Attention Deficit Disorder: A Review of the Past 10 Years

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ABSTRACT

Objective: To summarize knowledge about attention deficit disorder in the areas of epidemiology, etiology, clinical predictors, assessments, natural history and outcome, and management. Method: A literature review of articles, books, and chapters primarily published in the past 10 years was completed. Articles presenting new information, most relevant to clinical practice, were reviewed. Results: Key findings in the areas listed above are presented. Conclusions: Major advances have been made in all areas. The clinical picture has been refined and developmental manifestations have been delineated. Patterns of comorbidity have been detailed. Various etiological factors, particularly in the biological area, have been investigated. Multimodal management has been promulgated as the treatment of choice. J. Am. Acad. Child Adolesc. Psychiatry, 1996, 35(8):978–987. Key Words: attention deficit disorder, disruptive behavior disorders, stimulant treatment, multimodal treatment.

Attention deficit disorder (ADD) is one of the most important disorders that child and adolescent psychiatrists treat. It is important because it is highly prevalent, making up as much as 50% of child psychiatry clinic populations. It is a persistent problem that may change its manifestation with development from preschool through adult life. It interferes with many areas of normal development and functioning in a child’s life. Untreated, it predisposes a child to psychiatric and social pathology in later life. Most importantly, it can be successfully treated.

EPIDEMIOLOGY

The figure usually given for prevalence of ADD in the general population is approximately 3% to 5% of school-age children. This figure does not take into account preschool, adolescent, and adult populations. Prevalence rates, however, vary according to the population that is sampled, the diagnostic criteria, and diagnostic instruments that are used. More recent data suggest higher figures in school-age children.

Wolraich et al. (1996) and Baumgaertel et al. (1995) have recently completed two epidemiological studies using DSM-IV criteria (American Psychiatric Association, 1994). One was conducted in Tennessee and one in Germany. Teacher information was the sole source of data in both studies. The prevalence rates for the primarily inattentive, primarily hyperactive, and combined subtypes of DSM-IV ADD in the Tennessee sample were 4.7%, 3.4%, and 4.4%, respectively. In the German sample the rates for the same subtypes were 9.0%, 3.9%, and 4.8%, respectively. In the German sample the rates for the same subtypes were 9.0%, 3.9%, and 4.8%, respectively.

Both in clinical and epidemiological samples the condition is much more common in males—9 to 1 in clinical samples, 4 to 1 in epidemiological samples. This suggests selective referral bias since girls may have primarily inattentive and cognitive problems and less of the aggressive/impulsive conduct symptomatology which leads to earlier referral (Baumgaertel et al., 1995; Cantwell, 1994b; Wolraich et al., 1996).
ETIOLOGY

The etiology of ADD is unknown. It is unlikely that one etiological factor leads to all cases of what we call the clinical syndrome of ADD. Most likely there is an interplay of both psychosocial and biological factors that may lead to a final common pathway of the syndrome of ADD. Thus, there are some known conditions such as fragile X syndrome, fetal alcohol syndrome, very low birth weight children, and a very rare, genetically transmitted thyroid disorder that can present behaviorally with symptoms of ADD. However, these cases make up only a small portion of the total population of children with the diagnosis (Arnold and Jensen, 1995; Cantwell, 1994b).

Early ideas were that this condition was some type of “brain damage.” This idea was derived from the early studies of children who had suffered encephalitis in the encephalitis epidemic of 1917 and 1918. More recent studies of brain morphology involve modern and much more sophisticated measures. Hynd et al. (1990) produced magnetic resonance imaging findings, suggesting that children with ADD had normal plana temporal, but abnormal frontal lobes. Giedd et al. (1994) demonstrated reduced volume in the rostrum and rostral body of the corpus callosum. This has been interpreted as being consistent with an alteration of functioning of the prefrontal and anterior cingulate cortices of the brain in addition to altered premotor function (Steere and Arnsen, 1995).

