The medical management of attention-deficit/hyperactivity disorder: spoilt for choice?

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Abstract
This paper focuses specifically on the medical management of attention-deficit/hyperactivity disorder (ADHD) and the options currently available in South Africa. References are made to current thinking on the etiology of this disorder and the pharmacological principles involved in its treatment. This review will not try to address all aspects of ADHD but highlight the range of medical management options, their advantages or disadvantages, their clinical application and give some personal perspectives about the practicalities within the clinical setting. Although the treatment of co-morbidities are not systematically discussed in this paper, reference are made to specific co-morbidities where relevant.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is not a benign disorder. Children with ADHD experience severe and chronic impairment in daily functioning, including academic problems, disruptive behaviour and problematic relationships with parents, teachers and peers.

Follow-up studies of clinical samples suggest that sufferers are far more likely than normal people to drop out of school (32-40%), to have few or no friends (50-70%), to under perform at work (70-80%), to engage in anti-social activities (40-50%), and to use tobacco and elicit drugs. Children growing up with ADHD are more likely to experience teen pregnancy (40%), to speed excessively and have multiple car accidents, to experience depression (20-30%) and personality disorders (18-25%) as adults than the normal popullation.[1]

In the light of new developments in the pharmacological management of ADHD it is perhaps timeous to re-evaluate the different modalities of treatment available and the evidence that support their use. Perhaps the time has come where, in stark contrast to the recent past, clinicians, who treat patients with ADHD may indeed be ''spoilt for choice'' – or are they? This review will not try to address all aspects of ADHD but highlight the range of medical management options, their advantages or disadvantages, their clinical application and give some personal perspectives about the practicalities within the clinical setting.

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Etiology

ADHD is the most common neurobehavioural disorder that doctors will encounter. It is estimated that about 8% (3-10%) of the children of any population could have an ADHD, with persistence into adolescence in the order of 85% and into adulthood as great as 31%.[2,3] Boys are reported to be more affected than girls (3:1), although this impression is changing with the emergence of a group described to have Attention Deficit Disorder without Hyperactivity (ADD), where girls outnumber boys.

The etiology of ADHD appears to involve multiple factors. In probably more than 80% of cases, genetic factors play a role in the inheritance of this disorder. Parental ADHD elevates the risk for developing ADHD eight-fold. At least three chromosomes have been identified and inheritance appears to be polygenetic. These genes are of small effect but combine with each other and environmental risk factors to cause ADHD. In-utero cigarette and alcohol exposure have been shown to increase the odds of developing ADHD two- to three-fold.[4] The defective genes most likely to be associated with ADHD are the 7-repeat allele of the dopamine 4-receptor gene and the dopamine transporter gene.[5,6] These findings have been confirmed with twin studies.

The patho-physiology in children with ADHD has been localized to three areas in the brain; the frontal lobe, its connection to the basal ganglia and the relationship to the central aspects of the cerebellum,

using PET scans. In children with ADHD these areas show less activity and may also be relatively smaller. It appears that patients with ADHD have insufficient available dopamine in the synapses of these areas. Dopamine is responsible for behaviour (pleasure, reward, reinforcement) in the meso-limbic pathways, and attention arousal, concentration and higher cognitive functions in the meso-cortical pathways. Furthermore it is responsible for attention, signal enhancement, inhibition and integration in the cotico-striatal pathways. The perceived dopamine deficiency in these synapses is due to an overrepresentation of dopamine transporters (DAT) on the pre-synaptic membrane that bind to and eliminate dopamine so rapidly, as to make these synapses inefficient. The dopamine transporter is thought to be a critical regulator of dopamine homeostasis. The gene encoding this transporter is located on chromosome 5p15.3. Stimulants block these receptors.[7] In some cases the problem is not the quantity of available neuro-transmitter, but the presence of abnormal receptors on the distal neurons.

It is now recognized that the norepinephrine pathways are also important for attention, concentration and cognitive function (frontal), emotions, energy and agitation (limbic), tremors (cerebellum) and cardiovascular functions (brainstem). The patho-physiological processes involved in the malfunctioning of these pathways are not yet well understood, but may be similar to those of the dopamine pathways. The mode of action of atomoxitine for example, that has been shown to increase norepinephrine levels in the brain, has a similar action in blocking the reabsorption transporters of norepinephrine, as methylphenidate has on blocking dopamine transporters.

The different modalities for the medical management of ADHD usually imply some mechanism to increase dopamine and/or norepinephrine in the synapses of the relevant neuronal pathways in the brain.

