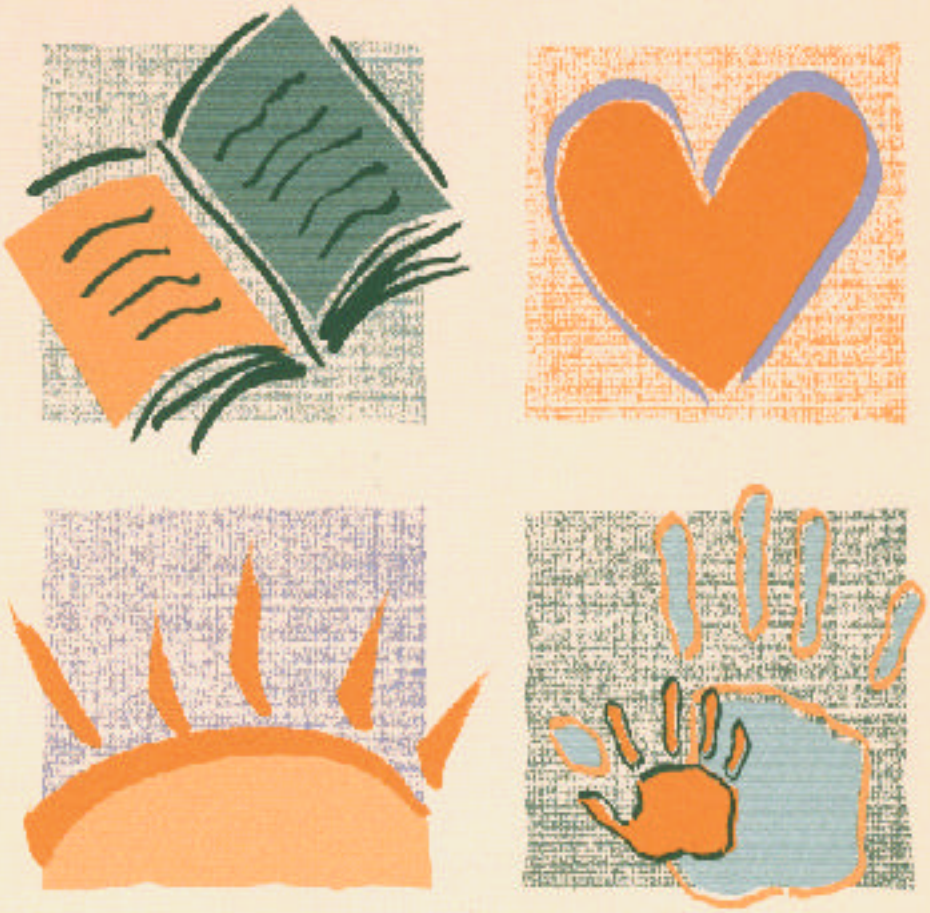
NIH Consensus Development Conference



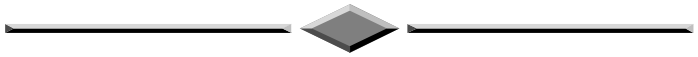
Diagnosis and Treatment of

Attention Deficit Hyperactivity Disorder

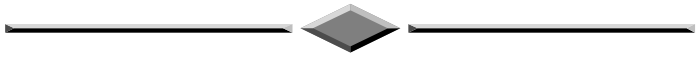
Program and Abstracts

Office of the Director • National Institutes of Health

NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder



November 16–18, 1998
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland



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Contents

Introduction

Attention deficit hyperactivity disorder, or ADHD, is the most common behavioral disorder of childhood, estimated to affect 3 to 5 percent of school-age children. Its core symptoms include an inability to sustain attention and concentration; developmentally inappropriate levels of activity; distractibility; and impulsivity. Although some persons have suggested that ADHD is just normal childhood behavior, children with ADHD usually have pronounced difficulties and impairment resulting from the disorder across multiple settings—in home, at school, and with peers—as well as resultant long-term adverse effects on later academic, vocational, social-emotional, and psychiatric outcomes. The ADHD symptoms, degree of impairment, and longitudinal course form a coherent pattern from which well-trained clinicians can reliably diagnose ADHD at a level of accuracy that rivals or exceeds many other medical diagnostic and assessment procedures. Moreover, many clinical treatment studies of the condition have also been conducted, resulting in substantial evidence of efficacy for a variety of treatments.

Despite the substantial progress in the assessment, diagnosis, and treatment of children and adults with ADHD, the disorder has remained controversial in many public and private sectors. The confusion resulting from diverse, frequently expressed opinions (often not based on research evidence) has made many families, health care providers, educators, and policymakers uncertain about the status of the disorder and its long-term consequences; whether it should be treated and, if so, how; which treatments yield the best outcomes; and what the personal, family, and societal costs and consequences of the disorder are, whether treated or not.

One of the major controversies regarding ADHD concerns the use of psychostimulants to treat the condition. Psychostimulants, including dextroamphetamine, methylphenidate, and pemoline, are by far the most widely researched, clinically effective, and commonly prescribed treatments for ADHD. These medications are regarded by many in the medical community as the psychopharmacologic treatment of choice for ADHD. The use of methylphenidate and amphetamine nationwide has increased significantly in recent years. The increased availability and use of psychostimulants have intensified the concerns about use, overuse, and abuse.

This 2½-day conference will bring together national and international experts in the fields of relevant medical research and health care as well as representatives from the public.

On the second day of the conference, 1 hour has been allocated for 5- to 10-minute formal oral presentations by individuals presenting statements on behalf of interested organizations regarding the conference issues.

After 1½ days of presentations and audience discussion, an independent, non-Federal consensus panel chaired by Dr. David J. Kupfer, Thomas Detre Professor and Chair, Department of Psychiatry, University of Pittsburgh, will weigh the scientific evidence and write a draft statement that will be presented to the audience on the third day. The statement will take into

account the panel's review of the scientific literature prepared during the preceding year. The consensus statement will address the following key questions:

- What is the scientific evidence to support ADHD as a disorder?
- What is the impact of ADHD on individuals, families, and society?
- What are the effective treatments for ADHD?
- What are the risks of the use of stimulant medication and other treatments?
- What are the existing diagnostic and treatment practices, and what are the barriers to appropriate identification, evaluation, and intervention?
- What are the directions for future research?

On the final day of the meeting, the conference chairperson, Dr. David J. Kupfer, will read the draft statement to the conference audience and invite comments and questions. A press conference will follow to allow the panel and chairperson to respond to questions from media representatives.

General Information

Conference sessions will be held in the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 5:30 p.m. on Monday, from 8:00 a.m. to 1:00 p.m. on Tuesday, and from 9:00 a.m. to 11:00 a.m. on Wednesday. The telephone number for the message center is (301) 496-9966. The fax number is (301) 480-5982.

Cafeteria

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7:00 a.m. to 2:00 p.m., serving breakfast and lunch.

Continuing Education Credit

American Medical Association

The NIH/FAES is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

The NIH/FAES designates this continuing medical education activity for a maximum of 15 credit hours in Category I of the Physician's Recognition Award of the American Medical

Association. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

In accordance with ACCME requirements regarding conflict of interest, each speaker presenting at this conference has been asked to submit documentation outlining any real or potential conflict of interest.

Sponsors

The primary sponsors of this meeting are the National Institute of Mental Health, the National Institute on Drug Abuse, and the NIH Office of Medical Applications of Research. The conference is cosponsored by the National Institute of Environmental Health Sciences and the National Institute of Child Health and Human Development of NIH; the Food and Drug Administration; and the Office of Special Education Programs, U.S. Department of Education.

Agenda

Monday, November 16, 1998

8:30 a.m.	Welcome **Steven E. Hyman, M.D.,** Director National Institute of Mental Health
	Alan Leshner, Ph.D., Director National Institute on Drug Abuse
	Charge to the Panel **John H. Ferguson, M.D.,** Director Office of Medical Applications of Research
	Panel Chair Remarks **David J. Kupfer, M.D.,** Thomas Detre Professor and Chair Department of Psychiatry, University of Pittsburgh

I. Overview and Introduction

9:00 a.m.	Overview of Attention Deficit Hyperactivity Disorder (ADHD) **C. Keith Conners, Ph.D., M.A.,** Duke University

II. ADHD as a Disorder in Children, Adolescents, and Adults

9:15 a.m.	Current Diagnostic Schema/Core Dimensions **Benjamin B. Lahey, Ph.D.,** University of Chicago
9:30 a.m.	Is ADHD a Valid Disorder? **William B. Carey, M.D.,** University of Pennsylvania School of Medicine
9:45 a.m.	Biological Bases of ADHD: Neuroanatomy, Genetics, and Pathophysiology **James Swanson, Ph.D.,** University of California, Irvine
10:05 a.m.	Etiology/Risk Factors: Cognitive and Behavioral Correlates **Rosemary Tannock, Ph.D.,** University of Toronto
10:20 a.m.	Discussion

Monday, November 16, 1998 (continued)

III. Impact

11:00 a.m.	The Prevalence and Cross-Cultural Validity of ADHD **Hector R. Bird, M.D.,** New York State Psychiatric Institute
11:15 a.m.	ADHD: Long-Term Course, Adult Outcome, and Comorbid Disorders **Russell A. Barkley, Ph.D.,** University of Massachusetts
11:30 a.m.	Discussion
11:50 a.m.	Lunch
12:50 p.m.	The Impact of ADHD on School Systems **Steven R. Forness, Ed.D.,** University of California, Los Angeles
1:05 p.m.	The Impact of ADHD on the Juvenile Justice System **Betty Chemers, M.A.,** Office of Juvenile Justice and Delinquency Prevention
1:20 p.m.	Discussion
1:40 p.m.	Impairment: Childhood and Adolescence **Stephen P. Hinshaw, Ph.D.,** University of California, Berkeley
2:00 p.m.	The Impact of ADHD on Social and Vocational Functioning in Adults **Charlotte Johnston, Ph.D.,** University of British Columbia
2:15 p.m.	Discussion

IV. Safety and Efficacy of Treatments—Short and Long Term

2:35 p.m.	Stimulant Medications **Laurence L. Greenhill, M.D.,** Columbia University
2:55 p.m.	Pharmacotherapy of ADHD: Nonstimulant Treatments **Joseph Biederman, M.D.,** Harvard Medical School
3:10 p.m.	Risks and Mechanism of Action of Stimulants **Peter R. Breggin, M.D.,** Center for the Study of Psychiatry and Psychology, Bethesda, Maryland

Monday, November 16, 1998 (continued)

3:25 pm.	Public Health Perspectives and Toxicological Issues Concerning Stimulant Medications **Andrew S. Rowland, Ph.D.,** National Institute of Environmental Health Sciences
3:35 p.m.	Psychosocial Interventions **William E. Pelham, Jr., Ph.D.,** State University of New York at Buffalo
3:55 p.m.	Treatment Alternatives for ADHD **L. Eugene Arnold, M.D., M.Ed.,** Ohio State University
4:10 p.m.	Behavioral and Medication Treatments for ADHD: Comparisons and Combinations **Peter S. Jensen, M.D.,** National Institute of Mental Health
4:30 p.m.	Matching Patients to Treatments **Howard Abikoff, Ph.D.**, New York University
4:45 p.m.	Discussion
5:30 p.m.	Adjourn Until Tuesday Morning

Tuesday, November 17, 1998

V. Substance Abuse Risks of Stimulant Treatments

8:00 a.m.	Alcohol, Nicotine, Stimulants, and Other Drugs **Rachel G. Klein, Ph.D.,** Columbia University and the New York State Psychiatric Institute
8:15 a.m.	Risk of Treatment Versus Nontreatment **Jan Loney, Ph.D.,** State University of New York at Stony Brook
8:30 a.m.	ADHD and Risk for Substance Use Disorders **Timothy E. Wilens, M.D.,** Massachusetts General Hospital
8:45 a.m.	Sensitization and the Risk of Exposure to Stimulant Medications **Peter W. Kalivas, Ph.D.,** Medical University of South Carolina
9:00 a.m.	Stimulant Treatment as a Risk Factor for Nicotine Use and Substance Abuse **Nadine M. Lambert, Ph.D.**, University of California, Berkeley

Tuesday, November 17, 1998 (continued)

9:15 a.m.	Diversion, Trafficking, and Abuse of Methylphenidate **Gretchen Feussner,** Drug Enforcement Administration
9:30 a.m.	Availability of Stimulant Medications: Nature and Extent of Abuse and Associated Harm **James R. Cooper, M.D.,** National Institute on Drug Abuse
9:45 a.m.	Discussion

VI. Existing Practices and Barriers Regarding Assessment and Treatment

10:15 a.m.	A National Perspective on Treatments and Services for Children With ADHD **Kimberly Hoagwood, Ph.D.,** National Institute of Mental Health
10:30 a.m.	Current Assessment and Treatment Practices **Mark L. Wolraich, M.D.,** Vanderbilt University
10:45 a.m.	Educational Policy: Educating Children With Attention Deficit Disorders **Thomas Hehir, Ed.D.,** U.S. Department of Education
11:00 a.m.	Use of Services and Costs for Youth With ADHD and Related Conditions **Kelly J. Kelleher, M.D., M.P.H.,** University of Pittsburgh
11:20 a.m.	Individual and Family Barriers **Sheila Anderson**, Children and Adults With Attention Deficit Disorders (CH.A.D.D.)
11:35 a.m.	Discussion
12:00 p.m.	Public Presentations
1:00 p.m.	Adjourn Until Wednesday Morning

Wednesday, November 18, 1998

9:00 a.m.	Presentation of the Consensus Statement
9:30 a.m.	Public Discussion
11:00 a.m.	Panel Meets in Executive Session
1:00 p.m.	Press Conference
2:00 p.m.	Adjournment

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Abstracts

The following are abstracts of presentations to the NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors, who have summarized their materials and made them available in a timely fashion.

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Overview of Attention Deficit Hyperactivity Disorder

C. Keith Conners, Ph.D., M.A.

Attention deficit hyperactivity disorder (ADHD) refers to a developmental disorder of childhood characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development (American Psychiatric Association, 1994). The diagnosis requires that some of the inattentive or hyperactive-impulsive symptoms be present before age 7, and some impairment from these symptoms must be evident in at least two settings, such as home, school, or work. Clear evidence of impairment of developmentally appropriate social, academic, or occupational functioning must be present.

Although the name is new, the behavioral syndrome of ADHD has been recognized since the early 1900s. The features of this syndrome gradually emerged from observations over many years from professionals working in pediatric medicine, neurology, education, and pharmacology. The core symptoms of hyperactivity, impulsivity, and inattention are a constant in the very earliest observations and throughout the numerous changes in terminology (Kessler, 1980). Changes in diagnostic terminology, definitional boundaries, conceptions of etiology, and preferred modes of treatment reflect changing scientific paradigms and professional allegiances, as well as empirical evidence derived from increasingly rigorous investigations (Conners, Erhardt, 1998).

Formal diagnostic criteria for the disorder underwent rapid changes as new syntheses and accumulation of data from field trials took place. The fact that the concept of ADHD has evolved with changing evidence should be taken as a strength, not as a sign of unreliability or vague conceptualization. Comprehensive review of the evidence regarding diagnosis and treatment carried out by independent expert medical reviewers concludes that diagnostic criteria for ADHD are based on extensive empirical research and, if applied appropriately, lead to the diagnosis of a syndrome with high interrater reliability, good face validity, and high predictability of course and medication responsiveness (Goldman, Genel, Bezman, et al., 1998).

ADHD appears to be among the most prevalent childhood disorders even when narrow and conservative criteria are employed. Estimates of prevalence vary with the particular criteria used to define the disorder. Past estimates have ranged from 1 to 20 percent. But when rigorous research criteria are employed, the figures range between 1 and 4 percent in North America. Despite some obvious differences in prevalence rates due to cultural variations, evidence from a number of studies now reveals that very similar rates appear in several other cultures, including China, Japan, Europe, India, and Latin America (Barkley, 1998a).

No single cause of ADHD has been discovered. Rather, a number of significant risk factors affecting neurodevelopment and behavioral expression have been implicated in ADHD.

Several of these risk factors, often present at one time, lead to the assumption that the disorder frequently reflects a summation of independent forces impinging on early development (Biederman, Milberger, Faraone, et al., 1995). The expression of the disorder appears to depend on both these risk factors and individual protective factors and subsequent interactions with the environment. Evidence for *genetic causes* derives from consanguinity studies of hyperactivity, family genetic studies, and recent transmission studies from several laboratories. Normal *variations in temperament* (which are also likely to be genetically determined) must also be considered a risk factor for ADHD. Data suggest that some individuals are merely at the extremes of normal distributions for activity, impulse control, and attentional control. *Medical causes*, particularly those affecting early development of the fetal brain, such as maternal alcohol and tobacco use, are well-established as causes, as demonstrated by large collaborative studies of natal and perinatal development (Nichols, Chen, 1981). Injury to the developing brain from environmental toxins, lead, smoking, lack of crucial nutrients such as iron and calcium, and a host of other hazards have also been implicated in the etiology of ADHD-like symptoms.

Recent studies in neuroimaging of ADHD children, adolescents, and adults lend support to several possible anatomic substrates affected by the many risk factors to brain development. A variety of relatively small-sample studies with PET, SPECT, and MRI technologies have demonstrated impairments in ADHD relative to control in frontal, prefrontal, parietal, splenial corpus callosum, and right caudate nuclei (Ernst, Zametkin, 1995). These studies have now been supplemented by a large, well-controlled MRI study at the National Institute of Mental Health (NIMH) demonstrating deficits in the right-sided, prefrontal-striatal systems in ADHD. These findings include a smaller total cerebral volume, loss of normal right-greater-than-left asymmetry in the caudate, smaller right globus pallidus, smaller right anterior frontal region, smaller cerebellum, and reversal of normal lateral ventricular asymmetry in the ADHD group (Castellanos, Giedd, Marsh, et al., 1996).

ADHD is a chronic, lifetime disorder that exacts a considerable toll on those suffering from it as well as on the families of those who must care for them. Although as many as 40 to 50 percent of ADHD children may become indistinguishable from normal children by young adulthood, careful long-term prospective followup studies (Weiss, Hechtman, 1993) demonstrate that a significant proportion of those with ADHD end up with serious social, emotional, interpersonal, and economic limitations. The risks of death by misadventure; driving accidents; teenage pregnancy; sexually transmitted diseases; alcohol and other substance abuse; and academic underachievement are high. Profound impairment of self-esteem and personal identity are frequent sequelae in adults with a childhood history of ADHD.

Important strides in the treatment of ADHD have been made over the past several decades. The evidence for the short-term efficacy and safety of psychostimulants from controlled clinical trials is overwhelming (Swanson, McBurnett, Wigal, et al., 1995). Many studies of psychosocial treatment are also suggestive of positive benefits on the short-term status of ADHD. However, selective and careful review of the literature led Richters and colleagues (1995) to conclude the following:

> "Despite decades of treatment research and clinical practice, there is an insufficient basis for answering the following manifold question: under

> what circumstances and with what childhood characteristics (comorbid conditions, gender, family history, home environment, age, nutritional/metabolic status, etc.) do which treatments or combinations of treatment (stimulants, behavior therapy, parent training, school-based intervention) have what impacts (improvement, stasis, deterioration) on what domains of child functioning (cognitive, academic, behavioral, neurophysiological, neuropsychological, peer relations, family relations), for how long (short versus long term), to what extent (effect sizes, normal versus pathological range), and why (processes underlying change)?"

This sobering conclusion led to the formation of the largest clinical trial in the history of NIMH (Arnold, Abikoff, Cantwell, et al., 1997) established through the mechanism of a Cooperative Agreement among seven university teams and NIMH. The results of that trial of a multimodal treatment strategy comparing medication management, psychosocial treatments, their combination, and a community-based control sample will form an important part of the empirical data presented in this consensus forum.

Important areas of our knowledge about ADHD remain to be clarified. Developments in cognitive neuroscience point to the multidimensional nature of both attentional processes and activity level, yet these concepts are poorly operationalized by current symptomatic criteria. Neuropsychological studies demonstrate a clear heterogeneity in samples of ADHD defined solely by symptomatic criteria (Conners, 1997). Doubts have been raised about the current nosological subtyping and the possibility that inattention and hyperactivity-impulsivity reflect separate disease entities (Barkley, 1998b). Current diagnostic criteria require that symptoms be more frequent and severe than are typically observed in individuals at a comparable level of development (American Psychiatric Association, 1994), but marked variations in the application of this rule lead to serious underdiagnosis or overdiagnosis, resulting in excesses or deficiencies of pharmacologic treatments (Angold, Costello, 1998). The embarassment of riches from neuroimaging studies reflects a poor understanding of any specificity for the neural basis of ADHD. The high levels of comorbidity of ADHD with oppositional, conduct, and mood disorders also call into question the specificity of the definition of the disease and whether current criteria are sufficient to allow further understanding of the neurobiology of the syndrome.

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Current Diagnostic Schema/Core Dimensions

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In DSM-II, hyperkinetic reaction of childhood was defined in terms of extreme levels of motor activity, impulsivity, and attention deficits. The definition of DSM-III attention deficit disorder (ADD) deemphasized hyperactivity and allowed the diagnosis of subtypes with either maladaptive levels of inattention, impulsivity, and motor activity (ADD with hyperactivity) or attention deficits and impulsivity only (ADD without hyperactivity). DSM-III-R dropped these two subtypes, however, and defined a single category of ADHD much like DSM-II. Many studies have indicated that the symptoms of ADHD are not unitary as assumed by the DSM-III-R definition of ADHD, but the three dimensions of DSM-III symptoms (inattention, impulsivity, and hyperactivity) have not been supported either (Lahey, Pelham, Schaughency, et al., 1988; Lahey, Carlson, Frick, 1997). Rather, two dimensions of symptoms underlie ADHD, one reflecting inattention and another comprising both hyperactivity and impulsivity (Lahey, Pelham, Schaughency, et al., 1988; Lahey, Carlson, Frick, 1997). Accordingly, DSM-IV distinguished three subtypes of youths who exhibit maladaptive levels of both dimensions (combined type), inattention only (inattentive type), and hyperactivity-impulsivity only (hyperactive-impulsive type) (Lahey, Applegate, McBurnett, et al., 1994). This two-dimensional structure of ADHD has since been supported by both confirmatory factor analyses (Burns, Walsh, Owen, et al., 1997; Burns, Walsh, Patterson, et al., 1997; DuPaul, Anastopoulos, McGoey, et al., 1997; DuPaul, Anastopoulos, Power, et al., 1998; Pillow, Pelham, Hoza, et al., in press) and discriminant validity studies. Inattention and hyperactivity-impulsivity differ in their correlations with types of functional impairment (inattention is associated with academic deficits and peer unpopularity, whereas hyperactivity-impulsivity is associated with peer rejection and accidental injuries) (Lahey, Applegate, McBurnett, et al., 1994; Lahey, McBurnett, Applegate, et al., unpublished), and hyperactivity-impulsivity is more strongly associated with conduct problems than is inattention (Lahey, Carlson, Frick, 1997; Lahey, Applegate, McBurnett, et al., 1994; Lahey, McBurnett, Applegate, et al., unpublished). In addition, inattention and hyperactivity-impulsivity follow different developmental courses, with inattention declining less than hyperactivity-impulsivity from childhood through adolescence (DuPaul, Anastopoulos, McGoey, et al., 1997; DuPaul, Anastopoulos, Power, et al., 1998; Hart, Lahey, Loeber, et al., 1995).

Correspondence of DSM-IV ADHD to DSM-III, DSM-III-R ADHD, and ICD-10

When only changes in symptom criteria are considered, DSM-IV ADHD is somewhat more prevalent than DSM-III-R ADHD (Lahey, Applegate, McBurnett, et al., 1994; McBurnett, Pfiffner, Wilcutt, et al., unpublished), but revisions to the age of onset criterion and the new requirement of impairment in two or more settings in DSM-IV reduce the prevalence of ADHD. These revised criteria particularly affect the prevalence of the inattentive and hyperactive-impulsive subtypes because youths who meet criteria for these subtypes tend to be impaired only at home or at school, and the inattentive type tends to have a later onset (Lahey, Applegate,

McBurnett, et al., 1994; Lahey, McBurnett, Applegate, et al., unpublished). As a result, when full diagnostic criteria are used, the prevalence of DSM-IV ADHD is approximately the same as, or lower than, that of DSM-III-R ADHD, with a substantial degree of overlap (Lahey, McBurnett, Applegate, et al., unpublished; Biederman, Faraone, Weber, et al., 1997). However, a higher proportion of girls and children younger than 7 years of age are among those youths who meet criteria for DSM-IV ADHD but do not meet DSM-III-R criteria (Lahey, McBurnett, Applegate, et al., unpublished). When compared with DSM-III ADD, full DSM-IV diagnostic criteria identify essentially the same number of cases, with substantial correspondence among the subtypes of the two definitions (Lahey, McBurnett, Applegate, et al., unpublished). ICD-10 hyperkinesis uses the same list of symptoms as DSM-IV ADHD but identifies only the equivalent of the combined type. In addition, unlike DSM-IV, ICD-10 requires that full diagnostic criteria be met independently according to both parent and teacher informants. As a result, the ICD-10 definition identifies half the number of children and adolescents as the DSM-IV definition and appears to under-identify impaired youths (Lahey, McBurnett, Applegate, et al., unpublished).

Validity of ADHD

Face Validity. Some view ADHD as a disorder with high face validity (Goldman, Genel, Bezman, et al., 1998), whereas others conceptualize ADHD as a valid syndrome of maladaptive behavior that warrants treatment but object to its being considered a mental disorder (British Psychological Society, 1996). Some researchers find the definition of ADHD to lack specificity (Prior, Sanson, 1986), and a few groups believe that ADHD simply describes the exuberant behavior of normal children and view efforts to treat ADHD as inappropriate "mind control" (Safer, Krager, 1992). For this reason, other forms of validity are of greater importance to an evaluation of ADHD.

Reliability, Concurrent Validity of DSM-IV ADHD, and Discriminant Validity of the Subtypes. The reliability of assessments of ADHD is quite high using both structured diagnostic interviews (Biederman, Faraone, Keenan, et al., 1992; Orvaschel, 1995; Schwab-Stone, Shaffer, Dulcan, et al., 1996; Shaffer, Fisher, Dulcan, et al., 1996) and parent and teacher rating scales (Conners, 1973; Quay, Peterson, 1983), and many, but not all, studies using mechanical measures have found that clinic-referred children who meet criteria for ADHD exhibit significantly higher levels of motor activity and less visual attending than comparison children (Paternite, Loney, Roberts, 1996; Porrino, Rapoport, Behar, et al., 1983; Teicher, Ito, Glod, et al., 1996). The concurrent validity of DSM-IV ADHD and the discriminant validity of its subtypes have been addressed in a number of ways (Goldman, Genel, Bezman, et al., 1998). The three subtypes have different gender ratios, with the combined type having a higher male-to-female ratio than the inattentive type (Lahey, Applegate, McBurnett, et al., 1994; Lahey, McBurnett, Applegate, et al., unpublished). Controlling for demographic differences, the subtypes also differ on the number of concurrent conduct problems (the inattentive type exhibits the fewest, and the combined exhibits the most) and symptoms of depression (the combined and inattentive types display more) (Lahey, McBurnett, Applegate, et al., unpublished). Two studies show that when differences in age, gender, intelligence, socioeconomic status, ethnicity, and concurrent psychopathology are controlled, the combined and hyperactive-impulsive types are

rated as more globally impaired by parents and interviewers (Lahey, McBurnett, Applegate, et al., unpublished) and are more likely to have had unintentional injuries than control youths without ADHD (Lahey, McBurnett, Applegate, et al., unpublished; Lahey, Pelham, Stein, et al., in press). The combined type has more homework problems (Lahey, McBurnett, Applegate, et al., unpublished), and the combined and inattentive types show lower academic achievement relative to intelligence than controls (Lahey, Pelham, Stein, et al., in press). All three subtypes show greater deficits in peer social relations and are more likely to have used special education services than controls (Lahey, Pelham, Stein, et al., in press). A third study of 6- to 12-year-old boys provides similar support for the validity of DSM-IV ADHD, but fewer confounds were controlled (Paternite, Loney, Roberts, 1996). Thus, there is substantial support for the validity of ADHD and its subtypes. On the other hand, several studies suggest that both the DSM-IV age of onset criterion and the DSM-IV requirement of cross-situational impairment reduce the accurate identification of impaired cases (Applegate, Lahey, Hart, et al., 1997; Barkley, Biederman, 1997). Thus, although the concurrent validity of the current DSM-IV definition is substantial, it may be possible to improve it by reconsidering these criteria in the future. No data have been published on potential differences among the DSM-IV subtypes of ADHD in response to treatment, but one study found differences in response to methylphenidate between youths who met criteria for DSM-III ADD with and without hyperactivity (Barkley, DuPaul, McMurray, 1991).

Predictive Validity of ADHD in Childhood. Numerous longitudinal studies support the validity of childhood ADHD by demonstrating adverse adult outcomes (Lilienfeld, Waldman, 1990), but the diagnostic criteria used in all such studies predated DSM-III-R. In addition, there is evidence that the most commonly cited adverse adolescent and adult outcomes of childhood ADHD are actually attributable to comorbid childhood conduct problems (Lilienfeld, Waldman, 1990; Lahey, McBurnett, Loeber, in press). There is growing evidence that adverse outcomes in academic achievement, occupational attainment, and driving violations are independently associated with childhood ADHD after controlling for childhood conduct problems, but better controlled adult followups are needed. (Mannuzza, Klein, Bessler, et al., 1993; McGee, Partridge, Williams, et al., 1991; Nada-Raja, Langley, McGee, et al., 1997; Taylor, Chadwick, Heptinstall, et al., 1996).

ADHD in Adulthood

Children with ADHD are increasingly less likely to meet diagnostic criteria for ADHD as they grow older, but some children continue to meet criteria for ADHD and to be impaired into adulthood (Hill, Schoener, 1996). Thus, there is little doubt that ADHD is a valid diagnosis in adulthood for some individuals. A number of issues create concern about the use of this diagnosis with adults, however. First, there are concerns that adults without ADHD who are impaired because of other mental disorders seek out the diagnosis because they find it less stigmatizing than other diagnoses (Shaffer, 1994). If so, the suddenly popular term “adult ADHD” may cause many individuals not to receive optimal treatment for other mental disorders. Second, it is not clear that the retrospective assessment during adulthood of childhood ADHD symptoms is valid or that the impairment experienced by many adults with ADHD is not better accounted for by other mental disorders. Finally, much remains to be learned about the response of adults to pharmacologic and other forms of treatment for ADHD.

Is ADHD Better Conceptualized in Diagnostic or Dimensional Terms?

Some have suggested that ADHD is more appropriately viewed as a dimension of maladaptive behavior than a taxonomic category (Fergusson, Horwood, 1995; Levy, Hay, McStephen, et al., 1997). At present, there is strong evidence that two continuous dimensions of impairing ADHD behaviors can be identified, but there is no evidence of a natural threshold between ADHD and "normal" behavior. The distributions of numbers of inattention and hyperactivity-impulsivity symptoms in the general population are not bimodal, associations between numbers of ADHD symptoms and impairment are linear rather than curvilinear (Lahey, Applegate, McBurnett, et al., 1994), and a twin study of the heritability of ADHD found no evidence of a natural diagnostic threshold based on differential heritability (Levy, Hay, McStephen, et al., 1997). This does not imply that ADHD cannot be treated as a diagnostic category, however. Even if ADHD is not naturally dichotomous, many individuals with higher numbers of ADHD behaviors present for treatment. This means that clinicians must make dichotomous decisions to treat or not treat each individual. Because all forms of treatment involve some iatrogenic risk, it seems more appropriate to adopt a well-considered diagnostic threshold than to require each clinician to make this decision individually, even if the threshold is viewed as more conventional than natural. This state of affairs is not unique to ADHD, as similar questions can be raised about many mental disorders. However, much remains to be learned about the taxonomic status of ADHD and other mental disorders.

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Is Attention Deficit Hyperactivity Disorder a Valid Disorder?

William B. Carey, M.D.

Attention deficit hyperactivity disorder (ADHD) is defined as consisting of six of nine inattention or six of nine hyperactivity/impulsivity symptoms for 6 or more months that have been present from before the age of 7 years, with impairment in two or more settings, and are not due to other conditions. Additional common assumptions about ADHD include that it is clearly distinguishable from normal behavior, constitutes a neurodevelopmental disability, is relatively uninfluenced by the environment, and can be adequately diagnosed by brief questionnaires. All of these assumptions and some others must be challenged because of the weakness of empirical support and the strength of contrary evidence.

There does seem to be general agreement on the existence of a small group of readily recognizable "hyperkinetic" children, about 1 to 2 percent of the population with pervasive high activity and inattention. Their condition is associated with early onset, antisocial behavior, cognitive deficits, neurological problems, and response to methylphenidate. But even for this group, it is generally not clear whether the symptoms come from abnormal brains or adverse environments.

This discussion describes the problems in the diagnostic terminology of ADHD as it is currently applied to the other 5 to 10 percent of American children.

ADHD Symptoms Are Not Clearly Distinguishable From Normal Temperament Variations

The literature of ADHD defines the inattention and high activity behaviors as abnormal and easily differentiated from normal temperamental variations, using "cutpoints" in numbers of symptoms.

However, temperament research shows a normal range of its several traits from high to low, with half of any population being more active and half less attentive than average. No solid data support the current cutpoints, where normal high activity and inattentiveness leave off and abnormal amounts begin (Levy, Hay, McStephen, et al., 1997). Yet, any temperament trait may, as a risk factor, induce a "poor fit" with the particular environment and dysfunction in the child. Children with the "difficult" temperament cluster (low adaptability, negative mood, etc.) are more likely to develop social behavior problems, and those with the "low task orientation" cluster (high activity, low persistence-attention span, high distractibility) are more likely to do poorly in academic achievement. But even at their extremes, these traits do not necessarily lead to dysfunction unless other factors are present.