Pathophysiology of ADD has also been investigated using other imaging techniques including single photon emission computed tomography (SPECT) and positron emission tomography (PET) (Lou et al., 1989; Zametkin et al., 1990). SPECT studies revealed focal cerebral hypofusion of striatum and hyperfusion in sensory and sensorimotor areas. The PET study by Zametkin et al. was of adults with ADD who had a child with ADD. Compared with normal adults, the adults with ADD had lower cerebral glucose metabolism in the premotor cortex and in the superior prefrontal cortex. These brain areas are involved in the control of motor activity and attention. The same authors used PET to study adolescents with ADD. The results were not as strong. Adolescent females with ADD did have reduced glucose metabolism globally compared with normal control females and males and compared with males with ADD (Cantwell, 1994b; Zametkin, 1993).

The results might be explained on the basis of the adults’ having a “familial” and a “persistent” subtype of ADD. All adults in the Zametkin study continued to manifest the syndrome from childhood on and had a child with ADD. It may be that the adolescents did not all have a “familial” subtype and/or that their ADD will not persist into adult life.

There is general agreement that psychophysiological studies have not revealed global autonomic underactivity in children with ADD. However, a more specific pattern of underreactivity to stimulation has been suggested by studies showing more rapid heart rate deceleration and smaller orienting responses on galvanic skin response, greater slow-wave activities of the EEG, smaller amplitudes of response to stimulation, and more rapid habituation on average evoked responses to stimuli (Barkley, 1990).

Family genetic factors have been implicated as etiological in ADD for some 25 years. Heritability is estimated to be between .55 to .92. Concordance was 51% in monozygotic twins and 33% in dizygotic twins in one study (Goodman and Stevenson, 1989). Family aggregation studies have shown that the ADD syndrome and related problems do run in close family members (Biederman et al., 1989). Adoption studies support that this “running in families” is genetic rather than environmental (Barkley, 1990; Cantwell, 1975). At this point, no gene has been described or found, but this is an active area of research and is likely to bear fruit in the foreseeable future.

The positive response of ADD individuals to CNS stimulants and antidepressants logically suggested catecholamine abnormalities in ADD. There is a substantial body of literature reporting both animal and human studies that used blood, urine, and CSF, but results are inconsistent (Zametkin and Rapoport, 1986). Low dopamine and norepinephrine turnover is suggested by most studies. However, there is interaction between the serotonin and catecholamine systems and any “one drug—one neurotransmitter” hypothesis is too simplistic.

Psychosocial factors are not thought to play a primary etiological role. Various types of parent–child relationships and family dysfunction are found in families of children with ADD. Interaction conflicts with their mothers are more common in younger children with ADD than in older children with ADD. In the older adolescent age range, more noncompliant and negative
verbalizations are reported in families of children with ADD than in families of normal children. These psychosocial factors are thought to be primarily related to development of oppositional defiant disorder and conduct disorder rather than to the core symptoms of ADD.

Some "environmental" etiological factors have been proposed. These include various pre- and perinatal abnormalities, toxins such as lead and various food additives, sugar intoxication, and orthomolecular theories of great need for vitamins and nutrients in children with ADD. None of these has received substantial empirical support (Arnold and Jensen, 1995; Barkley, 1990).