Diagnosis

It is important to realize that not every child that presents with some of the signs and symptoms of ADHD have this disorder. In some children it may be a normal variant or result of a medical condition or an affective disorder. It may be secondary to learning disabilities, partial sensory deficits or even low cognitive potential. The diagnosis therefore depends on an adequate history and subsequent collateral information from various sources. The more thorough the history taking and the more members of the team involved in providing additional data, the more likely the diagnosis will be correct.

The diagnosis is made based on the DSM IV[a] criteria, which divides the symptoms of ADHD into two groups. The first of these have to do with inattention. Nine possible scenarios are sketched and if a child fulfills six or more that have persisted for more than 6 months and is maladaptive and inconsistent with the child's developmental level, a case can be made for the diagnosis of an Attention Deficit. The second part of the DSM IV relates to hyperactivity and impulsivity. Again, there are nine scenarios of which a child should fulfil six to a degree that is maladaptive and considered abnormal for the child's developmental level for more than six months, to be considered to have a ''hyperactivity-impulsive disorder''. The DSM IV criteria state that the hyperactive, impulsive and inattentive symptoms should have caused impairment before the age of seven and present in more than one setting. An EEG plays no part in the diagnosis or prognosis of ADHD.

Based on the DSM IV criteria there are four types of ADHD:

A: Combined type. These children fulfil the majority of criteria of the DSMIV. They often present in the pre-school year but may present as late as Grade 2 or 3. They have inattention, impulsivity as well as hyperactivity.

B: Predominantly inattentive type. This group has been neglected in the past, but is being diagnosed more often now. They are more often girls than boys. They are not excessively impulsive or hyperactive and therefore are not noticed in the classroom. They are diagnosed usually at an older age (9 years).

C: Predominantly hyperactive impulsive type. These children (usually boys) often present very young (3-4 years) with unacceptable behaviour.

D: In partial remission. This represents ADHD diagnosed in older children who do not present with all the symptoms.

In this paper all subtypes are implied when the abbreviation ADHD is used. Although this paper will not specifically address the diagnosis of co-morbidities in ADHD, they will be referred to when they influence decisions regarding medical management. Co-morbidities include: Oppositional defiant disorder, conduct disorder, communication disorder, Tourette's Syndrome and learning disorders.

A positive response to stimulants should not be used to confirm the diagnosis of ADHD as these effects are non-specific.[8,9]

Medical management

The management of ADHD demands a multi-modal approach, as a single intervention is rarely effective. The main intervention modalities are:

1. Medical.
2. Educational.
3. Psychosocial (behaviour modification).
4. Diet manipulation and supplements.

This paper will discuss medical management only, but this does not imply that the other interventions are less important.

When a doctor is confronted with a child with a possible diagnosis of ADHD, it is important to exclude any other medical causes for these symptoms such as sleep apnea, obstructive airway disease, use of other medications and poorly managed allergies. A thorough history of the child's development needs to be taken and, if possible, also assessed in the consulting rooms. Make sure that the child's vision and hearing are adequate. Once the diagnosis is made, do not forget to refer the parents and children to social support groups and also to give some tips on behaviour management if necessary.

A. STIMULANTS

Psychostimulants were first used to treat disruptive behaviour in children in 1937.[10] The use of stimulants is the mainstay of the medical management of children with ADHD[9,11] and is one of two interventions that is evidence based (the other is behaviour modification).[12] In fact, of all treatments in child and adolescent psychiatry it has the best evidence to support its use.[13] It has been used for over 50 years and has been found to be beneficial in about 70% of children.

[a] *Diagnostic and Statistical Manual of Mental Disorders, 4th Edn. American Psychiatric Association, 1994.*

In a recent study, the Multi-modal Treatment Study of Children with ADHD[14], the effect of medication was compared to that of behaviour modification. Nearly 600 children took part in this study between the ages of 7 to 10 years. All the children had ADHD, combined type. A quarter received stimulant medication (not necessary methylphenidate) only, which was titrated after monthly visits. A quarter received intensive behavioural treatment, a quarter a combination of both and a quarter received usual community care. On virtually every outcome measure, the children who received stimulants only, did significantly better than the children who had behaviour modification only. The children who received both did not do significantly better than the group that received medication only. The children, who continued with community management only, were the worst off in the long run. This study is not quoted to indicate that stimulants are the only intervention worth considering in ADHD, but to highlight the fact that it is a very important component of its management.