Absence of Clear Evidence That ADHD Symptoms Are Related to Brain Malfunction

The ADHD behaviors are assumed to be largely or entirely due to abnormal brain function. The DSM-IV does not say so, but textbooks and journals do. Some preliminary brain imaging studies have shown inconsistent *differences* in children with the ADHD diagnosis, but there is no proof that they are *deviations.* We do know that various brain insults like lead poisoning, fetal alcohol syndrome, and low birth weight may lead to increased activity and decreased attention span.

Several lines of evidence oppose this supposed link for ADHD: (1) No consistent pattern of high activity or inattention is seen in children with established brain injury, (2) no consistent structural, functional, or chemical neurological marker is found with the current ADHD diagnosis (Cantwell, 1996), (3) on the other hand, differences in brain function have been demonstrated in healthy children with normal temperamental variations (e.g., frontal electroencephalogram differences). Therefore, proof is needed that any test differences demonstrated with the ADHD diagnosis are signs of a disorder and not just a temperamental predisposition. Evidence of a genetic basis for the current diagnosis of ADHD cannot be taken as proof of brain abnormality because normal temperamental variations and coping also reveal substantial genetic contributions.

Neglect of the Role of Environment and Interactions With It as Factors in Etiology

The DSM-IV criteria for ADHD describe only the behaviors in the child and require the child to be having problems at home, at school, and so forth. The varying contributions of the setting to the problem are typically ignored. Yet, there are indications that the environment can produce or at least worsen (Biederman, Milberger, Faraone, et al., 1995) the ADHD symptoms. Something else is needed besides the behavioral predisposition to cause a disorder, for example, family problems with difficult temperament to produce behavior problems, or family problems, or inappropriate teaching (or other factors in the child) with high activity and low attention span to result in academic underachievement.

Diagnostic Questionnaires Now in Use as Highly Subjective and Impressionistic

Current practice involves the widespread use of brief, vaguely worded parent and teacher questionnaires to diagnose the presumed complex neurodevelopmental disability of ADHD. These scales have not met adequate psychometric criteria; they generally consist of only small numbers of items, are vaguely worded (“often,” “excessively,” etc.), and place much of the responsibility for not only reporting but also making clinical judgments as to deviation on the observer. Variations in experience, tolerance, or criteria used among observers are not allowed for. Only modest agreement has been demonstrated between these scales. Yet this vagueness leads to an all-or-nothing diagnosis of ADHD. The consequences have included poor inter-rater reliability, overdiagnosis, misdiagnosis, and inclusion of other problems (the comorbidity issue);

various unvalidated techniques (e.g., electroencephalograms) have been proposed by some in an effort to improve the precision of the diagnosis.

Low Adaptability and Cognitive Problems May Be the Most Important Predisposing Factors

The DSM-IV definition says that high activity and low attention span are the disorder itself. Accumulating evidence is demonstrating that other factors may be more important in production of the behavioral or scholastic dysfunction: (1) a different behavioral predisposition, variously described as low adaptability, limited ability to modify behavior, a problem in regulation of responses, and a deficiency in response inhibition (Barkley, 1997) and (2) a developmental predisposition—there is a high frequency of cognitive disabilities in children who receive diagnoses of ADHD today (Levine, 1998).

Lack of Evolutionary Perspective

Embodied in the current ADHD diagnosis is the assumption that a child not fitting into the modern classroom has a defective brain. An evolutionary perspective informs us that the ADHD traits may have been highly adaptive in primitive times but may be less so now (Jensen, Mrazek, Knapp, et al., 1997).

Small Practical Usefulness and Possible Harm From Label

Some observers maintain that the ADHD label represents progress in mental health diagnosis because it takes the blame off the parents and schools, helps children get services, and justifies the use of medication. But there are several negative aspects of the labeling: (1) It is not helpful to teachers, psychologists, or physicians because it offers no articulation of the individual's problems and strengths and no suggestions for specific management other than medication, (2) the complex phenomenon of attention is analyzed in too simple a way, and (3) the label may be harmful and stigmatizing by stating or implying brain malfunction when it is unproven. Labels stick.

Conclusions

DSM-IV defines a mental disorder as a clinically significant behavioral syndrome arising from a dysfunction that results in present distress or disability. What is now most often described as ADHD in the United States appears to be a set of normal behavioral variations that sometimes lead to dysfunction through dissonant environmental interactions. This discrepancy leaves the validity of the construct in doubt.

Research for a better diagnostic system should include the following: (1) As the DSM-IV requires, any disorder should be defined in terms of areas of dysfunction (social relationships, school achievement, self-control, etc.) and service needs but not in terms of risk factors,

(2) diagnosis of brain malfunction should be substantiated by some objective test, and (3) broader individual assessments should be used regularly and encompass both child and setting and strengths and problems.

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Biological Bases of Attention Deficit Hyperactivity Disorder: Neuroanatomy, Genetics, and Pathophysiology

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In a multistage process for validation of a psychiatric disorder (Jensen, Martin, Cantwell, 1997), two preliminary steps have been taken for attention deficit hyperactivity disorder (ADHD): (1) a partial consensus has been reached in the two primary diagnostic manuals, DSM-IV and ICD-9, about an ADHD phenotype that can be reliably assessed (Swanson, Sergeant, Taylor, et al., 1998) and (2) in followup studies of children with the disorder from several different geographical locations, adverse adolescent outcome in social adjustment and educational attainment has been documented (e.g., Mannuzza, Klein, Bessler, et al., 1993; Satterfield, Swanson, Schell, et al., 1994; Taylor, Chadwick, Heptinstall, et al., 1996). In this process, a critical next step is the delineation of biological bases of ADHD by laboratory tests. We will review recent pivotal studies from neuroanatomy and molecular biology that address this issue.

Recent investigations of a refined phenotype defined by the ICD-10/DSM-IV consensus criteria (ADHD-combined type without serious comorbidities present in childhood) (ADHD/hyperkinetic disorder [HKD]) have produced some converging evidence about biological bases of this disorder. Multiple causes have been assumed (see Conners, 1998, this volume), and both neurological damage and genetic variation have been proposed as likely biological etiologies. We will discuss research exemplifying both proposals.

Recent Research on Neuroanatomical Abnormalities

One of the most important current developments has been the convergence of findings from magnetic resonance imaging studies of brain anatomy (aMRI). We will present a meta-analysis of studies from several independent laboratories that have reported ADHD/HKD abnormalities in two specific but still coarsely defined brain regions of the frontal lobes and basal ganglia. For example, Filipek and colleagues (1997) reported that a group of children with ADHD/HKD had brain volumes about 10 percent smaller than normal in anterior superior regions (posterior prefrontal, motor association, and midanterior cingulate) and anterior inferior regions (anterior basal ganglia), and Castellanos and colleagues (1996) reported that right anterior frontal, caudate, and globus pallidus regions were about 10 percent smaller in an ADHD/HKD group than in a control group.

The convergence of findings within and across investigators has not emerged for functional imaging studies using positron emission tomography (PET) (Ernst, Zametkin, 1995) as it has for aMRI studies. We will discuss possible reasons for this, as well as a variety of findings from studies based on other methods of functional imaging, such as single photon emission

tomography (SPECT), EEG event-related potentials (ERP), and functional magnetic resonance imaging (fMRI).

The reported aMRI findings may be localized in theoretical frameworks of neural networks, such as the parallel segregated circuits described by Alexander and colleagues (1986) and the neuroanatomical networks of attention described by Posner and Raichle (1996). We will discuss attempts to use these theories to organize the empirical findings from brain imaging studies of ADHD/HKD, and we will review some of the proposals that have been offered to account for executive function deficits of ADHD/HKD children documented by neuropsychological tests (see Tannock, 1998, in this volume).

Recent Molecular Genetic Investigations

Many family (e.g., Faraone, Biederman, Chen, et al., 1992), twin (e.g., Gjone, Stevenson, Sundet, 1996), and adoption (e.g., Deutsch, Matthysse, Swanson, et al., 1990) studies have documented a strong genetic basis for ADHD/HKD, but these studies do not identify specific genes linked to the disorder. Molecular genetic studies are necessary to identify allelic variations of specific genes that are functionally associated with ADHD/HKD. Dopamine genes have been the initial candidates for application of advances in molecular biology, based on the site of action of the stimulant drugs (Wender, 1971; Volkow, Ding, Fowler, et al., 1995), the primary pharmacological treatment for ADHD/HKD (see Greenhill, 1998, in this volume).

Two candidate dopamine genes have been investigated and reported to be associated with ADHD/HKD: the dopamine transporter (DAT1) gene (Cook, Stein, Krasowski, et al., 1995; Gill, Daly, Heron, et al., 1997) and the dopamine receptor D4 (DRD4) gene (LaHoste, Swanson, Wigal, et al., 1996; Swanson, Sunohara, Kennedy, et al., 1998). The associated polymorphisms of these genes are defined by variable numbers of tandem repeats (VNTR), which for the DAT1 gene is a 40-bp repeat sequence on chromosome 5p15.3 and for the DRD4 gene is a 48-bp repeat sequence on chromosome 11p15.5. Speculative hypotheses have been based on the notions that specific alleles of these dopamine genes may alter dopamine transmission in the neural networks implicated in ADHD/HKD (e.g., that the 10-repeat allele of the DAT1 gene may be associated with hyperactive re-uptake of dopamine or that the 7-repeat allele of the DRD4 gene may be associated with a subsensitive postsynaptic receptor). However, the literature on this topic is sparse, and not all studies agree about the association of ADHD/HKD with DAT1 (Sunohara, Kennedy, 1998) or DRD4 (Castellanos, Lau, Tayebi, et al., in press). This is an emerging area of research; so we will discuss its status at the time of the conference.

Investigations of Nongenetic Etiologies

Specific genetic models have incorporated a high phenocopy rate to account for a sporadic as well as a genetic form of the disorder (Faraone, Biederman, Chen, et al., 1992; Deutsch, Matthysse, Swanson, et al., 1990). In addition to rare genetic mutations, sporadic cases may be due to nongenetic etiologies such as acquired brain damage. For decades, theories of minimal brain damage and minimal brain dysfunction (MBD) have been proposed and rejected

(e.g., Wender, 1971; Brown, Chadwick, Shaffer, et al., 1981) because of the lack of empirical evidence of suspected brain damage in children manifesting behavioral soft signs and the lack of specificity of the behavioral consequences of traumatic brain injury. However, recent theories based on animal models and brain damage have revived this approach. For example, Lou (1996) proposed that during fetal development, bouts of hypoxia and hypotension could selectively damage neurons located in some of the critical regions of the anatomical networks implicated in ADHD/HKD (i.e., the striatum). Fetal exposure to alcohol, lead, nicotine, and other substances may produce similar neurotoxic effects. Also, severe traumatic brain injury may produce selective interneuron damage in the frontal lobes, which Max and colleagues (1998) suggest may produce new-onset symptoms of inattention and impulsivity, though often not hyperactivity (Brown, Chadwick, Shaffer, et al., 1981). We will discuss these new developments in the context of the historical questions about documentation of specific neuroanatomical abnormalities (which may be addressed with modern imaging methods) and selective expression of ADHD/HKD symptoms (which may be addressed by prospective followup investigations).

Neurobiological Bases for Pharmacological Treatment

The abnormalities in neuroanatomical networks associated with ADHD/HKD (smaller frontal and basal ganglia regions) and the biochemical pathways (specific alleles of dopamine genes) suggest a possible theoretical basis (e.g., a dopamine deficit) for the standard pharmacological treatments of ADHD/HKD with dopamine agonist drugs (see Greenhill, 1998, in this volume). Primary treatment with the stimulant medication methylphenidate has stood the test of time and the scrutiny of controlled research (Wilens, Biederman, 1992; Swanson, McBurnett, Wigal, et al., 1993). Recent investigations (Volkow, Ding, Fowler, et al., 1995) have identified the site of action of methylphenidate, which blocks the dopamine transporter. This increases the temporal and spatial presence of synaptic dopamine when it is released in the basal ganglia (e.g., putamen, caudate, and ventrostriatum) and cortex (e.g., temporal, insula, and cingulate gyri) for approximately the post-peak length of action following oral administration (2 to 3 hours). We will discuss site-of-action hypotheses that have been proposed to account for effects of clinical doses of stimulant medication. For example, Castellanos (1997) proposed that presynaptic effects may predominate in D2-rich subcortical regions where presynaptic receptors are abundant, producing decreased synaptic dopamine, and postsynaptic effects may predominate in D4-rich cortical regions, which lack presynaptic receptors, producing increased synaptic dopamine. Also, Seeman and Madras (in press) have proposed that clinically relevant doses of stimulants may increase extracellular background levels of dopamine more than action-potential released dopamine, which may account for why these dopamine agonist drugs result in a reduction in psychomotor activity.

Other etiologies of ADHD/HKD have been proposed (e.g., adverse reactions to foods or food additives, cortical underarousal, muscular tension), and on the basis of these proposals, specific nonpharmacological treatments have been suggested (e.g., special diets, EEG biofeedback, EMG relaxation training). These proposals and treatments have testimonial support, but empirical support from controlled studies is lacking. Since these areas will be covered by Arnold (1998, this volume), they will not be discussed here.

Summary

Recent investigations provide converging evidence that a refined phenotype of ADHD/HKD is characterized by reduced size in specific neuroanatomical regions of the frontal lobes and basal ganglia. These specific deficits suggest abnormalities in neural networks that affect input-output processing and attention (alerting and executive function). These neural networks are modulated by catecholamines, which are affected by stimulant drugs. The site of action of methylphenidate (the primary stimulant now used to treat ADHD/HKD) suggests that dopamine is the principal neurotransmitter involved, although norepinephrine has also been implicated. Recent molecular genetic studies have documented significant association of a refined phenotype of ADHD/HKD with polymorphisms in dopamine genes, which may alter the functions of the implicated neural networks. Recent investigations of brain development and brain injury also suggest that damage to these specific neural networks may produce symptoms of ADHD/HKD. Overall, the recent investigations in these areas have provided considerable evidence of multiple biological bases of ADHD/HKD.

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Cognitive and Behavioral Correlates

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Neuropsychological correlates provide useful criteria for examining the validity of attention deficit hyperactivity disorder (ADHD), because they do not share method variance with clinical measures used to assess psychiatric symptomatology. Performance is assessed directly and is not subject to confounding factors such as recall bias or halo effects. Also, these data provide insights into the neural substrates of the disorder (Halperin, McKay, 1998; Lezak, 1995).

A systematic review of the literature was undertaken using *Medline* and *Psychlit* bibliography databases and covering the following correlates: (1) general intellectual function, (2) academic achievement, (3) neuropsychological function (motor function, perception, visual-motor integration, language, memory, executive functions), and (4) cognitive processes (alerting, orienting, executive control). The following questions were addressed: (1) What are the impairments/strengths associated with ADHD? (2) Do these impairments/strengths vary by gender and/or by age? (3) Are these impairments/strengths influenced by the presence of concurrent disorders? (4) Are these impairments/strengths specific to ADHD? and (5) What neural networks are implicated?

General Intellectual Function

Intelligence tests provide a broad index of higher cortical functioning that can be used to generate hypotheses for further investigation using neuropsychological and experimental cognitive techniques. Their psychometric properties remain robust for the clinical group of ADHD (Schwean, Saklofske, 1998). Compared with normative data, ADHD is associated typically with lower full-scale IQ and subtest scores (particularly those comprising an index of working memory), but the mean levels of intellectual functioning are well within the normal range. These findings are robust across age (preschool through adulthood), gender (although girls may exhibit greater intellectual impairment), study design (cross-sectional, longitudinal) or source of sample (epidemiological, pediatric, or psychiatric clinic), and various test versions (Saklofske, Schwean, Yackalic, et al., 1994; Sonuga-Barke, Lamparelli, Stevenson, et al., 1994; Mariani, Barkley, 1997; McGee, Williams, Moffit, et al., 1989; Barkley, DuPaul, McMurray, 1990; Biederman, Faraone, Taylor, et al., 1998; Seidman, Biederman, Faraone, et al., 1997; Seidman, Biederman, Faraone, et al., 1997; Gaub, Carlson, 1997). Also, they generally hold for studies that have controlled for the presence of comorbid disorders (Faraone, Biederman, Lehman, et al.,1993; Faraone, Biederman, Weber, et al., 1998; Newby, Recht, Caldwell, et al., 1993). By contrast, the findings do not appear to hold for the predominantly hyperactive subtype of ADHD, suggesting that the intellectual profile may be a correlate of inattention rather than hyperactivity/impulsiveness (Gaub, Carlson, 1997; Semrud-Clikeman, Biederman, Sprich, et al., 1992; Hinshaw, 1992; Barkley, Anastopoulos, Guevremont, et al., 1991). Preliminary evidence that male (but not female) siblings of children with ADHD exhibit a similar intellectual profile

supports the hypothesis that ADHD is familial (Faraone, Biederman, Lehman, et al., 1993). This intellectual profile is not specific to ADHD; it is also associated with learning disabilities and other disruptive behavior disorders (Newby, Recht, Caldwell, et al., 1993). Thus, intellectual correlates of ADHD may have conceptual but not diagnostic significance.

Academic Achievement

Academic achievement tests provide a more detailed profile of strengths and weaknesses in underlying component skills that contribute to academic competency and indicate the presence of a learning disability. One of the most robust findings is a higher rate of school failure (Semrud-Clikeman, Biederman, Sprich, et al., 1992; Hinshaw, 1992; Barkley, Anastopoulos, Guevremont, et al., 1991). This is evidenced most clearly by low productivity but also by lower scores (on average, 0.5 S.D. lower) on reading (decoding, comprehension), spelling, and arithmetic, and elevated rates of grade repetition, learning disabilities, remedial tutoring, and special class placement, despite average levels of intellectual functioning. Academic underachievement is evident in both girls and boys as well as siblings, it occurs in preschool years and endures through adolescence (Barkley, DuPaul, McMurray, 1990; Faraone, Biederman, Lehman, et al., 1993; Faraone, Biederman, Weber, et al., 1998; Zentall, 1990). It is a correlate of ADHD per se and cannot be accounted for by psychiatric comorbidity (which tends to influence school placement rather than school failure or intellectual ability) or comorbid learning disabilities (Faraone, Biederman, Lehman, et al., 1993; Faraone, Biederman, Weber, et al., 1998). However, academic problems, particularly in arithmetic, are more common among predominantly inattentive and combined subtypes of ADHD, suggesting that these problems are related to inattention rather than hyperactivity/impulsivity (Hynd, Lorys, Semrud-Clikeman, et al., 1991; Baumgaertel, Wolraich, Dietrich, 1995; Lahey, Applegate, McBurnett, et al., 1994; Gaub, Carlson, 1997; Lamminmäki, Ahonen, Närhi, et al., 1995; Marshall, Hynd, Handwerk, et al., 1997. The nature of the academic impairments (particularly in individuals without comorbid learning disabilities) suggests problems in effortful processing. However, there is no evidence of a profile that is uniquely associated with ADHD.

Neuropsychological Function

Neuropsychological tests provide a detailed assessment of a wide array of cognitive functions that afford insights into brain-behavior relationships; they are sensitive to subtle deficits that interfere with learning and achievement. The most consistent (albeit not invariable) findings are impairments in "executive functions," an umbrella term denoting a range of higher order, effortful, self-regulatory functions whose formal definition and measurement (particularly in children) remain elusive and under debate (Pennington, 1997; Tannock, 1998; Pennington, Ozonoff, 1996). However, impairments in component functions, particularly those associated with *control* of motor responses (planning, inhibition) and *working* memory, are clearly evident during effortful tasks in preschoolers, children, and adolescents, using a variety of measures requiring both fast or slow processing of information (Mariani, Barkley, 1997; Seidman, Biederman, Faraone, et al., 1997; Seidman, Biederman, Faraone, et al., 1997; Pennington, Ozonoff, 1996; Nigg, Hinshaw, Carte, et al., in press; Seidman, Biederman, Faraone, et al.,

1995). These findings generally hold after controlling for comorbid psychiatric disorders and learning disabilities (Nigg, Hinshaw, Carte, et al., in press; Seidman, Biederman, Faraone, et al., 1995). Motor planning and inhibition problems are not typically associated with learning disabilities, although a combination of impairments in motor control, perception, speech-language, and attention is discernible in some children (Gillberg, Rasmussen, Carlstrom, et al., 1982; Hellgren, Gillberg, Bagenholm, et al., 1994). Reciprocally, verbal impairments associated with reading disabilities (phonological processing, verbal memory) are not associated with ADHD (Javorsky, 1996; Felton, Wood, 1989). Moreover, verbal impairments reflecting difficulties in *use* of language for organization of information and self-regulation (language-mediated processing) are more strongly associated with ADHD than with learning disabilities (Tannock, Schachar, 1996). These patterns of findings indicate at least some neuropsychological differentiation between these overlapping disorders. On the other hand, evidence of impairments in many component functions (including motor inhibition) in a wide range of clinical populations mitigates specificity for ADHD (Gold, Carpenter, Randolph, et al., 1997; Matier-Sharma, Perachio, Newcorn, 1995; Purcell, Maruff, Hyrios, et al., 1998).

Information Processing

Methods derived from information processing theory allow decomposition and more precise measurement (latency and accuracy) of the complex web of cognitive processes involved in most neuropsychological measures (Cohen, 1993). The most robust finding is of slow, variable, and inaccurate response latencies across a range of different measures, implicating impairments in energetic state regulation, preparation, maintenance, and inhibition or adjustment of motor control processes. Three component processing systems are implicated: sustained attention or vigilance, which refers to a state of readiness to respond (CPT paradigms) (Losier, McGrath, Klein, 1996; Corkum, Seigel, 1993; Van der Meere, 1996; Sergeant, Van der Meere, 1990), selective attention or spatial allocation of attention (visuospatial orienting paradigms) (Nigg, Swanson, Hinshaw, 1997; Pearson, Yaffee, Loveland, et al., 1995; Swanson, Posner, Potkin, et al., 1991; Tannock, Schachar, Logan, 1993), and response inhibition (stop-signal, delay-aversion paradigms) (Sonuga-Barke, Taylor, Hepenstall, 1992; Sonuga-Barke, Williams, Hall, et al., 1996; Oosterlaan, Logan, Sergeant, 1998; Schachar, Logan, 1990; Schachar, Tannock, Marriott, et al., 1995). The findings are not incontrovertible. For example, impairments in sustained attention are evident across the lifespan (preschool through adulthood) regardless of comorbidity, but findings are influenced strongly by temporal parameters (interstimulus interval, trial length, etc.), stimulus modality, memory load, and context (presence/absence of experimenter, rewards) (Purcell, Maruff, Hyrios, et al., 1998; Cohen, 1993; Van der Meere, 1996; Sergeant, Van der Meere, 1990; Halperin, Wolf, Greenblatt, et al., 1991b; Chee, Logan, Schachar, et al., 1989). In general, ADHD is associated with inefficient performance (slow, inaccurate) and vigilance decrements (faster than normal decline in performance) that occur with increased demand for effortful processing (Van der Meere, 1996; Sergeant, Van der Meere, 1990). However, performance impairments on vigilance tasks are exhibited by a wide range of clinical populations, once again challenging the notion of specificity for ADHD per se. Dysfunction of the visuospatial orienting system (particularly in the right hemisphere) is suggested by a few studies of covert orienting (shifts in allocation of visual attention in the absence of saccadic eye movements), including one study of biological parents,

suggesting the influence of genetic factors (Nigg, Swanson, Hinshaw, 1997; Pearson, Yaffee, Loveland, et al., 1995; Swanson, Posner, Potkin, 1991). However, inconsistency of findings across studies and across child and parent samples does not allow for firm conclusions.

Response inhibition deficits are demonstrated using theoretically distinct methods. One approach characterizes the impairment as delay avoidance, defined as a response style aimed at minimizing total time on task (Sonuga-Barke, Taylor, Hepenstall, 1992; Sonuga-Barke, Williams, Hall, et al., 1996). The continuity of this response style into adulthood or its variation with gender or comorbidity is unknown. Another approach demonstrates impairments in inhibiting prepotent courses of action (indexed by slow and/or variable inhibitory processes) (Oosterlaan, Logan, Sergeant, 1998; Schachar, Logan, 1990; Schachar, Tannock, Marriott, et al., 1995). The severity of impairment is attenuated in the situational and predominantly inattentive subtypes (suggesting a closer association with hyperactivity/impulsivity), as well as by comorbid anxiety (Schachar, Logan, 1990; Schachar, Tannock, Marriott, et al., 1995). These inhibition deficits are shared by other externalizing disorders (aggression, oppositional defiant disorder, conduct disorder) but are not evident in anxiety disorders or learning disabilities, suggesting some specificity with hyperactivity/impulsivity (Oosterlaan, Logan, Sergeant, 1998). Moreover, there is preliminary evidence of a link between performance decrements on response inhibition tasks and subtle anatomical anomalies in the frontal-striatal circuitry (prefrontal cortex, caudate, and globus pallidus) in children and adolescents with ADHD (Casey, Castellanos, Giedd, 1997). It is not known whether these deficits continue into adulthood, and there is little evidence that this central inhibitory control impairment relates to behavioral self-regulation (impulsivity, overactivity, inattention).

Implications for Neural Substrate and Pathophysiology of ADHD

The pattern of neuropsychological impairments associated with ADHD shows correspondence with findings of subtle anomalies in brain anatomy and neurochemistry in individuals with ADHD (Tannock, 1998). Specifically, vigilance deficits implicate neural networks in the right frontal lobe and locus ceruleus; impairments in response control and cognitively demanding information processing implicate the dopaminergically mediated "anterior" attentional system associated with anterior cingulate and frontostriatal circuitry; and the potential deficits in visuospatial orienting implicate "posterior" attentional systems comprising superior parietal cortex, pulvinar, and superior colliculus (Posner, Raichle, 1994). Moreover, the overall difficulties in dynamic, online adjustment and adaptation to changes in the immediate environment, which are evident in both clinical and cognitive studies of ADHD, implicate cerebellar networks that play a major integrative role in prediction and preparation of neural conditions needed for a particular motor or nonmotor operation (Courchesne, Allen, 1997).

Future Directions

Currently, ADHD is best characterized as reflecting a nonoptimal activation state and dysfunction in motor preparation and control (planning, execution, inhibition) not readily

explainable by comorbidity, but not necessarily specific to ADHD. This research is challenged by heterogeneity of this symptom complex, measurement problems, and the study of small samples. Future studies may be more informative if ADHD is conceptualized as a composite of two quantitative, continuously distributed dimensions of inattention and impulsivity/ hyperactivity, rather than as three categorical subtypes. Also, large samples are required to afford adequate statistical power for multivariate techniques to examine the impact of gender, age, symptom dimensions, and comorbidity. Comparisons with multiple clinical/medical groups are required to examine the issue of specificity of neuropsychological impairment. Measurement approaches are required that select measures of contrasting constructs (automatic versus controlled processing, linguistic versus non-linguistic, fast versus slow pace, motoric versus nonmotoric, high versus low working memory load, etc.) and incorporate the recent advances in brain imaging and psychophysiological techniques. Delineation of the neuropsychological and neural mechanisms of ADHD must be an iterative process in which clinical subtypes are defined, tested, and redefined, using more precisely controlled and validated measures.

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The Prevalence and Cross-Cultural Validity of Attention Deficit Hyperactivity Disorder

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This report reviews a number of epidemiologic studies carried out in child and adolescent populations in different cultural settings. It provides prevalence findings in different countries and cultural groups as well as information about the cross-cultural generalizability and validity of the syndrome of attention deficit hyperactivity disorder (ADHD) based on the results of studies carried out in widely disparate cultural settings.

Two types of studies are highlighted in this report: those that are based on categorical nosological constructs (primarily DSM and ICD) and those that have employed continuous measures (primarily CBCL and Conners ratings). These studies, carried out in different cultural settings throughout the world, including the United States and Canada, Great Britain, several other countries in Western Europe, China, India, Israel, Brazil, Chile, Puerto Rico, Australia, Indonesia, Nigeria, and Thailand, have found remarkable similarity in the syndromal construct of behaviors characteristic of ADHD.

Wide fluctuations in the reported rates of the disorder across cultures range from less than 1 percent to close to 20 percent. Although different rates might be expected in different settings, these differences may be more a function of the diagnostic system employed to classify the syndrome, the methods of ascertainment, and other methodological artifacts than an actual manifestation of cultural differences. Lowest rates are obtained with the ICD diagnostic classification of hyperkinetic syndrome and highest rates with the DSM-IV classification of ADHD. Studies that used DSM-III and DSM-III-R obtained rates somewhere between these two extremes. Moreover, there were important variations noted in the ratings of the behaviors and in the prevalence of ADHD resulting from cultural differences among raters. For example, when standardized videotape vignettes of subjects participating in individual and group activities were rated by clinicians proceeding from different cultural backgrounds, Chinese and Indonesian clinicians gave significantly higher scores for hyperactive-disruptive behaviors than did their Japanese and American colleagues. Such findings suggest that although different cultures conceptualize the ADHD syndrome in similar ways, the threshold for deviance, among both clinicians and other informants, may have strong cultural determinants, thereby producing an informant effect that could have a strong bearing on differences in rates.

Other studies are cited that provide validation of the syndrome in different cultures from both a statistical and a clinical perspective. Despite variations in the rates at which specific behaviors occur in different populations, the overall syndrome repeatedly shows high internal consistency across settings. When behavior questionnaires are subjected to factor analytic procedures, the results are invariably similar across cultural settings as disparate as the United States, Italy, China, Germany, Brazil, and Thailand. These analyses repeatedly show a syndrome that breaks down into two robust factors of inattention and hyperactivity/impulsivity. Moreover,

a study of Chinese schoolboys replicates neurobiological findings that have been associated with the attentional deficit syndrome in Western studies. These include inefficiency in the Continuous Performance Test (CPT), significantly higher activity and inattentiveness levels in terms of actometer readings and direct observations of body movements and gaze, more frequent reported histories of motor and language delays, and higher biological risk indices, including lower birth weights and complications during the neonatal period.

The findings from repeated studies over the past 15 years provide strong support for the cross-cultural validity of the syndrome of attentional deficits and hyperactivity as a clinical entity.

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Attention Deficit Hyperactivity Disorder: Long-Term Course, Adult Outcome, and Comorbid Disorders

Russell A. Barkley, Ph.D.

This presentation focuses on two issues: (1) the long-term course and adult status for attention deficit hyperactivity disorder (ADHD) specifically and (2) the likely comorbid psychiatric disorders found in association with ADHD across its developmental course into adolescence and adulthood. For each issue, the focus is on the two separate periods of adolescence (ages 13 to 19 years) and young adulthood (ages 20 to 30 years). The presentation relies chiefly on the prospective longitudinal studies that have been conducted on hyperactive children or children with ADHD. It does not address issues related to areas of impairment produced by or often seen in conjunction with the disorder, such as school performance problems, peer relationship difficulties, family interaction problems, or difficulties in occupational settings (in the case of adults with ADHD). Nor does it deal with the associated cognitive impairments or even health and accident risks that may be accentuated by the condition.

Limitations of Methodology

The interpretation of prospective followup studies on hyperactivity or ADHD is greatly constrained by a number of important limitations in methodology:

- Many of the longest running followup studies did not have available empirically based consensus diagnostic criteria for the disorder, such as DSM-III-R or IV, to employ as part of subject selection criteria to identify children as having ADHD at entry into the study. It therefore cannot be stated unequivocally that all subjects in these and other similar followup studies would have met today's standards for a diagnosis of ADHD.

- Most followup studies did not use the same assessment instruments across their followup points, making direct calculations of the stability, persistence, and desistance of disorder across development highly problematic.

- None of the followup studies attempted to correct their figures dealing with persistence of disorder for unreliability of measurement across time.

- The methods used to assess persistence of symptoms and disorder across time, as well as comorbid psychiatric disorders, are not similar or identical across studies, making straightforward comparisons of the results across those studies difficult.

- The method by which ADHD is diagnosed across development fails to take into consideration the strong probability that ADHD is a *developmental disorder* of a cognitive mechanism or set of such mechanisms. That is, subjects may appear to outgrow the item set used for diagnosis but would not be outgrowing their disorder.

- Some studies shifted the source of the information about the subjects and their disorder at different followup points. This is a problem because there is reason to believe that subjects with ADHD may have more limited self-awareness of their symptoms and so may underreport the extent of their disorder and comorbidities.

- The percentage of subjects relocated and reevaluated at followup varies markedly across studies, ranging from 51 to 98 percent. In studies with high attrition rates, it is highly likely that subjects lost to the followup evaluation are not similar to those who were able to be reevaluated and may well have been more likely to have had persistent disorder as well as greater comorbidity than those subjects who were evaluated.

Summary of Outcome Studies

It appears that a majority of hyperactive children continue either to manifest significant symptoms of disorder (70 to 80 percent) into adolescence or to qualify for a diagnosis of full disorder. Approximately 65 to 80 percent will have full disorder in early adolescence, whereas 30 to 50 percent may continue to have full disorder by late adolescence (16 to 19 years), assuming that parental report is the source of information. By adulthood, it first appears that only a small percentage of hyperactive children or children with ADHD retain their disorder if formal diagnostic criteria are used at the adult followup point and self-reports serve as the basis for diagnosis (3 to 8 percent). But there are numerous legitimate reasons for questioning such results. One major reason is the apparent developmental insensitivity of the diagnostic criteria to the disorder in this older group. Another is the apparent underreporting of symptoms by the subjects relative to reports given by their parents. Anywhere from 3 to 68 percent of hyperactive subjects have ADHD in adulthood depending on these various methodological factors, with rates being higher (25 to 68 percent) when based on parent reports and/or on empirically based (developmentally referenced) definitions of disorder. The persistence rates are dramatically lower when based on DSM criteria using self-reports (3 to 8 percent).