**CORE CLINICAL CRITERIA**

Although DSM-III, DSM-III-R, and DSM-IV differ on the exact core symptoms and how they are arranged, they are actually globally quite consistent. There is general agreement that the core symptoms consist of an inattention domain and a hyperactivity/impulsivity domain. DSM-III arranged these domains in three separate symptoms areas. DSM-III-R grouped them in one long symptom list and DSM-IV lists them as two core dimensions. There are nine symptoms of each dimension in DSM-IV. DSM-IV maintains the requirement of an early age of onset (before the age of 7 years), presence for 6 months or longer (to indicate chronicity), and presence in two or more settings (to indicate pervasiveness of symptoms). DSM-IV describes a combined subtype in which the individual has six or more symptoms out of nine from both the inattention dimension and the hyperactive/impulsive dimension. The predominantly inattentive subtype consists of six or more inattention symptoms and five or fewer hyperactive/impulsive symptoms. A predominantly hyperactive/impulsive type consists of six or more symptoms of the hyperactive/impulsive dimension and five or fewer of the inattention dimension. The symptoms must be more frequent and severe than those of children of comparable developmental level and must cause significant functional impairments. Across children the symptoms may vary in their frequency of occurrence, in their pervasiveness across settings, and in the degree of functional impairment in various areas. Also with the same child some settings may enhance or decrease symptom manifestation. For example, open classrooms may bring out more symptoms than classrooms that are more structured.

**DEVELOPMENTAL PSYCHOPATHOLOGY**

The core symptoms of ADD may change over time. Most of our knowledge base comes from studies of elementary school-age boys with ADD. There are fewer studies of younger children and adolescents and a growing body of literature on adults.

In the preschool age range, the most difficult differential diagnostic problem is with normally active, exuberant preschool children. Many parents of normal children describe their children as inattentive and hyperactive. The preschool child with true ADD, which persists over time, generally has such additional symptoms as temper tantrums, argumentative behavior, aggressive behavior (hitting others and taking others' possessions), and fearless behavior which leads to frequent accidental injury and noisy, boisterous behavior. Noncompliance is often a major problem with these youngsters as is sleep disturbance (Campbell, 1990). One follow-up study by Campbell (1990) showed that about one half of preschool children with a diagnosis of hyperactivity had a clear diagnosis of ADD by age 9. The children with more severe symptoms in preschool were likely to have the most persistent ADD over time.

The various DSM criteria have been based on the clinical picture in elementary school-age children. Cognitively effortful work is most difficult for these children. Thus, entering into the academic arena in the elementary school age range puts greater stress on the cognitive domain. In addition, their impulsivity, hyperactivity, and inattention often lead to difficulty in peer relationships, which first become manifest in the elementary school age range. Elementary school children also may begin to develop comorbid symptomatology such as noncompliant behavior.

The clinical presentation of ADD in adolescents has not been studied as systematically as in younger children (Barkley, 1990). Barkley suggests that not only do the symptom manifestations change with age, but that a lower number of symptoms should be considered as indicative of the diagnosis in the adolescent age range and possibly the adult age range. Adolescents are in junior high school or high school, where they no longer have one teacher in one class, but now have multiple teachers in multiple classes. In addition, adolescent
demands for a greater degree of independence and development of both same-sex and opposite-sex peer relationships may present conflicts. The core symptoms may be manifest now as an internal sense of restlessness rather than gross motor activity. Their inattention and cognitive problems may lead to poorly organized approaches to school and work and poor follow-through on tasks. Failing to complete independent academic work is a hallmark in the adolescent age range, and a continuation of risky types of behaviors such as more frequent auto and bike accidents may also be manifestations (Weiss and Hechtman, 1994).

The study of the adult syndrome is a much more recent phenomenon. A variety of different symptoms in adults have been described by Wender (1994), Barkley (1995), Conners (1995), and Hallowell and Ratey (1994). The presence of disorganization continues to have an impact in the workplace, often requiring written lists of activities to be used as reminders. Poor concentration may continue to persist into adult life, leading to shifting activities, not finishing projects, and moving from one activity to another. Procrastination is present as is the presence of intermittent explosive outbursts, which may be related to comorbid mood symptomatology or may be a special type of labile mood described by Wender (1994).