Stimulants are used to treat the core triad of symptoms of ADHD – inattention, impulsivity and hyperactivity.[15] Stimulant drugs result in immediate and often dramatic improvement in behaviour. There may be a marked improvement in handwriting, presumably due to enhanced motor planning. They may increase the child's responsiveness to other psychological and educational interventions. They improve functioning in the classroom, with reduced negative and off-task behaviour.[8,16] Lower doses treat concentration effectively, but social functioning appears to require higher doses.[9]

Previously it was not clear if stimulants improve learning or long-term academic achievement.[17] Stimulants have now been shown to improve measures of cognition, vigilance, reaction time, short term memory, learning of verbal and non-verbal material, school-based productivity and accuracy in children with ADHD.[16] Data suggest that, contrary to the current clinical practice of employing the lowest effective dose, stimulants should be titrated for optimal effect – best cognitive or behavioural effect balanced against adverse effects.

1. Methylphenidate

(i) Short acting (Ritalin IR®)

The stimulant medication, methylphenidate (MHP), has been used for nearly half a century to treat children with ADHD. The efficacy and safety of this clinical practice has been established by decades of clinical use and thousands of research studies.[18] The immediate-release formulation of MPH (Ritalin IR®) is rapidly absorbed, yielding effects within 30 minutes, peaking after 2 hours and typically lasting for about 4 hours.[19,20,21] Bioavailability is only 20-25%.

Methylphenidate binds to the dopamine transporter in the pre-synaptic cell membrane, blocking re-uptake of dopamine and causing a resultant increase in extracellular dopamine levels. This is in contrast to amphetamine which causes release of newly synthesized dopamine from the nerve terminal. At oral therapeutic doses MPH is estimated to occupy more than half of the brain's dopamine transporters.[22]

Once it has been decided to treat a child on stimulants, a two-week trial is usually prescribed. It is imperative that during the trial period the short-acting methylphenidate only is prescribed. Weight based dosing is not effective because of individual differences in metabolism.[23] In pre-school children and tiny Grade 1 children, 5mg should be adequate. Research suggests that stimulants are effective in preschoolers, refuting the notion that stimulants are ineffective or associated with pervasive adverse effects.[16] For the majority of other children, one tablet in the morning can be used. It is usually advisable to start at a lower dose and titrate higher.

The MPH is prescribed for two weeks and generally without the teacher's knowledge for the first week, although I do encourage parents to discuss it with the teachers, at least before the second week.

The reason for the two-week trial is two-fold:

1. To ascertain whether the medication has a beneficial effect which is usually evident within a day or two.
2. To monitor the side effects.

Once a clinician has decided to recommend a trial of stimulant medication, a counseling session is required to explain the expected positive effects and the potential side effects.[23] Because of strong placebo effects I never discuss the side effects of MPH in the presence of the child initially. The most common initial side effects include insomnia, appetite suppression, dysphoria (irritability, sadness) and the rebound effect, where children appear to be even worse in the afternoons than before, but are well controlled in the mornings. When managing perceived side effects, distinguish between inadequate dosage, medication effects and wear-off effects. Compare the timing of the symptoms with the timing of the medication administration.[23] Hyperactivity may increase when the medication is beginning to wear off and irritability may occur also. If hyperactivity increases within 1-2 hours of administration the dosage is suboptimal.

Discuss issues regarding mealtimes and nutrition with parents. Children with ADHD often are picky eaters prior to the introduction of MPH. It is important for these children to have breakfast (protein if possible) and then a small lunch and a mid-afternoon snack would suffice. It is probably advisable to serve supper only when the child is hungry. Fortunately the appetite suppressant effect of MPH appears to wane over time. In children with very poor appetite, it may be useful to introduce a protein shake as a meal replacement once a day. It is not imperative to use supplements, but in most children a vitamin supplement may be useful, especially if there is poor nutrition. Evidence based use of all other supplementation is lacking, except perhaps for free fatty acids, where there have been a few promising reports.

It is important to obtain an accurate history of sleep patterns before you start! Parents often blame sleep problems that existed prior to using MPH, on the medical intervention. A small percentage of these children develop sleep disorders with MPH. The majority have pre-existing problems. Manipulation of the timing and strength of the MPH dose might be necessary. Adding a tricyclic anti-depressant at night may sometimes be useful to establish acceptable sleep patterns. Remember that children with ADHD usually experience problems at the onset of sleep. When they have many night time awakenings, consider another medical or psychiatric diagnosis.

It is important to warn parents of a possible rebound effect, as it will often cause cessation of the MPH if parents are not informed prior to the trial. Increased irritability or hyperactivity in the afternoon usually implies that a second or even a third dose of MPH (or a long-acting formulation) may be necessary. It is interesting that wear off effects seldom occur after 16h00, probably due to body's natural biorhythms. It is therefore useful to postpone the rebound effects to later in the day, side effects permitting.