Approximately 20 to 50 percent of hyperactive children are likely to have conduct disorder (CD) by adolescence. It is not surprising then, given the link of CD to antisocial personality disorder (APD), that 25 percent of hyperactive subjects will have APD in young adulthood. And because APD is a known risk factor for substance use, dependence, and abuse, the elevated risk of 10 to 37 percent of these young people having a substance dependence or use disorder in adulthood, as found in several studies, is also not unexpected.

Studies differ in finding major depression present in the adolescent or young adulthood years of hyperactive subjects followed prospectively. The New York study (Mannuzza, Klein, Bessler, et al., 1998) found no significant elevation of risk at either age period. In contrast, the Boston study (Biederman, Faraone, Milberger, et al., 1996) found such an elevation in risk at

adolescence. The author's more recent Milwaukee study (Barkley, Fischer, Edelbrock, et al., 1990; Barkley, Fischer, Fletcher, et al., manuscript in preparation) found a rate of nearly 28 percent in young adulthood. Given the higher than normal rate of conduct disorder and subsequent APD in a substantial minority of hyperactive children and the known association of CD/APD with major depression, it should not be surprising to discover that this subgroup has a higher than normal risk for depression in young adulthood, as the Milwaukee study has recently discovered.

In conclusion, hyperactivity or ADHD is a highly persistent disorder from childhood to adolescence. It also conveys a greater risk for oppositional defiant disorder (ODD), CD, and APD among a substantial minority of these children as they progress through adolescence and into adulthood. Consequently, there may also be an elevated risk for substance use disorders among this subset of children with ADHD who have comorbid CD or APD. Whether ADHD conveys a greater risk for mood disorders, such as major depression, remains unsettled at this time. However, it apparently does not elevate the risk for later anxiety disorders. The extent to which ADHD persists into adulthood cannot be easily determined from the existing data. Where fixed (childhood-based) diagnostic criteria such as the DSM are applied to these formerly hyperactive or ADHD children as they become adults and their own self-reports are used, rates of persistence of disorder are low indeed. More than 90 percent of subjects no longer seem to meet criteria for full disorder. However, where developmentally referenced and empirically based definitions are employed (e.g., symptoms > 93rd percentile for age) and others, such as parents, serve as the source of information, persistence of disorder is present in the majority of subjects (68 percent). Which of these approaches to determining persistence of disorder into adulthood yields the more valid picture of the adult outcome for ADHD awaits further study.

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The Impact of Attention Deficit Hyperactivity Disorder on School Systems

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Although attention deficit hyperactivity disorder (ADHD) is not recognized as a separate category of special education, schools have been officially encouraged by the U.S. Department of Education to provide services for children with ADHD under existing special education categories, such as learning disabilities (LD), emotional disturbance (ED), and other health impairments (OHI), or to provide accommodations in general education classrooms under Section 504 of the 1973 Rehabilitation Act (Davila, Williams, MacDonald, 1991). The critical issues involve numbers of children with ADHD actually served in special education, costs of special education for these children, and problems in educating children with ADHD in both general and special education settings.

Special Education Eligibility for Children With ADHD

Eligibility for the LD category in special education requires a substantial difference between intellectual ability and academic performance, a problem for many children with ADHD whose measured reading or math skills may be low but not to the extent required (Forness, Walker, 1994). Eligibility for the ED category is likewise problematic in that existing diagnostic criteria do not necessarily correspond to ADHD symptomatology, and eligibility is sometimes denied if ADHD symptoms are mistaken merely for difficulties in social adjustment. The OHI category is reserved for children whose medical conditions significantly limit their classroom participation, and OHI functions as a category of convenience for certain children with ADHD who fail to qualify in other categories. Section 504 accommodations are usually requested only when children are denied eligibility for special education and are usually minimal since no funding follows this law as it does in special education.

Although children with ADHD often have learning disabilities or other comorbid psychiatric diagnoses, few data exist on their particular eligibility for special education or on children with ADHD who remain ineligible. Special education or school psychology research seldom addresses specific diagnostic entities such as ADHD, thus limiting such evidence. Table 1 summarizes the few available studies from which percentages of ADHD children actually found eligible for LD or ED categories of special education could be reliably determined. Different methods of diagnosis, sample selection, and other factors precluded systematic weighting of these percentages; therefore, approximate means across all studies were used as final estimates.

Table 1. Estimates of ADHD prevalence with LD, EDH, and OHI categories

Source	LD (%)	ED (%)	OHI (%)
Bussing et al. (1998)	16.2	31.1	
Cullwood-Brathwaite & McKinney (1998)	68.3		
Duncan et al. (1995)		24.7	
MacMillan et al. (in press)	33.1		
Mattison et al. (1992, 1993, 1997)		44.4	
McConaughy et al. (1994)	28.1	44.8	
U.S. Department of Education (1990–97)			39.7
Reasonable estimate	26.0	43.0	40.0

Note: See text for method of establishing reasonable estimate.

The estimate in the OHI category could be derived only by examining trends in this category in the 4 years before official recognition of ADHD (1988–92) and the 4 years after this recognition (1992–96) (U.S. Department of Education, 1990-97). These trends are depicted in table 2. Although average enrollments and annual increases were relatively similar for the LD and ED categories across these two periods, different trends were noticeable in the OHI category. In the absence of other plausible hypotheses, the average increase beyond that registered for the preceding 4 years appears to represent use of the OHI category for children with ADHD. Enrollment in this category more than doubled in size from 1992 to 1996 so that about 60 percent of children in the OHI category were newly identified by the end of this period. Since the excess increase was approximately two-thirds, the current estimate is that approximately 40 percent of children in the OHI category have ADHD.

Estimates were then applied to the numbers of children in each category as depicted in table 3. Using an estimate of approximately 2 million school children with ADHD, approximately 45 percent of all children with ADHD appear to be in special education classes.

Table 2. Percentages of school enrollment and of annual increase in children by year for LD, ED, and OHI categories

	LD		ED		OHI	
School Year	Enrollment	Increase	Enrollment	Increase	Enrollment	Increase
1988–89	4.71	3.0	0.89	0.7	0.12	7.8
1989–90	4.79	3.3	0.89	2.2	0.12	5.7
1990–91	4.88	4.0	0.89	5.0	0.13	8.5
1991–92	5.02	4.9	0.89	2.6	0.13	7.1
1992–93	5.25	5.3	0.89	1.0	0.14	13.4
1993–94	5.27	3.4	0.89	4.1	0.18	26.7
1994–95	5.34	3.5	0.91	3.2	0.23	28.2
1995–96	5.44	3.6	0.91	2.5	0.28	24.7

Source: Annual Report to Congress on IDEA, Volumes 12–19 (1990–97).

Table 3. Current available numbers of children in LD, ED, and OHI categories and best estimate of children with ADHD in each

Category	Children in 1995–96	Best Estimate (%)	Number With ADHD
LD	2,595,004	26	674,701
ED	438,150	43	188,404
OHI	133,354	40	53,342
Total	3,166,508		916,447

Note: See text and table 2 for source of estimates; numbers are from the Annual Report to Congress on IDEA, Volume 19 (1997).

Costs of Special Education for Children With ADHD

The estimate of the excess or marginal costs of special education (costs beyond those required to educate a child without disabilities) is currently $5,435 per pupil (U.S. Department of Education, 1990-97). This estimate includes all Federal, State, and local school district contributions. The estimate varies, however, depending on special education category and type of classroom environment. Percentages of children in the LD, ED, and OHI categories in various special education environments are depicted in table 4. Current cost estimates are available only for special classes or schools (combined) and regular classes or resource rooms (combined); therefore, the percentages in table 4 had to be collapsed into two types of settings, regular/resource and segregated (Chaikind, Danielson, Brauen, 1993). For such estimates, numbers of children with ADHD in the OHI category also had to be added to numbers of children in the LD category, since OHI is merely a category of convenience and thus more likely to contain children with mild cases of ADHD similar to children in the LD category.

Table 4. Percentage of children in LD, ED, or OHI categories in various special education environments

Category	Regular Classrooms With Special Education Support	Resource Rooms	Special Classes	Special Schools
LD	41.1	39.6	18.4	0.9
ED	22.0	24.0	35.2	18.7
OHI	42.6	28.9	18.5	10.0

Source: Annual Report to Congress on IDEA, Volume 19 (1997).

These estimates of children with ADHD in the combined LD/OHI categories and in the ED category (taken from table 3) are depicted in table 5, according to their numbers in each special education environment (derived from combined proportions in table 4). The per pupil costs for children in regular or resource room environments and segregated special classes or schools are also provided in table 5 and used to compute approximate costs for children with ADHD. Note that 3.2 billion dollars are currently spent on schooling of children with ADHD, with about 44 percent of that amount spent on the 26 percent of children with ADHD in segregated settings.

Table 5. Costs for children with ADHD in categories by setting

Category	Estimated Number	Estimated Per Pupil Costs ($)	Total Costs ($)
LD-OHI (Combined)			
Regular/resource	587,531	2,511	1,475,290,341
Segregated	140,512	4,712	662,092,544
ED			
Regular/resource	86,666	4,006	347,183,996
Segregated	101,738	7,446	757,541,148
Total	916,447		3,242,108,029

Educating Children With ADHD in General or Special Education

Although various instructional or behavioral methods are used with children who have ADHD, these are not necessarily different from approaches used with a wide variety of children with other behavioral or learning disorders. Recent meta-analysis of available research on these techniques reveals only 63 studies to date, of which more than 60 percent were single-subject designs with limited generalizability (DuPaul, Eckert, 1997). Effect sizes were .45 for 8 studies with control groups and .64 for 17 studies with only pretesting and posttesting on the same sample. These effect sizes suggest moderate to good outcomes. Effect sizes for techniques used in special education were 1.29 compared with .49 when used in general education.

Mainstreaming of children in special education at least part-time into general education classrooms has more recently begun to give way to full inclusion, an approach in which children with disabilities are placed full-time in general education, sometimes with minimal or no special education support. Despite controversy about full inclusion, many children with ADHD may be subject to this approach, even if they qualify for special education. As noted above, more than half of all children with ADHD may not even qualify for special education and thus remain in inclusive settings with either minimal 504 accommodations or no recognition or assistance whatsoever. Rank order of approaches favored by teachers in general versus special education for children with ADHD are depicted in table 6. Teachers in general education reported using only their first-ranked intervention (changing seating) more than 40 percent of the time, whereas teachers in special education reported using all but their last two interventions from 44 to 72 percent of the time (Reid, Maag, Vasa, Wright, 1994).

Table 6. Rank order of reported use of selected interventions for ADHD by teachers in general versus special education settings

Intervention	General Education	Special Education
Changing seating	1	5
Behavior modification	2	1
Timeout	3	4
Shortened assignments	4	7
One-to-one instruction	5	3
Special consultation	6	2
Peer tutoring	7	9
Frequent breaks	8	8
Assignment format	9	6

Note: Developed from data reported in Reid et al. (1994).

Conclusion

Since so little is known about the current status of children with ADHD in school, there needs to be expansion of the data base on numbers and types of children with ADHD in various special education categories and classroom environments, further study on use and effectiveness of classroom interventions, and additional training of both general and special education teachers on early detection and classroom implications of ADHD.

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The Impact of Attention Deficit Hyperactivity Disorder on the Juvenile Justice System

Betty Chemers, M.A.

Since 1995 the Office of Juvenile Justice and Delinquency Prevention has identified juvenile mental health issues as a priority for both research and program support. With increasing numbers of juveniles entering the juvenile justice system, there is great interest not only in expanding what is known about the specific behaviors or circumstances that bring youth to the attention of the juvenile justice system but also in understanding the underlying problems, including mental health disorders and substance abuse. As a partner with NIMH and NIDA, we are pleased that we have had the opportunity to support the research on attention deficit hyperactivity disorder (ADHD) and look forward to increased collaboration in the future.

Trends in Juvenile Offending

To assess the impact of ADHD on the juvenile justice system, it is useful to look at an updated picture of juvenile crime trends and their impact on juvenile justice agencies.

For many Americans, juvenile crime and violence are the most important issues facing our Nation today. From 1986 until 1994 crimes by juveniles increased at an alarming rate. In 1995 this trend stopped, and in 1996, for the second consecutive year, the number of juvenile arrests for violent crime index offenses—murder, forcible rape, robbery, and aggravated assault—declined (Snyder, 1997). This increase is reflected in the workload of the juvenile courts, which experienced an increase of 45 percent in the number of delinquency cases between 1986 and 1995 (Stahl, 1998). The increase in juvenile offending was also reflected in the increased number of juveniles held in detention, correctional, or shelter facilities. On February 15, 1995, the most recent date for which a count is available, more than 108,700 juveniles were in detention. For public facilities, this figure represents almost a doubling of the number of juveniles held from the period (1983) predating the great increase in juvenile arrests (Snyder, Sickmund, Poe-Yamagata, 1997).

Prevalence of Mental Health Disorders, ADHD, and Conduct Disorders Among Youth in the Juvenile Justice System

In his landmark report, Cocozza (1992) concluded from a review of prevalence studies that although it was not possible to offer an exact prevalence rate of mental health disorders for youth in the juvenile justice system, it was clear that the prevalence rate was substantially higher than in the general population. Although the estimates ranged as high as 22 percent, it was likely that the prevalence rate for youth in the juvenile justice system was higher. Although information on the specific types of conduct disorder was lacking, Cocozza offered a safe

estimate that at least 20 percent and perhaps as many as 60 percent of the youth in the juvenile justice system had conduct disorders.

Because conduct disorder is currently considered one of a trio of related diagnoses that also includes ADHD and oppositional defiance disorder (ODD), known collectively as disruptive behavior disorders, many studies do not identify the specific prevalence of ADHD. For those that do, the rates vary widely. In a recent literature review of 11 studies conducted from 1980 to 1997, Teplin (1998) looked at the prevalence of alcohol, drug, and mental health (ADM) disorders in nonreferred juvenile detainees. Prevalence rates of ADHD ranged from a low of 2 percent to a high of 76 percent.

Two States that have conducted recent statewide assessments of the mental health needs of juvenile detainees are Ohio and Virginia. Virginia authorities identified 8 percent to 10 percent of their youth in secure detention homes as having serious mental problems requiring immediate attention and an additional 39 percent of youth as having mental health problems requiring mental health services but not requiring immediate intervention. Attention problems, possibly ADHD as tested by Achenbach, were found in 6.9 percent of the youth detention population (Virginia Policy Design Team, 1994).

In a series of recent studies from 1994 to 1996 conducted in Ohio by the Department of Psychiatry at Case Western Reserve University School of Medicine, mental health needs of incarcerated male and female juveniles were assessed and compared with a 1988 study. In the earlier study (Davis, Bean, Schumacher, et al., 1991), 29 percent of the males exhibited serious mental disorders. In the later study (Timmons-Mitchell, Brown, Schulz, et al., 1997), males continued to exhibit high rates of mental illness (27 percent), whereas females exhibited an overwhelming presence of mental illness estimated to be about 84 percent. Conduct disorder was the mental health diagnosis for 100 percent of the males and 96 percent of the females. Attention deficit was identified as present in 76 percent of the males and 68 percent of the females (Underwood, 1997).

Although exact prevalence rates may vary, analyses show a consistently elevated rate of criminal behavior among children with hyperactivity/inattention (particularly if aggression is present) and other disruptive disorders. And this relationship appears to be consistent with later violent behavior. Unfortunately, the relationship is not well understood. Evidence from a wide range of studies consistently reveals a positive relationship between hyperactivity, concentration or attention problems, impulsivity and risk-taking, and later violent behavior (Loeber, Farrington, 1998).

Clearly, the juvenile justice system has a great interest in ADHD and conduct disorders, taken both individually and together. Both are significant risk factors for the development of less serious antisocial behavior as well as more violent behavior. Furthermore, there is evidence that the comorbidity is associated with more arrests and more antisocial behavior, which start at a younger age, than with conduct disorder alone. The comorbidity of the two disorders seems to combine the worst features of both (Foley, Carlton, Howell, 1996).

Juvenile Justice System Response

In the same way that we are beginning to get a sense of the magnitude of the problem, we are at the threshold of understanding what is required to address the needs of youth with ADHD and conduct disorder. We do know that these youth exert great stress on the system. Some of the stress is caused by the sheer numbers and the fact that early onset of ADHD and conduct disorders seems particularly resistant to treatment (Foley, Carlton, Howell, 1996). The most promising approaches incorporate multiple components with documented efficacy at the individual, family, and peer levels (Wasserman, Miller, 1998), but unfortunately the restrictive nature of the juvenile justice system, detention in particular, may not lend itself to a multisystemic approach to treatment. Although these youth and their families may have had multiple contacts with the juvenile justice, child welfare, and mental health service systems, these systems are just beginning to form systems of care, to share information, and to employ treatments established in one discipline for use in others. Reactive approaches rather than proactive approaches are the norm. Sanctions are more dominant than either treatment or prevention efforts.

Some important strides have been made to improve the delivery of mental health services to youth in the juvenile justice system. Notable is the Cook County Clinical Evaluation and Services Initiative (CESI), a joint project of Northwestern University School of Law, the University of Chicago, and the Juvenile Court of Cook County in Illinois, which is aimed at a comprehensive redesign of the Department of Clinical Services and a correlating reform of the use and acquisition of information obtained from the provision of clinical services by the juvenile court judges (Dohrn, Leventhal, 1997). As described earlier, Virginia and Ohio are among several States seriously committed to expansion of mental health services.

Increasing attention has also been focused on new organizational structures (community assessment centers) to better assess the needs of juveniles and on new assessment instruments (Massachusetts youth screening instrument).

An important strategy employed by the juvenile justice field focuses on youth at highest risk. One group at highest risk comprises very young juvenile offenders. Efforts are under way to use current knowledge about risk factors and the developmental course of young, serious, violent juvenile offenders to identify appropriate intervention strategies. Early diagnosis and treatment of ADHD and conduct disorders are an important key to preventing future delinquency.

Research Needs

There are numerous significant gaps in our knowledge about youth with ADHD and conduct disorders in the general population and in the juvenile justice system in particular. First, there is a need to identify youth with mental illness and identify appropriate treatment. As indicated, the juvenile justice system is not well equipped to handle juveniles with mental health disorders. Effective models for screening, diverting, and treating offenders and establishing comprehensive community-based systems of care are needed. Many disorders, including the less severe or pervasive ones, have the potential to be linked with a particular youth's involvement

with the juvenile justice system. Ways must be found to treat youth whose mental disorders may not be linked to their delinquent behavior while in the juvenile justice system (Cocozza, 1992).

Second, research is needed on prevalence of ADHD and conduct disorders in females. Increasingly, more girls are coming into the juvenile justice system charged with more serious crimes. There is preliminary evidence in at least three studies that we are seeing a higher incidence of ADHD and conduct disorders among female youth detainees. A majority of girls in the juvenile justice system have been physically abused and/or sexually assaulted, and this needs to be considered in the assessment and screening process as well as in programming and protocols.

Third, increased research on predictors of adolescent antisocial behavior is needed. Most serious violent offenders have a history of earlier childhood misbehavior. Research on the specific risk factors for these behaviors may yield important knowledge that can be used to prevent violent offending. Wasserman and Miller (1998) suggest that if a diagnosis of ADHD is a risk factor for a later conduct disorder, then ameliorating the symptoms of ADHD may decrease the chances of subsequent conduct disorder and violent offending.

Fourth, research is needed on mental disorders among youth of color and their representation in services. Little has been written or researched on this subject since the Cocozza report (1992), which summarizes Isaacs and Benjamin's analysis of the mental health needs of children and adolescents of color. Her observation that few researchers have explored systematically the reasons for or consequences of youth of color being overrepresented in the American juvenile justice system while also being underserved and inappropriately served by the child mental health system appears to still hold true 6 years later.

Finally, noting that one of this author's assigned issues for this paper was the estimated costs to society of conduct problems and services to ADHD children in the juvenile justice system and having been unable to come up with valid estimated costs, I respectfully propose this as a topic worthy of future attention by researchers.

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Impairment: Childhood and Adolescence

Stephen P. Hinshaw, Ph.D.

The symptom criteria for attention deficit hyperactivity disorder (ADHD) reflect developmentally extreme problems in focusing attention, controlling impulses, and refraining from extraneous motor activity (American Psychiatric Association, 1994). When careful diagnosis is made on the basis of pervasive and persistent difficulties in these problem areas, ADHD in childhood and adolescence is associated with marked impairment in key domains of functioning that are essential for optimal development: family relationships, peer status and social skills, academic achievement, self-esteem/self-perception, and accidental injury. I review these domains in turn and then comment on methodologic issues that influence documentation of such impairment. The chief conclusion from this review is that the impairments related to ADHD are severe, pervasive, and often debilitating, reflecting the clinical importance and public health significance of this disorder.

Family Relationships

The impact of raising a child with dysregulated attention, behavior, and self-control is noteworthy. Families of children with ADHD have higher levels of marital discord, suboptimal parenting practices, and parenting distress than do comparison families (Donenberg, Baker, 1994). In turn, the ensuing, negative parent-child interactions predict (a) persistence of ADHD-related symptomatology, (b) higher levels of noncompliant/disruptive behavior, and (c) peer disapproval (Anderson, Hinshaw, Simmel, 1994; Campbell, Pierce, Moore et al., 1996; Hinshaw, Zupan, Simmel, et al., 1997). Although debate has centered on the directionality of these effects—from parent to child versus child to parent—bidirectional and transactional models are needed for full explanation. That is, young children with difficult temperaments and early signs of ADHD tend to elicit discordant child-rearing practices that serve to exacerbate the child's behavioral tendencies (Hinshaw, in press). No evidence, however, exists that children with ADHD (unaccompanied by aggressive features) have lower levels of insecure attachments to caregivers than do comparison children, whereas aggressive-ADHD children have high rates of insecure attachment.

Peer Status and Social Skills

Perhaps the most devastating impact of ADHD is reflected in the strong tendency for children with this disorder to be rejected by their peers. Specifically, children with ADHD receive negative sociometric ratings and nominations from age-mates at extremely high levels (Hinshaw, Melnick, 1995). Such peer disapproval emanates from the intrusive behavioral styles, lack of reciprocation, and aggressive tendencies of children with ADHD. In fact, the comorbidity of ADHD with aggression incurs particularly severe peer disapproval (Hinshaw, Melnick, 1995;

Milich, Landau, 1989). Given that (a) peer rejection in childhood is a robust predictor of such negative long-term outcomes as school dropout, delinquency, and adult mental health problems (Parker, Asher, 1987) and that (b) such predictions hold even when initial levels of problem behavior are controlled (Greene, Biederman, Faraone, et al., 1997), the peer rejection of youth with ADHD is clinically and prognostically of the utmost importance. Recent evidence also points to the specific difficulties experienced by children with ADHD in making and keeping friends (Blachman, Hinshaw, unpublished data). These social difficulties do not appear to be related specifically to deficits in social knowledge or social skill; rather, children with ADHD have marked problems with the performance of appropriate social behavior (Whalen, Henker, 1992).

Academic Achievement

Children with ADHD also have noteworthy problems in terms of academic attainment and school-related functioning. Such problems are salient not only for the approximately 15 percent of ADHD children who have comorbid learning disabilities, but also for nearly all other ADHD youth, for whom behavioral disruption and poorly focused attention compromise optimal classroom behavior and learning (Hinshaw, 1992). In fact, the vast majority of children and adolescents with ADHD are not working up to their potential with respect to school grades and specific measures of academic achievement. By adolescence, poor organizational and study skills are extremely salient. Another indicator of academic impairment is that children with ADHD are overrepresented in special education settings. Given the clear importance of academic achievement for success in later life, the academic impairments that pertain to ADHD are of marked clinical significance.

Self-esteem/Self-perception

Far fewer investigations have been conducted on the self-esteem of children with ADHD, an area plagued by measurement and instrumentation problems. Some studies reveal that, as a group, children and adolescents with ADHD have lower self-perceptions and self-esteem than do comparison children (Treuting, Hinshaw, 1998). Such self-esteem deficits predict poorer social and occupational adjustment in adulthood (Slomkowski, Klein, Mannuzza, 1995). It is important to note that recent research has suggested that some children with ADHD may have self-perceptions and expectations that are actually inflated over levels displayed by comparison children (Diener, Milich, 1997). In other words, ADHD youth may approach tasks with exaggerated levels of confidence, perhaps as a compensation for skill deficits. This domain of impairment bears closer scrutiny.

Accidental Injury

The small amount of relevant research suggests strongly that children with ADHD experience higher rates of accidental injuries than do comparison children (Lahey, Pelham, Stein, et al., 1998; Matheny, Fisher, 1984). Since such accidental injuries may be a significant

contributor to head trauma or other debilitating conditions, this area of impairment is of clear significance. Cormorbidity with aggressive behavior patterns is a related risk for accidents.

Several methodologic points are important to consider in interpreting the above results.

a. Methodology and sampling: First, impairments are most pronounced in clinical samples, but impairment is also salient in unreferred epidemiologic samples. Second, current diagnostic criteria (e.g., DSM-IV) require significant impairment before an ADHD diagnosis can be made, leading to potential circularity (American Psychiatric Association, 1994). Crucially, however, several investigations have documented significant impairment in ADHD samples for whom impairment criteria were deleted from the diagnostic algorithm (Lahey, Applegate, McBurnett, et al., 1994). Third, it is important to document impairment either with objective measures or by informants who do not supply the symptoms used to make diagnosis. ADHD-related impairment has, in fact, been demonstrated by such means (Lahey, Applegate, McBurnett, et al., 1994; Lahey, Pelham, Stein, et al., 1998).

b. ADHD subtypes: All three DSM-IV subtypes (Inattentive, Hyperactive-impulsive, and Combined) have been shown to display clear impairment (Lahey, Applegate, McBurnett, 1994; Lahey, Pelham, Stein, et al., 1998). In addition, evidence exists that the Hyperactive-impulsive and Combined types are particularly likely to receive active peer rejection compared with the Inattentive type (Wheeler, Carlson, 1994), but the latter subtype may have more difficulties in the domain of academic achievement. (Evidence for this latter contention is mixed; see Lahey, Applegate, McBurnett, et al., 1994.)

c. Comorbidity: Some investigations have found that ADHD-related impairment is attributable specifically to comorbid conditions (oppositional-defiant or conduct disorder, anxiety disorders or depression, learning disabilities) rather than to ADHD per se (Paternite, Loney, Roberts, 1996). Recent, careful research, however, demonstrates that ADHD is related to clear impairment even with statistical control of comorbid symptoms or diagnoses (Lahey, Pelham, Stein, et al., 1998). For example, nonaggressive children with ADHD are still rejected by peers (but aggressive ADHD children are even more rejected [Hinshaw, Melnick, 1995]); furthermore, young children with ADHD display social and academic impairments with careful statistical control of oppositional-defiant, conduct-disordered, and internalizing symptomatology (Lahey, Pelham, Stein, et al., 1998).

d. Developmental issues: More research is needed to document the types of impairment in adolescents with ADHD, particularly when comorbid diagnoses are controlled.

Overall, ADHD is a condition that, in childhood and adolescence, is accompanied by clear impairments in domains of functioning that are essential for optimal development. Any accounting of the impact of ADHD must recognize the familial, peer-related, academic, and self-esteem-related impairments that frequently accompany the disorder, as well as its risk for accidental injury.

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The Impact of Attention Deficit Hyperactivity Disorder on Social and Vocational Functioning in Adults

Charlotte Johnston, Ph.D.

This paper addresses the impairments associated with attention deficit hyperactivity disorder (ADHD) in adulthood, with an emphasis on functioning in social and occupational roles. In the first section, general issues in the study of ADHD in adulthood are considered, and a framework for the evaluation of the available literature is provided. The middle portions of the paper review data from both prospective and retrospective studies of functioning in adults with ADHD. Case studies and clinical descriptions are used to supplement areas where the empirical literature is sparse. The strengths, weaknesses, and comparability of the designs and methodologies of the various studies will also be considered. The paper concludes with recommendations for future research.

In the past 10 years, the persistence of ADHD into adulthood has been increasingly recognized (Wender, 1997). Although not entirely resolved, advances have been made in developing criteria for reliable and valid diagnosis of the condition in adulthood (Kane, Mikalac, Benjamin, et al., 1990; Ward, Wender, Reimherr, 1993). Beyond issues of identification of the disorder, most studies of the impact of ADHD in adulthood have examined the prevalence of the disorder, its psychiatric comorbidities, and the use of medication for its treatment. The impact of ADHD on adult academic and occupational outcomes and functioning in interpersonal areas is less well studied. However, several sources of data offer insight and converge to suggest that the profile of interpersonal and academic/vocational problems associated with the disorder is similar across the lifespan.

One source of data regarding the impact of ADHD on social and occupational functioning in adults comes from prospective studies that have followed children diagnosed with ADHD into adulthood. For example, Weiss and Hechtman (1993) conducted 5-, 10-, and 15-year followups of children diagnosed with ADHD. Data gathered when participants were 25 years of age indicated that, compared with controls, the young adults in the ADHD group had completed less education, were rated by their employers as having more work-related difficulties (e.g., trouble completing tasks), had more often quit or been laid off from their employment, and held lower status jobs. In addition, the adults in the ADHD group had more social skills difficulties (e.g., as assessed in simulated job interviews or heterosexual interactions). Mannuzza and colleagues (1997) have also provided prospective data on the outcome of children diagnosed with ADHD and confirm the findings of less schooling and lower occupational ranks for these children as young adults compared with controls. This impact on vocational functioning has significant legal and societal ramifications. For example, a recent survey of calls to an international toll-free consulting service that provides information on job accommodations indicated that between 1993 and 1995, there was a 407 percent increase in calls related to the impact of ADHD on adult work performance (Means, Stewart, Dowler, 1997).

Other information concerning the impact of ADHD in adulthood comes from studies of adults who are usually self-referred to mental health centers and have been diagnosed with ADHD on the basis of current functioning and retrospective accounts of childhood behavior. As in the prospective studies, educational and occupational functioning is noted to be impaired in adults with ADHD compared with controls (Barkley, Murphy, Kwasnik, 1996; Roy-Byrne, Scheele, Brinkley, et al., 1997). Studies using samples of adults with ADHD diagnosed retrospectively have also found elevated rates of divorce, separation, and marital dissatisfaction compared with controls (Biederman, Faraone, Spencer, et al., 1993; Murphy, Barkley, 1996). The few reports of the impact of ADHD on parenting indicate impairment in child-rearing strategies, parent-child relationships, and couples' co-parenting (e.g., Arnold, O'Leary, Edwards, 1997; Evans, Vallano, Pelham, 1994).

The impact of ADHD in adulthood can also be discerned from reports of elevated rates of the disorder among adults suffering from problems such as gambling, depression, and alcoholism. Finally, genetic and familial transmission studies reveal that many parents of children with ADHD also suffer from the disorder; therefore, characteristics of these parents will be reviewed briefly.

Regarding recommendations for the future, an argument is made for more extensive and well-controlled research into the social and occupational impact of ADHD in adulthood. Specific recommendations include the need for a consensus regarding adult diagnostic criteria, resolution of the existing discrepancies in characteristics of childhood-identified samples versus samples identified in adulthood, greater consideration of the impact of comorbidities, and extension of research beyond young adulthood and beyond samples of predominantly white middle-class males.

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Stimulant Medications

Laurence L. Greenhill, M.D.

The most commonly prescribed medication treatments for attention deficit hyperactivity disorder (ADHD) are the psychostimulants, including methylphenidate (Ritalin), amphetamine (Dexedrine and Adderall), and pemoline (Cylert). Prescribing patterns suggest that stimulants are a mainstay of treatment for ADHD children. Outpatient visits devoted to ADHD increased from 1.6 to 4.2 million per year during the years 1990 to 1993 (Swanson, Lerner, Williams, 1995). During those visits, 90 percent of the children were given prescriptions, 71 percent of which were for the stimulant methylphenidate (MPH). MPH production in the United States increased from 1,784 kg to 5,110 kg during the same time period, so that over 10 million prescriptions for MPH were written in 1996 (Vitiello, Burke, in press), and epidemiological surveys have estimated that U.S. school-age children's 12-month stimulant prescription prevalence ranges from 6 percent urban (Safer, Zito, Fine, 1996) to 7 percent rural (Angold, Costello, 1997).

Psychostimulant use has increased over the past 12 years, and this has raised concerns at the U.S. Drug Enforcement Administration (DEA)—which regulates their production—about the risk of abuse and diversion. Production of MPH has tripled over a 10-year period, and 90 percent of U.S.-produced MPH is used in this country.

Increased MPH use could mean increases in ADHD prevalence, a change in the ADHD diagnosis, improved recognition of ADHD by physicians, broadened indications for use, or an increase in drug diversion and prescription for profit or abuse (Goldman, Genel, Bezman, et al., 1998). Analyses of managed care datasets reveals a 2.5-fold increase in prescribing in the 1990 to 1995 time period, accounted for by longer durations of treatment, inclusion of girls and those with predominantly inattentive symptoms, and treatment of high school students (Safer, Zito, Fine, 1996). Estimates suggest that 2.8 percent of U.S. youth between the ages of 5 and 18 years were taking the medication in 1995 (Goldman, Genel, Bezman, et al., 1998).

Although the abuse liability of MPH and other stimulants has been established in animal research, the evidence that MPH's ability to generate euphoria and lead to abuse is less clear. National surveys indicate that snorting ground-up MPH tablets does occur among high school seniors, although it occurs far less frequently than marijuana or cocaine use (Loney, Milich, 1982); however, the lifetime nonmedical use has remained constant at 1 percent for years (Goldman, Genel, Bezman, et al., 1998). Analyses of annual school surveys of drug use and the Drug Abuse Warning network data on emergency room visit monitoring have not suggested growing abuse of MPH (Goldman, Genel, Bezman, et al., 1998).

