Attention-Deficit Hyperactivity Disorder

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ATTENTION-DEFICIT HYPERACTIVITY DISORDER

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The term “attention-deficit hyperactivity disorder” (ADHD) is a contemporary term used to describe a behavioral disorder of childhood. Historically, behavioral and cognitive disorders were linked together and characterized as the notion of minimal brain dysfunction (MBD). Included were a broad array of characteristics such as hyperactivity, distractibility, impulsivity, learning disabilities, and emotional instability (1). The term ADHD is used throughout this chapter as it reflects the separation of this syndrome from learning disabilities, except as a related disorder. This term also implies no specific etiology, no pathognomonic signs, and no particular similarity in course of the disorder, or treatment duration. Evolution of operational definitions can be traced through three revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association. In the second edition, DSM II published in 1968, the phrase “hyperkinetic reaction of childhood” was used (2). DSM III (1980) presented two subtypes of a more broad-based concept, attention-deficit disorder with and without hyperactivity (3). The most recent revision, DSM III-R, (1987) combines the subtypes into one disorder to reflect the prominent and often disturbing role that hyperactivity plays in the disorder.

Table 55.1 shows the behaviors that a child with ADHD may exhibit with corresponding treatment goals and multimodal treatment plans for increasing the availability of the child to learning. Current practice suggests a patient-oriented healthcare team, including a primary care physician, clinical pharmacist, special educator, psychologist, and parent, and interactive pharmacologic and behavioral management that occurs within the child’s primary environments. The primary concern is for children who are producing chronic ADHD behaviors at home, at school, and in their communities because they present the greatest challenges, and with multimodal treatment, they may experience recovered potential rather than failure and despair (5).

ADHD is more common in boys than girls. The exact cause is unknown, although it is presumed to be neurologic. The affected children are not “available” for learning whether it is academic, social, or emotional skills that are involved.

A major and obvious symptom of ADHD is excessive motor activity. Movement, however, is also a primary form of normal expression in young children. During the first 6 years of their lives, children learn by touching, tasting, feeling, holding, and manipulating. Furthermore, children tend to translate their anxiety into excessive motor behavior; this often helps them communicate their unhappiness to adults in the absence of language. These normal developmental conditions often complicate diagnosis, particularly for for 4- and 5-year-old children enrolled in inappropriately structured and overly demanding academic preschool programs, where they must sit still to “learn” before they are ready to do so.

Therefore, ADHD could be described as purposeless, chronic, pervasive, driven behavior that interferes with a child’s availability to social, emotional and academic learning. The definition is assessed by an examination of the three characteristics—hyperactivity, impulsivity, and distractibility.

The term hyperactivity brings to mind the stereotypical wound-up child, unable to slow down for anything short of a brick wall. However, to label a child hyperactive simply on the basis of miles traveled per hour is to disregard some of the hallmarks of ADHD. Any child who is producing behavior that is purposeful, even at high energy, need not be considered hyperactive. To illustrate purposeless behavior in the extreme, consider a sandbox situation where four or five 6-year-old children are making roads in the sand and playing with toy trucks. The child with ADHD might use the truck to knock down another child’s sand house or throw the truck while moving rapidly from one part of the play area to the next, but this child will not typically be observed playing together or in common with the other children or “driving” the toy truck on the roads while making contextually appropriate “truck” sounds.

The impulsive ADHD child is likely to be viewed as disruptive and perhaps mean or “bad” by his peers and by adults. Very often with the impulsive ADHD child there is a one-to-one correspondence between feelings a child might have and the expression of these feelings—no matter how inappropriate—through verbal behavior or physical action. Therefore, a feeling of anger will be expressed without reflectivity or any recognition as to what impact
the words "I hate you" or "I want to smash you" for example, might have on the recipient. Even a hug, impulsively given at the wrong time and wrong place, can result in embarrassment and surprise for the unwilling recipient and corresponding rejection and hurt feelings for the ADHD teen. Adults and children often react negatively, which sets up a vicious cycle with the child producing even more impulsive behavior.

The distractible ADHD child has a short attention span and seems to be more interested in what is going on in the next room than in the activity at hand. However, distractible children often are more on-task than they might appear and respond well to behavioral modification techniques and educational modifications.

