/d or max of 300 mg/d as tolerated	Nausea, insomnia, rash, tics, dose- related risk of seizures.	Lowers seizure threshold; contraindicated if current seizure disorder. Usually given in divided doses bd for children and tds for adolescents for both safety and effectiveness.		
	Imipramine	1–4 mg/kg/d with a maximum of 200 mg/d	Sedation, dizziness, constipation, heart block, weight gain, overdose toxicity,	Obtain baseline ECG before starting.		
	Desipramine	0.5–1 mg/kg/d increase as tolerated to 2–3 mg/kg/d maximum of 300 mg/day (adults only)	rapid heartbeat.			
	Nortriptyline	0.5-2 mg/kg/d with a maximum of 100 mg/d				
	Clonidine	< 45 kg 0.05 mg at bedtime; titrate in 0.05 mg increments bd, tds, qds > 45 kg 0.1 mg at bedtime; titrate in 0.1 mg increments bd, tds, qds Max dose 27–40.5 kg:0.2 mg; 40.5–45 kg:0.3 mg; > 45 kg: 0.4mg	Sedation, dizziness, heart block, constipation.	May be used alone or as adjuvant to another med for ADHD. Effective for impulsivity and hyperactivity; modulating mood level; tics worsening from stimulants; sleep disturbances.		
	Risperidone	0.25–0.5 mg bd may titrate every 3-4 days as tolerated to response (1–4 mg/d)	Extrapyramidal symptoms, dizziness, ↑ prolactin, hepatotoxicity, weight gain.	Short-term use (1–4 months) only for severe aggression associated with ADHD.		
	Olanzepine	2.5–5 mg bd may titrate every 3–4 days as tolerated to response (usual range 7.5–15 mg/d)	Sedation, weight gain, restlessness, diabetes, hyperlipidaemia.			
	Ziprasidone	10–20 mg bd may titrate every 3–4 days as tolerated to response (usual range 40–120 mg/d)	Nausea, restlessness, insomnia, QT prolongation.			
	Haloperidol	0.5–1 mg bd may titrate every 3–4 days as tolerated to response (usual range 0.5–5 mg/d)	Extrapyramidal symptoms, dizziness, ↑ prolactin, sedation.			







18



Bupropion blocks the reuptake of noradrenaline and dopamine and has more stimulant properties than the TCAs'.²² It has been found to have a modest efficacy in decreasing hyperactivity and aggressive behaviour.²² It can cause motor tics and lower the seizure threshold.²²

Clonidine

Clonidine an alpha-2-adrenergic agonist has been found to be effective in reducing symptoms in ADHD but is not as effective as stimulants.22 It may be useful in overaroused, easily frustrated, highly active or aggressive individuals.22 It has been used in patients with ADHD who also have tics or Tourette syndrome.²² It has been used alongside methylphenidate to reduce the incidence of tics. 10 Side effects include sedation, depression, bradycardia, headache and hypotension.²² When discontinuing treatment, clonidine should be withdrawn slowly (0.05mg reductions every three days) to prevent rebound hypertension or behavioural dyscontrol.8

Antipsychotics

Antipsychotic medications such as risperidone, olanzepine, zisprasidone and haloperidol are not recommended for use in children but may have a place in patients with ADHD who are severely aggressive. Treatment is usually only recommended for a short period of time (one to four months).⁸ Risperidone is registered for disruptive behaviour disorders in children five years and older with sub-average intellectual functioning or mental retardation where destructive behaviour is prominent.²¹

Evidence-based recommendations

The evidence-based recommendations listed below are based on the following guidelines:

- American Academy of Pediatrics, Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder.⁹
- American Academy of Pediatrics. Clinical Practice Guideline: Treatment of the School-Aged Child With Attention Deficit/Hyperactivity Disorder.¹⁸
- AACAP Work Group on Quality Issues. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder.¹
- NICE clinical guideline 72. Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults.³
- Recommendation one: Screening for ADHD should be part of every patient's Mental Health Assessment.¹
- Recommendation two: Evaluation of the preschooler, child or adolescent for ADHD should consist of clinical interviews