A delay in setting production quotas, coupled with the increase in stimulant prescribing in the United States, led to shortages in 1993. Parent support groups then filed a petition to

declassify MPH (Horn, Parker, Evans, et al., 1994). Although this failed, procedures for final quota notice approval were improved (Goldman, Genel, Bezman, et al., 1998).

Epidemiologically based surveys that include child diagnoses and treatment services have been used to evaluate whether stimulant drugs are overused or misused in the United States. One survey in four different communities found only one-eighth of children with diagnosed ADHD received adequate stimulant treatment (Jensen, Kettle, Roper, et al., 1998), while another survey in rural North Carolina found that many school-age children on stimulants did not meet criteria for ADHD (Angold, Costello, 1997).

Pharmacology

The psychostimulants in clinical use for treatment of children with ADHD have putative effects on central norepinephrine (NE) pathways (Pliszka, McCracken, Maas, 1996). Their action may enhance the functioning of executive control processes, overcoming the deficits in inhibitory control and working memory reported in children with ADHD (Douglas, Barr, Amin, et al., 1988). These effects are brief because of the rapid absorption and metabolism of these drugs (Patrick, Mueller, Gualtieri, et al., 1987) and do not continue after the stimulant has been stopped. The pharmacodynamic (PD) effects of the immediate-release (IR) formulations of MPH, Dexedrine, and Adderall appear within 30 minutes, reach a peak within 1 to 3 hours, and are gone in 5 hours (Swanson, Wigal, Greenhill, et al., 1998), making in-school dosing a necessity, despite the resulting problems of peer ridicule and added adult supervision requirements. Sustained-release formations of MPH, Dexedrine, and pemoline have been shown to have effects on attention up to 9 hours after dosing (Pelham, Greenslade, Vodde-Hamilton, et al., 1990). However, clinicians have not found that these drugs successfully cover the entire school day with only one morning administration. In addition, hepatoxicity has been reported for children chronically treated with pemoline (Berkovitch, Pope, Phillips, et al., 1995; Wroblewski, Leary, Phelan, et al., 1992).

Short-Term Efficacy

Over 170 controlled studies involving more than 6,000 school-age children—all but 22 lasting no more than 12 weeks (Schachar, Tannock, 1993)—have demonstrated that 70 percent respond when a single stimulant is tried (Spencer, Biederman, Wilens, et al., 1996). Compared with placebo in short-term, double-blind trials, stimulants demonstrate robust efficacy in improving both ADHD symptoms and associated conditions (Spencer, Biederman, Wilens, et al., 1996; Greenhill, 1998; Jacobvitz, Sroufe, Stewart, et al., 1990; Swanson, 1993). Effect sizes in short-term trials range from 0.8 to 1.0 standard deviations on teacher reports (Thurber, Walker, 1983; Elia, Borcherding, Rapoport, et al., 1991) for both methylphenidate and dextro-amphetamine. The beneficial effects of stimulants on behavior and attention reported for children with ADHD also have been shown for children with other disorders and with normals (Rapoport, Buchsbaum, Weingartner, et al., 1980), so their clinical actions are neither "paradoxical" nor specific for ADHD. Clinicians should not use a positive response to stimulants to diagnose ADHD in children. Stimulant medications continue to play a therapeutic

role in other medical conditions, such as narcolepsy and depression (Goldman, Genel, Bezman, et al., 1998).

Stimulant medications ameliorate disruptive ADHD behaviors cross-situationally (classroom, lunchroom, playground, and home) when repeatedly administered throughout the day in short-term trials. In the classroom, stimulants decrease interrupting, fidgetiness, and finger tapping; increase on-task behavior (Abikoff, Gittelman, 1985); and ameliorate peer nomination rankings (Whalen, Henker, Buhrmester, et al., 1989). On the playground, stimulants reduce overt aggression (Gadow, Nolan, Sverd, et al., 1990), covert aggression (Hinshaw, Heller, McHale, 1992), and signs of conduct disorder (Klein, Abikoff, Klass, et al., 1997) and increase attention during baseball (Richters, Arnold, Abikoff, et al., 1995). At home, stimulants improve parent-child interactions and compliance (Barkley, 1989). Stimulants decrease response variability and impulsive responding on cognitive tasks, increase the accuracy of performance, and improve short-term memory, reaction time, seatwork computation, problem-solving games with peers, and sustained attention. Studies of time-action stimulant effects show a different pattern of improvement for behavioral and attentional symptoms, with behavior affected more than attention (Swanson, Wigal, Greenhill, et al., 1998). While stimulant drugs show a large 0.8 to 1.0 effect size for behavioral measures, smaller 0.6 to 0.8 effect sizes are reported on cognitive measures (Spencer, Biederman, Wilens, et al., 1996).

Although there is a large database of controlled stimulant medication studies attesting to the overall efficacy and safety of these medications in children with ADHD, most data are group-based and do not inform the clinician about fine points of management for the individual patient (Greenhill, Abikoff, Conners, et al., 1996). Questions remain unanswered about the best dose to initiate treatment in young children; how to identify the optimal stimulant drug for preschoolers; how to determine whether twice-daily or three-times-daily dosing is best; how to choose to increase, decrease, or keep the stimulant dose the same throughout the day; and whether to stop stimulants at the first sign of a motor tic.

Multimodal therapy, which combines stimulant medication therapies with parent training, educational, or school-based interventions (Horn, Ialongo, Pascoe, et al., 1991), has not been shown in recent studies (Schachar, 1998; Abikoff, Hechtman, 1998; Jensen, Arnold, Cantwell, et al., 1998) to be superior to medication, despite the assertions of its superiority in the majority of review articles (Richters, Arnold, Abikoff, et al., 1995).

Limitations of Published Studies of Stimulants for Children With ADHD

Despite the large number of published stimulant trials in school-age children, many issues remain unanswered. The majority of controlled trials of stimulants in ADHD have been run for less than 3 months (Schachar, Tannock, 1993), so the risk-benefit ratio of stimulants during chronic, maintenance treatment is largely unknown. Clinicians are unable to predict response from patient characteristics (Buitelaar, Gary, Swaab-Barneveld, et al., 1995); stimulant effects vary by domain (Pelham, Milich, 1991); there is a lack of consistent therapeutic effects across the IQ range (Aman, Marks, Turbott, et al., 1991); there are variable effects of other comorbid Axis I disorders on stimulant response (Pliszka, 1992); there is no widely accepted method for

managing short, time-action effects of stimulants with rapid changes during the school day (Swanson, Kinsbourne, Roberts, et al., 1978); the hepatoxicity of pemoline (Berkovitch, Pope, Phillips, et al., 1995) limits its use as a first-line treatment; and many parents are concerned about the potential abuse liability of psychostimulants. Most studies do not individually titrate medication doses to optimize each child's response. Similarly, most published studies rely on averaged group data to evaluate medication effects, possibly missing important subgroup differences in treatment response.

Long-Term Treatment Effects of Stimulant Medications

Although short-duration stimulant studies have shown robust efficacy, this has not been true for studies lasting longer than 3 months (McBride, Anderson, Hertzig, et al., 1989). Multiyear followup studies conducted in the 1970s failed to show the persistence of benefits in academic or social areas for children who stayed on stimulants. However, they were severely constrained by their retrospective methods and lack of nonstandard outcome measures or the monitoring of compliance with pill-taking (Schachar, Tannock, 1993). Futhermore, treatment programs for chonic conditions have their own difficulties. One study using triplicate prescription records showed that Suffolk County physicians most often prescribed only one 30-day stimulant per year, even though ADHD problems are stable and chronic over years (Sherman, 1991).

More recently conducted, long-duration randomized clinical trials have shown the maintenance of stimulant medication effects over periods ranging from 12 months (Gillberg, Melander, von Knorring, et al., 1997) to 24 months (Abikoff, Hechtman, 1998). The NIMH Multimodal Treatment Study of Children With Attention Deficit Hyperactivity Disorder (MTA Study) was established to examine the effects of long-duration treatment in children randomly assigned to four different groups, including stimulants alone or stimulants in combination with psychosocial interventions (multimodal therapy). This study will also allow an evaluation of the moderating effect of baseline patient characteristics on stimulant treatment response. To have sufficient power to address these questions, it utilized a large sample size of 576 children with ADHD gathered at multiple performance sites (Richters, Arnold, Abikoff, et al., 1995; Arnold, Jensen, Richters, et al., 1997). Including the MTA Study, four stimulant medication randomized controlled trials have been completed that have lasted 12 months or longer (Schachar, 1998; Abikoff, Hechtman, 1998; Arnold, Jensen, Richters, et al., 1997). These are depicted in Table 1.

Table 1. Long-duration methylphenidate clinical trials in medication-only treatment arm: Within-subjects effects

Study	Med Group Number (Study Total)	Design	Duration (Months)	Compliance	Total mg Daily Dose (schedule)	Measure	Effect Size at Study End
Abikoff 1998	33 (103) in med only	Parallel RCT	24	Saliva Levels	33.7 (TID)	Teacher CTRS	2.7
Gillberg 1997	56 (62)	Double-blind Discontinuation RCT	15	N/A	17 (BID) Amphetamine	Teacher CTRS Hyperactivity	27–40 percent
Schachar 1998	24 (91) in med + self-help	Parallel RCT	12	Pill Counts	33.5 (BID)	Telephone Interview Probe	0.7
Jensen, Arnold 1998	133 (576) in med only	Parallel RCT	14	Saliva Levels; Pill Counts	38.7 (TID)	SNAP Teacher Hyperactivity	1.4

Collectively, these studies show a persistence of medication effects over time, in contrast with earlier reports. Within-subject effect sizes reported after 12 to 24 months of MPH treatment resembled those previously reported in short duration studies (Thurber, Walker, 1983; Elia, Borcherding, Rapoport, et al., 1991). Domain of greatest improvement differs among studies, with some (Gillberg, Melander, von Knorring, et al., 1997) showing greater effects at home and another (Schachar, 1998) showing greater effects at school. The total mean MPH daily doses reported by three long-duration studies ranged between 33 and 37.5 mg. The Dexedrine study reported a mean dose one-half of this level, agreeing with the general ratio of Dexedrine to MPH doses. Family-initiated treatment discontinuation was associated with persistent stimulant drug side effects or assignment to placebo treatment. Surprisingly, attrition from placebo assignment is slow, allowing ample time for standard 8-week efficacy trials to be conducted.

Stimulant Adverse Events

Adverse events in short-duration controlled stimulant studies of children with ADHD most often include insomnia, reduced appetite, stomachache, headache, and dizziness. They average 4 percent of those treated in short-term studies (Barkley, McMurray, Edelbrock, et al., 1990). A third, mid-afternoon dose of MPH added to the usual twice-daily regimen does not lead to additional sleep problems, although it may affect appetite (Meltzer, Arora, 1991). Staring, daydreaming, and irritability decrease with increasing stimulant dose. Children also develop motor tics while on stimulants, but it is not clear whether the medication caused the tics or unmasked an underlying condition. Other studies have shown inconsistent effects of stimulant medications on chronic tic disorder, such as Tourette's disorder (Castellanos, Giedd, Elia, et al., 1977). No consistent relationship has been found in short-term controlled studies between stimulant dose and the less frequently reported adverse events—behavioral rebound, motor tics, compulsive picking of nose or skin, emotional or cognitive constriction, and growth delays (Spencer, Biederman, Wilens, et al., 1996). One 12-month study reported a 15 percent incidence

of persistent and worsening side effects—over-focusing and affective symptoms—that eventually led to discontinuation of stimulants (Schachar, 1998), going against the popular notion that children adjust to adverse events of stimulant medications.

Long-Term Risks of Stimulant Use

Growth delays, particularly failure to attain weight at an expected rate during development (Gillberg, Melander, von Knorring, et al., 1997), have been cited as a possible long-term risk of stimulant treatment. These effects were thought to respond to short periods off drugs ("drug holidays") (Gittelman-Klein, Landa, Mattes, et al., 1988). However, prospective followup into adult life (Mannuzza, Klein, Bonagura, et al., 1991) has revealed no significant impairment of height attained among stimulant-treated children. A later single-observation, cross-sectional study of adolescents with ADHD suggested that untreated children with ADHD may show significantly slowed growth in early years, and later catch up, compared with nonaffected children (Spencer, Biederman, Harding, et al., 1996). In contrast, other long-term studies that incorporate pretreatment and multiple measures show a decrement in weight gain during stimulant treatment when MPH-treated children are compared with those on nondrug treatments (Schachar, 1998).

Hepatic tumors in rodents treated with high oral doses of 4 to 47 mg/kg of MPH (Dunnick, Hailey, 1995) have been reported. However, hepatic tumors are species-specific, and these MPH doses are far higher than ever used in treatment of children with ADHD. Furthermore, hepatic tumors have not been reported in children with ADHD treated with MPH and are exceedingly rare in preschool and school-age children. Other studies show hepatic damage in mice from high MPH doses, particularly when given with B-adrenergic agonist drugs (Roberts, Harbison, Roth, et al., 1994). Altered liver function tests and fulminant hepatoxicity were reported in 44 children treated with pemoline (Berkovitch, Pope, Phillips, 1995), which is 4 to 17 times the expected rate, leading to a warning placed in the drug's package insert.

Summary

The percentage of U.S. youth being treated with psychostimulants is well within the estimates of the prevalence of ADHD, which suggests that the increases in MPH prescribing do not represent overuse or diversion of stimulant medication. A recent AMA Council report concluded that more cases are being recognized and treated and the duration of treatment with stimulants is increasing (Goldman, Genel, Bezman, et al., 1998). Other surveys suggest that ADHD is being misdiagnosed at times, perhaps because the evaluation is not long enough or thorough enough or does not follow recently published guidelines (Dulcan, 1997). The safety, dosing, and efficacy of stimulant medication has been extensively studied across the lifespan (Spencer, Biederman, Wilens, et al., 1996). Stimulant medication provides short-term behavioral and academic improvement for symptoms of ADHD, but children must remain on stimulants long term to maintain these benefits. The risk-benefit of stimulant treatment in ADHD has been determined to be highly favorable (Goldman, Genel, Bezman, et al., 1998) but must be monitored on a continuous basis over time.

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Pharmacotherapy of Attention Deficit Hyperactivity Disorder: Nonstimulant Treatments

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Although stimulants are the most established treatment for this disorder, as many as 30 percent of affected individuals do not respond to or may not tolerate such treatments (Wilens, Biederman, 1992). Moreover, multiple concerns about stimulants remain, including their short duration of action, necessitating multiple administrations during the day; insomnia, which precludes their use in the evening; concerns about their effect on growth and development; and medicolegal concerns. Although various alternative approaches have been proposed and evaluated, questions remain about their effectiveness, tolerability, and safety.

Tricyclic Antidepressants

After the stimulants, the tricyclic antidepressants (TCAs) are the most established agents in the treatment of ADHD. The beneficial effects of this class of drugs in ADHD are assumed to be secondary to their effect on noradrenergic neurotransmission. There have been 31 TCA studies (58 percent controlled) of more than 1,000 children, adolescents, and adults with ADHD. The vast majority of these studies (87 percent) reported substantial improvement in ADHD symptoms. However, as in the case of the stimulants, most studies were relatively brief and included primarily latency-age children. A number of recent studies have examined extended treatment for up to 2 years and noted sustained improvement (Biederman, Gastfriend, Jellinek, 1986; Gastfriend, Biederman, Jellinek, 1985; Wilens, Biederman, Geist, et al., 1993). Although some studies have touted the benefits of low-dose TCAs in the treatment of ADHD, only studies using aggressive doses of TCAs have reported sustained improvement for up to 1 year with desipramine (DMI) (>4 mg/kg) (Biederman, Gastfriend, Jellinek, 1986; Gastfriend, Biederman, Jellinek, 1985) and nortriptyline (2.0 mg/kg) (Wilens, Biederman, Geist, et al., 1993). Despite TCAs' potential benefit, concerns have been raised regarding their safety in children after several reports of sudden unexplained death in children treated with DMI (Abramawicz, 1990). Although a recent report estimated that the magnitude of DMI-associated risk of sudden death in children may not be much larger than the baseline risk of sudden death in this age group (Biederman, Thisted, Greenhill, et al., 1995), uncertainties regarding their safety persist. Thus, TCAs should be used as second-line treatment for ADHD and only after carefully weighing the risks and benefits of treating or not treating an affected child.

Bupropion

Bupropion hydrochloride is a novel-structured antidepressant of the aminoketone class related to the phenylisopropylamines but pharmacologically distinct from known antidepressants (Casat, Pleasants, Schroeder, et al., 1989). Bupropion appears to possess both indirect dopamine

agonist and noradrenergic effects. Bupropion has been shown to be effective for ADHD in children in a large, controlled multisite study (N = 72) (Casat, Pleasants, Schroeder, et al., 1989; Casat, Pleasants, Van Wyck Fleet, 1987; Conners, Casat, Gualtieri, et al., 1996) and in a comparison with methylphenidate (N = 15) (Barrickman, Perry, Allen, et al., 1995). In an open study of ADHD adults, sustained improvement was documented at 1 year (Wender, Reimherr, 1990). In that study, dosing for ADHD, an average of 360 mg of bupropion for 6 to 8 weeks, appeared to be similar to that recommended for depression. Bupropion has been associated with an increased risk for drug-induced seizures relative to other antidepressants. However, this risk has been linked to high doses, a previous history of seizures, and eating disorders.

Monoamine Oxidase Inhibitors

Although monoamine oxidase inhibitors (MAOIs) have been shown to be effective in the treatment of ADHD in a few small studies (Zametkin, Rapoport, Murphy, et al., 1985), because of potentially severe reactions resulting from dietetic restrictions and potential drug-drug interactions, their use is severely restricted in children. One MAOI, selegiline, has been successfully used in children with tic disorders (Jankovic, 1993). Preliminary evidence indicates that this agent at low doses may have fewer side effects than the other MAOIs. Major general limitations to the use of MAOIs are the dietetic restrictions of tyramine-containing foods (e.g., most cheeses), pressor amines (e.g., sympathomimetic substances), or drug interactions (e.g., most cold medicines, amphetamines) that can induce a hypertensive crisis or the serotonergic syndrome when MAOIs are combined with predominantly serotonergic drugs.

Serotonin Specific Reuptake Inhibitors

Although a small open study (Barrickman, Noyes, Kuperman, et al., 1991) suggested that fluoxetine may be beneficial in the treatment of children with ADHD, the available evidence does not support the usefulness of these compounds in the treatment of core ADHD symptoms (NIMH, 1996). Nevertheless, because of the high rates of comorbidity in ADHD, these compounds are frequently used to treat comorbid mood and anxiety disorders.

Venlafaxine

Venlafaxine is chemically unrelated to other antidepressants and has both noradrenergic and serotonergic activity. Four open studies of venlafaxine in adults with ADHD (N = 59) reported an overall response of 79 percent in completers with a 20-percent rate of dropout due to side effects (Adler, Resnick, Kunz, et al., 1995; Findling, Schwartz, Flannery, et al., 1996; Hornig-Rohan, Amsterdam, 1995; Reimherr, Hedges, Strong, et al., 1995). In addition, an open study of 16 children with ADHD reported a 50-percent response rate in completers with a 29-percent rate of dropout due to side effects, most prominently increased hyperactivity (Luh, Pliszka, Olvers, et al., 1996).

Antipsychotics

Although 12 controlled studies including 242 children and young adolescents reported on the efficacy of antipsychotics for ADHD, much of this literature is dated and confounded by diagnostic uncertainty. As reviewed by Klein (Gittelman, 1980), not more than 50 percent of ADHD subjects improve on antipsychotics. Eighty-three percent (N = 10/12 studies) of the available studies evaluated phenothiazines, and two evaluated haloperidol. Ten of the twelve studies were relatively brief, lasting 3 to 12 weeks. Daily dosage ranged widely from 0.25 to 1.75 mg/kg for the phenothiazines and 0.025 to 0.05 mg/kg for haloperidol. Considering the concerns about tardive dyskinesia, antipsychotics should not be part of the routine care of ADHD patients.

Adrenergic Agents

Clonidine is an alpha-2, noradrenergic agonist. Four pediatric studies (N = 2 controlled [Gunning, 1992; Hunt, Minderaa, Cohen, 1985], N = 1 open [Hunt, 1987], and N = 1 retrospective review [Steingard, Biederman, Spencer, et al., 1993]) reported beneficial effects of clonidine in the treatment of ADHD in children and adolescents (N = 122) with daily doses of up to 4 to 5 mg/kg (average, 0.2 mg/day). All studies reported positive behavioral response, with 50 to 70 percent of subjects having at least a moderate response but limited effects on cognition. There is one open study (N = 13) of the more selective alpha-2a agonist, guanfacine, in children and adolescents with ADHD. Beneficial effects on hyperactive behaviors and attentional abilities were reported (Hunt, Arnsten, Asbell, 1995). There has been a single small open study (N = 13) of the antihypertensive propranolol for adults with ADHD and temper outbursts. This study reported beneficial effects (85 percent improved) on ADHD symptoms at very high doses (average, 528 mg/day) over 9 weeks (Mattes, 1986).

Other Agents

One report (Greenhill, Rieder, Wender, et al., 1973) described a controlled, 3-month trial of lithium in the treatment of children (N = 9) with ADHD. However, these authors found that the children without comorbid affective disorders were unresponsive to lithium treatment. Other compounds found to be ineffective in the treatment of ADHD include antianxiety drugs (meprobamate and hydroxyzine) (Cytryn, Gilbert, Eisenberg, 1960); a sympathomimetic amine, fenfluramine (Donnelly, Rapoport, Potter, et al., 1989); dopamine agonists (amantidine and L-Dopa) (Gittelman-Klein, 1987); amino acid precursors (DL-phenylalanine and L-tyrosine) (Reimherr, Wender, Wood, et al., 1987); and caffeine (Firestone, Davey, Goodman, et al., 1978; Garfinkel, Webster, Sloman, 1975; Garfinkel, Webster, Sloman, 1981; Harvey, Marsh, 1978).

ADHD and Comorbid Disorders

Studies of antidepressants for children with ADHD and comorbid conduct disorder (N = 4 studies; N = 137 children) are few, but they indicate improvement of aggressive symptoms (Biederman, Baldessarini, Wright, et al., 1993; Simeon, Ferguson, Van Wyck Fleet,

1986; Wilens, Biederman, Geist, et al., 1993; Winsberg, Bialer, Kupietz, et al., 1972) (N = 4/4 studies) (N = 2/2 studies) (Simeon, Ferguson, Van Wyck Fleet, 1986; Winsberg, Bialer, Kupietz, et al., 1972). All four TCA studies of ADHD with comorbid anxiety or depression (N = 134 children and 32 adults; one controlled [Biederman, Baldessarini, Wright, et al., 1993], one open [Cox, 1982], and 2 retrospective reviews [Wilens, Biederman, Geist, et al., 1993; Wilens, Biederman, Mick, et al., 1995]) reported response of ADHD symptoms in comorbid subjects. In the two TCA studies that examined the effect of medication on comorbid depressive symptoms, TCAs decreased symptoms of depression in children with ADHD (Biederman, Baldessarini, Wright, et al., 1993; Garfinkel, Wender, Sloman, et al., 1983). Recent case reports and case series of the TCAs imipramine (Dillon, Salzman, Schulsinger, 1985), nortriptyline (Spencer, Biederman, Wilens, et al., 1993), and desipramine (Hoge, Biederman, 1986; Riddle, Hardin, Cho, et al., 1988; Spencer, Biederman, Kerman, et al., 1993) have reported a high rate (82 percent; 42/51 of subjects) of improvement of ADHD symptoms with no change or improvement of the tic disorder over an extended followup period (Spencer, Biederman, Kerman, et al., 1993; Spencer, Biederman, Wilens, et al., 1993). In a controlled study (N = 34), Singer and colleagues (1994) reported that desipramine was significantly better than both clonidine and placebo in its ability to improve ADHD symptoms associated with the full Tourette's syndrome. In this study, desipramine was tic neutral and clonidine did not improve tics. In an open study (N = 29) of a (selective) monoamine oxidase (B) inhibitor, deprenyl improved ADHD symptoms in 90 percent of children with ADHD and tics and was generally well tolerated. Last, a small case series described precipitation (N = 2) or exacerbation of tics (N = 2) in four children with comorbid ADHD treated with bupropion (Spencer, Biederman, Steingard, 1993). Although a retrospective study (N = 24) and an open study (N = 7) of clonidine (Steingard, Biederman, Spencer, et al., 1993) reported a high rate (96 percent) of response of ADHD symptoms in ADHD children and adolescents with comorbid tics, a controlled study (Singer, Brown, Quaskey, et al., 1994) found that clonidine was not better than placebo in its ability to improve ADHD symptoms associated with the full Tourette's syndrome. Finally, there is one open study (N = 10) of the more selective alpha-2a agonist, guanfacine, reporting beneficial effects on phonic tics and neuropsychological measures of attention and impulsivity (the continuous performance test) in children with ADHD and tics (Chappell, Schahill, Schultz, et al., 1994).

New Horizons

Several ongoing efforts are under way to evaluate new agents in ADHD. These include noradrenergic-specific compounds, nicotinic analogs, and cholinergic agents.

Summary

The armamentarium of anti-ADHD compounds includes not only the stimulants but also antidepressants with dopaminergic and noradrenergic activity, antipsychotics, and alpha-2 adrenergic drugs. However, concerns remain regarding the efficacy and safety of these alternative treatments. Active efforts are under way to identify new, effective, nonaddictive, and safe treatments for ADHD.

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Risks and Mechanism of Action of Stimulants

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Table 1 summarizes the adverse drug reactions caused by methylphenidate and amphetamine stimulant drugs. Table 2 provides estimated frequencies of these reactions and adds those to pemoline. Younger children are especially vulnerable to these harmful effects (Dulcan, Popper, 1991; Schleifer, Weiss, Cohen, et al., 1975).

Results of various studies are as follows.

CNS Adverse Effects in Double-Blind Placebo-Controlled Studies

Mayes and colleagues (1994) (partially controlled): 18.8 percent lethargy "variously described by raters as tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive"; 26.1 percent "irritability"; 7 percent severe adverse reactions including one manic-like reaction with "incessant talking," one "wild" and "out of control," and one "aggressive behavior."

Schachar and colleagues (1997): 10 percent of children dropped out because of adverse drug reactions, including serious behavioral aberrations, such as "sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior," "withdrawal and mild mania," and "withdrawal and dysphoria."

Barkley and colleagues (1990): the "percentage of children experiencing proneness to crying also increased by at least 10 percent during the low-dose condition" ($p<.05$) (p. 187); 3.6 percent were unable to complete the protocol because of serious adverse reactions including one with manic-like symptoms (p. 186).

Gillberg and colleagues (1997): three children developed hallucinations (4.8 percent).

These four controlled clinical trials found psychotic symptoms in at least 2 percent (6 of 260) and higher rates for other CNS effects.

Borcherding and colleagues (1990): "perseverative/compulsive behaviors" in 51 percent administered amphetamine and methylphenidate and one drop out "due to both the severity of the tic he developed during his initial treatment phase (dextroamphetamine) and exacerbated symptoms of separation anxiety." Solanto and Wender (1989): 42 percent of completers "overaroused"with "cognitive perseveration"(overfocused, obsessive/compulsive reaction). Castellanos and colleagues (1997): 25 percent of children (comorbid for ADHD and Tourette's) developed "largely transient" obsessive/compulsive behavior during a 3-week exposure to methylphenidate.

Table 1. Adverse effects caused by methylphenidate and amphetamines

Cardiovascular	Central Nervous System	Gastrointestinal	Endocrine/ Metabolic	Other	Withdrawal and Rebound
Palpitations	Psychosis with hallucinations (skin crawling or visions)	Anorexia	Pituitary dysfunction [including growth hormone and prolactin]	Blurred vision	Insomnia
Tachycardia	Excessive CNS stimulation [convulsions]	Nausea	Weight loss	Hypersensitivity reaction with rash, conjunctivitis, or hives	Evening crash
Hypertension [arrythmias] [cardiac arrest]	Insomnia (nightmares)	Vomiting	Growth suppression	Anemia‡	Depression
	Nervousness	Stomach pain, cramps	Growth retardation	Leukopenia‡	Overactivity and irritability
	Irritability	Dry mouth			Rebound ADHD symptoms
	Anxiety				
	Emotional oversensitivity, easy crying				
	Dysphoria (especially at higher doses)				
	Impaired cognitive test performance (especially at higher doses)				
	Dizziness				
	Headache				
	Attacks of Tourette's or other motor or vocal tic syndromes				
	Nervous habits (e.g., picking at skin, pulling hair)				
	Stereotyped activities or compulsions				
	Depression				
	Decreased social interest				
	Zombie-like constriction of affect and spontaneity*				
	Amphetamine look (pinched, somber expression)†				

Sources: Combination of Dulcan (1994, Table 35-6, p. 1217), Arnold and Jensen (1995, Table 38-5, p. 2306), and Drug Enforcement Administration (1995, p. 23). Any additional material indicated by brackets.

* "Zombie" references from Arnold and Jensen (1995, Table 38-5, p. 2306; Table 38-7, p. 2307; and column 2, p. 2307); Swanson, Cantwell, Lerner, et al. (1992, p. 15); Fialkov and Hasley (1984, p. 328).

†Arnold and Jensen (1995).

‡For methylphenidate only.

Table 2. Percentages of children experiencing ADRs from stimulants*

Side Effects	Dextroamphetamine	Methylphenidate	Pemoline
Central Nervous System Effects			
Dyskinesias	<1	3	5.5
Tourette's syndrome	<1	<1	<1
Tics	<1	—	—
Headache	18.3 (1-31)	9.3 (0-15)	13.8 (1-22)
Drowsiness, less alert	5.5	5.7 (0-17)	5.5
Psychosis (normal dose)	<1	<1	<1
Difficulty arousing	—	15 (11-19)	—
Insomnia	19 (5-43)	16.9 (0-52)	28.7 (<10-42)
Tremor	5.5	6.5	—
Confused, “dopey”	10.3 (8-12)	3.9 (2-10)	—
Mood changes	<1	>10	5.5
Depression	39	8.7 (0-16)	—
Agitation, restlessness (motoric)	>10	6.7 (3.3->10)	—
Irritability, stimulation	25 (17-29)	17.3 (11-19.6)	13.3 (1-21)
Cardiovascular Effects			
Dizziness, lightheadedness	11.5 (1-23)	7.7 (0-13)	5.5
Lower blood pressure	—	<1	<1
Higher blood pressure	>10	15.8 (1-26)	—
Tachycardia	5.5	15 (1-20)	5.5
Palpitations	5.5	4.4 (1-10)	5.5
Cardiac arrhythmias	<1	5.5	—
Chest pain	<1	4.4 (1-10)	—
Gastrointestinal Effects			
Dry mouth and throat	>10	8.7 (0-17.4)	—
Anorexia, lower appetite	23.1 (1-56)	26.9 (0-72)	14.5 (1-34)
Nausea	5.5	5.1 (1-10)	5.5
Vomiting	5.5	—	—
Bad taste	5.5	—	—
Dyspepsia, upset stomach	5.5	9.7 (1-28)	5.5
Diarrhea	5.5	—	—
Constipation	5.5	6.5	—
Hepatotoxicity	—	—	2
Weight loss	29.5 (1-63)	13.5 (3-27)	5.5
Weight gain	—	4.3	—
Renal Effects			
Enuresis	—	9 (3-20)	—
Endocrine and Sexual Effects			
Impotence	5.5	—	—
Disturbed sexual function	5.5	—	—
Growth suppression	See text.	See text.	See text.
Hematologic Effects			
Easy bruising	—	5.5	—
Eye, Ear, Nose, and Throat Effects			
Blurred vision	5.5	<1	—
Nystagmus	—	—	5.5
Skin, Allergy, and Temperature Effects			
Unusual sweating	5.5	—	—
Rashes	<1	5.5	5.5
Hives	<1	5.5	—
Exfoliative dermatitis	—	5.5	—
Fever, unexplained	—	5.5	—
Joint pain	—	5.5	—

*These figures are based primarily on reports of children and adolescents treated for ADHD.
—Indicates nonexistence of information, not nonexistence of adverse effects. All data taken from Maxmen and Ward (1995, pp. 365-6).

Psychostimulant-Induced Motor and Vocal Tics

Borcherding and colleagues (1990): approximately 59 percent abnormal movements. Barkley and colleagues (1990): 10 percent increase in tics. Handen and colleagues (1991): (mentally retarded with ADHD) 11 percent stopped methylphenidate because of motor tics.

Lipkin and colleagues (1994) (retrospective): 9 percent tics or dyskinesias, one severe, irreversible case.

Psychostimulant Addiction, Withdrawal, and Rebound

Rapoport and colleagues (1978) (controlled, single amphetamine dose of 0.5 mg/kg): 71 percent of normal children suffered "marked behavioral rebound," including "excitability, talkativeness, and, for three children, apparent euphoria." Case reports of "crashing" with depression (Dulcan, 1994; also see Porrino, Rapoport, Behar, et al., 1983). The Drug Enforcement Administration (1995) and International Narcotics Control Board (1996, 1997) express concern about clinical use encouraging addiction and about abuse through illegal diversion.

Psychostimulant Growth Suppression and Retardation

Methylphenidate disrupts growth hormone cycles (Aarskog, Fevang, Klove, et al., 1977; Barter, Kammer, 1978; Brown, Williams, 1976; Joyce, Donald, Nicholls, et al., 1986; Shaywitz, Hunt, Jatlow, et al., 1982; reviewed in Dulcan, 1994, and Jacobvitz, Sroufe, Stewart, et al., 1990). Stimulants inhibit growth (height and weight) (Klein, Mannuzza, 1988; Safer, Allen, Barr, 1975). Spencer and colleagues (1996) conclude that growth deficits are related to ADHD, but the study is flawed, including the use of only one measurement per child and a control group that is 1 year older.