While the young ADHD child may be observed producing purposeless motor behavior, the ADHD adolescent may be sophisticated enough to control the external behavior, even though his mind is racing a mile a minute. Distracted by anything and everything, he is preoccupied with his own thoughts.

Although often described as a disease of childhood, some symptoms of ADHD, such as impulsivity and distractibility may persist into adult life (6, 7).

PATHOGENESIS

Studies of causative factors have focused on the relationship between scholastic underachievement and central nervous system (CNS) disorder. Table 55.2 lists abnormalities and lesions that have been postulated to be responsible for the symptoms of ADHD, which is presumed to be a neurological disorder (8). The most promising of the contemporary postulates on CNS-related causative factors is assumed neurotransmitter deficiency or breakdown. It is thought that psychostimulants increase the production of norepinephrine so that the child can function as normally as possible (9). However, the actual etiology of ADHD remains elusive.

DIAGNOSTIC AND CLINICAL FINDINGS

Diagnosing ADHD begins the process of change, but making that diagnosis is complex. The typical ADHD child has good health, but the history reveals that, from the earliest days, the child has been different and his purposeless behavior has been chronic. Whereas ADHD was once thought of as a global syndrome, it is now differentiated into two general types: the chronic or neurologically based and the situational or anxiety-based (10).

The two types have striking similarities in that the child may be producing hyperactive behavior. The chronic or neurologically based hyperactivity however, is recognized very early in life. Some mothers report that even in utero, the child was very active. Often the medical history will indicate a child who was very colicky and had very disruptive sleeping and eating patterns. From early on, the child was fearless and charged headlong into situations that were dangerous or even life-threatening, such as running out into the street, whereas normally developing preschoolers are more likely to be put off by loud noises made by cars and, therefore, tend to avoid the street. Approximately 1% of the school-aged population would be considered ADHD if only those children who fit the "chronic rule" were considered.

In contrast, situational or anxiety-based hyperactivity has no chronic history of problems with attention deficits. For example, the child may be 10 years old, with a good disposition and perfect school attendance record. Then, suddenly, the child no longer pays attention in class, and is fidgety, nervous, and upset. His behavior is suddenly and acutely purposeless, and not directed toward goal completion. In most cases, these are young people experiencing anxiety over an unpleasant situation in their lives.
such as a parent's impending divorce or loss or change of
jobs, the death of a pet, problems with a bully who wants
to fight or visit by relatives. The anxiety is then translated
into motor behavior. Children sometimes become symp-
tom-bearers for family issues, particularly when family rou-
tine, predictability, and structure are altered or lost. These
children are not thought to be good candidates for drug
treatment, and individual counseling and family therapy
are indicated. While controversial, it might be best to not
consider these children as ADHD patients.

Although there is not a critical diagnostic test for
ADHD, it is important to attempt to rule out other syn-
dromes, such as borderline schizophrenia. The schizo-
phrenic child will usually appear more fearful, will have
pronounced phobic symptoms, and will avoid social con-
tact while exhibiting undue preoccupation with violent or
sexual matters.

Learning disabilities and ADHD are now no longer
thought of as a common syndrome with differing clinical
manifestations. Rather they are conceptualized as distinct
conditions (11). Table 55.3 highlights the similarities and
differences noted for both syndromes. Similarities include:
(a) presumed neurological cause and (b) school failure.
Differences include (a) impact of presumed neurological
involvement; (b) reason for school failure; and (c) entitle-
ment to special education classes by law. On this last point,
federal lawmakers have recently agreed to drop a proposal
explicitly entitling ADHD children to special education
classes under the federal special education law. How this
will turn out is of serious concern to education, mental
health, and civil rights groups who believe that a dispro-
portionate number of minority children could be miscal-
beled and consequently placed in special education classes.
Furthermore, services for deserving special education chil-
dren might be diluted (19). For children with learning
disabilities, ADHD should be thought of as a separate but
"related" disorder when these children also demonstrate
hyperactivity, distractibility, and/or impulsivity.