COMORBIDITY

Comorbidity is a major problem in children, adolescents, and adults with the ADD syndrome. As many as two thirds of elementary school-age children with ADD who are referred for clinical evaluation have at least one other diagnosable psychiatric disorder (Arnold and Jensen, 1995; Cantwell, 1994b; Nottelmann and Jensen, 1995). The actual comorbid conditions and their prevalence rates may vary across different types of samples, depending on whether the sample is clinical or epidemiological and whether a clinical sample is psychiatric or pediatric. Conduct disorder and oppositional defiant disorder seem to be higher in psychiatric samples, learning disorders in pediatric samples. The major comorbid conditions include language and communication disorders, learning disorders, conduct and oppositional defiant disorder, anxiety disorders, mood disorders, and Tourette’s syndrome or chronic tics (Cantwell, 1994b). A type of comorbidity described by Cantwell as “lack of social savoir-faire” is not a diagnosable condition in the DSM sense. However, it does describe a common problem that many ADD children, adolescents, and adults have. It is an inability to pick up on social cues, leading to difficulties in interpersonal relationships.

Comorbidity complicates the diagnostic process and can have an impact on natural history and prognosis and the management of children, adolescents, and adults with ADD. Assessment and treatment of the comorbid disorder is often equally as important as assessing and treating the ADD symptomatology. It may be that some of the comorbid conditions, such as ADD plus Tourette’s syndrome or ADD plus conduct disorder, may identify subgroups of ADD children with different natural histories and possibly different underlying etiological factors and different responses to treatment. At present, the practicing clinician simply must carry a high index of suspicion for other types of disorders when assessing the child who has ADD. In particular, the internalizing problems such as anxiety and mood disorders may be underreported by parents and teachers, who are better able to see the externalizing behaviors.

DIFFERENTIAL DIAGNOSIS AND ASSESSMENT

It should be kept in mind that in the differential diagnosis of ADD in children there are conditions that in some cases may be comorbid and in other cases may mimic “true” ADD. A good example would be absence seizures, which may mimic the clinical presence of ADD in some cases and may be associated with a true ADD syndrome in others. The differential diagnosis must rule out the presence of other psychiatric disorders, developmental disorders, and medical and neurological disorders and determine whether these are comorbid or whether they are mimicking an ADD syndrome.

The diagnosis of ADD is a clinical diagnosis. It is made on the basis of a clinical picture that begins early in life, is persistent over time, is pervasive across different settings, and causes functional impairment at home, at school, or in leisure time activity. There is no laboratory test or set of tests that currently can be used to make a definitive diagnosis of ADD (Arnold and Jensen, 1995; Barkley, 1990). The clinician has a number of diagnostic tools, including parent and child interviews, observations of the parent and child, behavior rating scales, physical and neurological examinations, and cognitive testing. Laboratory studies, such
as audiology and vision testing, may be useful in some cases but not others. Detailed speech and language evaluation may be appropriate in some cases. Developmental questionnaires and behavior rating scales for completion by the teacher and parents can be mailed out prior to the first visit. The initial parent visit should consist of a detailed developmental and symptomatic history and a detailed medical, neurological, family, and psychosocial history. The diagnostic process must occur in a developmental context. Symptoms are considered to be present and meaningful only if they are in excess of what would be expected of a child of the same age and cognitive level.

The nature and content of the interview with the child vary, of course, with age and developmental levels. Nevertheless, the goal is the same: to obtain, both spontaneously and in response to direct questions, the patient's report of various types of psychiatric symptoms and their impact on the patient's life.

In the assessment process a variety of rating scales can be used to gather information from parents, teachers, significant others, and in some cases the patient. These can be generally divided into broad- and narrow-range scales. An example of a broad-range scale is the Child Behavior Checklist developed by Achenbach (1993). It contains items on a variety of dimensions, not just inattention and hyperactivity. It is useful as a broad-based screener. There is a parent and a teacher version. More specific scales have been developed for ADD (Hinshaw, 1994), such as those developed by Conners (1994); the SNAP-IV, developed by Swanson (1995); and the Disruptive Behavior Disorder Scale, developed by Pelham (1992). A diagnosis is not made on the basis of a score on one scale. Rather, it is made when the clinician has collected all the available information and on that basis determines that ADD is present, determines whether there is or is not comorbidity, and determines what possibly important biological and psychosocial factors should be considered. Good measures of current intellectual functioning and current level of academic achievement are useful for every child. The need for further testing will then depend on the results of the clinical evaluation.