Methylphenidate Cardiovascular Adverse Effects

FDA's Spontaneous Reporting System (SRS) (1985 through March 3, 1997): 2,821 reports with 8 percent cardiovascular, including arrhythmias and conduction problems (120) and heart arrests and failures (13) (Breggin, 1998b). Psychostimulants have direct cardiotoxic effects (Henderson, Fischer, 1994; Ishiguro, Morgan, 1997).

Further Review of the FDA Spontaneous Reporting System

FDA SRS reports indicate symptom clusters often overlooked in reviews: drug dependency, addiction, and withdrawal (117 reports); hair loss (250); various skin disorders; various blood disorders, including leukopenia; abnormal liver function tests (also see National Toxicology Program, 1995, for cancer threat); and convulsions (69). Adverse mental reactions: depression (48); psychotic depression (11); combined categories of overdose, overdose

intentional, and suicide attempt (50); personality disorders (89); agitation (55); hostility (50); abnormal thinking (44); hallucinations (43); psychosis (38); and emotional lability (33).

Methylphenidate-Induced Abnormalities of Brain Function

Porrino and Lucignani (1987) (conscious rats): alterations in glucose metabolism in the brain. Bell and colleagues (1982) (rat brain tissue): glucose metabolic rates reduced in the motor cortex and increased in the substantia nigra and other deep structures.

Volkow and colleagues (1997) (PET in normals): reduced relative metabolism of basal ganglia and varied other effects. Wang and colleagues (1994) (PET in normals): decreased overall flow of blood into brain by 23 to 30 percent. Nasrallah and colleagues (1986) (PET): brain atrophy in more than 50 percent of 24 young adults with stimulant-treated hyperactivity in childhood. They conclude "cortical atrophy may be a long-term adverse effect of this treatment." Brain scan studies that attempt to show pathology of ADHD (Lou, Henriksen, Bruhn, 1984; Giedd, Castellanos, Casey, et al., 1994; Hynd, Semrud-Clikeman, Lorys, et al., 1991) are almost certainly measuring pathology caused by psychostimulants.

Psychostimulant-Induced Abnormalities of Brain Chemistry in Animals

Methamphetamine: chronic exposure can produce irreversible CNS damage to dopamine receptors and norepinephrine function (Wagner, Ricaurte, Johanson, et al., 1980). Large chronic doses cause the death of serotonergic nerves in animals (Battaglia, Yeh, O'Hearn, et al., 1987). Melega and colleagues (1997b) found persistent "neurotoxic" changes in dopamine function (dopamine depletions of 55 to 85 percent) in vervet monkeys at 10 to 12 weeks (2 doses of 2 mg/kg). Sonsalla and colleagues (1996) found dopaminergic cell death in the substantia nigra of mice (approximate cell loss, 40 to 45 percent) (4 i.p. injections at 10 mg/kg).

Amphetamine: in rhesus monkeys, demonstrated long-lasting loss of dopamine and dopamine uptake sites (receptors) (Wagner, Ricaurte, Johanson, et al., 1980); down-regulation (subsensitivity) in the dopamine neurotransmitter system (Barnett, Kuczenski, 1986). Melega and colleagues (1997b) using PET in vervet monkeys found marked decreases in dopamine synthesis (25 percent at 10 to 12 weeks) with a 16 percent reduction in one amphetamine-treated animal at 32 weeks (2 doses of 2 mg/kg). Melega and colleagues (1997a) recorded gradual recovery from neurotoxicity in the striatum over 2 years (4 to 18 mg/kg over 10 days).

Methylphenidate: down-regulation of dopamine receptors (Barnett, Kuczenksi, 1986); reduction of the density of the norepinephrine receptors (Mathieu, Ferron, Dewar, et al., 1989); locus coeruleus loses responsiveness (Lacroix, Ferron, 1988).

Fenfluramine: (chemically related to amphetamine) causes death of serotonergic neurons (McCann, Seiden, Rubin, et al., 1997).

Psychostimulant Indirect Adverse Effects

Children lose their sense of responsibility for their own behavior (Breggin, 1997, 1998a; Jensen, Bain, Josephson, 1989) and experience many negative emotional reactions that they may not report (Sroufe, Stewart, 1973).

Psychostimulant Mechanism of Action

Spontaneous or self-generated activities—play, mastery, exploration, novelty seeking, curiosity, and zestful socialization—are central to the growth and development of animals and humans and necessary for the full elaboration of CNS synaptic connections (Greenough, Black, 1992; Weiler, Hawrylak, Greenough, 1995).

Psychostimulants consistently cause two specific, related adverse drug effects in animals (and also humans). First, stimulants suppress normal spontaneous or self-generated activity and socialization (Arakawa, 1994; Hughes, 1972; Randrup, Munkvad, 1967; Schiørring, 1979, 1981; Wallach, 1974). Second, stimulants promote abnormal stereotyped, obsessive/compulsive, asocial behaviors that are repetitive and meaningless (Bhattacharyya, Ghosh, Aulakh, et al., 1980; Costall, Naylor, 1974; Koek, Colpaert, 1993; Kuczenski, Segal, 1997; Mueller, 1993; Randrup, Munkvad, 1967; Rebec, Bashore, 1984; Rebec, Segal, 1980; Segal, 1975; Segal, Weinberger, Cahill, 1980; early studies reviewed in Wallach, 1974, and Schiørring, 1979). The effects occur in rats at doses as low as 0.63 mg/kg methylphenidate (Koek, Colpaert, 1993) or 0.3 mg/kg amphetamine (Rebec, Bashore, 1984).

The drugs suppress *normal* spontaneous, self-generated behaviors and socialization; they promote *abnormal* compulsive, asocial, compliant behaviors deemed suitable to structured and often suppressive situations, such as many classrooms (Breggin, 1997, 1998a; Breggin, Breggin, 1996, 1998; Ellinwood [in Kramer, Lipton, Ellinwood, et al., 1970]; Fialkov, Hasley, 1984; Rie, Rie, Stewart, et al., 1976; Rebec, Bashore, 1984). This drug-induced suppression of behavior and mental function is independent of the child's mental state; it occurs in healthy animals and children. When children seem to be overactive, impulsive, or distractible, psychostimulants will also suppress these behaviors regardless of the cause, including ADHD-like behaviors that signal boredom, frustration, abuse, conflict, lack of rational discipline or age-appropriate attention, or inadequate educational interventions. This mutes the child's distress or needs, allowing them to be ignored.

Table 3 lists some of the ADRs that are mistakenly seen as "improvements" when they reflect suppressed, overfocused, asocial behavior.

Risk/Benefit Ratio

There are no positive long-term psychostimulant effects (beyond 7 to 18 weeks) and no improvement in academic performance or learning (Swanson, 1993; also see Breggin, 1998a; Jacobvitz, Sroufe, Stewart, et al., 1990; Popper, Steingard, 1994; Richters, Arnold, Jensen, et al., 1995; Whalen, Henker, 1997). Studies claiming that ADHD leads to bad outcomes have studied

children who have been diagnosed and treated with drugs (Mannuzza, Klein, Bessler, et al., 1993, 1998; Weis, Hechtman, Milroy, et al., 1985). Diagnosis, treatment, and other non-ADHD factors may contribute to any bad outcome. Meanwhile, there are many common, severe stimulant hazards. The "therapeutic effects" are in reality toxic effects (Table 3). *The use of psychostimulant drugs for the control of behaviors labeled ADHD in children should be stopped.*

Future Research Directions

Before the clinical use of psychostimulants for ADHD is continued, large animal psychostimulant studies are needed that focus on (1) the extent and potential irreversibility of abnormalities in gross brain function (blood flow and energy consumption), (2) the extent and potential irreversibility of neurotransmitter down-regulation and receptor loss, (3) neuronal death and atrophy, (4) reduced brain plasticity (fewer synaptic connections), (5) disruption of pituitary and hormonal functions, (6) developmental retardation of growth and behavior, and (7) cardiac toxicity.

Table 3. Adverse drug reactions (ADRs) from stimulants mistakenly labeled "beneficial"

Obsessive Compulsive ADRs That Abnormally Focus a Child	Social Withdrawal ADRs That Isolate a Child	Suppressive ADRs That Enforce Compliance, Apathy, and Submissiveness
Stereotypical activities (2, 6, 23, 25)	Social withdrawal and isolation (1, 3, 6, 19, 24, 25)	Compliance, especially in structured environments (13*,15*,16*)
Obsessive-compulsive behavior (2, 6, 12, 28)	Reduced social interactions, talking, or sociability (6, 13, 15*,17, 21)	Fewer social interactions and diminished responsiveness (26*)
Perseverative behavior (2, 14, 28)	Decreased responsiveness to parents and other children (15*)	Hypoactive, unusual stillness, too quiet, lost sparkle (18, 25)
Cognitive perseveration (12)	Increased time spent alone (1, 21)	Reduced curiosity (12)
Inflexibility of thinking (14)	Increased solitary play (7, 13*)	Somber (5), and somber, quiet, and still (1)
Overfocusing or excessive focusing (1, 12, 14, 25)	Diminished play (26*)	Subdued (6,10)
	Autism and schizophrenia (3, 23)	Apathetic; lethargic: "tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive" (6) (also 23, 25)
		Bland, emotionally flat, affectless (9, 27)
		Depressed, sad, easy or frequent crying (6, 7, 8, 18, 19, 20, 22)
		Little or no initiative or spontaneity (9)
		Diminished curiosity, surprise, or pleasure (9)
		Humorless, not smiling (9, 22)
		Drugged, spaced out (22, 25)
		Social inhibition—passive and submissive behaviors (11)
		Amphetamine look (pinched, somber expression) (1, 4)
		"Zombie" effect ("zombie-like constriction of affect and spontaneity") (1, 4, 25)

*Considered positive or therapeutic by the source.
cct = controlled clinical trial

1. Swanson, Cantwell, Lerner, et al. (1992) [confirms many ADRs in list]
2. Borcherding, Keysor, Rapoport, et al. (1990) [cct]
3. Schiørring (1981)
4. Arnold, Jensen (1995)
5. Tannock, Schachar, Carr, et al. (1989) [cct]
6. Mayes, Crites, Bixler, et al. (1994) [cct]
7. Schleifer, Weiss, Cohen, et al. (1975) [cct]
8. Dulcan (1994) and Dulcan, Popper (1991) [open trial]
9. Rie, Rie, Stewart, et al. (1976) [cct]
10. Bradley (1937) [open trial]
11. Granger, Whalen, Henker (1993) [cct]
12. Solanto, Wender (1989) [cct]
13. Cunningham, Barkley (1978) [cct]
14. Dyme, Sahakian, Golinko, et al. (1982) [cct]
15. Barkley, Karlsson, Pollard, et al. (1985) [cct]
16. Cotton, Rothberg (1988) [cct]
17. Jacobvitz, Sroufe, Stewart, et al. (1990)
18. Davy, Rodgers (1989)
19. Schachar, Tannock, Cunningham, et al. (1997) [cct]
20. Barkley, McMurray, Edelbrock, et al. (1990) [cct]
21. Pelham (1989)
22. Sleator, Ullmann, von Neuwman (1982)
23. Ellinwood, Tong (1996)
24. Handen, Feldman, Gosling, et al. (1991) [cct]
25. Fialkov, Hasley (1984)
26. Barkley, Cunningham (1979) [cct]
27. Whalen, Henker, Granger (1989) [cct]
28. Castellanos, Giedd, Elia, et al. (1997) [cct]

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Public Health Perspectives and Toxicological Issues Concerning Stimulant Medications

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During the past 10 years, there has been a marked increase in the use of stimulant medication to treat attention deficit hyperactivity disorder (ADHD). Present estimates are that between 1.5 and 2 million children in the United States are taking these medications (Safer, Zito, Fine, 1996). In other parts of the world, there is increasing use of stimulant medication as well. In the past, ADHD was considered primarily a disease of childhood. The clinical perspective on this has been shifting as ADHD among adults has received renewed attention. Increasingly, ADHD is believed to be a chronic, lifetime disorder that may require long-term management and treatment. This has encouraged additional use of stimulant medication to treat teenagers and adults (Safer, Krager, 1994). A recent clinical trial suggests that stimulant medication may be effective in treating children who have conduct disorder without ADHD (Klein, Abikoff, Klass, et al., 1997). This could further increase the number of children receiving these medications.

Much of the literature about the toxicity and side effects of stimulant medications has focused on short-term effects. Relatively little research has been done on possible chronic effects. The National Institute of Environmental Health Sciences (NIEHS) has conducted 2-year carcinogenicity studies for dl-amphetamine sulfate and methylphenidate hydrochloride (Dunnick, Eustis, 1991; Dunnick, Hailey, 1995). These studies found a decrease in tumor rates among rats and mice treated with amphetamines and a decrease in tumor rates among rats treated with methylphenidate. Mice treated with methylphenidate also showed a decrease in the incidence of mammary gland fibroadenomas. However, a dose-dependent increase in liver abnormalities (eosinophilic foci) and liver tumors (hepatocellular adenomas) was seen among male and female mice. Dose-dependent increases in a relatively rare type of tumor, hepatoblastomas, were also seen among male mice. The mice in these studies lost weight, which usually is a strong protective factor against the development of tumors, including mouse liver tumors. On the other hand, mouse liver tumors may not always be predictive of human cancers; therefore, these bioassay results should be interpreted with caution when extrapolating to risk in humans.

In this talk, potential gaps in the toxicologic and epidemiologic data on the chronic toxicity and adverse effects of stimulant compounds will be presented. The current system of post-market surveillance of pharmaceutical treatment has been able to identify rare instances of liver failure among children taking Pemoline and sudden deaths among children taking Clonidine and stimulant combinations (Swanson, Flockhart, Udrea, et al., 1995; Marotta, Roberts, 1998). It is less clear that the mechanisms are in place to identify possible chronic adverse effects of stimulant medications on human health unless additional toxicologic and epidemiologic studies are conducted. Additional experimental and observational studies are needed to identify whether these compounds are safe during key developmental periods (in utero, toddler, adolescent) and whether there are susceptible subpopulations that may be at increased risk of chronic adverse effects. Because some of these compounds alter liver metabolism, more studies are needed to

determine whether this might affect the way the body handles endogenous or exogenous chemicals.

The long-term efficacy of stimulant therapy has not been adequately proven, and this has been identified as an important area for future study among ADHD researchers. Because of the large number of people being treated with stimulants and the increasing length of treatment, good public health practice suggests that additional laboratory and epidemiologic research on the long-term safety of these compounds is also needed.

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Psychosocial Interventions

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Children with attention deficit hyperactivity disorder (ADHD) have serious impairment in many areas of functioning and skill development, including school, family, and peer domains, that are not sufficiently addressed through pharmacological treatments. Because functioning in some of these areas—particularly with peers and family—not only highlights the seriousness of ADHD as a childhood problem but also predicts the development of even more serious problems and a poor outcome in adolescence and adulthood, effective intervention for these difficulties is a major public health agenda.

Various treatments have been tried and are widely used for ADHD, including traditional one-to-one therapy, restrictive or supplemental diets, allergy treatments, chiropractics, biofeedback, perceptual-motor training, treatment for inner ear problems, and pet therapy. However, only three treatments have been shown to be evidence-based as effective short-term treatments for ADHD: (1) behavior modification, (2) central nervous system stimulants, and (3) a combination of the two. We will discuss two of these validated treatments—behavioral and combined interventions. Pharmacological approaches, alternative approaches, and treatment comparisons are covered in other papers.

Behavioral interventions have been used for children specifically diagnosed as having ADHD for more than two decades, and they have been used for more than 30 years to treat disruptive children, some of whom, although not diagnosed as ADHD, very likely had the disorder. Thus, there is an extensive literature on behavioral treatments for ADHD. Behavioral treatments can be examined in five categories (Pelham, Murphy, 1986; Pelham, Wheeler, Chronis, 1998): (1) cognitive-behavioral interventions, (2) clinical behavior therapy, (3) direct contingency management, (4) intensive, packaged behavioral treatments, and (5) combined behavioral and pharmacological treatments. These categories differ in the amount of evidence for their effectiveness, as well as in the nature and efficacy of their interventions.

First, consider cognitive-behavioral treatments, which include verbal self-instructions, problem-solving strategies (used in isolation), cognitive modeling, self-monitoring, self-evaluation, social skills training (used in isolation), and self-reinforcement. These techniques are typically implemented in a series of individual or small group sessions by a therapist with a child. Although these treatments are widely used, controlled investigations are virtually uniform in failing to provide evidence that the treatments work (Abikoff, Gittelman, 1985). Despite their intuitive appeal, these interventions are ineffective with ADHD children.

In contrast, the other behavioral approaches to treatment work quite well. Applications of traditional, outpatient-based, clinical behavior therapy have typically involved training parents to implement contingency-management programs with their children and consulting with the children's teachers with the same goal. In typical behavioral treatment programs, parents are

given assigned readings and in a series of 8 to 20 weekly group sessions are taught standard behavioral techniques such as time-out, point systems, and contingency management. Similarly, therapists work with teachers to develop classroom management strategies that can be implemented by the teacher with the target children and daily report cards that provide feedback to parents on the children's school performance, for which parents provide a consequence at home. Contingency management approaches involve using the same behavioral treatment techniques but generally implemented directly with children by paraprofessionals or teachers in controlled settings.

The efficacy of such behavioral approaches has been evaluated in numerous controlled studies (Pelham, Wheeler, Chronis, 1998). These studies have revealed meaningful treatment effects on a variety of dependent measures, with larger effects not surprisingly coming from more intensive, contingency management approaches. Indeed, behavioral parent training and classroom management approaches are among the most widely used and well-documented treatments for children with disruptive behavior. Thus, behavior therapy of the sort that is likely to be implemented by therapists in community mental health and primary care settings and by educators in school settings results in clinically important improvement on multiple measures in home and school settings for most treated children.

Despite clear evidence for the effectiveness of behavioral parent training and behavioral classroom interventions for ADHD, there is growing consensus among professionals that outpatient treatment may not be adequate for many ADHD children and that intensification of psychosocial treatment programs and/or concomitant medication are often necessary. A summer treatment program (STP) for ADHD children is one such intensive treatment program (Pelham, Hoza, 1996). The STP is based on the premise that combining an intensive summer treatment program with a school year, outpatient followup program will provide a maximally effective intervention for ADHD. The STP runs for 9 hours on weekdays for 8 weeks. Various empirically supported treatments (e.g., point system, time-out, skills training, parent training, group problem-solving) are combined to focus on improved peer relations and recreational and academic competencies. Effects from such intensive treatment programs are quite substantial, with large changes in indices of children's behavioral disruptiveness, low treatment dropout rate, excellent parent participation and satisfaction ratings, and children's overall improvement. Programs such as the STP must be combined with parent training and school-based followup to be effective. That package—STP, parent training, and school-based intervention—constitutes the psychosocial treatment package for the MTA Study (Arnold, Abikoff, Cantwell, et al., 1997).

The addition of medication to behavioral interventions has been another approach taken to maximize the effectiveness of treatment for ADHD. A number of studies have shown that the combination of behavioral treatment and psychostimulant has unique advantages over either treatment alone (Pelham, Waschbusch, in press). These include improved efficacy with less intensive levels of psychosocial treatment and lower dosages of medication (e.g., Carlson, Pelham, Milich, et al., 1992). Further, when medication is removed from children who received combined pharmacological and psychosocial treatment, a substantial portion of the treatment effect remains (Klein, Abikoff, 1997).

In summary, behavior modification in the form of parent training and classroom management, whether implemented by parents, teachers, or paraprofessionals, appears to be an efficacious treatment for ADHD. Intensive treatment programs for the children or adjunctive medication appears helpful for many ADHD children who receive a standard regimen of parent and teacher intervention.

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Treatment Alternatives for Attention Deficit Hyperactivity Disorder

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Alternate treatments (Tx) are defined for this conference as any treatment other than prescription drugs or standard behavioral treatments. In contrast with those two established general treatments, many alternate treatments are etiologically targeted (see Table 1) and consequently applicable to a smaller subpopulation of patients with attention deficit hyperactivity disorder (ADHD). Therefore, scientific evaluation and clinical use of such treatments require a deeper level of diagnosis than the phenomenological criteria of DSM-IV.

Elimination Diets (Oligoantigenic or Few-Food Diets)

The 1982 consensus development conference on defined diets in hyperactivity (NIH, 1982) called for more controlled research. Since then, at least seven controlled studies (Breakey, 1997) have demonstrated either significant improvement compared with a placebo condition (disguised full diet) (Kaplan, McNicol, Conte, et al., 1989) or deterioration on a placebo-controlled challenge of offending substances after an open diet trial and open challenge to identify the substance (Egger, Carter, Graham, et al., 1985; Pollock, Warner, 1990; Carter, Urbanowicz, Hemsley, et al., 1993; Rowe, Rowe, 1994; Boris, Mandel, 1994; Schmidt, Mocks, Lay, et al., 1997). The finding of scientifically acceptable documentation of efficacy since 1982 appears associated with broadening the range of suspected food items, selecting subjects more carefully (e.g., for allergic diathesis), and allowing for the timing peculiarities of food sensitivities. A related Tx possibility arises from the documentation of successful desensitization to the offending food by enzyme-potentiated desensitization (Egger, Stolla, McEwen, 1992). The main scientific task is to refine the diagnostic characteristics of diet responders and delineate what percentage they constitute of the ADHD population. Preliminary evidence suggests that the profile of a probable responder is a middle- or upper-class preschooler with atopy and prominent irritability and sleep disturbance, with physical as well as behavioral symptoms.

A related dietary strategy, simple elimination of sugar or candy, has not garnered convincing scientific support from repeated placebo-controlled challenge studies (Krummel, Seligson, Guthrie, 1996) despite a few encouraging reports (e.g., Goldman, Lerman, Contois, et al., 1986).

Nutritional Supplements. Both macronutrients (amino acids, lipids, carbohydrates) and micronutrients (vitamins and minerals) have been proposed as Tx for ADHD.

Table 1. Scientific status of alternate treatments for ADHD

Treatment	Etiology or Mechanism	Type of Data	ES or *p*	Rating* (0-6); Recommendation	Risks
Few-foods diet (oligoantigenic)	Food or additive sensitivity	Controlled trial; placebo challenges	ES 0.5-1.5 *p*,.05-.001	5; Define subgroup (profile; % ADHD)	Nuisance, expense, nutrition
Enzyme-potentiated desensitization	Food or additive sensitivity	Controlled comparison with placebo injections	*p*,.001	4; Replication Define subgroup	Injection
Sugar elimination	Sugar malaise	Placebo-controlled challenges	*p*>.1	0 for acute; Take FH of DM	Delay std Tx
Amino acid supplementation	Precursors of catecholamines	Placebo-controlled comparisons	ES up to 0.6, *p*,.01	0 despite short-lived effect of little utility	Eosinophilia, neurotoxicity
Essential fatty acid supplementation	Prostaglandins neur. membrane	Serum level cf. cntrl plac-contr. trials	ES 0.5 .1>*p*>.05	3; trials of n-3	Upsetting balance
Glyconutritional supplementation	Need for glycoconjugates	Open trials, SNAP-IV, blind teachers	*p*,.05-.002	3; placebo trials	Upsetting balance
Vitamins	Deficiency vs. Idiopathic need for higher dose	Placebo-controlled trials megavitamin cocktails, not RDA	Megadose cocktail no benefit	0 for megacocktail; 1 for RDA, specific megavit; pilot trials	Hepatotoxicity, neuropathy in megadose
Iron supplementation	Co-factor make catecholamines	Open trial supplementation	ES 1.0 *p*<.05	3†; controlled trials	Hemochroma-tosis
Zinc supplementation	Co-factor for many enzymes	Comparison Zn lvl of ADHD with control	ES 2.4 *p*<.001	2†; controlled trials	Excess
Magnesium supplementation	Deficiency cf. to controls	Open trial with control group	ES 1.2-1.4 *p*<.05	3†; placebo trials	Aggression from excess
Chinese herbals	Clinical exper.	Open trials, one with MPH control	*p*<.05; no diff. MPH	3; placebo trials	Delay of other Tx
Other herbals	Clinical exper.	No data	N.A.	1; pilot trials	Delay Tx
Homeopathic prep	Clinical exper.	No data	N.A.	1; pilot trials	Delay Tx
Laser acupuncture	Stimulate foci for calming	Open trial	ES 1.0	2; controlled trial	Delay other Tx, burn

Table 1. Scientific status of alternate treatments for ADHD (continued)

Treatment	Etiology or Mechanism	Type of Data	ES or *p*	Rating* (0-6); Recommendation	Risks
EEG biofeedback	Suppress theta, increase beta	Open & randomized wait list ctrl trials	$p<0.05$	3; sham-controlled trial	Expense, time
EMG biofeedbck, relaxatn, hypnosis	Lower arousal, muscle tone	Randomized trials with controls	ES 1.0-1.3 $p<0.01$	0 for hypnosis; 4 for EMG/relaxn; cf. med	Delay other Tx
Meditation	Autonomic effect focused attn	Cf. relaxation, wait list ctrl, med	$p<.05$	3; rigorous replication, sham ctrl	Delay other Tx
Channel-specific perceptual training	Basic readiness skills, focus	Randmzd prev trial with 2 control grps	ES 0.9 $p<0.01$	3; controlled Tx trials	Delay other Tx
Vestibular stimulation	Modulate behav attn, perception	Open and single-blind trials	ES 0.4-1.2 *p* ns-0.001	3; randomized sham-controlled trials	Nausea, accident
Antifungal Tx	GI yeast	No systematic data	N.A.	1; pilot trials	Med risk
Thyroid Tx	Thyroid Fx affects AD Sx	Placebo trial: 5/8 GRTH, 1/9 other	ns if thyr not abnrml	0 if thyroid nl; 6 if thyroid abnl	Thyroid toxicity
Deleading	Lead toxicity causes AD Sx	Placebo-ctrl trial of chelation (=MPH)	ES 0.7-1.6 *p*,.05-.001	4 if blood Pb>20; 2 if Pb<20; ctrl trial	Toxicity of chelator

* Ratings: 0 = not worth considering further (despite, in the case of amino acids, some evidence of short-lived effect); 1 = credible hypothesis or collateral support or wide clinical experience, needs pilot data; 2 = promising systematic data, but not prospective trial; 3 = promising prospective data (perhaps with random assignment to control or objective/blind measures) lacking some important control -OR- controlled trial(s) with trends suggesting further exploration; 4 = one significant double-blind controlled trial needing replication -OR- multiple positive controlled trials in a treatment not easily blinded; 5 = convincing double-blind controlled evidence but needs further refinement (e.g., define target subgroup) for clinical application; 6 = should be considered established Tx for the appropriate subgroup.

† The rating would be 6 for patients showing frank deficiency of vitamins, iron, zinc, or other nutrients.

Amino Acid Supplementation. Amino acid supplementation is theoretically supported by reports of low levels of amino acids in ADHD, including the precursors of catecholamines and serotonin (Bornstein, Baker, Carroll, et al., 1990; Baker, Bornstein, Rouget, et al., 1991). Several open and controlled studies reported a short-term benefit from tryptophan, tyrosine, or phenylalanine supplementation (Nemzer, Arnold, Votolato, et al., 1986; Reimherr, Wender, Wood, et al., 1987; Wood, Reimherr, Wender, et al., 1985a). However, no lasting benefit beyond 2 to 3 months has been demonstrated (tolerance develops) (Wood, Reimherr, Wender, et al., 1985b), and even short-term benefit was not found in some studies (Eisenberg, Asnis, van Praag, et al., 1988; Zametkin, Karoum, Rapoport, 1987; Ghose, 1983). Further, such supplementation, while originally considered benign, may carry real dangers beyond that of eosinophilia. Therefore, amino acid supplementation does not appear a promising area to explore further.

Essential Fatty Acid Supplementation. Neuronal membranes are composed of phospholipids containing large amounts of polyunsaturated fatty acids, especially the n-3 and n-6 acids, which humans cannot manufacture de novo and hence are essential in the diet. Essential fatty acids (EFA) are also metabolized to prostaglandins, which modify many metabolic processes. Both the n-3 series (progenitor alpha-linolenic acid) and the n-6 series (progenitor linoleic acid) have been reported to be significantly lower in children with ADHD than in comparison controls (Mitchell, Lewis, Cutler, 1983; Mitchell, Aman, Turbott, et al., 1987; Stevens, Zentall, Deck, et al., 1995). Even total serum-free fatty acids were lower in ADHD, with ES = 2.4; $p<.001$ (Bekaroglu, Yakup, Yusof, et al., 1996). Aggression has been significantly inhibited in young adults by docosohexaenoic acid of the n-3 series (Hamazaki, Sawazaki, Itomura, et al., 1996). Two double-blind placebo-controlled trials of gamma-linolenic acid (n-6 series) supplementation yielded equivocal results from ADHD subjects not selected for low n-6 acids (Aman, Mitchell, Turbott, 1987; Arnold, Kleykamp, Votolato, et al., 1989); in one, the serum triglyceride gamma-linolenic acid correlated inversely with Conners scale scores (Arnold, Kleykamp, Votolato, et al., 1994). A controlled pilot trial of n-3 supplementation in ADHD subjects selected for symptoms of EFA deficiency showed a trend of advantage for the supplement despite a huge placebo effect (pre-post ES 1.8 vs. 1.4), and changes in serum phospholipid n-3 acids correlated negatively with changes in Conners scores (Burgess, Stevens, 1998). The data suggest further controlled trials in subjects selected for low serum levels.

Glyconutritional Supplements. Glyconutritional supplement contains basic saccharides necessary for cell communication and formation of glycoproteins and glycolipids: glucose, galactose, mannose, N-acetylneuraminic acid, fucose, N-acetylgalactosamine, and xylose. Only the first two are abundant in the ordinary diet. Dykman and Dykman (1998) found in an open trial of glyconutritional and phytonutritional (flash freeze-dried fruits and vegetables) supplements with 17 ADHD subjects a significant ($p<.01$) reduction in parent and teacher SNAP-IV ratings. Dykman and McKinley (1997) found in a second open trial with the same supplements in 18 children reductions in parent inattention ratings from 2.47 to 2.05 ($p<.05$) and hyperactivity-impulsivity ratings from 2.23 to 1.54 ($p<.002$), sustained for 6 weeks. Placebo-controlled trials are needed.

Vitamin Supplementation. Three strategies for vitamin supplementation are (1) RDA multivitamin preparations, (2) megavitamin cocktails, and (3) megadoses of specific vitamins. The first is noncontroversial, but no research has been done on its effects in diagnosed ADHD, even though some reports suggest mild deficiencies in diet and blood levels that might be addressed. However, in a randomly assigned double-blind placebo-controlled trial of RDA vitamin and mineral supplementation in 47 6-year-old children not selected for ADHD, Benton and Cook (1991) found an 8.3 point IQ advantage ($p<.001$), mainly in nonverbal ability, an increase in concentration and decreased fidgeting on a frustrating task ($p<.05$), and advantage on a reaction time task assessing sustained attention (ES = 1.3; $p<.05$). The second strategy has been found ineffective in double-blind placebo-controlled short (2 weeks) and longer (up to 6 months) trials in ADHD and the related comorbidity of learning disorder (Arnold, 1978; Haslam, Dalby, Rademaker, 1984; Kershner, Hawke, 1979). Further, megadosage carries risks, including hepatotoxicity (Haslam, Dalby, Rademaker, 1984; Shaywitz, Siegel, Pearson, 1977). Therefore, megavitamin cocktails are not worth pursuing. The third possibility, judicious use of single vitamins in megadosage to alter neural metabolism in specific ways, is actually more like

psychopharmacology and has not been adequately explored despite some encouraging early reports (e.g., Coleman, Steinberg, Tippett, et al., 1979; Brenner, 1982).

Mineral Supplements. The main mineral candidates for supplementation are iron, zinc, magnesium, and calcium, all of which have been reported deficient in ADHD compared with matched controls (e.g., Kozielec, Starobrat-Hermelin, Kotkowiak, 1994).

1. **Iron Supplementation.** Iron is a co-enzyme in anabolism of catecholamines. In an open 30-day supplementation trial with 17 nonanemic boys ages 7 to 11 with ADHD, Sever and colleagues (1997) found improvement in Conners parents' scores from 17.6 to 12.7 (ES = 1.0), but not in teacher ratings. In a double-blind placebo-controlled trial in 73 teenage nonanemic but iron-deficient girls, Bruner and colleagues (1996) found improvements in verbal learning and memory. In a trial of gastroprotected ferritin in 33 iron-deficient children, Burattini and colleagues (1990) reported a decrease of hyperactivity. Iron supplementation merits further study, with focus on whether any benefit found is confined to those with laboratory evidence of iron deficiency and with due concern for possibly toxicity of excess iron.

2. **Zinc Supplementation.** Animal data suggest involvement of zinc deficiency in hyperactivity (e.g., Halas, Sandstead, 1975; Sandstead, Fosmire, Halas, et al., 1977), and human deficiency syndrome includes impairment of concentration and jitters (Aggett, Harries, 1979). Zinc has been reported deficient in ADHD compared with controls, with ES up to 2.4 ($p<.001$) (Bekaroglu, Yakup, Yusof, et al., 1996; Toren, Sofia, Sela, et al., 1996). However, McGee and colleagues (1990) did not find a significant correlation of parent and teacher hyperactivity ratings with hair or serum zinc in the epidemiologic Dunedin sample. Arnold and colleagues (1990) reported data suggesting that stimulant response may depend on adequate zinc nutriture. Despite clinical advocacy of zinc supplementation, no systematic prospective trials could be found. The obvious need is a placebo-controlled double-blind trial of RDA zinc supplementation with pretreatment assessment of zinc status to determine whether zinc deficiency is a prerequisite for any benefit found.