Social withdrawal is usually secondary to an excessive dose of medication. Dysphoria often settles down after the first three days, but if it should continue for the entire two week trial this may imply that MPH cannot be used in that particular case.

The effect of the medication is usually visible within 15 to 30 minutes, and the effect lasts for about two to four hours. Stimulants should not be started with other changes, like starting a new year at school or an altered classroom setting. If a beneficial effect of the medication is obvious, therapy should be continued and monitored with rating scales (such as a Conners Questionnaire). Dosage and time of administration need to be tailored to the child's specific needs. Although a total daily dosage of over 60mg is not advised, it is important to realize that the optimal dose is determined by the expected benefits and the presence of unacceptable side effects. The child may not be aware objectively of the benefits. If the effect is not noticeable or uncertain, increasing dose can be considered. If this does not have any effect or unwanted side effects appear, the trial should be abandoned and other options pursued.

The medication does not have to be taken before breakfast. This practice was advocated to improve absorption. Given with food, the absorption of MPH is enhanced. Authors agree that in most cases the best time to take the tablet is just before leaving for school in the morning. The tablet should not be chewed but swallowed whole.

Results from recent research suggest that it is beneficial to prescribe stimulants three times a day, to be of benefit during homework also.[23] It is also recommended by some, depending on side effects, that children do not have weekend or vacation breaks, but use the medication continuously to modify all ADHD symptoms.

Termination of medication should be based on a clinical trial off stimulants during which behaviour is monitored closely. Frequently there are brief, accidental trials off medication when a dose is forgotten. If ADHD behaviours return immediately, the child is not yet ready for a planned trial off medication. If not, a planned trial off medication for 2 weeks is arranged, usually during less stressful periods. Thereafter the medication can be stopped if there is no deterioration of ADHD symptomatology. The child should still be monitored for at least a year.

Experiments in rats have shown long-lasting changes in the development of the central dopaminergic system caused by MPH administration in early juvenile life.[24] A decrease in the density of dopamine transporters was reported. It appears that clinical efficacy persists if treatment is maintained for at least one year or more.[25] Currently it is recommended that, with an aim to ''cure'', MPH be prescribed for a period of at least three years continuously.

(ii) Long acting methylphenidate

Specific problems were identified in the use of the short acting MPH. These problems include:

a. Multiple daily doses[26,27] produce problems with compliance.
b. The standard dosing at breakfast and lunchtime may leave the child experiencing a trough in medication level during some times of the day. As the morning dose is wearing off, inattention may increase during the late morning. Similarly, when the midday dose is wearing off, the child may experience difficulty concentrating on after-school homework.
c. Taking medication at school is an event that many children with ADHD would want to avoid. This lack of privacy effects especially teenagers.
d. School staff often administers the medication unreliably.[28]
e. Children with ADHD, who are disorganized to start with, often are required to go to a designated place in the school at the appropriate time to take their midday pills. They do not manage to do this consistently.
f. The third dose often has to be administered when children are involved in extra-curricular activities.
g. Shorter acting stimulants do not exert a major effect on functioning at home in the evening hours. There is growing awareness that children with ADHD are impaired in the home domain, in their peer contacts that occur after school and in the evenings and in their ability to perform homework tasks.[20,26]
h. Research on the efficacy of third dose short acting MPH is limited.[29]
i. Disconcerting waxing and waning effects
j. Concerns regarding security and diversion

The awareness of the above mentioned problems stimulated researchers to develop longer acting formulations.

a. Ritalin SR®

With the introduction of Ritalin SR® (sustained release), a longer acting methylphenidate was available. The Ritalin SR® formulation is based on a wax-matrix delivery system.[30] Because of its plateau-like profile, it is not as effective as two short-acting tablets daily, and appears to have a delayed onset of action.[31] Another problem is that it is only available in a 20mg tablet format, and therefore manipulation of the dosage is quite difficult. The time course for Ritalin-SR appears to be variable, and individual responsiveness to the preparation may be highly variable.[32,33] Ritalin SR® should be given with meals to enhance absorption. It is useful in children who require a low but persistent dose of MPH during the day to function optimally (e.g. children with ADD), and can be supplemented with Ritalin IR®.