Specialized tests, such as the Continuous Performance Task (in its various permutations), the Wisconsin Cart-Sorting Test, the Matching Familiar Figures Test, and subtests of the WISC-R, should not be considered "diagnostic" of ADD (DuPaul et al., 1992). Tests that measure cognitively effortful work, such as the Paired Associate Learning (PAL) Task, may be useful because they most approximate a laboratory measure of classroom learning. The PAL is likely to pick up "cognitive toxicity" caused by high dosages of medication, which may not be noticed simply by the use of behavior rating scales. However, the PAL is not diagnostic of ADD either. There is no specific diagnostic test for ADD (Cantwell and Swanson, 1992).

The core symptoms of ADD may occur in other psychiatric conditions and may be precipitated by medical and neurological conditions. In some cases a child, parent, or teacher may be unreliable as an informant. There may be negative findings in a brief, one-time interview with the child. All of these lead to pitfalls in the diagnostic process, but they can be overcome with the proper diagnostic approach. Such a diagnostic approach involves the following (Reiff et al., 1993):

1. A comprehensive interview with all parenting figures. This interview should pinpoint the child's symptoms so that the clinician can discern when, where, with whom, and with what intensity these symptoms occur. This should be complemented by a developmental, medical, school, and family social, medical, and mental health history.

2. A developmentally appropriate interview with the child to assess the child's view of the presence of signs and symptoms; the child's awareness of and explanation of any difficulties; and, most importantly, at least a screening for symptoms of other disorders—especially anxiety, depression, suicidal ideation, hallucinations, and unusual thinking.

3. An appropriate medical evaluation to determine general health status and to screen for sensory deficits, neurological problems, or other physical explanations for the observed difficulties.

4. Appropriate cognitive assessment of ability and achievement.

5. The use of both broad-spectrum and more narrowly ADD focused parent and teacher rating scales.

6. Appropriate adjunct assessments such as speech and language assessment, and evaluation of fine and gross motor function in selected cases (Braswell and Bloomquist, 1994).
NATURAL HISTORY

In the past it was believed that all children with ADD “outgrew their problem.” This “outgrowing” was supposed to occur with puberty. We now know from prospective studies that this is not true. Cantwell (1985) has described three potential types of outcomes. One is described as a “developmental delay” outcome. This may occur in 30% of the subjects. With this outcome, sometime early in young adult life the individual no longer manifests any functionally impairing ADD symptoms. The second outcome has been called the “continual display” outcome. This may occur in about 40% of child subjects. In this case, functionally impairing symptoms of ADD continue into adult life. In addition, these symptoms may be accompanied by a variety of different types of social and emotional difficulties. The last outcome, which may occur in as many as 30% of subjects, Cantwell describes as a “developmental decay” outcome. In these cases not only is there a continual display of core ADD symptoms, but there is the development of more serious psychopathology such as alcoholism, substance abuse, and antisocial personality disorder. One of the strongest predictors of this most negative outcome is the presence of comorbid conduct disorder with ADD in childhood.

Recent studies of adults with retrospectively diagnosed ADD suggest there may be people (particularly females) who had unrecognized ADD in childhood, who were not evaluated in childhood, and yet who seem to make a reasonable adjustment in adult life. They present with a wide range of comorbid adult disorders such as anxiety disorders and mood disorders (Wender, 1994), even though they have made a reasonable adjustment without treatment. A combination of psychosocial and medical interventions improves their functioning (Hallowell and Ratey, 1994; Wender, 1994). It is interesting that in most samples of those who present as adults with no childhood evaluation or treatment, a substantially greater number of females has been present.