3. **Magnesium Supplementation.** Kozielec and Starobrat-Hermelin (1997) found 95 percent of 116 children ages 9 to 12 with ADHD deficient in magnesium (34 percent by serum alone). They assigned 50 children ages 7 to 12 with DSM-IV ADHD and magnesium deficiency to 6 months open supplementation with 200 mg/day and 30 similar controls to usual treatment without magnesium; the supplemented group significantly decreased their Conners ratings compared with the control group (Starobrat-Hermelin, Kozielec, 1997). Thus, magnesium supplementation merits a placebo-controlled double-blind trial and replication by other investigators. Dosage of supplementation may be important, because animal work suggests a U-shaped behavioral dose-response curve (Izenwasser, Garcia-Valdez, Kantak, 1986).

Herbal and Homeopathic Treatments. In a randomly assigned open trial, Zhang and Huang (1990) compared a Chinese herbal cocktail (80 Ss) with methylphenidate 5-15 mg b.i.d. (20 Ss) for 1 to 3 months; 23 of 80 herbal cocktail cases were "cured" (disappearance of all

clinical symptoms and no recurrence for 6 months) compared with 6 of 20 taking methylphenidate. Including improved cases, the effectiveness rates were 86 percent versus 90 percent; the groups did not differ except for lower side effects and greater IQ rise in the herbal group. In an open trial with 100 hyperkinetic children, Wang and colleagues (1995) found an effectiveness rate of 94 percent, including reduction of hyperactivity, improved attention, and improved academics from the herbal Tiaoshen Liquor. In another open trial in 66 hyperkinetic children, Sun and colleagues (1994) found an effectiveness rate of 85 percent with Yizhi wit-increasing syrup, including significant improvement in behavior, school records, and soft neurological signs. Thus the open pilot data warrant placebo-controlled double-blind trials of Chinese herbals. No systematic data in ADHD could be found for Calmplex, Defendol, Gingko biloba, hypericum, or pycnogenol, but the first few listed may be worth pilot trials based on clinical experience.

Acupuncture. Despite the popularity of acupuncture, no published systematic data in ADHD could be found. Loo (1998), in unpublished preliminary pre-post single-blind data from students in grades K to 3, found improvements in Conners 10-item scores by teachers (n = 7) from 17.0 to 12.0 and in analogous parent scores (n = 6) from 23.1 to 15.5. She noted that children with the most severe ADHD could not cooperate with the Tx.

EEG Biofeedback. Electroencephalographic (EEG) biofeedback involves induction of sensorimotor or higher beta band EEG rhythms (12-18 Hertz) and suppression of theta rhythms by visual and auditory feedback. It arose from the observation that some children with ADHD have more theta and less beta rhythm than controls and animal work demonstrating reduction of motor activity associated with sensorimotor rhythm (Shouse, Lubar, 1978; Mann, Lubar, Zimmerman, 1992). There are several promising pilot trials. Lubar (1991) and Lubar and Shouse (1977) reported that in a single-subject ABA design four hyperactive children selected for low arousal showed better behavior and work habits without stimulant at the end of all treatment (ABA) than at the beginning with or without stimulant, and their unmedicated level of undesirable behaviors dropped by over half to the level of the normal controls; three of them showed synchrony of behavior with the ABA shifts. An uncontrolled open trial with 37 hyperactive children yielded significant grade point and achievement score improvements (Lubar, 1991). In an intensive summer treatment regimen, 12 children who showed EEG changes also improved on significantly more TOVA scales than did 7 who failed to show EEG changes (Lubar, Swartwood, Swartwood, et al., 1995). Linden and colleagues (1996) randomly assigned 18 children with DSM-III-R ADD/ADHD to either a wait list (n = 9) or 40 EEG biofeedback sessions over a 40-week period. The treated group showed a 9 point IQ rise compared with the wait list rise of less than 1 point ($p<.05$) and a 28 percent reduction in the SNAP inattention score compared with a 4 percent increase in the wait list group ($p<.05$). Thus, this treatment merits a sham-controlled randomized trial.

EMG Biofeedback, Relaxation Training, and Hypnosis. These three related Tx modalities are typically used in some combination. The few published data on hypnotherapy or breathing control alone for ADHD are discouraging (e.g., Calhoun, Bolton, 1986; Simpson, Nelson, 1974). However, the hypnotic techniques of imagery and progressive relaxation have often been incorporated into successful EMG biofeedback protocols. There are more literature citations for EMG than for EEG biofeedback (Lee, 1991). Denkowski and colleagues (1983)

randomly assigned hyperactive junior high boys to six 25-minute EMG-assisted relaxation training sessions (n = 24) or a control condition (n = 24); the treated group attained significantly higher reading and language performance and made a significant internal shift in locus of control. In 10 hyperactive boys ages 6 to 12, Dunn and Howell (1982) found significant improvement in behavior observations, parent ratings, and psychological tests after 10 relaxation training sessions but none after 10 neutral sessions. Omizo and Michael (1982) randomly assigned hyperactive boys ages 10 to 12 to either four sessions of EMG biofeedback-induced relaxation (n = 16) or sham treatment of equal length; compared with the sham, the relaxation induced significant improvements in attention and impulsivity on the Matching Familiar Figures test (ES = 1.0 to 1.3; $p<.01$). Krieger (1985) found in 27 children ages 7 to 11 with DSM-III ADHD significant improvement on Conners parent and teacher scales compared with an equal-n matched wait list control group. Success is largely moderated by baseline locus of control (Denkowski, Denkowski, Omizo, 1984). Despite recent neglect, the data suggest that EMG biofeedback-facilitated relaxation training merits further study.

Meditation. Meditation, though resulting in relaxation, is different from the preceding treatments in not directly targeting relaxation but achieving it indirectly. Kratter (1983) randomly assigned 24 children ages 7 to 12 with DSM-III ADD-H to either meditation training, progressive relaxation, or wait-list control, with 4 weeks of twice-weekly sessions; both active treatments, but not wait list, reduced impulsivity and improved scores on parent behavior scales but not teacher scales; only meditation training showed significant improvement on a test assessing selective attention. Moretti-Altuna (1987) randomly assigned 23 boys ages 6 to 12 with ADD-H to meditation training, medication, or standard therapy; meditation showed significant advantage in classroom behavior but not in parent ratings or psychological tests.

Perceptual Stimulation/Training. Perceptual and sensory stimulation and training include a wide variety of modalities, some with few or no data. The literature search found no systematic data on sensorimotor integration or optometric training for ADHD despite their widespread use. Neither were studies in ADHD found for massage, which has documented efficacy in other applications. The Interactive Metronome provides perceptual-motor concentration training with biofeedback about accuracy from motion sensors as the child taps to the beat provided by the program; open trials show improvements in timing that correlate at 0.2-0.4 with teacher ratings of attention, but there are no controlled data (Synaptec, 1998). In a single-blind prevention paradigm, Arnold and colleagues (1977) randomly assigned matched triplets and quads of first-graders selected for vulnerability on a perceptual screening battery to either 6 months of channel-specific perceptual training (n = 23), the same length of regular academic tutoring (n = 23), or no-contact control (n = 40); at 1-year followup, the trained group surpassed both control groups in blind teacher Conners ratings ($p<.01$), WRAT reading achievement, and Wechsler IQ ($p<.05$), although baseline measures were not different.

Mulligan (1996) reported significant impairment of vestibular processing in 309 children with ADHD compared with 309 matched children without ADHD ($p<.01$). In a single-blind crossover in 18 children with DSM-II hyperkinetic reaction, Bhatara and colleagues (1981) found improvement in Conners teacher ratings from rotational vestibular stimulation compared with a sham condition ($p<.05$), with benefit mainly confined to the 14 children younger than age 10 and those without comorbid conduct disorder. In another single-blind crossover with 12 children

identified through teacher scale screening, Arnold and colleagues (1985) found an ES of 0.5 between vestibular rotational stimulation alone and two control conditions (missing significance at the sample size), compared with an ES of 0.2 between visual rotational stimulation alone and the same control conditions in a similar group of 18 children. The Comprehensive Motion Apparatus provides vestibular stimulation in all vectors through complex motion; an open trial in 14 dyslexic children (mean age, 12 ± 2.6 years) showed pre-post improvement in parent rating of attention (ES = 1.5; $p<.003$) and objective cognitive/achievement tests (ES = 0.4–1.2; $p = .05–.001$) (Stillman, 1998). Thus, stimulation and/or training of specific perceptual channels merit further research in controlled trials, especially targeting subgroups that test deficient in the particular perceptual modality.

Antifungal Treatment. Treatment with antifungal agents such as nystatin (in combination with sugar restriction and other measures) is advocated by Crook (1985, 1989, 1991) and others on the hypothesis that repeated antibiotic use for otitis media changes intestinal flora, allowing yeast overgrowth, which compromises immune function and changes the gut mucosal barrier to allow absorption of food antigens. Several components of this hypothesis are supported by collateral documentation from other fields, and the hypothesis would make sense of the reported association of chronic high sugar intake with ADHD symptoms (e.g., Prinz, Riddle, 1986) without acute effects, in that sugar could promote yeast overgrowth chronically without showing acute effects on behavior. However, this hypothesis is not supported by any systematic prospective trial data in ADHD, and a trial of nystatin alone for another syndrome (fatigue, premenstrual tension, gastrointestinal symptoms, and depression) was negative (Dismukes, Wade, Lee, et al., 1990). A systematic randomly assigned trial in ADHD should be carried out, preferably double-blind placebo-controlled and accompanied by the sugar restriction and other supportive measures recommended by the advocates of this treatment.

Thyroid Treatment. Despite initial enthusiasm about resistance to thyroid hormone as a key to a large proportion of ADHD, this genetic syndrome appears extremely rare in ADHD samples. The same studies, however, reveal a rate of other thyroid dysfunction ranging from 2 percent to 5 percent (e.g., Weiss, Stein, Trommer, et al., 1993; Valentine, Rossi, O'Leary, et al., 1997), and the rate may be higher in those with comorbid mood disorder (West, Sax, Stanton, et al., 1996). In children with thyroid dysfunction, it seems related to attentional and hyperactive-impulsive symptoms (Rovet, Alvarez, 1996; Hauser, Soler, Brucker-Davis, et al., 1997). In a double-blind placebo crossover trial of thyroid supplementation, only one of nine children with ADHD and normal thyroid function improved compared with five of eight with ADHD and resistance to thyroid hormone (Weiss, Stein, Refetoff, 1997). Thus, thyroid treatment does not seem promising in children with ADHD with normal thyroid function but would seem the treatment of choice for those with thyroid dysfunction. Therefore, all children with ADHD should be screened for historical and physical exam signs of possible thyroid dysfunction (Weiss, Stein, in press).

Deleading. Animal data (e.g., Silbergeld, Goldberg, 1975) document hyperactivity as one symptom of chronic lead poisoning and suggest that lead-induced hyperactivity depends on blood lead levels and can be reversed by chelation (Gong, Evans, 1997). In humans, the level considered toxic for subtle neuropsychiatric symptoms has declined with increasing knowledge, with some authors placing it as low as single digits (Kahn, Kelly, Walker, 1995) and many

recommending 10 mcg/dL as the threshold. Whether such lead levels correlate with behavioral and cognitive measures is the subject of some controversy, partly depending on the sample size and consequent power. David and colleagues (1976) openly treated 13 children who had hyperkinetic (HK) reaction and blood lead levels greater than 25mcg/dL with penicillamine (CaEDTA if allergic to penicillin); the 7 with no other probable medical cause of their HK reaction improved in teacher hyperactivity rating (ES = 1.4; $p<.01$) and parent hyperactive-impulsive rating (ES = 2.2; $p<.05$) but not significantly in teacher inattention rating (ES = 0.6), whereas the 6 with another probable medical cause did not improve. In a double-blind placebo-controlled 12-week trial, David and colleagues (1983) randomly assigned hyperactive children with "minimally elevated lead levels" (mean, 28 ± 6 mcg/dL) to either penicillamine plus methylphenidate placebo (n = 22), methylphenidate (5–40 mg/day) plus penicillamine placebo (n = 11), or double placebo (n = 11); compared with placebo, penicillamine improved Conners teacher hyperactivity scores (ES = 1.6; $p<.001$), parent Werry-Weiss-Peters hyperactivity scores (ES = 0.7; $p<.05$), and CGI (ES = 1.4; $p<.01$); across measures the penicillamine group did nonsignificantly better than the methylphenidate group. Thus, it appears that deleading would be the treatment of choice for children with ADHD who have blood lead elevations in the range treated by Oliver and associates. To how low a blood lead level this treatment should extend is a research question of high priority.

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Behavioral and Medication Treatments for Attention Deficit Hyperactivity Disorder: Comparisons and Combinations

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Background

Abundant evidence has accumulated over the last three decades indicating that both medication and behavioral treatments are efficacious in improving the symptoms of attention deficit hyperactivity disorder (ADHD) (Richters, Arnold, Jensen, et al., 1995). Because of both the well-established efficacy of these two major forms of treatment and the lack of total normalization of symptoms and behavior with any single form of treatment for most children with ADHD, since the late 1970s investigators have contrasted the potential benefits of these two forms of treatment, alone and in combination. In particular, researchers have sought to determine whether the combination of these two approaches yields any advantages over unimodal (i.e., only medication or only psychotherapeutic approaches) treatments. Although early investigators (Satterfield, Cantwell, Satterfield, 1979; Satterfield, Satterfield, Cantwell, 1981; Satterfield, Satterfield, Schell, 1987) reported reduced antisocial behavior among youngsters with ADHD receiving intensive, long-term combined (multimodal) treatment, these early studies did not use random assignment or employ appropriate control groups, and followup assessments were hampered by attrition.

Since Satterfield and colleagues' (1979) first report, a total of 15 well-controlled studies have been conducted that have compared psychostimulant medication, alone and in combination with various psychotherapeutic approaches, including parent training in behavioral modification approaches, child-focused cognitive treatments, social skills training, other forms of behavioral therapy or contingency management, and combinations of these psychotherapeutic approaches (see Table). These 15 studies were identified through two major sources: first, the Agency for Health Care Policy and Research commissioned a systematic review of seven major areas concerning the safety and relative efficacy of various ADHD treatments. This review, completed by the McMaster University Evidence-Based Practice Center (1998), constitutes the most rigorous review of treatment efficacy to date. This review identified a total of 13 studies conducted since 1971 that have tested various psychosocial and medication treatments alone and in combination. Of these, four studies did not focus on change in ADHD symptoms as a primary outcome and were therefore excluded from further consideration. Two additional studies from this group provided so little methodological detail concerning the nature of the medication and/or psychosocial treatment conditions as to render their findings uninterpretable, leaving only seven studies for review. Beyond this small group of studies, however, we identified an additional eight studies of significant interest, some ongoing and in prepublication status, others completed,

Table 1. Behavioral, medication, and combined treatments of ADHD: comparative studies

Authors, year	Sample	Design	Duration	Type of PS	Type of Med	Outcome Measures	Results
MTA Coop Group, 1998	n = 579; ages 7-9.9	4 groups: Individually titrated meds vs. intensive behavior training at home, school, and peer settings; vs. combination; vs. referral back to community providers.	14 mo, with 24 mo addn'l follow-up.	Parent BT in grp. and indiv. settings, classroom conting. Mgmt. tchr. consultn. summer tx prgrm.	Med blindly and individually titrated in 1st month, best dose and best drug found for each child, MPH doses 20-50 mg/day in 3 doses.	Teacher and parent rating scales, blind observers in class; WISC, WIAT, parent satisfaction, self-esteem, anxiety, depression, sociometrics, video-taped parent-child behavior ratings done blindly.	To be presented at Consensus Conference
Hechtman, Abikoff, 1995	n = 103; ages 6-10	MPH + multimodal tx ("MMT"); or MPH + PS "placebo" via an intense, but non-active PS tx; or MPH alone.	12 mo, with 12 more mo of 'booster' sessions.	Parent BT, indiv. Rx for child and prnt, acad. remed.; vs. "placebo" PS treatments of similar intensity vs. no PS tx.	Med response determined before randomiztn. indiv. titration 20-60 mg/day in 3 doses, vs. PBO; PBO challenge at 18 and 24 mo.	Teacher and parent rating scales, blind observers in class; WISC, WIAT, parent satisfaction, self-esteem, anxiety, depression.	− MPH + multimodal tx (MMT) = MPH alone = MPH + PS placebo for all comparisons.

Table 1. Behavioral, medication, and combined treatments of ADHD: comparative studies (continued)

Authors, year	Sample	Design	Duration	Type of PS	Type of Med	Outcome Measures	Results
Horn, Ialongo, et al., 1991, 1993	n = 96, ages 7-11	3x2:factorial: med = low or hi dose vs. PBO, PS = none, or Parent Training + child Self-Control training (PT/SC).	12 90-min sessions, 9 mo follow-up.	Parent Training + child Self-Control training. (PT/SC), plus 3 sessions of teacher consultation.	MPH 0.4 mg/kg; 0.8 mg/kg, or PBO.	12 checklists rating ADHD features, academics, or behavior.	– Repeated measures MANOVA showed sig. Main effects for Med and PT/SC status, and a sig. Interaction of Med status by PT/SC for *teacher* (but not parent) behavior ratings. Tchr. Hyperkinesis Index showed sig. Interaction with Med x BT/SC over time. PBO alone, Lo dose alone, and PBO+PT/SC did not yield pre-post improvements. Lo dose + PT/SC equivalent to Hi dose alone and Hi dose with PT/SC. PT/SC + Lo dose led to significant improvement over PBO + PT/SC, Lo dose, and PBO only. – PT/SC led to increased knowledge of behav. principles. – Direct child measures showed sig. Main effects for Med status only, including WRAT, self-concept, CPT commission errors, and observational ratings. – 9-month followup indicated that children receiving PT/SC showed continued accumulation of parent-reported benefits after the end of treatment, compared with Med only subjects who showed no further gains or modest deterioration.

Table 1. Behavioral, medication, and combined treatments of ADHD: comparative studies (continued)

Authors, year	Sample	Design	Duration	Type of PS	Type of Med	Outcome Measures	Results
Schachar et al., 1997	n = 91	2x2; Meds: MPH vs. PBO, PS: Parent training vs. parent.	12 mo	Behav. parent training vs. regular parent support grps.	3-4 wk open titration; then 0.7 mg/kg b.i.d. vs. PBO.	Parent and teacher behav. ratings; WISC-R; anxiety scale, self-esteem.	– Substantial attrition in PBO group (only 29 of 45 adhering after 4 mo; of these only 18 taking PBO meds regularly); substantial "cross-overs" preclude comparisons.
Klein, Abikoff, 1997	n = 89; ages 6-12	MPH; Behavior Therapy (BT) + PBO; BT+MPH.	8 weeks	BT at home and school: operant conditioning.	10 mg/day during 1st wk, individualized during rest of study; MPH or placebo.	Teacher and parent rating scales, blind observers: disruptive behavior, minor motor movement, solicitation.	– MPH + BT > MPH for tchr. cooperation, attention-seeking, impulse control, and trend for aggrsv. behavior. Also, tchr. and psychiatrist CGI ratings showed similar advantages for combo. Also, classroom obs. codes showed combo > MPH minor and gross motor; obs. overall severity ratings, for attention-seeking and impulse control. – For almost all other comparisons; MPH + BT = MPH > BT + placebo, or simply no diff. between med groups vs. BT.
Firestone et al., 1986	n = 73, age 5-9	Parent BT w/PBO; w/med; or med alone.	3 mo w/ 2-year followup	Parents read book: child management, then worked in groups.	Titration to optimal MPH dose, ranging from 10-30 mg/day.	Mean reaction time, impulsivity; academics, behav. ratings.	− Combo = med > placebo for decreasing hyperactivity and rxn time, but no academic effect; no residual effects found at 2-year followup.
Abikoff, Gittelman, 1985	50 kids ages 6-12	Compare 3 psy training programs, attn. cntl., cog. training, and med only	16-week cognitive program	Social prblm-solving, self-eval., verbal control of impulsive responses.	All kids on meds, MPH up to 80 mg qd, dex to 50, or pem to 150 mg.	Teacher/parent reports, achv. and cog. tests.	− Med = Attention cntl. + Med = CBT + Med on all outcomes.

Table 1. Behavioral, medication, and combined treatments of ADHD: comparative studies (continued)

Authors, year	Sample	Design	Duration	Type of PS	Type of Med	Outcome Measures	Results
Brown, et al., 1985	n = 40; ages 6-12	2x2 factorial, PS: Cog. behav. training (CBT) or Cog. Ther. (CT); Med: MPH or PBO.	3 mo	24 sessions, (1hr 2x/wk) modeling, self-verbaliz. strategy training.	.3 mg/kg MPH; doses ranged from 5-15 mg/day.	Attentional deployment and cog. style measures, behavioral and self ratings, achvmnt. tests.	− CT + MPH; CBT + MPH = MPH > CT, CBT. – Medication was continued at time of follow-up assessments.
Gittelman-Klein, Klein, Abikoff, et al., 1976	36 kids ages 6-12	Compare MPH, BT + MPH, and BT + PBO.	8-week cognitive behav. training program	Social problem-solving, self-eval., verbal control of impulsive responses.	All kids on meds, MPH up to 80 mg qd, dex to 50, or pem to 150 mg.	Teacher/parent reports, achv. and cog. tests.	− BT + Med = Med > PBO + BT, on all outcomes.
Brown, et al., 1986	n = 40; ages 6-12	Cognit. behav. training (CBT); MPH; combo, and untreated.	3 mo	24 sessions, (1hr 2x/wk) modeling, self-verbalization, and strategy training.	.3 mg/kg MPH; doses ranged from 5-15 mg/day.	Attentional deployment and cognitive style measures, behavioral and self ratings, achievement tests.	− CT + MPH = MPH > CT > control for attention; only MPH improved behavior. No differences in academic measures – Medication discontinued at follow-up assessment. – Medication effects dissipate rapidly, and testing children off medication shows decrement of gains achieved while on medicine.
Long et al., 1993	n = 32, ages 6-11	Compare "standard" MPH Rx vs. MPH + bibliotherapy.	2 mo, parent-paced program	Parents given BM protocol reading material.	All kids on meds, doses indiv. adjusted per clinician.	Teacher/parent reports, parental knowledge of behav. principles.	– Med + Bibliotherapy > Med alone for parents' and teachers' ratings of behav. probs. Trend (p<.06) for improvement in parents' knowledge in Med + BiblioRx group.
Kim et al., 1998	n = 24, ages 5-11	Compare MPH only vs. MPT + PT, vs. wait list.	9 wks + 4 wks of 'booster' sessions	Not noted, except for "weekly" sessions.	MPH 0.5-0.7 mg/kg total daily dose.	Parent behav. ratings; home situations, par-child relations, Tx satisf.	– MPH + PT generally showed greater gains than med only across all outcomes. Statistical tests uncorrected for multiple comparisons.

Table 1. Behavioral, medication, and combined treatments of ADHD: comparative studies (continued)

Authors, year	Sample	Design	Duration	Type of PS	Type of Med	Outcome Measures	Results
Carlson et al., 1992	n = 24, ages 6-12	2x3 factorial: low or hi dose vs. PBO, regular class vs. BM (behavioral mod.) classroom.	8-week summer treatment program	BM class w/ token econ., vs. "regular" class.	0.3 mg/kg or 0.6 mg/kg MPH vs. PBO.	Daily home report card, accuracy of work, off-task behavior.	− PS + 0.3 mg/kg MPH equivalent to 0.6 mg/kg for behavioral effects; only MPH improved academics. 0.3 mg/kg = BM + PBO
Hinshaw et al., 1984	n = 24 ages 8-13	Med vs. PBO, CBT vs. extrins. reinf.(x-over factorial design).	2 days in 5-week summer program	Reinforced self-eval.; Match Game = behav. mod.	Individualized doses, ranging from 5-40 mg MPH q.d.	Direct observ. of appropriate and neg. social interactions.	− Med + CBT > med or CBT > PBO, extrinsic reinforcement, or PBO + extrinsic reinforcement alone.
Thurston, 1979	n = 18, age 6-9	Wait list control vs. Med vs. PT + Med	4-6 wks	Parent training by behavioral therapist.	10 mg MPH, 2x/day.	Behaviors: activity level and impulsivity.	− No significant differences in impulsivity for any groups, PT + Med > med > control for decreased activity level.

that were not included in the McMaster review. Thus, there were 15 studies available for this review. Fourteen of these 15 studies employed complete random assignment across all treatment arms, whereas 1 contrasted 2 different classroom-based treatments, within which subjects were randomly assigned to different medication doses. With one exception, sample sizes of these studies were relatively modest, ranging from 18 to 103 subjects.

Given the fact that most of these studies utilized 3 or 4 treatment groups (sometimes more), 14 of these 15 studies are underpowered to establish the presence of any incremental benefits of combination over unimodal treatments, except for moderate-to-large effects. For example, based on a review of established literature (MTA Cooperative Group, 1995), the likely advantage of combined treatments (medication plus psychotherapy) over unimodal treatment has been estimated to have an effect size $d = \sim 0.4$, over and above the already substantial and well-established effect size $d = 1.0$ of stimulant medication versus placebo. With *alpha* set at .05, *beta* = .20, power = .80, with an assumed effect size $d = .40$ for any 2 group contrast (i.e., unimodal vs. combined treatment, one-tailed comparison), 75 or more subjects would be needed *per treatment arm*. Even this small-to-moderate estimated effect size may be generous, given the probability that only a subgroup of children would show a substantial incremental benefit from the combined versus unimodal treatments. The only study to date that has had sufficient power to examine unimodal versus additive effects, as well as to explore which subgroups might require combined treatments, is the recently completed Multimodal Treatment Study of Children with ADHD (the MTA study), which randomized 579 subjects to 4 treatment arms (Arnold, Abikoff, Cantwell, et al., 1997; Greenhill, Abikoff, Arnold, et al., 1996).

A second major difficulty with treatment studies so far has been the fact that most have been relatively short term, with treatments lasting generally no more than 3 months. Only two studies have spanned a longer active treatment period—the Multimodal Treatment study (MMT) by Hechtman and Abikoff (1995) (12 months of active treatment) and the MTA (14 months of active treatment). The longer period to assess treatment outcomes is of great interest because among the critical outcomes of ADHD and its treatments must be included the onset and maintenance of comorbidities, such as oppositional and conduct problems, school failure, decreased self-esteem, and substance use. An exclusive focus on ADHD symptoms alone is insufficient to examine the more wide-ranging and far-reaching outcomes of clinical interest.

A third difficulty with comparative treatment studies to date is that most psychosocial treatments have not been sufficiently intensive. Given the well-known difficulties with generalization and maintenance of psychosocial treatment effects (Richters, Arnold, Jensen, et al., 1995), it is questionable whether the likelihood that any relatively modest, single-setting, short-term psychosocial treatment is sufficiently robust to secure longer term benefits. Only two studies have been of sufficient intensity to offer some promise of maintenance of treatment gains after the immediate treatment period (the MMT and MTA studies).

A fourth difficulty with studies until now is that most have not optimally adjusted the treatment, whether medication or behavioral, to the child's specific level and type of symptoms. In the case of medication, this would require some form of individual titration to achieve optimal symptom control versus standard dosing procedures (e.g., mg/kg, fixed dose, etc.). With psychosocial/behavioral treatments, this would require the careful selection of target symptoms

and behaviors, toward which the psychosocial treatments should be directed. Only 5 of the 15 studies identified above conducted individual titration of medication to achieve an optimal response for each child, and only 2 conducted this titration under double-blind conditions (MTA and MMT studies).

Previous Studies' Findings

Despite the limitations of past studies, a review of the major findings of these 15 studies is illustrative and provides evidence in a number of instances of the relative benefit of various unimodal and combined treatment approaches. Findings from the largest and most rigorously controlled treatment studies are detailed briefly below.

Klein and Abikoff (1997) performed an 8-week experimental clinical trial comparing twice-daily stimulant medication, behavior therapy plus placebo medication, and the combination of behavior therapy plus active medication. These investigators found that the medication-only and combination groups outperformed the behavior-therapy-only group, despite the considerable improvements that accrued to the behavior-treatment-only condition. The two medication groups were statistically indistinguishable on most, but not all, measures. Specifically, the combined group showed significantly more improvement than the medication-only group in teacher ratings of cooperation, impulse control, and attention-seeking behavior. Similar findings for attention-seeking behavior and motor activity were reported by blind observers as well. Compared with children treated with medication alone, significantly more children treated with combination therapy were rated by teachers and psychiatrists (but not parents) as clinically improved. Interestingly, only the combined-treatment group yielded full normalization in several crucial functional domains. Unfortunately, the active treatment period spanned only 8 weeks, and modest sample sizes precluded determination of which subgroups of children (e.g., by comorbidity or parental psychopathology status) benefited most from combined treatment.

In a 2x3 factorial design study with 96 children with ADHD, Horn and colleagues (1991) examined the additive and interactive effects of methylphenidate (placebo, low-dose, and high-dose) and two psychosocial treatment groups (none vs. parent behavioral training and child self-control training [PT/SC]). Results showed significant main effects for Medication and PT/SC status and a significant interaction of Medication status *x* PT/SC for teacher (but not parent) behavior ratings. Moreover, teacher Hyperkinesis Index ratings showed significant interactions with *Med x PT/SC* status over time. The result of examination of these findings was most consistent with the interpretation that placebo, low-dose, and low-dose-plus did not yield meaningful pre-post improvements. In addition, findings suggest that low dose + PT/SC condition was equivalent to the high dose alone and high dose with PT/SC conditions. Moreover, in post hoc analyses, PT/SC + low dose proved significantly superior to low dose only. In contrast with these promising findings, direct child measures showed significant main effects for Medication status only, including academic measures, children's self-concepts, continuous performance task measures, and observational ratings.

Interestingly, 9 months posttreatment, Horn, Ialongo, and colleagues (Ialongo, Horn, Pascoe, 1993) assessed 71 of their original 96 subjects. Their followup findings indicated that

children receiving the behavioral PT/CS treatment showed continued accumulation of parent-reported benefits after the end of treatment, compared with Medication-only subjects, who showed either no further gains or even modest deterioration.

Thus, two of the largest and most rigorous short-term studies conducted to date, despite their relatively modest sample sizes and brief treatment periods, suggest that under some conditions, combined treatments appear to offer some advantages over Medication-only treatments for some outcomes of interest. In addition, these studies, as well as the majority of smaller sized or otherwise less methodologically stringent studies noted in the Table, suggest that medication treatments alone are generally superior to psychosocial-only treatment over a range of short-term outcomes when tested in head-to-head comparisons. These conclusions are consistent with the McMaster University Evidence-Based Practice Center report, titled The Treatment of Attention-Deficit/Hyperactivity Disorder: An Evidence Report, recently completed for the Agency for Health Care Policy and Research (1998).

Although evidence for *additive* effects of medication and behavioral procedures has not always resulted from extant investigations, *complementary* benefits have been reported. Thus, medication may provide benefits in domains like impulsivity or hyperactive behavior, whereas psychosocial interventions may improve behavior at home during unmedicated periods (e.g., Horn, Ialongo, Pascoe, et al., 1991; Pelham, Murphy, 1986). In addition, combined treatments have enabled a reduction in stimulant medication dosage needed for optimal behavior control in other studies (Horn, Ialongo, Pascoe, et al., 1991; Pelham, Schnedler, Bologna, et al., 1980; Pelham, Schnedler, Bender, et al., 1988).

Although most studies to date suggest clear superiority of medication over behavioral treatments in the short term, as well as the possible incremental benefit of combination treatments over medication-only treatments under some conditions, it is not clear from these findings whether a treatment that is most effective in the short term offers similar advantages in the long term. Some clues to this as a real possibility are found in the report by Ialongo and colleagues (1993), who noted that children receiving the PT/SC treatments during the 4-month treatment period showed evidence of continuing gains at 9 months posttreatment, compared with subjects receiving only medication, where no further gains or even modest deterioration was noted. Thus, examination of studies that have employed longer term treatments is essential, both to examine the extent to which these longer term treatments bode potentially different outcomes as a function of treatment duration and to take more fully into account the development of children with ADHD over time as their development is impacted by various forms of treatment.

Long-Term Treatment Studies

A recent study by Schachar and colleagues (1997) is one of the few randomized treatment studies of relatively long duration. The authors compared the effectiveness of yearlong treatment with methylphenidate (MPH) plus parent training (PT), MPH plus parent self-help and advocacy (SH), placebo plus PT, and placebo plus SH. Although no evidence was found for the efficacy of the PT interventions, either alone or in combination with MPH, the study was hampered by limited sample sizes, a 50-percent crossover rate to active medication in the placebo groups

(parents had the latitude to request reassignment to the alternative treatment during the course of the study), and poor parental participation (25 percent of parents never attended any parenting sessions, and those attending averaged only 40 percent attendance across all sessions). Other limitations included the b.i.d., 5-days-a-week MPH-dosing regimen, perhaps accounting for the fact that few behavioral improvements were reported at home.

Hechtman and Abikoff (1995) conducted a 12-month treatment study comparing stimulant alone, stimulant plus psychosocial placebo treatment, and stimulant plus active multimodal psychosocial treatment (parent training/counseling, social skills training, academic skills training and remediation, and individual psychotherapy). The 12-month active treatment period was augmented by an additional 12-month followup period during which subjects received monthly booster sessions to sustain the potential benefits of treatment. This study failed to demonstrate any evidence of superiority of combined treatments over stimulant alone, whether at the 12-, 18-, or 24-month assessment points. Moreover, rechallenging children with placebo at 18 and 24 months resulted almost universally in significant symptom relapse, regardless of the group to which the children had been assigned. However, as noted above in the discussion of the problems with studies to date, definitive interpretation of the findings from this study may not be possible, given power limitations resulting from the small number of subjects per treatment group (33 or 34) and some evidence that the 2 combined treatment groups had fewer children meeting ADHD criteria by study end (10 percent for both vs. 20 percent for the medication-only group). Also, inclusion in this study was limited to youngsters who had already demonstrated short-term benefit with MPH, precluding any head-to-head comparison of the two unimodal treatments and already giving the medication condition a slight edge in subsequent comparisons. Moreover, this study did not include intensive direct contingency management or a psychosocial-only treatment group, and children who met full criteria for conduct disorder were not eligible for inclusion in the study. Nonetheless, before the MTA, the MMT had been the most intensive and well-designed study.