**GENERAL MEASURE OF TREATMENT**

The major nonmedical treatment approaches for children
with ADHD are behavior therapy and individual and fam-
ily psychotherapy. Behavior therapy techniques include
(a) establishing baseline data; (b) recognizing and reinforcing
desirable behaviors; and (c) modifying instructional se-
quencies at home and school. Because desirable and un-
desirable behaviors cannot occur at the same time, it is
often advantageous to use a behavior therapy approach
referred to as incompatible alternatives, where the ADHD
child's desirable behaviors, which occur spontaneously and
fleeting, are recognized and reinforced by the teacher
and/or parents (14). According to Bax, "manipulation of
the external environment of the hyperactive child, rather
than changing the internal environment pharmaco-
logically, is in the long run the most likely to be helpful" (15).

Individual psychotherapy is indicated so the child can
learn to cope with family and friends during the recuper-
ative phase. The child is often acclimated to censure from
teachers and parents along with abuse from peers, result-
ing in the formation of many psychological scars. These
problems must be ameliorated with adequate psychother-
apy because most of the medications currently used can
only relieve the immediate symptoms of ADHD. They will
not aid coping with the indirect consequences of the child's
former behavior on the other individuals.

Family psychotherapy is indicated when family rela-
tionships and interactions become dysfunctional. Child-
focused and problem-oriented parenting, which may serve
to keep a child dependent, confused, and defensive are a
concern when special needs are present (16, 17). In many
families the behavior of the parent mirrors that of the child.
For example, if the child with ADHD is angry, a parent
is angry. If a child starts crying, a parent starts crying, and
if the ADHD child is happy, a parent is happy. If parents
are that emotionally enmeshed with their child, they only
heighten the child's anxiety. A family with this structure
needs to work on becoming less emotional and more cog-
nitive through family therapy, which also focuses on build-
ing predictability, limits, consequences, and routines for
all members of the family, not just the child with ADHD.

Most parents seek help for their hyperactive, distrac-
tible, and/or impulsive child because the purposeless be-
behavior has caused problems for the whole family. When
family members are willing to look at their part in this
relational-systemic process (understanding that if one
member of a relational system has a problem then every
member of that system also has a problem), the use of
available technology results in a very positive prognosis.
Unfortunately, there are cases where families hope that
the problem will just go away. That may be encouraged,

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**Table 55.3.**

**Comparison of Attention Deficit–Hyperactivity Disorder
and Learning Disabilities Syndromes**

<table>
<thead>
<tr>
<th>Attention Deficit–Hyperactivity Disorder</th>
<th>Learning Disabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed to be neurological resulting in impaired control of motor activity levels</td>
<td>Presumed to be neurological resulting in impaired basic psychological learning processes</td>
</tr>
<tr>
<td>School failure due to not being available to learning</td>
<td>School failure due to imperfect ability to listen, read, write, etc.</td>
</tr>
<tr>
<td>Not entitled to special education classes</td>
<td>Entitled to special education classes*</td>
</tr>
</tbody>
</table>

*Note: 15-50% of children with learning disabilities have ADHD as a "related" disorder (13).
unfortunately, by well-meaning professionals, who say "your child is just immature" or "boys will be boys."

In families with other achieving children, the sibling with ADHD may be subjected to unfavorable comparisons or simply be written off as the only one with the problem. In those cases, there may be enough positive relational activity going on that the family is not hurting to the point where they are motivated to seek needed family therapy.

PHARMACOTHERAPY

Many pharmacotherapeutic approaches have been taken in the treatment of ADHD. The use of medications in these children is most likely to be effective when it is an aspect of a multimodal treatment plan along with instructional modification, behavioral intervention, and family therapy. The use of selected drugs, such as dextroamphetamine or methylphenidate, is considered an acceptable therapy for managing specific inappropriate motor activities of children with ADHD, particularly where the hyperactivity is neurologically and not anxiety-based (10). Medications do not cure ADHD, but they may help make the child more available to the learning experience. The likelihood that medications will be effective is enhanced when there is an interdisciplinary diagnostic approach and when there is complete cooperation and communication between the physician and the child's home and school, where the ADHD child is most likely to be at odds with his parents and school authorities because of hyperactivity, impulsivity, and distractibility. Perhaps the greatest difficulty with drug use is that children are often put on medications before any specific baseline behaviors have been identified and documented. Without this information from home and school, positive changes in behavior become difficult to evaluate. Furthermore, with pinpointed behaviors, other forms of behavior management, such as positive reinforcement and modified curriculum, can be instituted once the child becomes available to learning, with the ultimate goal being the gradual withdrawal of the drugs.