MANAGEMENT

It is now recognized that management of the ADD syndrome requires a multiple-modality approach (American Academy of Child and Adolescent Psychiatry, 1991; Braswell et al., 1991; Hechtman, 1993; Pelham, 1994; Swanson, 1992). A multiple-modality approach combines psychosocial interventions and medical interventions. The psychosocial interventions that have proven to be effective for children with ADD can be classified as those psychosocial interventions which focus on the family, the school, and the child. Among the family-focused interventions are education about what ADD is and what it is not. Support groups such as CHADD and ADDA are quite helpful in the psychosocial and educational process and are useful for other reasons such as providing group support and knowledge about working with school systems and about resources in the community. A number of books now available for parents, teachers, and the children themselves are useful adjuncts to treatment.

Parent management training is almost a sine qua non of psychosocial interventions with ADD. Training parents to use contingency management techniques and to cooperate with the school in a school–home daily report card and point/token response cost system is highly effective. Parent management training has been shown not only to reduce the child’s disruptive behavior in the home setting, but also to increase the parents’ own self-confidence in their competence as parents and to decrease family stress. Both individual and group formats have been used for parent management training. Some clinicians such as Brown and Cantwell (1976) have used older siblings in addition to parents to serve as positive reinforcement and to make positive interactions. Assessment and treatment of parental psychopathology and more specific assessment and treatment of family dysfunction such as marital conflict are always indicated.

School-focused intervention should target academic performance. However, classroom behavior and peer relationships are also important. The most appropriate classroom environment is probably a structured classroom with the child placed in the front of the room, close to the teacher, where he or she may be less easily distracted and more able to focus. Children with ADD respond to predictable, well-organized schedules with rules that are known and clearly reinforced in the classroom setting. The use of contingency management and daily, teacher-completed report cards showing the child’s progress in targeted areas of improvement are hallmarks of this type of intervention (Braswell and Bloomquist, 1994). Incentives and tangible rewards, reprimands, and timeouts in the classroom setting can also be used in school as well as in the home.
School placement is a crucial issue. While many if not most children with ADD will remain in a regular classroom setting, some may need individual tutoring, some may need a resource program, some may need a self-contained special class (primarily for academic reasons), and others with complex problems may need a special school. The clinician can play a major role in assessing the need for specialized school intervention and in facilitating school placement.

The child-focused interventions include the use of individual psychotherapy to treat any depression, low self-esteem, anxiety, or other types of associated symptomatology. There should be a concerted effort to improve the child's impulse control, anger control, and social skills. Social skills-training programs focus on the child's entry into the social group, the development of conversational skills and problem-solving skills, as well as those factors noted above. Impaired social skills are an extremely important part of the negative aspect of children with ADD (Pelham and Bender, 1982). Problems caused by the "in your face" type of behavior associated with impulsivity and hyperactivity may be more easily treated than the lack of social savoir-faire described by Cantwell (1994b).

A number of summer treatment programs have been developed in which the child is in an intense school program for 8 weeks, 8 hours per day. The day involves not only academic work but behavioral management, social skills, and individual work with the child. There is then an attempt to carry over the school program into the regular school by the use of paraprofessionals in the regular classroom setting (Swanson, 1992).

The primary psychopharmacological agents used to treat ADD are the CNS stimulants (Cantwell, 1994a; Wilens and Biederman, 1992). The prototype drugs are dextroamphetamine, methylphenidate, and pemoline. There are a number of amphetamines including methamphetamine and dextroamphetamine, but dextroamphetamine probably enjoys the greatest use. Methylphenidate is probably used more than any of the other stimulants. At least 70% of children will have a positive response to one of the major stimulants on the first trial. If a clinician conducts a trial of dextroamphetamine, methylphenidate, and pemoline, the response rate to at least one of these is in the 85% to 90% range, depending on how response is defined (Elia, 1993).