b. Ritalin LA ®

Ritalin LA® (long acting) is available in different dosages, 20, 30 and 40mg and it mimics the effectivity profile of a short-acting methylphenidate given twice a day. Ritalin LA® is for oral administration once daily in the morning. It is an extended-release formulation of methylphenidate with a bi-modal release profile. The fluctuations between peak and trough plasma concentrations are smaller than for Ritalin IR® given twice a day. Ritalin LA® uses the proprietary SODAS (TM Spheroidal Oral Drug Absorption System) technology. Each bead-filled capsule contains half the dose as immediate release beads and half as enteric-coated, delayed release beads, thus providing an immediate release of MPH and a second delayed release of MPH, about 4 hours apart. It may be swallowed as a whole capsule or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce or in food with a similar consistency (but not in a liquid). The capsules should not be crushed, chewed or divided. Only switch from Ritalin IR® when a dose of about 10mg twice daily has been reached. The dosage can be increased by 10mg in weekly intervalseither until the required effect has been achieved or unacceptable side effects have occurred. Ritalin LA® is ideal for children who require treatment of their symptoms in the school hours only, where compliance may be a problem and where there are no obvious rebound phenomena.

c. Concerta®

Concerta® represents a new dosage formulation of MPH that combines the established active ingredient with OROS (osmotic, controlled-release oral system) technology. The rationale for developing Concerta® was for once a day dosing that would eliminate the need for in- and after-school dosing, with an efficacy comparable to 2-3 times daily Ritalin IR®, 12 hour duration of effect and rapid onset of action. Its ascending profile is produced by the delivery of a loading dose followed by delivery of small increasing doses over a 7-9 hour period.[34] Following a single dose of Concerta® , plasma levels of MPH increase rapidly for the first one to two hours, followed by a more gradual increase over the subsequent 3-4 hours. Peak plasma concentrations are noted 6-8 hours after dosing and decline gradually thereafter. No food effects were demonstrated and adverse effects on Concerta® are comparable to Ritalin IR®.[35]

Concerta® doses are usually 20% higher on a by milligram daily basis than a comparable three times a day regimen of short acting MPH.[29] Available as 18mg (similar to Ritalin IR® 5mg three times daily or Ritalin SR® 20mg a day), 36 mg (similar to Ritalin IR® 10mg three times daily or Ritalin SR® 40mg daily) and soon 54mg capsules (similar to 15mg Ritalin IR® three times daily or Ritalin SR® 60mg daily), the dosage can be increased at weekly intervals until the desired efficacy is reached. In a laboratory classroom setting Concerta® was as effective as Ritalin IR three times a day and lasted 12 hours after dosing.[29,36] Concerta® is useful in children who have a long academic day (senior students who do their homework till late in the night, where mothers do homework only after a day's work or when homework is done after sport) and also to prevent late afternoon rebound effects. Its use can also be considered for those children who appear to be rapid metabolizers, and for whom other long acting agents have a short therapeutic effect.

Contra-indications to the use of methylphenidate:

There are probably no absolute contra-indications to the use of methylphenidate.[37] Relative contra-indications may include:

a. ''Pure'' learning disorders: Because learning disabilities do not respond to stimulants, it is important to identify these deficits to help define remedial intervention.[16]
b. Developmental disorders: Stimulants have been found to be useful in children with mild to moderate developmental difficulties, but they may have lower response rates or higher incidence of adverse effects such as tics, obsessions, epilepsy anxiety or psychotic features.[38]
c. Emotional disturbances
d. Mental retardation: Several studies have shown that individuals with developmental disabilities have lower response rates to stimulants in comparison to people without. It appears to be more helpful in patients with mild to moderate developmental disabilities and ADHD, than those with severe to profound degrees of developmental disabilities.[382]
e. Uncontrolled epilepsy: For MPH and safety in epilepsy patients see study by Gross-Tsur, Manor, Van der Meere, Joseph and Shalev (1997).[39]
f. Gilles de la Tourette: Recent studies have found that the recommendations to avoid MPH in these children because of concerns of worsening tics are unfounded.[40]

Side effects of methylphenidate

Although some of the side effects of MPH have already been discussed under the short acting formulations, some of the more controversial side effcts are discussed here for completeness sake. Methylphenidate has been shown to be very safe.[41] Worldwide clinical experience over a period of more than 30 years has yielded remarkably few reports of adverse effects or serious toxicity, even when there has been intentional overdose. In children most side effects disappear as tolerance develops to the medication or resolve when the dose is decreased.[37] Yet resistance to its use in the management of ADHD persists mainly because of reputed side effects. In a double blind, methylphenidate-placebo trial the frequency of side effects was similar for both the stimulant and the placebo.[41] In more than 95% of the subjects side effects were reported to be in the mild range. Many of the side effects that were reported were similar to the symptoms of ADHD per se!

a. Anorexia and weight loss

Less than half the treated population is affected and it is usually mild. In most instances anorexia affects only the midday meal and decreases after two to three weeks' treatment. Short-term weight loss is virtually never significant.