Centrally Acting Symptomomimetics

The primary agents used in the treatment of ADHD are the centrally acting sympathomimetics, such as methylphenidate, dextroamphetamine, and magnesium pemoline (18). Dextroamphetamine was used initially in 1937 and continued to be the agent of choice until the late 1960s; when the use of methylphenidate increased in association with reports of a lower rate of side effects with the latter drugs. It would appear that these reports of greater safety with methylphenidate are of questionable clinical importance (19). There are also studies attesting to the greater clinical efficacy of methylphenidate (20) over dextroamphetamine by some authorities who prefer the former drug; proponents of dextroamphetamine indicate that, in their hands, it has comparable clinical efficacy at a lower cost (21). Some clinicians recommend that a trial of both dextroamphetamine and methylphenidate be given to each child. This allows identification of the most useful agent, i.e., whichever one gives the greatest improvement and lowest incidence of adverse effects (22). With the availability of sustained-release preparations, many clinicians now prefer to use these formulations. They provide sustained therapeutic levels with a single daily dose: methylphenidate, 20 mg SR; pemoline, 56.25 mg; or dextroamphetamine Spansule, 10 mg. The duration of effect was noted to be from 1 to 9 hr after ingestion, and all were equieffective; however, pemoline was associated with a greater frequency of difficulty in falling asleep (23).

Many studies have demonstrated that the centrally acting sympathomimetics are effective in 70 to 80% of affected children. The drugs are most effective in improving attentiveness and decreasing hyperactivity, but they may also be of use in ameliorating deficits in fine motor coordination, particularly handwriting. Although the action of these drugs on cognition is questionable, the improvement in attention span may help create a more positive atmosphere for learning (24). Identification of target symptoms is of particular importance, since some researchers have reported that low doses of stimulants improve cognitive performance, while higher doses are recommended for controlling undesirable behavior (25). A summary of the dose characteristics of CNS stimulants is provided in Table 55.4.

Use of the psychostimulant medications also carries inherent risk, as these agents are known to cause a number of adverse effects (29). The most commonly reported side effects include anorexia, weight loss, GI pain, and insomnia. These tend to decrease with time in many patients, but they must be carefully monitored. The sympathetic activation of these agents, particularly methylphenidate or dextroamphetamine, can cause palpitations, tachycardia, and increased blood pressure. Routine monitoring must include measurement of blood pressure and pulse, as there is a risk of myocardial hypertrophy from the chronic use of agents of this type (30). If significant increases in either

<table>
<thead>
<tr>
<th>Drug (Reference)</th>
<th>Daily Dosage (mg/kg)</th>
<th>Dosing Interval (hr)</th>
<th>Elimination Half-Life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine (26)</td>
<td>0.3–1.5</td>
<td>4–6</td>
<td>6.6</td>
</tr>
<tr>
<td>Methylphenidate (27)</td>
<td>0.3–3.5</td>
<td>4–6</td>
<td>2.5</td>
</tr>
<tr>
<td>Pemoline (28)</td>
<td>2.0–6.7</td>
<td>8–12</td>
<td>7.2</td>
</tr>
</tbody>
</table>
BP or HR are noted, the drug dosage should be reduced or an alternative agent (usually pemoline) should be used.

The actual decision to initiate drug therapy with CNS stimulants must be based on the characteristics of each case; however, two factors considered to be critical are proper class placement and use of target symptoms (24). Proper class placement appears to be most critical, so it is imperative that the school system properly evaluate the academic level of the child. Otherwise, medication will be of little use because of the problems of inappropriate coursework and negative peer interaction. Identification of target symptoms, i.e., hyperactivity, impulsivity, cognitive skills, or social interactions is also imperative for proper selection and dosage adjustment.