While it is clear that the medications target classroom behavior, academic performance (Evans and Pelham, 1991), and productivity (Swanson et al., 1991), there is also good evidence to show that ADD children with oppositional and conduct symptomatology and aggressive behavior also respond positively in these areas as well. Interactions between the child and peers, family, siblings, teachers, and significant others (such as scout masters and coaches) also improve. In addition, participation in leisure time activity, such as playing baseball, improves (Cantwell, 1994b). The main message is that stimulants are not "school time drugs." They should be used throughout the waking day and on the weekends as well. There is no way to pick the first stimulant to be tried because, essentially, they are all equally effective (Pelham et al., 1990). Some children respond better to one than they do to another, but response is idiosyncratic and cannot be predicted.

Side effect profiles may be better for one child with one drug than another, but in general, all stimulants share side effects of decreased appetite, insomnia, stomachache, headache, and irritability. Most side effects will dissipate with time and many can be managed with various types of manipulation (Cantwell, 1994b). Growth suppression appears to be dose-related, if it occurs at all. There does not seem to be strong evidence that adverse effects on the patient's ultimate height has been present in the long-term follow-up studies that have been done. However, there are individual children who do not seem to be able to adjust and adapt to the growth suppression. There is good evidence that the drugs do not lose their effect after puberty and that tolerance to the medication does not develop and lead to substance abuse (Greenhill and Setterberg, 1993). While there are some concerns about the use of stimulants in the ADD individuals who themselves have substance abuse in their past history or who have family members who are current substance abusers, this has not been a major problem.

The relationship of stimulant drugs to the development of tics is controversial. It is clear that a substantial number of children with ADD who are referred for clinical evaluation have motor or vocal tics or both. Some of these children experience worsening of their tics when stimulants are used. Recent data by Gadow et al. (1995) suggest that a substantial majority of those children return to baseline, even when stimulants are continued. If this does not occur, adjunct treatment
of the tics with medications such as haloperidol, pimozide, or clonidine is usually effective.

"Rebound" is a deterioration in behavior that follows the wearing off of short-acting stimulants (Johnston et al., 1988). This rebound period may be one-half hour or more, and it is actually a worsening of behavior above baseline behavior. This occurs in a minority of children. Rebound can be managed by the use of longer-acting drugs which seem to have a smoother onset and offset.

Cantwell and Swanson (1992) have reported "cognitive toxicity" in a subgroup of patients at doses at which the behavioral effects of the medication are maximized. Thus, the maximum dosage the child receives for behavioral effects will have less than a maximal effect on cognitive functioning. In these cases the dose should be lowered.

The literature on stimulants consists of more than 100 studies of more than 4,500 elementary school-age children. There are several small studies of preschool children (approximately 130 subjects), a small number of studies of adolescents (approximately 113 subjects), and eight studies of adults (180 subjects). In general, the response rate is 70% or more in the elementary school age range and in the adolescent range. A more variable effect has been found in studies with preschool children and with adults (Cantwell, 1994b).

The use of nonstimulant medication to treat attention-deficit hyperactivity disorder has recently been reviewed by Cantwell (1994a). The medications that have been evaluated include the antidepressants, anti-anxiety agents (clonidine and guanfacine), neuroleptics, fenfluramine, lithium, and the anticonvulsants. The best studied of the nonstimulants are the heterocyclic antidepressants (Elia, 1991). Some studies suggest that approximately 70% of children with ADD will respond to desipramine at dosages up to 5 mg/kg per day with blood levels of 100 to 300 ng/ml per milliliter (Biederman et al., 1989; Pliszka, 1987). All of the heterocyclics produce positive effects on hyperactivity, impulsivity, inattention, and most likely on anxiety and depressed mood. There is some question about whether there is a major effect on learning. The major side effects that are of concern are cardiovascular, especially the possible induction of arrhythmias. The report of the sudden death of several young children has led to a reconsideration of the use of the heterocyclics (Riddle et al., 1991).