The MTA Study

The inconsistent results so far have not yielded definitive information to guide clinical practice and policy. Design limitations in previous studies include short duration, small sample sizes, failure to include the most severely impaired, children with comorbid ADHD; restriction of samples to stimulant responders; failure to include the most intensive behavioral therapy; and failure to compare alternative yet credible treatments. The MTA, which included a very intensive, integrated psychosocial treatment (alone and in combination with medication), was developed to clarify the discrepant reports concerning relative merits of medication and psychosocial treatments, test possible benefits of combined treatments over short- and long-term durations, and compare these more intensive state-of-the-art treatments with the less intensive treatments generally available in the community. There were 579 children, ages 7 to 9, with ADHD treated at 6 different performance sites (96 to 98 per site). Subjects were randomly assigned to one of three manualized, intensive, 14-month treatments (medication plus brief supportive care, intensive behavioral treatment alone, or both) or to community standard care. Assessments included repeated measures (up to 14 months) of core ADHD symptoms; aggression and oppositional-defiant symptoms; anxiety/depression; social skills; academic

achievement; parenting measures; objective classroom observations and peer ratings; and videotaped, blindly scored ratings of parent-child interactions (Arnold, Abikoff, Cantwell, et al., 1997; Greenhill, Abikoff, Arnold, et al., 1996).

Final analysis of the MTA end-of-treatment outcome data is being completed and will be presented at the Consensus Development Conference.

Summary and Conclusion

Generally speaking, careful medication management (MM) alone appears consistently superior to psychosocial-only (PS) treatments across all studies that have conducted rigorous head-to-head comparisons of ADHD symptoms. The superiority of MM over PS for other areas of functioning (i.e., non-ADHD symptoms) is not well established, however. Across studies, combined cognitive therapy (CT) and MM approaches usually appear comparable in achieving short- and long-term treatment gains, although there is evidence in three of the four most rigorous studies conducted to date (Horn, Ialongo, Pascoe et al., 1991; Klein, Abikoff, 1997; MTA Cooperative Group, 1995) that for some outcomes, CT offers some advantages over MM alone.

Additional followup analyses of the long-term outcomes of the MTA subjects will be needed to determine whether PS or CT treatments offer increasing advantages over MM strategies as subjects mature. In addition, careful exploration of which subjects seem to benefit most from which forms of treatment will be needed. For example, if a subset of subjects with certain characteristics (e.g., comorbidity) can be shown to specifically require and benefit from CT and PS treatments, substantial benefits to these patients may accrue with targeting of such treatments to their specific needs. Similarly, more efficient guidelines and policies can be established to guide clinicians, health care providers, and third-party payors.

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Matching Patients to Treatments

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A primary goal in working with individuals with attention deficit hyperactivity disorder (ADHD) is to optimize the match between patients and treatments. This is a key clinical issue for a number of reasons. First, as attested to in the voluminous amount of treatment literature (Spencer, Biederman, Wilens, et al., 1996; Hinshaw, Klein, Abikoff, 1998), there are several treatment strategies available in the ADHD clinical armamentarium, including pharmacotherapy, psychosocial treatment (particularly behavioral interventions), and multimodal interventions, which combine pharmacologic and behavioral treatment. Second, for most individuals with ADHD, no one treatment, including stimulant medication, results consistently in improvement across all key functional domains. Third, ADHD is associated with a wide range of comorbid conditions. The high rate of comorbidities, coupled with individual differences in other salient child and family characteristics, increases the need to match individual patients with the most appropriate treatment regimen.

Knowledge about patient-to-treatment matching is gleaned most directly from studies that yield information about moderators of treatment effects. To this end, the most informative studies should have large sample sizes, include a heterogeneous group of children with ADHD and comorbid disorders (CD), obtain detailed demographics and information about parental and family functioning, and randomize youngsters to different treatment modalities. The National Institute of Mental Health (NIMH) Multimodal Treatment Study of Children with ADHD (MTA) (Arnold, Abikoff, Cantwell, et al., 1997), in which 579 children were randomized to pharmacotherapy alone, psychosocial treatment alone, the treatment combination, or community treatment, is the only study with all of these characteristics. Analyses are currently under way to evaluate the impact of specific moderators, including initial symptom severity and impairment, comorbidity, prior treatment history, parental psychopathology, and family insularity, on treatment outcome. The results of these analyses are forthcoming; it is anticipated that they will be available in time for the Consensus Development Conference on ADHD.

There are other multimodal treatment studies that have evaluated and compared the efficacy of pharmacologic and behavioral treatment, alone and in combination, in children with ADHD (Hechtman, Abikoff, 1995). Unfortunately, because these investigations are characterized by relatively small sample sizes and/or comorbid exclusion criteria, they have been insufficiently powered to evaluate or detect patient-by-treatment interactions, as well as other potential moderator effects.

The treatment literature does, however, provide heuristic information about potential patient-to-treatment matching options. These findings take several forms. The first pertains to

studies that yield information regarding differential treatment effects on specific behaviors. For example, two randomized clinical trials offer suggestions regarding treatment of associated disruptive behaviors in ADHD. In one clinical trial, long-term (2-year) treatment with methylphenidate (MPH) was found to be as effective as the combination of MPH and intensive multimodal psychosocial treatment in reducing oppositional behaviors in children ages 7 to 9 years with ADHD and in reducing the percentage of children who met diagnostic criteria for oppositional defiant disorder (ODD) (Hinshaw, 1991). The second found that aggressive classroom behavior is reduced significantly not only with methylphenidate (a common finding with stimulant treatment) (Klein, Abikoff, 1997), but also with clinical behavior therapy alone (Klein, Abikoff, Klass, et al., 1997). Although not all children with ADHD are aggressive, the clinical relevance of this behavior is well documented, and replication of the efficacy of behavioral approaches in other naturalistic settings is important.

The second, more common set of studies pertains to investigations of medication response in youngsters with ADHD alone versus those with a comorbid disorder.

Conduct disorder. A recent placebo-controlled clinical trial indicates that youngsters comorbid with ADHD and CD benefit from short-term (5-week) treatment with methylphenidate. There were significant reductions in multiple aspects of CD, including overt and covert antisocial behavior with MPH (Klein, Klass, Abikoff, et al., 1994). These findings have also been demonstrated with longer term (1-year) MPH treatment (Tannock, in press) and suggest that stimulant medication may be an important treatment component in patients with comorbid CD.

Anxiety disorder. Anxiety disorders co-occur in approximately 25 percent of clinic-referred children with ADHD (Pliszka, 1989). Several studies suggest a less robust response to stimulants in the comorbid compared with the noncomorbid group. With stimulants, children with a diagnosed comorbid anxiety disorder (or with high levels of self-reported anxiety) are less likely to benefit from stimulants (and show a higher placebo response rate) (Tannock, Ickowicz, Schachar, 1995), demonstrate less improvement in working memory (Urman, Ickowicz, Fulford, et al., 1995), and show alterations in diastolic blood pressure (Taylor, Schachar, Thorley, et al., 1987). There are other indications that children with internalizing symptomatology do less well on stimulants, as indicated by reduced responsivity to stimulant treatment in children with ADHD with symptoms of emotional disorder (Du Paul, Barkley, McMurray, 1994), and a report of adverse medication response in ADHD children with high levels of parent-rated internalizing problems (Biederman, Baldessarini, Wright, et al., 1993).

Mood disorders. Evidence from a placebo-controlled trial suggests that tricyclic medication may ameliorate both ADHD and depressive symptomatology in children comorbid with ADHD and depression (Findling, 1996). In contrast, an open-label series of case reports suggests that individuals with co-occurring ADHD and major depression whose comorbid symptomatology did not improve with treatment with a single pharmacologic agent demonstrated substantial clinical improvement with combined stimulant and SSRI treatment (Mayes, Crites, Bixler, et al., 1994). These disparate findings call for controlled trials of single versus polypharmacy regimens in youngsters comorbid not only with depression but also with other internalizing disorders as well.

Mental retardation. Children with ADHD and mild mental retardation are likely to benefit from stimulant treatment, although the rates of improvement tend to be slightly lower (62-68 percent) (Aman, Kern, McGhee, et al., 1993; Jensen, Abikoff, in press) than the 80 percent rate typical in nonhandicapped children.

Future Research

There is still a relatively small empirical database that can inform on matching patients to treatments. In particular, several issues relevant to this decision-making process have gone almost entirely unexplored (Jensen, Abikoff, in press). For example, clinical wisdom suggests that parental ADHD or depression can compromise the implementation of behavioral treatments. These observations require empirical confirmation. Information is needed about how parental psychopathology, as well as family factors such as marital discord, impact on the effectiveness and ordering of treatment strategies. Also unknown is whether differential outcomes occur in families who are provided their preferred treatment(s) (e.g., medication and/or psychosocial treatment) versus those who are randomized to treatment. Finally, the ideal procedure for matching patients to treatments involves the application of validated tailored treatment strategies. To this end, research designs are needed that compare standard treatments with tailored approaches based on patients' needs, impairments, and goals. Coincidentally, parallel research efforts are called for in two areas: (1) the development of measures to assess these patient characteristics and (2) the development of clinical treatment algorithms that facilitate the formulation of tailored treatment strategies (Jensen, Abikoff, in press).

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Alcohol, Nicotine, Stimulants, and Other Drugs

Rachel G. Klein, Ph.D.

Concern about substance abuse in children with attention deficit hyperactivity disorder (ADHD) coincided with the development of pharmacotherapy for ADHD in the 1960s. The establishment of effective medications for behavior control in ADHD sparked the belief in some persons that drug treatment in childhood promoted drug-taking behavior and facilitated future drug abuse.

Another concern stems from nonprimate animal studies that show that an affinity for psychostimulants can be induced experimentally through early exposure to these compounds (Schenk, Partridge, 1997). Brain sensitivity to reinforcing properties of stimulants, secondary to drug exposure in childhood, could occur in humans. If so, stimulant abuse should be greater than other abuse in children with ADHD treated with stimulants.

Finally, it has been suggested that the use of stimulants, including nicotine, may serve self-medicating purposes in adolescents and adults with ADHD (Kaminer, 1992; Khantzian, 1985; Levin, Conners, Sparrow, et al., 1996; Pomerleau, Downey, Stelson, et al., 1995). This clinical model of drug abuse in ADHD also predicts that stimulants will be used preferentially.

Thus, several lines of reasoning foster the expectation that children with ADHD will be more likely to abuse stimulants than other compounds compared with individuals without ADHD. The hypothesis does not refer to a differential rate of substance use disorders (SUD) per se, but to a specific pattern of abuse. Although extant studies have not examined the question directly, relevant evidence can be derived from several investigative approaches.

Retrospective Reports of Childhood ADHD in Adults and Adolescents With SUD

Do adults and adolescents with distinct patterns of substance use or abuse report dissimilar rates of childhood ADHD? Several studies have assessed the presence of a childhood history of ADHD in adults with SUD, allowing a comparison of rates of ADHD across different types of substance abusers. All groups have elevated rates of ADHD compared with population rates. Findings, summarized in Table 1, do not point to a specific relationship between a childhood history of ADHD and type of substance abuse (Carroll, Rounsaville, 1993; De Obaldia, Parsons, Yohman, 1983; Eyre, Rounsaville, Kleber, 1982; Goodwin, Schulsinger, Hermansen, et al., 1975; Horner, Scheibe, 1997; Milin, Loh, Chow, et al., 1997; Rounsaville, Anton, Carroll, et al., 1991; Tarter, McBride, Buonpane, et al., 1977; Whitmore, Mikulich, Thompson, et al., 1997; Wood, Wender, Reimherr, 1983), except perhaps for a reduced rate of ADHD in opiate addicts relative to other types of SUD (Eyre, Rounsaville, 1982). Results are difficult to compare across studies for several reasons: (1) abuse of a single substance is almost never the rule, precluding clarity in the relationships reported; (2) approaches to assessing

Table 1. Rates of ADHD in individuals with substance abuse disorder

	N	% of ADHD	ADHD Definition
Alcohol (adults)			
Goodwin et al., 1975 (133 Danish male adoptees)	14	50% (vs. 15% in non-ADHD, $p<.01$)	Clinical Interview About Childhood
Tarter et al., 1977 (inpatients and outpatients)	66	Significant*	Self-Rating Scale of Symptoms
De Obaldia et al., 1983 (inpatients)	55	Significant†	Tarter's Self-Rating Scale
Wood et al., 1983 (inpatients)	27	33% Residual Type	Clinical Interview, Parent Rating Scale
Milin et al., 1997 (inpatients)	15	13% Childhood Only 27% Childhood and Adulthood 7% Adulthood Only	2 Self-Rating Scales (Child and Adult Symptoms)
Cocaine			
Rounsaville et al., 1991 Carroll and Rounsaville, 1993 (inpatient applicants and outpatients) (community Ss)	 298 101	 35% 24%	
Milin et al., 1997	21	57%	Self-Rating Scale
Opiates			
Eyre et al., 1982 (treatment applicants)	157	22%	Interview (?)
Mixed SUD			
Milin et al., 1997	21	57%	Self-Rating Scale
Horner and Scheibe, 1997 Adolescents: (4 outpatients) (26 inpatients)	30	50%	Diagnosed ADHD in Childhood or 3 Self-Rating Scales
Whitmore et al., 1997 Adolescents			
(inpatient males) (outpatient females)	285 82	11% 11%	Disc-C Diagnosis
(males) (females)	285 82	22% 25%	Disc-C: 8 ADHD Sx

*Significantly elevated in severe (primary) alcoholics (N = 38) compared with milder (secondary) cases (N = 28), psychiatric controls (N = 49), or normals (N = 27).

†Significantly elevated in severe (primary) alcoholics (N = 22) compared with milder (secondary) cases (N = 33), (19.00% vs. 10.67% Hk/MBD).

childhood ADHD vary greatly and are bound to yield divergent rates. Further complicating interpretation of results is (3) the suggestive evidence that referred drug abusers are more likely to report childhood ADHD than similar people in the community (Carroll, Rounsaville, 1993); (4) the findings of relatively poorer test-retest reliability of psychiatric diagnosis in current drug abusers than in past abusers (Bryant, Rounsaville, Spitzer, et al., 1992); and (5) poor agreement between reports of function provided by individuals with SUD and their relatives (Rounsaville, Kleber, Wilber, et al, 1981). It is probable that considerable error occurs in the retrospective assessment of childhood adjustment in populations of substance abusers. Consistent with this likelihood are some findings that the patients with and without ADHD are equivalent in levels of education and sex ratios. These findings call the validity of the childhood diagnosis into question since lowered educational attainment and a relative excess of males typify the ADHD syndrome.

Retrospective Reports of Drug Use and Abuse in Adults With ADHD

Another retrospective approach has been to obtain histories of substance use and abuse from adults and adolescents with ADHD. Do the adults with ADHD have a unique profile of drug use or abuse? The two relevant studies, summarized in Table 2, have found that marijuana is the most frequently used and abused illicit compound, regardless of the presence of ADHD in adulthood (Biederman, Wilens, Mick, et al., 1995; Murphy, Barkley, 1996). Thus, the evidence, admittedly scant, does not suggest a specific association between a current adult diagnosis of ADHD and stimulant abuse. A report of cigarette smoking notes that adults with ADHD have elevated rates of smoking, as well as relatively less likelihood of desisting; these findings support a self-medicating model of nicotine abuse in ADHD (Pomerleau, Downey, Stelson, et al., 1995). However, comparisons are between a clinical sample of adults with ADHD and the general population, rather than with appropriately matched individuals.

Table 2. Rankings* of substances reported abused by adults with ADHD

	Biederman et al., 1995		Murphy and Barkley, 1996	
	ADHD (N = 62/120)†	Comparisons (N = 73/268)†	ADHD (N = 172)	Comparisons (N = 30)
Alcohol	1	1	2	2.5
Marijuana	2	2	1	1
Cocaine	3	3	4	5
Stimulants	4	4	–	–
Hallucinogens	5	5	3	4
Sedatives	6	7	5	2.5
Opiates	7	6	6	6

*Among those with SUD.
†Nominator = Ss with a SUD; denominator = total N.

Retrospective Reports in the General Population

A total population of high school students was assessed for current substance use and childhood attention deficit, the latter rated by students and parents (Windle, 1993). Perusal of the results fails to reveal specificity in the relationships between type of substance used and childhood attention deficit (Table 3).

Table 3. Relationships of adolescent and parent ratings of childhood attention deficit with adolescents' ratings of substance use

	Self-Ratings of Attention Deficit		Parent Ratings of Attention Deficit (N = 479)*	
	Boys (N = 520)	Girls (N = 564)	Boys	Girls
Alcohol	0.19†	0.31†	0.23†	0.16‡
Cigarettes	0.14†	0.29†	0.09	0.17
Marijuana	0.14†	0.16†	0.13†	0.14‡

*N of girls and boys not specified.
† $p<.01$.
‡ $p<.05$.

Current Diagnosis of ADHD and Types of SUD in Adolescents

Some cross-sectional studies of SUD and ADHD have targeted adolescents with primary diagnoses of SUD, whereas others have examined SUD in adolescents with ADHD. A clinical sample of adolescent substance abusers, all of whom also had conduct disorder, was evaluated for the presence of ADHD (Horner, Scheibe, 1997; Thompson, Riggs, Mikulich, et al., 1996). The ranking of drugs used or abused does not distinguish between adolescents with and without a childhood history of ADHD (Table 4), although in one instance (Thompson, Riggs, Mikulich, et al., 1996) but not in the other (Horner, Scheibe, 1997), amphetamine abuse was the only significant difference between substance-abusing adolescents with and without ADHD (27 percent vs. 11 percent, respectively, $p = .02$). However, it is not clear that this contrast exceeds other group differences.

The nature of substance abuse in siblings of children with ADHD has been found to be opposite from the predicted pattern in that cigarette smoking was the most prevalent abuse in siblings *without* ADHD (Milberger, Biederman, Faraone, et al., 1997b). Siblings with ADHD did not differ from normal comparisons in pattern of substances abused; alcohol was favored by both, followed by other drugs and cigarettes (Milberger, Biederman, Faraone, et al., 1997a) (Table 5).

Table 4. Ranking of substance used/abused in adolescents with SUD and ADHD

	Thompson et al., 1996		Horner and Sheibe, 1997	
	ADHD (N = 64)	Not ADHD (N = 79)	ADHD (N = 15)	Not ADHD (N = 15)
Alcohol	2	2	1.5	1
Cigarettes	3	3	NI	NI
Marijuana	1	1	1.5	2
Cocaine	5.5	5	4.5	3
Stimulants	5.5	6.5	6	6
Sedatives	9	8.5	7	7.5
Hallucinogens	4	4	3	4
Inhalants	7	6.5	4.5	5
Opiates	8	8.5	8	7.5

Table 5. Ranking of substances abused by siblings of ADHD children

	Siblings		
	ADHD (N = 28)	Not ADHD (N = 121)	Normals (N = 117)
Alcohol*	1	2	1
Cigarettes†	2.5	1	2.5
Other Drugs*	2.5	3	2.5

*Milberger S, Biederman J, Faraone SV, et al., 1997b.
†Milberger S, Biederman J, Faraone SV, et al., 1997a.

Prospective Studies of Children With ADHD

Longitudinal studies of clinical samples of children with ADHD provide the most cogent evidence regarding the specificity of drug use and abuse in persons with a history of ADHD. In all instances, the majority had been treated with stimulants. Several investigations conducted over followup periods from 8 to 17 years do not support the expectation that stimulants are preferentially used by individuals with a documented diagnosis of ADHD in childhood (see Table 6) (Barkley, 1998, unpublished data; Barkley, Fischer, Edelbrock, et al., 1990; Klein, Mannuzza, in press; Mannuzza, Klein, 1998, unpublished data). Longitudinal studies of nonclinically identified children with ADHD (Hartsough, Lambert, 1987; Lambert, 1988; Lynskey, Fergusson, 1995) are consistent in failing to demonstrate a specific pattern of substance use among individuals who had been diagnosed with ADHD in childhood (Table 7).

Preferred Substances of Abuse in Individuals With a Childhood History of ADHD

If the self-medicating models of drug abuse or brain sensitivity are correct, individuals with a positive history of ADHD should have a preference for stimulants over other substances. The relative frequency of abused drugs, noted above, may not be a valid indicator of drug of choice, because market availability, rather than user predilection, may determine the form of abuse. To address the issue, several studies have inquired about the drug of choice (Table 8).

The expectation of preference for stimulants is not supported by studies of adolescents with SUD whose childhood history was elicited retrospectively (DeMilio, 1989; Horner, Scheibe, 1997). A controlled prospective 4-year followup of children with ADHD (Biederman, Wilens, Mick, et al., 1997) included clinic cases likely to have received stimulants. No evidence was found for preference for stimulants among the individuals with ADHD. A study of siblings of ADHD children and comparisons also failed to note a differential pattern of drug preference among siblings who themselves had ADHD compared with siblings without ADHD, or with normal comparisons (Milberger, Biederman, Faraone, et al., 1997b).

Comment and Summary

The expectation that children with ADHD are more likely to abuse stimulant drugs than their non-ADHD counterparts has been fostered by a social learning model of drug abuse, a model of sensitization to the reinforcing properties of stimulants, and a self-medication model of stimulant use in ADHD. Much of the empirical literature on types of substance abuse in childhood ADHD consists of retrospective studies. Although potentially heuristic, these studies are plagued by the proverbial limitations of retrospective reports. It is self-evident that the longitudinal prospective study of children with ADHD is methodologically superior to the others, but it is not without its own limitations. So far, it has been almost exclusively restricted to referred children with ADHD. None of the investigative approaches reviewed have generated support for a specific elevation of stimulant use and abuse in individuals with a past or current history of ADHD.

Table 6. Ranking of substances abused by ADHD children grown up (prospective studies)

	Hechtman and Weiss, 1986		Barkley et al., 1990		Barkley, 1998		Klein and Mannuzza, in press	
	ADHD (N = 61)	Comparison (N = 41)	ADHD (N = 123)	Comparison (N = 66)	ADHD (N = 148)	Comparison (N = 76)	ADHD (N = 194)	Comparison (N = 178)
Age: Range, M	21-33, 25		12-20, 15		19-27, 21		16-23, 18	
Alcohol	1	1	2	2	15	1.5	3	2.5
Cigarettes	–	–	1	1	–	–	1*	1*
Marijuana	2	2	3	3	1.5	1.5	2	2.5
Cocaine	3	3	4.5	4.5	3.5	3	5.5	5.5
Stimulants	5	4	4.5	4.5	3.5	4	5.5	5.5
Sedatives	–	–	–	–	5	5	5.5	5.5
Psychedelics	4	5.5	–	–	–	–	5.5	5.5
Opiates	6.5	5.5	–	–	–	–	8	8
Barbiturates	6.5	5.5	–	–	–	–	–	–

*Mannuzza S, Klein RG. New York Longitudinal Study, 1998. Unpublished data.

Table 7. Ranking of substances used by ADHD "community children" grown up (prospective studies)

	Hartsough and Lambert, 1987		Lynsky and Fergusson, 1995	
	ADHD (N = 54)	Comparison (N = 47)	ADHD* (N = 168)	Not ADHD (N = 778)
Alcohol	1	1	1	1
Cigarettes	3	3	2	2
Marijuana	2	2	–	–
Cocaine	4	4	–	–
Stimulants	5	5.5	–	–
Sedatives	6.5	8	–	–
Hallucinogens	6.5	5.5	–	–
Opiates	8	7	–	–

*ADHD = children rated 5 and 6, on 6-point scale, at age 8.

Table 8. Rates of preferred substances among children and adolescents with ADHD and SUD

	DeMilio, 1989		Horner and Scheibe, 1997		Biederman et al., 1997		Milberger et al., 1997b		
Substance	ADHD,* % (N = 12)	Non-ADHD, % (N = 44)	ADHD, % (N = 15)	Non-ADHD, % (N = 15)	ADHD, % (N = 13)	Non-ADHD, % (N = 8)	1† (N = 9)	2† (N = 17)	3† (N = 8)
Alcohol	17	30	47	33	–	–	–	–	–
Marijuana	17	7	7	27	100	100	89	94	87
Cocaine	17	21	47	40	8	0	14	35	12
Stimulants	–	–	0	0	0	13	0	17	25
Sedatives	–	–	0	0	–	–	33	6	62
Hallucinogens/ LSD	–	–	0	0	23	38	–	–	–
Opiates	–	–	–	–	–	–	0	12	25
Alcohol or marijuana first, then cocaine	50	43.2	–	–	–	–	–	–	–

*4 patients with intermittent explosive disorder.

†Group 1 = ADHD siblings; group 2 = non-ADHD siblings; group 3 = non-ADHD comparisons.

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Risk of Treatment Versus Nontreatment

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It is well established that large numbers of children diagnosed with attention deficit hyperactivity disorder[1] (ADHD) are treated with central nervous system stimulants and that a substantial portion of ADHD children develop substance use disorders. It is therefore inevitable that some stimulant-treated children will develop substance use disorders. Of course, this does not mean that stimulant treatment increases later drug use or causes substance use disorders. The real question is whether children with ADHD who are treated with stimulant medication become more involved with substances than comparable unmedicated children with ADHD.

A completely adequate prospective study of the long-term effects of treatment with stimulant medication is difficult to carry out because fully informed random assignment to either long-term medicated or unmedicated groups is ethically and pragmatically impossible. Most studies of the impact of central nervous system (CNS) stimulant treatment on the subsequent use of illegal substances have had to rely on naturally occurring groups of children who were unmedicated because they were less severely hyperactive, they had not responded to medication, or their parents declined medication—that is, unmedicated groups that may have differed from medicated groups in their risk for later substance abuse. Further, many early investigators studied initial experimentation with alcohol and marijuana in small numbers of young adolescent subjects who had barely entered the risk period for many illegal substances. Finally, few early studies controlled for the co-occurring oppositional and conduct problems that later proved to be more important predictors of substance involvement than ADHD as such (Barkley, Fischer, Edelbrock, et al., 1990; Biederman, Wilens, Mick, et al., 1997; Mannuzza, Klein, Bonagura, et al., 1991). All of these factors have combined to reduce the number of adequate and relevant studies of substance involvement in medicated and unmedicated children with ADHD.

Much of the early literature was reviewed by Kramer and Loney (1982). Major studies from that period (Beck, Langford, MacKay, et al., 1975; Blouin, Bornstein, Trites, 1978) described minimal effects of stimulant treatment on later substance use. In the adolescent followup phase of the Iowa study (to be described in more detail), there were relatively few medication-related differences in substance use experiences, but adolescents who had not been medicated had more experience with marijuana and binge drinking, as well as more drunk driving and alcohol-related police contacts, than their medicated counterparts (Kramer, Loney, Whaley-Klahn, 1981). The earliest studies of adult ADHD subjects (Hechtman, Weiss, Perlman, 1984) also failed to find increased substance involvement in medicated hyperactive individuals. During this period, Goyer, Davis, and Rapoport (1979) described a hyperactive (and aggressive)

[1]The modern term ADHD is used here to include largely overlapping populations of children who are referred to in earlier studies as having childhood hyperactivity, minimal brain dysfunction (MDB), the hyperkinetic reaction of childhood, and attention deficit disorder with and without hyperactivity. The application of the term ADHD does not imply that all members of an ADHD group have ADHD only, because many children with ADHD have additional complicating diagnoses.

teenaged boy who took more medication than prescribed and said it made him feel "high," and a similar case was later reported by Jaffe (1991). These cases, while important and sobering, appear to be isolated instances, and their relevance is mainly cautionary (Goldman, Genel, Bezman, et al., 1998). Subsequent accounts have suggested that, with appropriate care, substance-abusing adolescents and adults can be treated with methylphenidate (Schubiner, Tzelepis, Isaacson, et al., 1995).

The Iowa Study

Perhaps the most comprehensive database on substance use in medicated and unmedicated children with ADHD (Loney, Kramer, Salisbury, 1998) is based on a study of 219 Caucasian boys with ADHD who were born between 1954 and 1968, referred for outpatient evaluation and treatment, and followed up as young adults between ages 21 and 23. Because of nonsystematic assignment to physicians with different treatment preferences, 182 of these boys received a trial of stimulant medication, and 37 were unmedicated (their parents and teachers were given short-term, behaviorally oriented counseling). A few of the medicated boys (8 percent) discontinued medication within the first month, but 84 percent continued to take medication for at least a year (average duration of treatment, 36 months). The average daily maintenance dosage was 32 mg of methylphenidate. At young adult followup, a Medication Attitude Interview and Questionnaire were administered. A standard epidemiological instrument, the National Survey on Drug Abuse (NSDA), was used to survey attitudes about, exposure to, and involvement with a wide range of substances, allowing the study data to be compared with national norms obtained during a comparable period of time. A structured interview (SADS-L) was used to obtain adult psychiatric diagnoses. Hierarchical regression analyses were carried out to determine the relationship between childhood medication status and a set of variables measuring subsequent substance attitudes, intentions, exposure, and involvement, as well as substance-related adult psychiatric diagnoses. For each analysis, statistical controls were applied for the effects of the era in which each boy grew up (year of birth) and the severity of his childhood symptoms (inattention-overactivity and aggression-defiance).

Attitudes Toward Medication

Attitudes are important because little is known beyond anecdotal and "TV" evidence about how a large group of adults (the most credible informants) actually feel about their childhood treatment with CNS stimulants. More important, theories about the negative effects of medication often suggest that treatment causes later substance abuse by changing children's attitudes toward the use of substances (e.g.,"It's OK to use drugs"). The young Iowa men who had been medicated in childhood had generally negative recollections of many aspects of their treatment with stimulant medication—about two-thirds said they disliked taking their medication (62 percent), avoided taking it (67 percent), or considered it a nuisance (68 percent); many (42 percent) reported having been embarrassed about taking medication, and some (28 percent) said they were teased; and between 6 and 18 percent experienced unpleasant initial side effects (e.g., throwing up, stomachaches, headaches). However, most of them described presumably

positive effects of medication on their behaviors and feelings (63 percent reported that medication had made them calmer, 59 percent found it easier to concentrate, and 60 percent said that medication made it easier for them to control their temper). Upon reflection, about two-thirds of the medicated young men thought medication had been a good or partly good idea for them. Consistent with these reports, 17 percent of these medicated men reported ever having taken more than their prescribed amount of methylphenidate; about half of those did so before a test or a game. Although 15 percent reported that someone had wanted pills from them at least once, fewer than 3 percent reported ever taking their pills to feel good or get "high." And although 8 to 10 percent said that medication made them more likely to try other medications or drugs, 28 to 31 percent said that medication made them less likely to try other medications or drugs, and another 56 to 64 percent saw no relationship between their medication and subsequent use of medication or drugs (Kramer, Loney, 1998).

Relationships Between Early Effects of Medication and Attitudes Toward and Intentions To Use Substances

For a variety of substances, including tobacco and alcohol, over-the-counter medications, prescription drugs (barbiturates, tranquilizers, and stimulants), marijuana, glue, cocaine, LSD, heroin, and opiates, there were no discernible differences between medicated and unmedicated individuals in their attitudes toward use or users. Medicated individuals did not differ significantly from unmedicated ones in their intentions to use any of a variety of illegal substances in the future.

Relationships Between Early Medication and Exposure to and Involvement With Substances

Exposure was the sum of responses to two NSDA questions about whether the respondent had ever known someone who used the particular substance and whether he had ever had the chance to use the substance himself. *Involvement* was the sum of responses to three NSDA questions about whether the respondent had ever tried the substance (experimentation), whether he had used it in the past month (continuation), and whether he was among the most frequent one-third of users during that month (escalation).

For 6 of 11 surveyed substances—alcohol, illegal barbiturates and tranquilizers, marijuana, cocaine, and heroin—childhood medication was associated with neither exposure to the substance nor actual extent of involvement. Most notably, there was no significant association between having taken stimulant medication in childhood and overall involvement with illegal stimulants as an adult. There was, however, a statistical trend for *fewer* medicated than unmedicated boys to later try illegal stimulants at least once ($p = .059$). Medicated boys were older than comparable unmedicated boys when they first had an opportunity to use LSD ($p = .008$), but there was no apparent difference between the groups in their actual involvement with LSD. For two surveyed substances, glue and opiates, medicated boys were significantly *less* involved in later use than comparable unmedicated boys ($p = .03$ and .04, respectively). Involvement with tobacco was positively associated with the severity of aggressive symptoms in

childhood (p = .02), and there was also a weak trend (p = .07 one-tailed) for medicated boys to be less involved with tobacco as young adults.

Relationships Between Early Medication and Adult Psychiatric Diagnoses

Similar results were obtained when four adult psychiatric diagnoses were examined (alcoholism, drug use disorder, antisocial personality disorder, major depression). Significantly *fewer* medicated boys than unmedicated boys had adult diagnoses of antisocial personality disorder (p = .004) and alcoholism (p = .002).

Conclusions and Future Directions

Although these data have limitations for predicting the specific results of treating an individual child, they should alleviate the general concern that treatment with CNS stimulants such as methylphenidate (Ritalin©) has significant negative effects on children's subsequent attitudes toward or use of legal or illegal substances. The data demonstrated few differences between medicated and unmedicated groups in substance use attitudes, intentions, exposure, or actual involvement. Where there were differences between medicated and unmedicated groups, it was the unmedicated individuals who were more involved with substances and more likely to have developed adult alcoholism and antisocial personality disorders, suggesting that the risk of substance abuse and related psychiatric disorders is greater for children who are *not* medicated than it is for children who are. It is hoped that these data will be examined by those who advocate replacing medication with treatments of questionable effectiveness (Robbins, 1998).