**Methylphenidate**

Methylphenidate is the most commonly used agent for pharmacotherapy of ADHD (31). In contrast to therapeutic agents used in other childhood disorders, the dosing of methylphenidate and other agents used in ADHD is somewhat empirical because of the lack of sensitive analytical methods prior to the 1980s. Recent studies indicate that oral methylphenidate has a lag phase of 0.5 to 1.0 hr and reaches a peak 2.5 hr after administration (24), with a positive correlation between plasma levels and response in ADHD (32). The drug is given orally in doses of 5 to 10 mg twice daily (in the morning and at noon, to avoid the potential iatrogenic insomnia that can ensue from the drug) or in a single 20-mg sustained-release form (RitalinSR) in the morning. Therapy should be initiated with a dose of 0.3 mg/kg either in the morning or twice daily. If a satisfactory response is not noted after 2 weeks, the dose is increased by 0.1 mg/kg every 2 weeks until the maximal dose is reached. If there is still no response at this point, switching to another medication is considered.

Most patients respond well at 10 to 20 mg twice a day, and the daily dose should be limited to 60 to 120 mg maximum. A single-dose study of methylphenidate revealed that a morning dose of 20 mg had clinical efficacy similar to a sustained-release form of dextroamphetamine. However, 15% of the children did not retain a therapeutic response for the entire school day (33). In addition, children will often experience decreased blood levels in the hours after school and social conflicts may develop, so the SR preparation is particularly useful in these cases.

Methylphenidate has a 70 to 85% response rate and appears to reduce hyperactivity and restlessness, prevent distraction, and increase the attention span. These factors all aid in making the child more available for the learning environment, so that a secondary, but important effect of the drug is to increase learning ability. Motor ability and coordination are also enhanced by the drug (34).

Methylphenidate has also been used for treatment of ADHD, residual type, which is noted in adult patients. Doses of 10 to 80 mg/day were significantly more effective than placebo in the amelioration of attention difficulty, affective lability, motor overactivity, and impulsivity (35).

In children with ADHD, methylphenidate can cause certain undesirable side effects. Suppression of growth has been reported, with both decreased weight and height being noted (36); however, when medication was discontinued over vacations, a spurt in growth returned the treated children to control levels (37, 38). A subsequent study in 100 patients has revealed no stunting of growth in children treated with methylphenidate, dextroamphetamine, or imipramine/desipramine on a long-term basis (39). It appears that a temporary decrease in the rate of growth in weight or height occurs during the first few years of therapy at conventional doses, dependent upon both dose and use of drug holidays. Any weight or height decrement should be compensated for during the drug-free period, and there does not appear to be any effect on adult height or weight (40). The current treatment approach allows the child to remain drug free, if pragmatically possible, over weekends and vacations, to both prevent any transient growth retardation and allow for continual reevaluation of the need for pharmacotherapy (41). If a child's hyperactive behavior is pronounced at home as well as in school, drug-free holidays may be difficult to institute in the absence of behavioral and counseling therapies. The child whose hyperactive behavior was primarily a school problem is a better candidate for intermittent drug therapy.

Cardiovascular side effects, usually either increased diastolic blood pressure or tachycardia, have been reported. It is important to monitor both blood pressure and pulse rate to evaluate excessive systemic sympathetic response (see above). Insomnia and anorexia resulting in weight loss have also been reported, but they occur less commonly than with other amphetamine derivatives. Cases of Gilles de la Tourette's syndrome have also been precipitated or exacerbated by this drug (42). Methylphenidate has been reported to inhibit hepatic drug metabolism, and the half-lives of several substances, such as desipramine and phenytoin, may be prolonged, resulting in potential toxicity. It is particularly important to consider the potential interactions with the anticonvulsant drugs, because these are often used concurrently in the child with ADHD, and there have been several reports of ataxia in patients on phenytoin and methylphenidate (34).

The use of methylphenidate (or other CNS sympathomimetic agents) is contraindicated in patients with symptomatic cardiovascular disease, hypertension, hyperthyroidism, or glaucoma, and in patients that are using or have taken monoamine oxidase inhibitors within the previous 14 days due to the drug interaction between indirect sympathomimetic agents and the MAOI drugs (29).
Dextroamphetamine

Dextroamphetamine is used similarly to methylphenidate in the treatment of ADHD, and although some studies indicate similar clinical efficacy (21), most of the clinical literature indicates an approximately 10 to 15% higher improvement rate with methylphenidate (20, 36). The use of dextroamphetamine in ADHD rather than levodopaamphetamine or racemic amphetamine mixtures is based on the established superiority of the former agent in various clinical trials (43). The usual dosing schedule for dextroamphetamine is 2.5 to 20 mg twice daily, morning and at noon, or the sustained-release dosage forms that are available can be used in a single morning dose. The use of 5-mg tablets allows greater latitude in dose adjustment and better evaluation of clinical response over time (41). Dextroamphetamine in the ADHD child has a peak effect at 1 to 2 hr after dosing and a duration of action of 4 to 6 hr. The dose is generally titrated from an initial dose of 5 mg twice a day up to an effective level by increasing the dose by 5 mg/day every 2 to 3 days until either the symptoms subside or side effects occur.