b. Insomnia/Nervousness

Stimulants may theoretically cause insomnia. If it does occur, most children will return to their original sleeping patterns (which may not have been good to start with) after two to three weeks. Fourty percent of children have insomnia, before treatment.[41]

c. Vague stomach aches/Dry mouth/Nausea

Symptoms usually disappear within two to three weeks.

d. Dysphoria

Dysphoria refers to a state of being sensitive to criticism and subject to tears. It usually decreases after the first three days of the trial. In their study, Barkley, McMurray, Edelbrock & Robbins, 1990[41], found that 49% of their cohort with ADHD was prone to crying, 72% were irritable, 58% were anxious and 43% presented with sadness when given placebo.

e. Transient dyskinetic states, tremors, and tics

In a study of 120 children diagnosed as ADHD, 9% developed tics or dyskinesias on stimulant therapy (not only methylphenidate). In all but one, who developed Tourette syndrome, it was transient in nature. Barkley, McMurray, Edelbrock & Robbins, 1990[41] found a similar percentage (about 30%) of children developed tics in both the stimulant and placebo treated groups. Based on the outcomes of recent literature, it is recommended that it is safe to treat the co-morbid attention deficit/hyperactivity disorder in patients with Tourette syndrome with stimulant medications.[42]

f. Cardiac symptoms

Although children using MPH may complain of mild palpitations, more severe cardiac symptoms such as severe palpitations, pulse and blood pressure changes, angina and cardiac arrhythmias are side effects restricted to intravenous drug abusers. Mild elevations in blood pressure and cardiac rate have been reported, but do not seem to be clinically significant with prolonged use.[43]

g. Drug abuse

Methylphenidate is a very mild stimulant and has a low potential for abuse. Eight outcome studies concluded that stimulant therapy

does not promote drug abuse in adolescents. Although it is true that MPH binds to the dopamine transport protein in a fashion similar to cocaine, the slower clearance of MPH seems to be related to its lower potential for abuse.[44] It should be appreciated that individuals with ADHD have a far higher risk for substance abuse than the normal population. ADHD adolescents with conduct or bipolar disorder are the highest at risk for substance abuse.[45] In fact, recent reports seem to indicate that stimulants may protect children against later drug abuse.[46] The use of stimulants decreased this risk to levels similar in the general population.[47] Of concern is that methylphenidate is being diverted from legitimate use to abuse, although non-medical use is probably about 1%. It can be abused by crushing the tablets and snorting the powder, or dissolving the powder and injecting it. These routes are more common when MPH is taken to induce euphoria. Oral abuse is preferred for the purposes of trying to stay awake. Intravenous abuse of methylphenidate may lead to multiple organ failure and even death, usually related to the insoluble excipients in the tablets.[48] Abusers may take 200mg or more MPH per day.

h. Long-term effects on weight and height

Treatment with stimulants has been associated with small but significant decrease in body weight and height, but does not appear to be clinically significant. Furthermore these decreases are temporary. Children receiving stimulants have not demonstrated body weight or height reduction persisting into adulthood, compared to family, community and untreated controls.[49] There appears to be a subset of children with ADHD who are smaller than their peers to begin with. They need careful monitoring.[50] If there is not significant appetite suppression, drug ''holidays'' are no longer advised, as it has been shown that most children will have a rebound catch up on height within two years. It has been suggested that growth deficits in ADHD children may represent a temporary delay in the tempo of growth, but that the final height is not compromised and that the effect is mediated by the ADHD and not by the stimulant treatment.[51]

i. Other

Side effects such as skin rashes, fixed drug reactions and conjunctivitis have been reported in less than 1-2% of children.

B. THE NON-STIMULANTS

There has always been an interest in developing non-stimulant medication for ADHD, despite the fact that the stimulants have been proven to be both effective and safe. Reasons for this include the fact that 20-30% of children with ADHD may not respond to stimulants or have significant side effects that are difficult to accept.[52] They may not be suitable for use when there is a high risk for tic disorders or abuse or when tolerance appears to have developed against stimulants and they no longer appear effective.[53]

With the exception of Atomoxetine, non-stimulants are still considered second line medications in the management of ADHD, because they do not always improve all three core symptoms of ADHD. Potential advantages of non-stimulants include a longer duration of action, the treatment of co-morbidity such as anxiety and a minimal risk of abuse.