SA Pharmaceutical Journal - September 2010

- with the patient and parent, obtaining information about the patient's school or day care functioning, evaluation for co-morbid psychiatric disorders, and review of the patient's medical, social, and family histories.¹
- Recommendation three: If the patient's medical history is unremarkable, laboratory or neurological testing is not indicated.¹
 - Recommendation four: Psychological and neuropsycho-logical tests are not mandatory for the diagnosis for ADHD, but should be performed if the patient's history suggests low general cognitive ability or low achievement in language or mathematics relative to the patient's intellectual ability.^{1,9}
 - Recommendation five: The patient with ADHD must be evaluated for the presence of co-morbid psychiatric disorders.^{1,9}
 - Recommendation six: A well-thought out and comprehensive treatment plan should be developed for the patient. 1,18
 - Recommendation seven: The initial treatment of ADHD should be with a trial with an agent indicated for the treatment of ADHD i.e. methylphenidate or atomoxetine.
 - Methylphenidate (and other stimulants available outside South Africa) are considered first-line in the treatment of ADHD. Atomoxetine may be considered first-line for ADHD in patients with an active substance abuse problem, co-morbid anxiety, or tics. Atomoxetine is preferred if the patient experiences severe side effects to stimulants such as mood lability or tics.
- Recommendation eight: If none of the above agents result in satisfactory treatment of the patient with ADHD, the diagnosis should be carefully reviewed and then behaviour therapy and/or other agents used (but not licensed) for ADHD should be considered.^{1,18}
- Recommendation nine: During pharmacological treatment for ADHD, the patient should be monitored for treatmentemergent side effects.^{1,18}
- Recommendation ten: If the patient with ADHD responds
 well to pharmacological treatment alone by showing full
 remission of symptoms and normative functioning it is not
 mandatory that behaviour therapy be added to the regimen.¹
- Recommendation eleven: If a patient with ADHD has a less than optimal response to medication, has a co-morbid disorder, or experiences stressors in family life, then psychosocial treatment in conjunction with medication is often beneficial.¹
- Recommendation twelve: Patients should be assessed periodically to determine whether there is a continued need for treatment or if symptoms have remitted. Treatment of ADHD should continue as long as symptoms remain present and cause impairment.¹
- Recommendation thirteen: Patients treated with medication for ADHD should have their weight and height monitored throughout treatment.¹







Factors to consider

- No single treatment is the answer for every patient a number of factors are involved in determining the best treatment for the individual.10
- Drug treatment is not recommended as first line in children under the age of five.3,10
- If using methylphenidate the choice of preparation needs to be considered3: modified-release preparations are convenient due to their pharmacokinetic profile, improving adherence, reducing stigma (drug does not need to be taken at school); and immediate-release preparations are preferred if more flexible dosing is required or during initial titration to determine correct dosing levels.
- Co-morbidities must be treated1,3,18
- It is recommended by manufacturers that drug treatment is suspended every one to two years so that the child's condition can be reassessed.10
- Patients not continuing with therapy need to be given appropriate withdrawal strategies. 10

Adult ADHD

Drug treatment for adults with ADHD should always be part of a comprehensive treatment programme that takes into account psychological, behavioural and educational or occupational needs.3 Behavioural therapy usually involves life coaching which can assist patients in restructuring dysfunctional life patterns.¹¹ Pharmacological treatment includes both stimulant i.e. methylphenidate and non-stimulant i.e. atomoxetine medications. These medications can help patients focus and organise their lives. 11 Both Ritalin® and Straterra® have adult registration in South Africa.6 NICE guidelines recommend that once a decision has been made to start drug treatment in adults then methylphenidate should normally be tried first.3 Blood pressure and heart rate should be closely monitored when initiating stimulant therapy as cardiovascular effects are more of a concern in adults than they are in children. 11 Co-morbidities must also be treated and considered when selecting pharmacological treatment. Depression can be treated with an antidepressant with noradrenergic effects (venlafaxine, duloxetine, mirtazapine, imipramine) or bupropion with dopaminergic effects.²⁴ It may be possible to treat both the ADHD and depressive symptoms with one drug.24 Atomoxetine is quite effective for anxiety and may be used when there is co-morbid anxiety.6

Conclusion

ADHD should be treated as a chronic illness that requires ongoing management, monitoring and treatment to prevent relapse. Treatment may need to be continued through adolescence and into adulthood. Pharmacological therapy should form part of a comprehensive treatment plan which should include psychological, educational and social measures that is implemented on an individual patient basis after consultation with patients, parents and teachers.

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