Side effects reported with dextroamphetamine are similar to those of methylphenidate and usually tend to decrease a few weeks after initiation of therapy. Persistent insomnia may be treated with a mild hypnotic agent such as diphenhydramine (25 mg) or can occasionally be alleviated by taking the child off dextroamphetamine and initiating therapy with methylphenidate. When this type of change in stimulant therapy is attempted, a 24-hr period should elapse prior to initiation of therapy with the new stimulant drug (21).

The question of potential abuse of psychostimulant drugs by children previously treated with these agents has been one of concern to many health professionals. However, at present, studies indicate that abuse of drugs in later life is not a sequel to amphetamine therapy in childhood (19, 44, 45).

Magnesium Pemoline

Magnesium pemoline has also been used in children with ADHD. This drug is a CNS stimulant with psychostimulant actions, similar to dextroamphetamine. It possesses similar beneficial actions to those of dextroamphetamine as well as similar side effects, with insomnia and anorexia being most prevalent. However, a more serious problem is hypersensitivity reactions that usually involve the liver; these are noted in 1 to 2% of patients, and liver function tests should be performed periodically in treated children (24, 29). Pemoline has a slower onset of action than the other CNS stimulants (2 to 4 hr), but a longer duration of action (8 to 12 hr). It may be given as a single morning dose or in two divided doses (morning/after school), depending upon patient response. The initial dose should be 37.5 to 75 mg/day, with incremental increases of 18.75 mg/day at weekly intervals until maximal therapeutic response or a maximum recommended dose of 112.5 mg/day is attained. Magnesium pemoline does not give as rapid a clinical response as dextroamphetamine, but after 8 weeks of treatment with either drug, a similar clinical response can be anticipated. This drug may be considered as an alternate agent for those patients that cannot tolerate either of the stimulants previously discussed.

Tricyclic Antidepressants

A variety of other agents have been used in attempts to treat cases of ADHD that are nonresponsive to or inappropriate for psychostimulant therapy. Many reports have indicated that tricyclic antidepressants, usually imipramine or desipramine, may benefit these patients, even though the only childhood use approved by the FDA is in the treatment of enuresis. However, although most studies have indicated their superiority over placebo, they are still not as effective as the psychostimulants. When a response is noted, it is usually seen within 3 to 4 days, as contrasted to the 2 to 4 weeks necessary for the antidepressant action. Effective doses range from 1 to 2 mg/kg/day in the majority of patients (29). Prior to starting therapy, patients should have a baseline EKG, CBC, platelet count, and liver and renal function tests. Drawbacks to the use of tricyclics include the development of tolerance in children and the numerous side effects of these agents (46). Side effects may be somewhat limited by the maximum daily dose approved by the FDA (5 mg/kg/day), but autonomic effects, weight loss, gastrointestinal irritation, fine tremors, hyperirritability, and mood alterations must be evaluated continually. The incidence of anticholinergic side effects with desipramine is generally less than with other first-generation tricyclic antidepressants, so it may be preferred in some patients. In addition, the more severe effects on the CNS (e.g., seizures) and the cardiovascular system (e.g., increased pulse and diastolic blood pressure) must be monitored. Sudden death has also been reported in three pubertal boys that received desipramine for ADHD (47). Since abrupt withdrawal of these drugs can cause rebound cholinergic symptoms, it is important to taper the dose during drug discontinuation. This cholinergic syndrome is marked by anxiety, nausea, diarrhea, and flu-like symptoms (48). Thus, although the tricyclic antidepressants are useful in the child with ADHD, their use at this point is limited primarily to nonresponders to CNS stimulants, and precautions must be taken if they are used (19, 49).