(i) Atomoxetine (Strattera®)

Nearly one third of children with ADHD will not respond to stimulants or are unable to tolerate them[54], and require an alternative medication to treat their symptoms. Atomoxetine is a potent inhibitor of the pre-synaptic norepinephrine transporter and therefore increases concentrations of extracellular norepinephrine. Low concentrations of norepinephrine in the right dorsal and orbital sections of the prefrontal cortex have been associated with many symptoms of ADHD such as decreased concentration, increased motor activity and lack of self control.[2]

Atomoxetine has been found to be effective in the treatment of ADHD in children and adolescents.[55,56] In the data reviewed, atomoxetine was more effective than placebo in children with ADHD ($p < 0.05$ to $p < 0.01$). Therapeutic doses ranged from 1.2 to 1.4mg/kg per day (maximum 100mg/day) in children.[57,58] It has alsobeen demonstrated to be an effective treatment in adults.[59,60]

Atomoxetine appears to be safe and well tolerated, and the incidence of adverse effects is low (about 5% of patients) with nausea being its main side effect. The majority of side effects are related to the acidity (low pH) of the active ingredient. Other adverse effects include decreased appetite, somnolence, dizziness and abdominal pain.[57,58] Although decreased appetite appears to be a significant side-effect, the incidence reduced by about 50% over 30 weeks follow-up and continued to resolve over time.[61] Anorexia and somnolence may be dose dependent.[56] Children experience a slight transient weight loss of 0.4kg versus placebo.[61]

Atomoxetine has shown no abuse potential[62] and is an alternative for parents seeking non-stimulants for their children. It is also particularly useful in children with co-morbid anxiety. Because of its long intra-cerebral half life (effective for 24 hours) it is also ideal in managing early morning and late night unwanted behaviours of ADHD.

In children weighing 70kg or less it is recommended that atomoxetine should be initiated at 0.5mg/kg/day and increased after at least 3 days (7days preferably) to reach the target dose of 1.2mg/kg/day.[56] For children and adults weighing more than 70kg, atomoxetine should be initiated at 40mg/day and increased after at least 3 days to reach a daily dose of 80mg. The lower initial dose is to prevent side effects. Atomoxetine (Strattera ®) is available in the following capsule strengths; 10mg, 18mg, 25mg, 40mg and 60mg. It is useful always to prescribe the next higher dose, rather than the next lower dose. If optimal effects are not obtained after 2-4 weeks, the dose can be increased to a maximum of 100mg/day for adults or 1.8mg/kg/day for children.

The dose may be administered once daily in the morning or twice daily in the morning and late afternoon/early evening. Most published data have utilized a twice-daily dosing regimen, but studies have found a once-daily administration of atomoxetine effective.[63] No tapering is required when discontinuing therapy. Unwanted gastric side effects (due to its acidity) can be managed by giving the atomoxetine with meals, at night rather than the morning, or splitting the difference. Research has found the morning dosage to be the most efficacious. Once the side effects have diminished, the evening dose could be switched back to a morning dose again.

When switching a child from a stimulant to atomoxetine, the technique may vary depending on the effects/side effects of the stimulants. It is recommended that the stimulant be continued as usual for the first week of the cross-over, and then halved in the second week, when the atomoxetine dose is administered at full strength. The stimulants can then be stopped in the third week. A more gradual withdrawal of stimulants can be followed if required. It may happen that in the process of stimulant withdrawal a situation is reached where the child enjoys maximum effect and

least side-effects on the combined therapy. It would be acceptable to keep the child on combination therapy at those dosages.

(ii) Antidepressants

Several antidepressants have been used for the treatment of ADHD, but the tricyclic antidepressants (TCAs) have been used most commonly.[11] Selective serotonin reuptake inhibitors have not yet been proven to be helpful or reliable in children with ADHD.[64]

Over 25 studies, mostly of imipramine (Tofranil®) and desipramine (Pertofran®), have been conducted in school aged children to establish the efficacy of TCAs in treating ADHD.[52] They do not appear to provide as much benefit in treating the cognitive symptoms of ADHD as stimulants, but they help to reduce impulsive and hyperactive behaviour.[64] Response rates of 70%-90% have been reported.[8,52]

Up until recently they were the preferred second choice of treatment in South Africa, and are specifically indicated when co-morbid conditions such as depression, anxiety and tic-disorders are present.[65] Further advantages to choosing the TCAs over MPH include potentially fewer disruptions of sleep, appetite and growth patterns and lower abuse potential. They may be effective in patients who are unresponsive to stimulants, although atomoxetine would now be the first non-stimulant drug of choice. Combined therapy with stimulants is often useful especially in complex cases.[11]

TCAs generally are initiated at doses of 0.5-3mg/kg (usually 10 to 25 mg) and increased every 3-4 days to 2-3 mg/kg. There appears to be no relationship with the dose needed to treat and body weight. Imipramine may take one to two weeks before an observable effect is evident, so usually the dose is increased every two weeks till the desired effect has been obtained. Often with children 10-25 mg daily or twice a day is enough.[53] Its benefit is that a once a day dose may be effective, but twice daily doses can be given to minimize side effects. If higher doses (over 50mg) per day are prescribed, a pre-treatment ECG is usually required, although cardiac effects in children are usually benign.[65,66]

Imipramine cannot be used with a monoamine oxidase inhibitor, and should be used with caution in patients with a history of cardiac conduction disorders and seizure disorders.[9] The most common side effects are fatigue and sedation and they may decrease over time. Less common side effects include dry mouth, constipation, decreased appetite and blurred vision.