Bupropion is an antidepressant that is not a serotonin reuptake blocker and is not a tricyclic. The side effect profile is very positive, and efficacy has been suggested in several studies published since 1986 in doses 5 to 6 mg/kg per day in three divided dosages.

The literature on serotonin reuptake blockers such as fluoxetine, sertraline, paroxetine, and fluvoxamine is limited, but it suggests that some individual children may get a positive response (Barrickman et al., 1991). Gammon and Brown (1993) reported on 32 subjects, aged 9 to 17 years, all with a diagnosis of ADD with multiple comorbid conditions. Mood disorders such as dysthymia were present in 78% of cases and major depressive disorder in 80% of cases. The addition of fluoxetine to the ongoing methylphenidate treatment led to a significant improvement in many measures in 30 of the 32 subjects.

Monoamine oxidase inhibitors have been shown in small studies to be effective in a substantial number of children, and in one study (Zametkin et al., 1986) their effect was equal to that of dextroamphetamine; however, multiple possible drug and diet reactions severely limit their use.

Clonidine and guanfacine are α2-adrenergic agonists. The literature suggesting their efficacy alone in ADD is limited. In conjunction with stimulants, they may offer some adjunctive help in the treatment of associated aggressive hyperactive/hyperarousal behavior and they may benefit those children who have tics. The clonidine-methylphenidate combination has recently been associated with idiosyncratic episodes in a small number of cases; there have been three cases of sudden death. The exact role, if any, of the drugs in these deaths is unclear. Fenfluramine is a synthetic stimulant not shown to be useful in the usual case of ADD. Clinical data suggest a possible positive effect on ADD symptoms (Cantwell, 1994a) in those with mental retardation and pervasive developmental disorders.

The mood stabilizers, such as lithium, carbamazepine, and valproic acid, do not seem to have a positive effect on core ADD symptoms. Symptoms of episodic dyscontrol in some ADD individuals may be positively affected.

Early studies with neuroleptics suggested an effect on certain symptoms. Neuroleptics may be cognitively dulling, although the early studies at smaller doses did not show that. They are very rarely used today because
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of their negative side effect potential. However, haloperidol or pimozide plus stimulants may be a useful combination for those who have ADD plus Tourette's syndrome or tics.

It is now accepted that a multimodal approach to therapy that uses both psychosocial intervention and medication has the greatest chance of alleviating the multiple symptoms and domains of dysfunction with which ADD children present. Medical treatment and psychosocial treatment have complementary effects. Thus a wider range of symptoms may be treated than with either intervention alone. Psychosocial intervention may improve symptoms during the period of time that medication has worn off. The use of both interventions together may lead to lower medication dosage and a less complex psychosocial intervention program than with either treatment alone.

SUMMARY AND CONCLUSIONS

This review has attempted to highlight advances in ADD over the past 10 years. It does seem that advances have been made on all fronts. Neuroimaging and family genetic studies are providing enticing leads to possible underlying etiological factors. Treatment studies have added to the staple of treatment, which has remained psychostimulant medication. Various psychotherapeutic and psychosocial interventions play a major role in treatment. School-based interventions have become more common and are quite effective. More work needs to be done on long-term results of treatment in childhood. The syndrome of ADD remains a subject of intense research as one of our best-studied child psychiatric problems.

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The new Clinical Perspectives Section of the *Journal* reflects an attempt to acknowledge formally the value of clinical observations, perspectives, wisdom, guidelines, and pearls. Submissions should be short (750 to 1,500 words), concise, clear, pithy, and focused. Clinical Perspectives reflects the *Journal's* continuing attempt to provide the latest information for clinical practice in addition to building a knowledge base for the field grounded on formal research. We encourage questions, comments, and submissions sent to Michael Jellinek, M.D., Assistant Editor, Clinical Perspectives, Massachusetts General Hospital, 15 Parkman Street—ACC 725, Boston, MA 02114.