Antipsychotic Agents

Several antipsychotic drugs have been used in ADHD, including chlorpromazine, thioridazine, haloperidol, and reserpine. Chlorpromazine has been reported to be sig-
significantly more effective in treatment of hyperactivity than placebo, and in some studies it has equivalent efficacy to that of dextroamphetamine, which is generally effective in approximately 55 to 70% of cases. However, the psychostimulants have a broader spectrum of action in ADHD, because chlorpromazine was found to control hyperactivity, but failed to result in significant attention improvement (50). Studies with thioridazine have provided results essentially similar to those described for chlorpromazine (50). A report of the effect of haloperidol on cognitive behavior in children with hyperactivity indicated that methylphenidate and low-dose haloperidol (0.025 mg/kg) both facilitated cognitive performance, while high-dose haloperidol (0.05 mg/kg) appeared to cause a slight deterioration of performance (51). Therefore, low doses of the antipsychotic agents should be used to obtain an optimal response. Use of these drugs in combination with psychostimulants is inappropriate, since haloperidol has been shown to block the positive effects of methylphenidate (52). Reserpine has been shown to produce improvement in 34% of the children with ADHD, and this limited success rate negates its use in this disorder (20). Thus, the antipsychotic agents may be useful occasionally in therapy of ADHD, but they are capable of depressing the higher CNS functions of attention, and more importantly, cognition. These latter concerns coupled with the multiple autonomic and extrapyramidal side effects associated with the antipsychotic agents, including the potentially irreversible syndrome of tardive dyskinesia, preclude their use as primary agents. They can be viewed as an alternate choice of therapy only in patients who are poor candidates for psychostimulant therapy.

Other Therapeutic Approaches

Many other therapeutic approaches have been used in an attempt to find the ideal drug for treatment of ADHD. The monoamine oxidase inhibitors clorgyline and tranylcypromine have been shown to be equieffective to dextroamphetamine in ADHD, but they must be carefully monitored and strict dietary compliance is mandatory (29). These drugs have an "immediate" clinical effect, in contrast to the time lag to their antidepressant response. Clonidine, an α2-receptor agonist in the CNS, has also been reported to produce improvements in both behavior and attentional difficulties, with minimal side effects (53). In one clinical trial, clonidine, 0.05 to 0.6 mg/kg/day was found to have equal activity to methylphenidate in ADHD. The availability of a transdermal administration system for this drug, its low abuse potential, and the relative lack of adverse effects (as contrasted to the oral preparations of this agent) make it an agent worthy of further investigation. Antianxiety agents have been evaluated on a limited basis and appear to be of little use. The benzodiazepines are of no value in therapy (54), and phenobarbital is similarly not useful and has been reported to worsen the child's behavior (19, 55). Therefore, use of these agents should be avoided in the child with ADHD. Similarly, anticonvulsant drugs (19, 55), caffeine (56), antihistamines (57), lithium salts (58), and fenfluramine (59) are either unacceptable for therapy or inadequately evaluated.

There is evidence that chronic low-level lead exposure can result in subtle CNS damage and hyperactivity. In one reported study, 13 hyperkinetic children with blood and urinary lead levels that were elevated, but in a nontoxic range, were treated with the lead-chelating agents penicillamine or calcium disodium acetate. Six of the children had a positive medical history of perinatal or developmental CNS insult and did not respond, while the other seven ADHD children that had unremarkable histories and a possible lead-induced hyperactivity showed marked improvement. The authors concluded that lead may play an important role in the etiology of ADHD, and measurements of blood and urinary lead levels may become a part of the standard work-up in cases of ADHD with no previous history of CNS insult (60).

There have also been isolated reports on the use of megavitamin therapy in ADHD (61). This approach is to be discouraged because of the potential toxic effects of vitamins A and D (62, 63); however, it is important to ensure adequate nutrition in the child with ADHD via monitoring of diet.

In 1973 an allergist postulated that hyperactivity was caused by food additives (64). Subsequent studies have failed to demonstrate any benefit of dietary regulation deleting food additives in the treatment of children with ADHD (65, 66). As mentioned previously, the causes of ADHD are not definable and may be multiple; therefore, the success of the Feingold diet should be viewed with some pessimism. Although there are individual testimonials to the positive outcome of dietary treatment of hyperactivity, studies carried out by numerous investigators over a 5-year period provide "sufficient evidence to refute the claim that artificial food colorings, artificial flavorings, and natural salts/yeasts produce hyperactivity" (66).