(iii) Clonidine (Dixarit®)

The usefulness of clonidine in ADHD has been controversial, partly because of the lack of placebo-controlled studies (although there are many case studies), and partly due to concerns that clonidine and MPH could lead to sudden death. The latter fear has been put to rest.[67,68] One recent controlled study[69] found no significant cardiovascular effects from this drug combination in a blind parallel study of 24 patients.[70]

One series of double-blind placebo-controlled studies has suggested a significant therapeutic effect of clonidine on ADHD.[71,72] They reported behavioural improvements (decreased hyperarousal, hyperactivity and disinhibition) with fewer effects on cognition (inattention). Clonidine may be useful to treat the insomnia caused by stimulant medication and is then administered at night. A slightly higher dose is required than would have been used during the day. Clonidine is used predominantly for hyper-aroused, aggressive states and it can be used in Tourette's disorder and in children with tics.[8,40,42,73] It has many side effects, including somnolence, sedation, irritability and hypotension or rebound hypertension.[2]

Clonidine is usually administered in doses of 0.1 to 0.3 mg/day and should be titrated up to these levels slowly at the beginning of treatment with no more than 0.05 mg increases every 3 days.[53] Blood pressure and pulse rate should be monitored.[73] When clonidine is discontinued the dose should be tapered slowly to prevent side effects such as headaches, dizziness or even a rebound adrenergic overdrive (hypertension, agitation, fever, headache, chest pain, sleep disturbance, nausea and vomiting).

(iv) Risperidone (Risperdal ®)

Risperidone is not registered for the treatment of ADHD. It is useful for aggressive, violent behaviour and sleep disorders. It is therefore of great benefit in children with behaviour disorders, Tourette's syndrome and other tic disorders[42], developmental delay, autism, pervasive developmental delay and mental retardation. In children with pervasive developmental disorders risperidone was found not only to significantly decrease disruptive behaviours, agitation and anxiety, but it also had a positive effect on attention.[74,75] Risperidone was initiated at a starting dose of 0.25 mg twice a day and increased in 0.25mg/day increments every 5-7 days. Optimal doses ranged from 0.75-1.5mg daily in divided doses.[74] Risperidone is often effective as monotherapy. Extrapyramidal side effects and tardive dyskinesia appear to be less common than standard neuroleptics, but weight gain and polyphagia have been described.[76]

(v) Modafinil (Provigil ®)

Modafinil is a novel wake-promoting agent that is chemically and pharmacologically distinct from the psycho-stimulants. It is registered for the treatment of narcolepsy, and although it has existed for almost 20 years it has been studied sparingly.[77]

Modafinil has a half-life of 11-14 hours. It is not known by which mechanism modafinil exerts its therapeutic effects. One suggested mechanism is that modafinil may increase the excitatory amino-acid glutamate and decrease the inhibitory neuro-transmitter GABA in the posterior hippocampus.[78]

Although the effectiveness of modafinil in ADHD is currently being investigated in controlled studies, there are few published data to support its use. It appears to be more efficacious for the hyperactive-impulsive features of ADHD, than the inattention. Overall side effects are minimal in the dose range of 100-400mg daily, with the common adverse events being headaches (13%) and insomnia (10%) on higher dosages (>300mg). Severe tremors required one (of four) children to discontinue the modafinil.[79]

Conclusion

Medication is the most effective treatment for ADHD. As the choice of medical interventions expand, the choice of optimal medication, the evaluation of its efficacy and the planning for appropriate follow-up require an increasing level of expertise by the clinician.[8] Factors that affect medication choice include

- the nature and characteristics of the response to medication
- the duration and consistency of the effects
- tolerability and safety
- patient/parent preference
- physician expertise and preference
- previous treatment experience
- whether stimulants or non-stimulants are required
- presence of co-morbid conditions (tics, anxiety, insomnia, substance abuse, depression etc.)

With new formulations of old drugs, the launch of new effective treatments and new applications of standard medications we are indeed ''spoilt for choice''. Certainly these are exciting times for the medical management of ADHD.

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