THE ADULT ADHD PATIENT

Children with ADHD do not always "outgrow" this disorder. Longitudinal studies indicate that 31% of these patients will continue with full symptoms (attention deficit, hyperactivity, impulsivity), with another 9% showing two of the three symptoms. Twenty percent of these patients had an antisocial disorder of some type, while another 12% had a substance abuse disorder. In another study, 66% of ADHD patients were found to have residual symptoms after 15 years (67).

The psychostimulants (methylphenidate, pemoline) have demonstrated efficacy in both adolescent and adult ADHD patients (67). However, the distribution of these
scheduled substances in the adult population may result in diversion. The antidepressant drug bupropion or the monoamine oxidase inhibitors paroxetine and deprenyl may offer therapeutic alternatives. Paroxetine (68) and deprenyl (69) provide moderate-to-marked improvement of symptoms in approximately 60% of adults with ADHD. Bupropion was found to benefit 14 of 19 patients in an open trial. However, tolerance to the therapeutic action was noted, and dosage had to be increased to an average of 359 mg/day. Ten of the 19 patients elected to remain on the drug rather than return to their former medication (70). Further studies are needed on this agent and on other therapeutic alternatives to psychostimulant therapy for the adult ADHD patient.

THERAPEUTIC CONSIDERATIONS
Methylphenidate or dextroamphetamine are the drugs of choice in this disorder. When these drugs are not effective, magnesium pemoline is the second agent to consider. If none of these agents are successful, the use of tricyclic antidepressants, antipsychotic agents, or clonidine might be attempted in hope of a response. Appropriate doses for commonly used agents are given in Table 55.5.

The child and family will need supportive counseling to promote compliance with the medication regimen as well as to ensure therapeutic success. As mentioned previously, behavior therapy, remedial education, and individual and family psychotherapy may all be indicated in addition to pharmacotherapy.

The duration of therapy is somewhat empirical, based on the response of the child during drug-free periods such as weekends and vacations. A number of children with ADHD continue to show characteristics of the disorder into adult life, and therapy of some type may be needed for the remainder of the patient’s life. Some clinicians have treated patients into the fourth decade of life, and interestingly, these patients do not appear to become tolerant to the effects of the psychostimulant drugs, and they do not become dependent upon the psychological attraction of their euphoric actions (45, 46). However, there may be concern for patients who view drugs as responsible for the control of their behavior without a corresponding increase in the development of personality skills, such as assertiveness and open, direct communication.

PROGNOSIS
The prognosis of the ADHD child is questionable. It is generally assumed that ADHD is outgrown by puberty or in early adolescence. However, ADHD has been causally linked to a variety of persistent disorders into adult life. Adjustment to continued schooling, jobs, and intimate personal relationships may continue to be a source of extreme reaction for the ADHD adult. Academic underachievement due to unavailability to learning during younger years, impulsive character disorder, sociopathy, and other recognized psychiatric disorders may then become the diagnosis. It is difficult with the present medical evidence to give an adequate prognosis on recovery per se, in light of limited follow-up data.

CONCLUSIONS
ADHD is a common disorder of primary grade school children which can persist into adult life. The cardinal features involve hyperactivity, impulsivity, and distractibility in the presence of normal intelligence. Treatment with psychostimulants is effective in approximately 75 to 80% of affected children when used as part of a multimodal treatment plan including behavior management, both at home and school, and educational modification. However, lingering affective aspects of the disorder are rarely totally alleviated by drug therapy, and other nonpharmacologic individual and family psychotherapy measures must be used concomitantly with these agents. When all of these approaches are used effectively, there is no reason for the quality of life of these patients to be any different from that of the rest of the populace.

Table 55.5.
Daily Dosage Ranges of Drugs Useful in Therapy of Attention-Deficit Disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychostimulants</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>5–120</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>2.5–60</td>
</tr>
<tr>
<td>Pemoline</td>
<td>55.25–112.5</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>10–1000</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>20–600</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>10–175</td>
</tr>
<tr>
<td>Desipramine</td>
<td>10–175</td>
</tr>
</tbody>
</table>

REFERENCES