Although the short-term effectiveness of treatment with CNS stimulant medication is undeniable, it is important to note that few other studies have produced convincing evidence for long-term positive effects of childhood medication. It is therefore important that additional ethically designed longitudinal studies of matched treated and untreated samples be attempted. Also, the association between aspects of early medication treatment (symptom reduction, dosage, side effects, treatment duration) and later substance abuse should be examined in existing longitudinal data sets.

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Attention Deficit Hyperactivity Disorder and Risk for Substance Use Disorders

Timothy E. Wilens, M.D.

The overlap between attention deficit hyperactivity disorder (ADHD) and alcohol or drug abuse or dependence (referred to here as substance use disorders [SUDs]) in adolescents and adults has been an area of increasing clinical, research, and public health interest. Onset of ADHD occurs in early childhood and affects from 6 to 9 percent of juveniles and up to 5 percent of adults. Longitudinal data suggest that childhood ADHD persists in 75 percent of cases into adolescence and in approximately 50 percent of cases into adulthood. SUDs usually begin in adolescence or early adulthood and affect between 10 and 30 percent of U.S. adults and a less defined but sizable number of juveniles. Recent reviews support an excessive and bidirectional overlap between ADHD and SUD.

The study of comorbidity between SUD and ADHD is relevant to both research and clinical practice in developmental pediatrics, psychology, and psychiatry with implications for diagnosis, prognosis, treatment, and health care delivery. For instance, impulsivity as part of ADHD may impair a patient's quality of life while adversely affecting substance moderation or abstinence and treatment retention. The identification of specific risk factors of SUD within ADHD may permit more targeted treatments for both disorders at earlier stages of their expression, potentially dampening the morbidity, disability, and poor long-term prognosis in adolescents and adults with this comorbidity.

In adolescents, there have been three recent studies assessing ADHD and other disorders in substance abusing groups. These studies indicate that approximately one-quarter of adolescents with SUD had current ADHD, with an overrepresentation of both mood and conduct disorders in these youth.

Studies of adults with SUDs are similar to those of adolescents. Including both alcohol and drug addiction, from 15 to 25 percent of adult addicts and alcoholics have current ADHD (See Table 1). Furthermore, adults with ADHD and SUD have been reported to have SUD chronicity, treatment difficulties, and poorer SUD outcomes.

An overrepresentation of SUD also has been consistently observed in studies of adults with ADHD. All of the eight investigations of adults with ADHD reported higher rates of SUD in adults with ADHD than in the general population: 17 to 45 percent of adults with ADHD have alcohol abuse or dependence and 9 to 30 percent have drug abuse or dependence. The risk of SUD developing over the lifespan in an individual with ADHD is twofold compared with adults without ADHD (52 percent vs. 27 percent, respectively). Hence, the aggregrate literature strongly indicates a bidirectional overrepresentaion of SUD and ADHD among subjects with these disorders.

Table 1. ADHD and substance use disorders overlap

Rate	Alcohol	Cocaine	Opiates	Polydrug
Studies (N)	3	2	2	2
Subjects (N)	120	450+	306	157
ADHD Rate (%)	33-71	10-35	5-22	17-21

Reference: Wilens, Biederman, Mick, et al., 1997.

The association of ADHD and SUD is particularly compelling from a developmental perspective because ADHD manifests itself earlier than SUD; therefore, SUD as a risk factor for ADHD is unlikely. Thus, it is important to evaluate to what extent ADHD is a precursor of SUD. Longitudinal studies of children with ADHD or children who develop SUD provide the most compelling data on this developmental hypothesis.

Prospective studies of children with ADHD have provided evidence that the group with conduct or bipolar disorders (BPD) co-occurring with ADHD have the poorest outcome with respect to developing SUD and major morbidity. For example, as part of an ongoing prospective study of ADHD, we found differences in the risk for SUD in ADHD adolescents (mean age, 15 years) compared with non-ADHD controls which were accounted for by comorbid conduct or bipolar disorders. In the older siblings of these probands, we were able to show that ADHD is an independent risk factor for the development of an SUD. These data support retrospectively derived data from ADHD adults indicating that ADHD was an independent risk for SUD and that there was an earlier age of SUD onset in adults with ADHD (mean age of full SUD, 19 years) compared with non-ADHD adult controls (mean age, 22 years, $p<.01$).

Clarification of the critical influence of ADHD treatment in youth on later SUD remains hampered by methodological issues. Whereas concerns of the potential kindling of specific types of abuse (e.g., cocaine) secondary to early stimulant exposure in children with ADHD have been raised, the preponderance of clinical data and consensus in the field do not appear to support such a contention. Nonrandomized investigations following adolescents and young adults with ADHD naturalistically treated with stimulants indicate that treated youth, particularly noted responders to treatment, were less likely to demonstrate subsequent irritable behavior and illegal drug use.

Similar to data from studies of children with ADHD, longitudinal research of children who later develop SUD also indicates that ADHD (plus conduct disorder) may be an important antecedent in some individuals who develop SUD. For instance, in the Chicago-based Woodlawn Study, children who were rated aggressive, impulsive, and inattentive as first graders had higher rates of substance use 10 years later as adolescents.

Cigarette smoking in youth is often a gateway to more severe alcohol and drug use disorders. In this context, an increasing body of literature shows an intriguing association between ADHD and cigarette smoking. For example, we found in boys that ADHD was a significant predictor for early initiation of cigarette smoking (before age 15) and higher risk for cigarette use. In addition, ADHD probands with comorbid conduct, mood, and anxiety disorders had especially high rates of cigarette smoking.

The presence of ADHD also appears to influence the transition into and out of SUD. Recent work indicates that ADHD and related comorbidities accelerate the transition from less severe drug or alcohol abuse to more severe dependence (1.2 years vs. 3 years, $p<.05$). Furthermore, ADHD may heighten the risk for a drug use disorder, particularly in individuals with an alcohol use disorder. Conduct or bipolar disorder co-occurring with ADHD tends to markedly heighten the risk for SUD and accelerate the process. ADHD also affects remission from SUD. In a study of 130 referred adults with ADHD and 71 adults without ADHD, all with a history of SUD, the rate of remission and duration of SUD were quite different in the ADHD subjects relative to controls: the median time to psychoactive substance use disorders remission was more than twice as long in subjects with ADHD as in control subjects (144 vs. 60 months, respectively), with SUD lasting more than 3 years longer in the adults with ADHD compared with their non-ADHD peers.

Family studies are highly informative in examining the nature of the association between two co-occurring disorders. The child and adolescent children of alcoholic and drug-abusing parents have elevated rates of ADHD compared with the children of parents without a substance use disorder. Conversely, elevated rates of SUD have consistently been demonstrated in controlled family studies of ADHD. The mode of SUD transmission in families with ADHD remains under study with a preferentially elevated risk for SUD in relatives of ADHD children with conduct disorder and models showing the independent transmission of ADHD and SUD in families.

Although the influence of prenatal substance exposure is confounded by many factors, such as the transmission of parental psychopathology, followup studies of children diagnosed with fetal alcohol syndrome demonstrate that two-thirds of these youth have ADHD in adolescence. In contrast, data in cocaine- and opiate-exposed youth do not support the teratogenic effects of these agents in producing ADHD in offspring.

The mechanism of SUD development in ADHD is probably multifactorial, including self-medication and family genetic vulnerabilities. Given that the demoralization and failure associated with ADHD are also independent risk factors for SUD, albeit lacking confirmatory data, the self-medication hypothesis is compelling in ADHD. Moreover, youth with ADHD plus conduct or BPD have poor judgment, aggressivity, and impulsivity, which may be particularly noxious for development of SUD during adolescence. Of interest are open reports in substance-abusing adolescents and adults with ADHD that show that treatment of ADHD with stimulants or antidepressants results in the reduction of both ADHD and SUD.

The robust findings of a family genetic component of SUD development, coupled with recent findings of postsynaptic dopamine D4 receptor polymorphisms association with ADHD,

suggest that a polygenic mechanism may be operant. It may also be that ADHD and early onset SUD may represent variable expressivity of a shared risk factor. Clearly, more work needs to be done to examine the contribution of psychiatric symptoms, deficits, and familiality to explain the relationship of SUD and ADHD.

In summary, there is a robust literature supporting a relationship between ADHD and SUD. Combined data from retrospective accounts of adults and prospective observations of youth suggest that juveniles with ADHD are at increased risk for cigarette smoking and SUD during adolescence. Youth with ADHD and bipolar or conduct disorder are at risk for very early cigarette use and SUD (i.e., beginning before the youth reach 16 years of age), whereas the typical age of risk for the onset of SUD accounted for by ADHD itself is probably between 17 and 22 years of age. Recent work suggests that ADHD youth disproportionately become involved with cigarettes, alcohol, and then drugs. Substance abusers with ADHD tend to prefer the class of drugs over alcohol, with no evidence of a preference for specific types of drugs. ADHD accelerates the transition from less severe alcohol or drug abuse to more severe dependence. Conduct or bipolar disorder co-occurring with ADHD tends to further heighten the risk for SUD and accelerate the process. Individuals with ADHD, independent of comorbidity, tend to maintain their addiction longer compared with their peers without ADHD. Given the prevalence and major morbidity and impairment caused by SUD and ADHD, prevention and treatment strategies for these patients need to be further developed and evaluated.

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Sensitization and the Risk of Exposure to Stimulant Medications

Peter W. Kalivas, Ph.D.

Behavioral sensitization refers to the progressive augmentation of certain psychostimulant-induced behaviors in individuals who repeatedly use the drugs. Although behavioral sensitization has been reported only in experimental animals using a broad spectrum of psychostimulants ranging from caffeine to cocaine, in humans clear psychostimulant sensitization has been reported only with the amphetamine-like psychostimulants (Pierce, Kalivas, 1997). Amphetamine-like psychostimulants include a number of drugs of abuse such as methamphetamine, cocaine, and MDMA (ecstasy). In addicts who repeatedly abuse these drugs, a well-documented sensitization profile emerges, which includes an increase in anxiety and paranoid ideation, sometimes culminating in neuropsychiatric disorders such as paranoid psychosis and panic attacks. In addition, there is some preclinical and clinical evidence that with repeated use, the abuse liability of these drugs may also sensitize, thereby increasing the propensity for relapse of drug-seeking behaviors (Bartlett, Halldin, Chapman, et al., 1997; Robinson, Berridge, 1993). Also classified as amphetamine-like psychostimulants are many drugs used to treat attention deficit hyperactivity disorder (ADHD), such as methylphenidate, dextroamphetamine, and pemoline. Of these drugs, only dextroamphetamine has been reported to produce behavioral sensitization. However, sensitization to dextroamphetamine occurred in individuals taking the drug for indications other than ADHD, such as using the drug for its anorectic properties (Ellinwood, Sudilovsky, Nelson, 1973). The focus of this abstract is to describe the pharmacological characteristics of drugs that produce behavioral sensitization and to provide a preliminary evaluation of the literature regarding possible induction of behavioral sensitization by the use of amphetamine-like psychostimulants in the treatment of ADHD.

Behavioral sensitization can be broken into two temporally and mechanistically distinct components, termed “initiation” and “expression” (Kalivas, Stewart, 1991). The initiation of sensitization is the process of developing the augmented behavior, whereas expression refers to the manifestation of the sensitized behavior. Thus, the repeated use of a psychostimulant such as cocaine initiates behavioral sensitization by binding to the dopamine transporter, increasing dopamine transmission in the brain, and ultimately producing long-term changes in neurotransmission both presynaptic and postsynaptic to the dopamine synapse (White, Kalivas, in press). During initiation, the primary behavioral response to cocaine is motor stimulation and a sense of well-being. Once initiated by repeated use, the expression of sensitized behaviors typically arises in response to the readministration of cocaine and manifests as anxiety, paranoia, and craving for more drug.

Requirements for the initiation of behavioral sensitization are both pharmacokinetic and pharmacodynamic. A primary pharmacokinetic requirement is that the drug be administered intermittently and that the organism be permitted time between drug exposures when blood and brain drug levels are near zero (Post, 1980). If amphetamine-like psychostimulants are

administered continuously to experimental animals, classic forms of behavioral sensitization do not initiate. A pharmacodynamic requirement appears to be an interaction with the dopamine transporter. All of the amphetamine-like psychostimulants that produce behavioral sensitization with intermittent administration bind dopamine transporters (Gatley, Pan, Chen, et al. 1996; Reith, Meisler, Sershen, et al., 1986). The question then arises as to what extent the use of methylphenidate or other amphetamine-like psychostimulants in the treatment of ADHD fulfills these requirements for the initiation of behavioral sensitization.

Methylphenidate fulfills the pharmacodynamic requirement by being a relatively potent antagonist of dopamine transport and increasing the extracellular concentration of dopamine (Hurd, Weiss, Koob, et al., 1989; Volkow, Gatley, Fowler, et al., 1996). Although relative affinities for the different monoamine transporters may affect the profile of the sensitized behaviors (White, Kalivas, in press) on the basis of the general pharmacological action of methylphenidate, the drug should be capable of producing behavioral sensitization. Indeed, in experimental animals, repeated injections of methylphenidate have been reported to induce behavioral sensitization of motor behaviors (Crawford, McDougall, Meier, et al., 1998; Gaytan, al-Rahim, Swann, et al., 1997). In contrast with the pharmacodynamic criterion, the use of methylphenidate in the treatment of ADHD may not meet the pharmacokinetic criterion. The drug is typically taken orally and in a continuous rather than intermittent fashion. Thus, the large swings in brain concentration that are optimal for inducing behavioral sensitization (i.e., intravenous administration and binges of drug-taking followed by periods of abstinence) are not associated with the treatment of ADHD. Indeed, the literature indicates that treatment of ADHD with psychostimulants may not lead to an increase in abuse of psychoactive substances (Klein, Wender, 1995; Levin, Kleber, 1995; Spencer, Biederman, Wilens, et al., 1996; St. Dennis, Synoground, 1996). However, there may be some motor sensitization indicated by the dose-related exacerbation of motor tics (Borcherding, Keysor, Rapoport, et al., 1990; Castellanos, Giedd, Elia, et al., 1997).

A final consideration is that in the treatment of ADHD, amphetamine-like psychostimulants are generally administered to prepubescent individuals, whereas psychostimulant sensitization is experimentally evaluated almost exclusively in adult experimental animals and addicts. However, most studies conducted to date in prepubescent rats indicate that with the appropriate dosing regimen, it is possible to induce behavioral sensitization with methylphenidate and other amphetamine-like drugs (Gaytan, al-Rahim, Swann, et al., 1997; McDougall, Duke, Bolanos, et al., 1994); in contrast with responses in adults, the sensitized behavioral responses may not be as enduring in prepubescent animals (Fujiwara, Kazahaya, Nakashima, et al., 1987; McDougall, Duke, Bolanos, et al., 1994).

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Stimulant Treatment as a Risk Factor for Nicotine Use and Substance Abuse[2]

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Children who have been diagnosed with attention deficit hyperactivity disorder (ADHD) are often treated with the central nervous system (CNS) stimulant methylphenidate. Although the therapeutic efficacy of methylphenidate has been established (Greenhill, 1992; Klein, 1993), very few studies have examined the long-term effects of treatment with the drug. In longitudinal research (Barkley, Fischer, Edelbrock, et al., 1990; Gittelman, Mannuzza, Shenker, et al., 1985; Lambert, 1988; Weiss, Hechtman, Milroy, et al., 1985), ADHD and childhood use of CNS stimulants have been shown to predispose children to early tobacco use and to adult use and dependence on tobacco and substances with stimulating properties (Hartsough, Lambert, 1987; Lambert, Hartsough, in press).

This investigation explores the predisposing properties of CNS stimulant medication in childhood in the uptake of regular smoking during the developmental period, daily smoking in adulthood, adult DSM-III-R psychoactive dependence diagnoses, and lifetime use of cocaine and stimulants. In addition to childhood CNS use, other independent variables in the analyses are a research diagnostic proxy for the severity of DSM-IV ADHD symptoms, severity of childhood conduct problems, gender, the age of initiation into tobacco, and birth year cohort.

There are four major, most likely complementary, explanations regarding the relationship of ADHD and CNS use to adolescent and adult use of substances.

The first hypothesis predicts that general behavior dysfunction in childhood and adolescence, characterized by psychosocial unconventionality or the presence of antisocial behavior (all of which are also prevalent among ADHD groups in adolescence), leads to both more smoking and more intensive substance use (Jessor, Jessor, 1980; Loney, 1980; Robins, 1980).

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Another perspective targets tobacco as a gateway drug and predicts that early tobacco use is likely to be common among all who use other substances (Fleming, Leventhal, Glynn, et al., 1989; Henningfield, Clayton, Pollin, 1990; Kandel, Yamaguchi, Chen, 1992). Tobacco dependence is an important addiction on its own merits, and tobacco also appears to be involved in the development of a variety of other drug dependencies.

Another hypothesis proposes that tobacco serves a self-medicating role for ADHD subjects and that initiation into and continued use of nicotine are sought because of its beneficial behavioral effects. Research with human subjects has suggested that both tobacco and cocaine may be used for self-medication, depending on the particular type of presenting symptomatology (Cocores, Davies, Mueller, et al., 1987; Rounsaville, Anton, Carroll, et al. 1991; Weiss, Mirin, 1986). Methylphenidate has pharmacological properties that closely resemble those of other stimulant drugs including cocaine and amphetamine (Robinson, Jurson, Bennett, et al., 1988; Volkow, Wang, Gatley, et al., 1996); therefore, repeated exposure to methylphenidate may be expected to produce effects similar to those engendered by repeated exposure to these other psychostimulants.

The fourth hypothesis is the methylphenidate/amphetamine sensitization hypothesis, founded primarily on animal studies. Pursuing a tobacco-cocaine sensitization hypothesis, animal research has shown that preexposure to nicotine predisposes rats to the reinforcing impact of cocaine (Horger, Shelton, Schenk, 1991). Likewise, evidence from the animal studies implicates the use of amphetamines as predisposing to the rewarding impact of cocaine (Schenk, Snow, Horger, 1991; Schenk, Valadez, McNamara, et al., 1993). The sensitization hypothesis posits that early exposure to either nicotine or amphetamines predisposes to adult stimulant and cocaine use because the increased neurochemical sensitization enhances responsiveness to cocaine's reinforcing properties. Thus, although subjects with ADHD may have more risk factors predisposing to adult tobacco and cocaine abuse, the fundamental processes involved in the sensitization hypothesis are thought to hold regardless of psychiatric symptomatology.

The participants in this investigation are adults who have been subjects since childhood in a prospective longitudinal investigation of the life histories of ADHD subjects and their age-mate controls. DSM-IV ADHD research diagnostic criteria based on 1974 parent and teacher ratings on the Children's Attention and Adjustment Survey (CAAS) (Lambert, Hartsough, Sandoval, 1990) of inattention and hyperactive-impulsive symptoms and age of onset of symptoms classified all 492 subjects on the presence and severity of ADHD in childhood. Of the 492 subjects, 22 percent were female and 23 percent were members of minority ethnic groups. Of the 492, 132 were classified as severe DSM-IV ADHD, 99 were moderate ADHD, 61 were mild ADHD, and 200 subjects did not satisfy DSM-IV ADHD research criteria. Of those originally receiving medical diagnoses of hyperactivity with no competing explanations for their condition (Lambert, Sandoval, Sassone, 1978), only 4 percent failed to satisfy the DSM-IV ADHD diagnostic proxy. On the other hand, 3 percent of the age-mate controls met the criteria for

DSM-IV ADHD and might have been identified as ADHD in 1974, when they entered the study, had the 1994 DSM-IV diagnostic criteria been used (American Psychiatric Association, 1994).

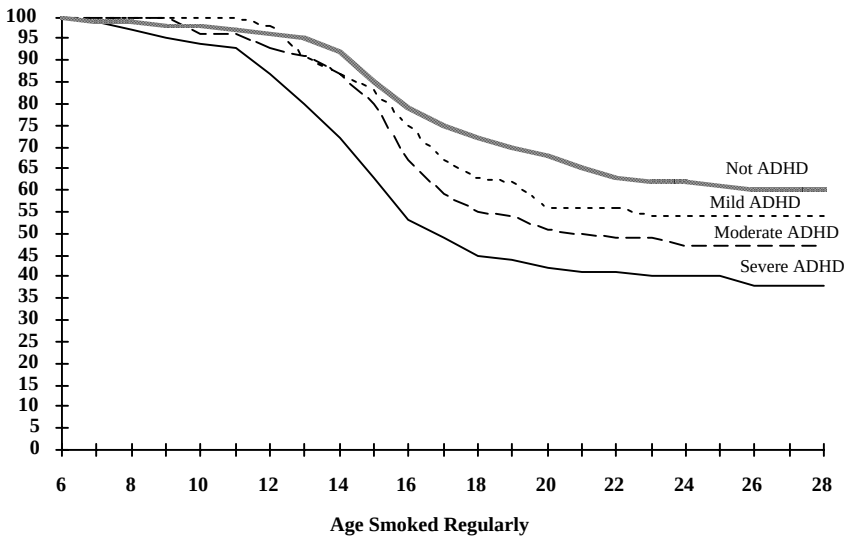
Histories of treatment interventions in childhood, derived from parent and subject reports, included the age at which CNS stimulants were first prescribed and duration of use. Among those subjects who used CNS stimulants, 69 percent used only methylphenidate, 16 percent used combinations of methylphenidate and other CNS stimulants, and 15 percent used other CNS stimulants (Dexedrine, Benzedrine, Cylert, or Deaner). CNS stimulants were used by 45 percent of the severe ADHD, 51 percent of the moderate ADHD, 15 percent of the mild ADHD, and 5 percent who were not classified as ADHD.

Other independent variables included severity (pervasiveness) of early ratings of conduct problems on the CAAS; age of initiation into tobacco; gender; and birth-year cohort groups. Social status and cognitive ability measures were explored as well.

Research goals were realized through use of an adult interview comprising eight major sections, among which were adult ADHD symptoms and treatment history, lifetime reports of tobacco use and current smoking status, and the Quick Diagnostic Interview Schedule, III-R (QDIS III-R) (Marcus, Robins, Bucholz, 1990). Adult interview protocols were obtained for 81 percent of the original 492 subjects (77 percent of those with ADHD and 86 percent of the controls), and analyses of differential loss indicated no appreciable impact on reported rates of tobacco and substance use that could be attributed to loss at followup (Hartsough, Babinski, Lambert, 1996).

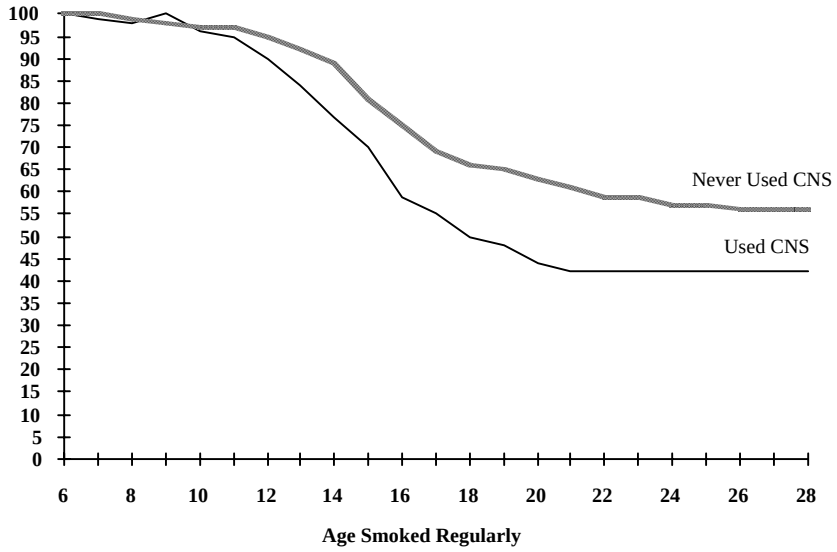
Three sets of statistical analyses were completed. The survival analyses (Cox, Oakes, 1984) of the age subjects became regular smokers during the child-adolescent-early adult developmental period used both ADHD and CNS use as independent variables. Next, chi-square statistics explicated the association between ADHD and CNS use and adult daily smoking. Logistic regressions were conducted with the QDIS III-R dependence measures of tobacco, cocaine, stimulants, marijuana, and alcohol. The dependency criteria do not assess high rates of use, but they do focus on using more than intended, difficulty in cutting down despite problems, and developing a tolerance to the drug. Logistic regressions were also conducted with lifetime use measures for tobacco, cocaine, stimulants, and use of cocaine and stimulants combined. For substances other than tobacco, lifetime use was divided into a low-use group (1 to 19 times) and a high-use group (20+ times). The results of the investigation were as follows:

1. Tobacco use in the survival analyses was measured as “age smoked on a regular basis.” Subjects who had never smoked were given a later age, and those cases were censored in the analysis. The survival analyses for severity of ADHD and use of CNS in childhood (Figures 1 and 2) show that both severe ADHD symptoms and childhood CNS treatment are childhood risk factors that predispose to earlier onsets of regular smoking in childhood and adolescence.



Overall comparison: Lee Desu Statistic 15.166, df = 3, $p \leq .01$. Pairwise comparisons: Severe vs. Never, $p \leq .000$; Severe vs. Mild, $p \leq .05$; Severe vs. Moderate, $p \leq .10$; Moderate vs. Never, $p \leq .10$.

Figure 1. Survival analysis—percentage not smoking regularly during the developmental period by ADHD classification.



Overall comparison: Lee Desu Statistic 5.825, df = 1, $p \leq .05$.

Figure 2. Survival analysis—percentage not smoking regularly during developmental period for subjects who used CNS treatment before they became regular smokers and those who never used CNS.

2. There is evidence for a "protective" effect of CNS use. Survival analysis that groups subjects by the age CNS terminated (Figure 3) shows that the longer the CNS treatment was used, the longer the delay in the "age smoked on a regular basis." This suggests that subjects begin regular smoking when CNS treatment ends, implicating support for both the self-medicating and sensitization hypothesis. Even so, the adult rates of daily smoking for each of the three CNS treatment groups are comparable, indicating that this protective effect may be short-lived.

3. Childhood CNS treatment for more than 6 months is significantly related to rates of adult daily smoking (Figure 4). Rates of daily smoking (Figure 5) in adulthood are significantly higher for ADHD (Severe and Moderate groups combined) compared with Not ADHD (Mild and Not ADHD combined).

4. The logistic regressions of the independent variables with adult smoking and substance use variables produced the following results:

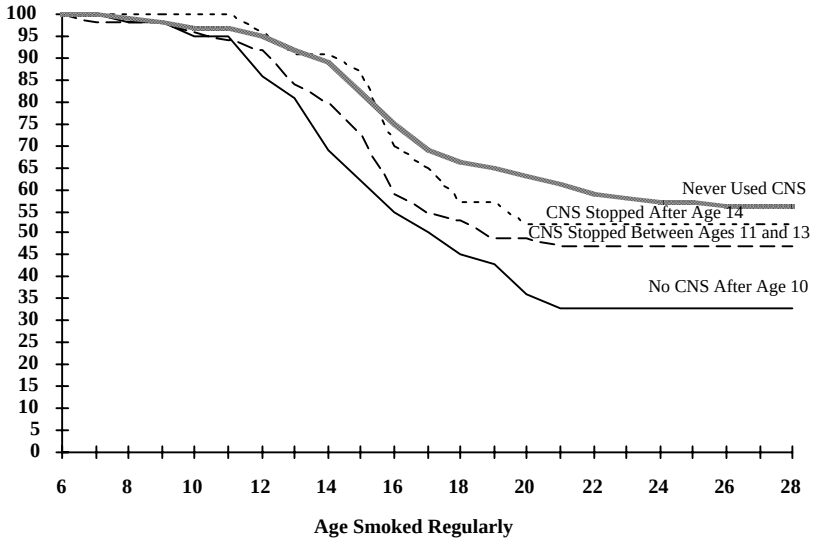
    a. There was a significant odds ratio for early initiation into tobacco in the regressions for all of the DSM-III-R dependence diagnoses. Severity of ADHD was significantly related to tobacco, cocaine, and stimulant dependence but not to marijuana and alcohol dependence. There was a significant odds ratio for CNS stimulants in the prediction of cocaine dependence. Although early initiation into smoking was prevalent for all substance dependencies, ADHD contributed significantly to the predictions for dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants. Subjects with severe ADHD symptoms are more likely to become involved with substances with stimulating properties and have greater difficulty reducing or eliminating their use.

    b. Adult daily smoking and lifetime use of cocaine and stimulants were predicted by early initiation into smoking and use of CNS stimulants for a year or more. This supports hypotheses on the early use of nicotine and CNS stimulants as sensitizing agents in greater lifetime use of tobacco, cocaine, and stimulants.

    c. There was a significant odds ratio for gender only for alcohol and marijuana dependence, with males more likely to be dependent. Severity of ADHD was not related to marijuana or alcohol dependence.

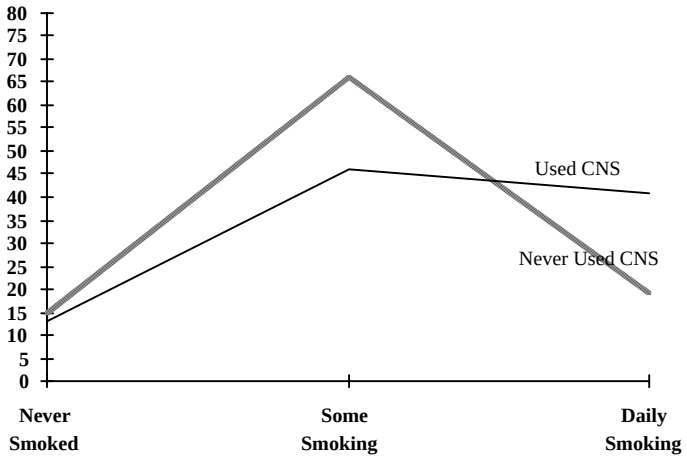
    d. Support for the stimulant sensitization hypothesis was shown by significant odds ratios for CNS treatment in the regressions for adult daily smoking, cocaine dependence, lifetime use of stimulants, and a combined measure of lifetime use of both cocaine and stimulants.

5. When subjects who became cocaine-dependent were grouped as (1) neither smoker nor CNS user, (2) CNS user only, (3) smoker only, and (4) smoker and CNS user, there was a significantly higher rate of cocaine dependence for subjects who were both smokers and CNS users (Figure 6).



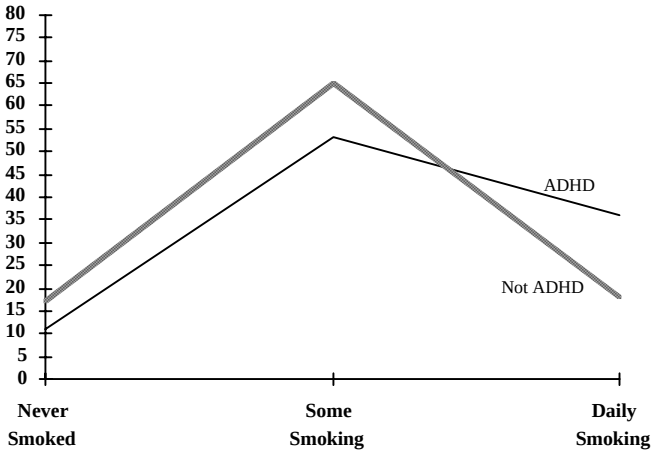
Overall comparison: Lee Desu Statistic 15.280, df = 3, $p \leq .01$. Pairwise comparisons: no CNS after age 10 vs. no CNS, $p \leq .001$; no CNS after age 10 vs. off CNS after age 14, $p \leq .10$.

Figure 3. Survival analysis—percentage not smoking regularly during developmental period for subjects with different CNS stimulant medication histories.



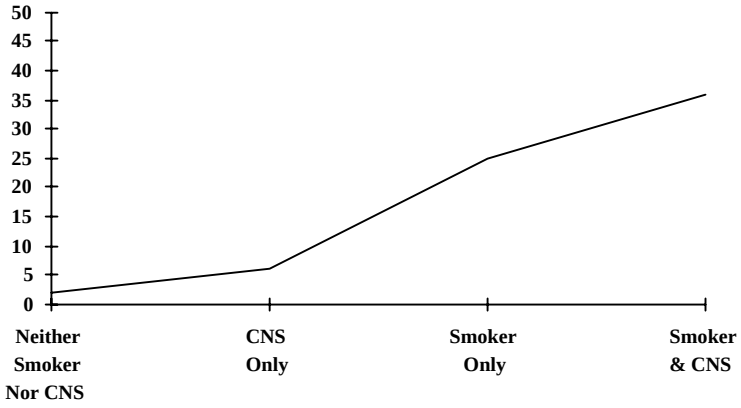
Pearson $X^2_{df=2} = 23.156$, $p \leq .000$; Mantel-Haenszel $X^2_{df=1} = 13.850$, $p \leq .000$.

Figure 4. Adult smoking status for subjects with CNS treatment in childhood compared with those who never used CNS treatment (percentage).



Pearson $X^2_{df=2}$ = 16.835, $p \leq .001$; Mantel Haenszel $X^2_{df=1}$ = 13.818, $p \leq .001$.

Figure 5. Adult smoking status for ADHD and not ADHD subjects (percentage).



Pearson $X^2_{df=3}$ = 52.61, $p \leq .000$; Mantel-Haenszel $X^2_{df=1}$ = 50.689, $p \leq .000$. Among those who were cocaine-dependent, 62 percent were ADHD and 39 percent were not ADHD.

Figure 6. Adult cocaine dependence as a function of childhood ADHD, CNS treatment, and smoking history.

No support was apparent for the problem behavior hypothesis of higher rates of smoking and substance abuse. It is important to distinguish between childhood evidence for conduct problems based on parent and teacher ratings and subsequent adolescent diagnoses of conduct disorders and oppositional defiant disorders. Other investigators (Hinshaw, 1987; Loeber, Stouthamer-Loeber, 1998; O'Donnell, Hawkins, Abbott, 1995) have summarized evidence to refute the commonly held belief that individuals who have a history of early aggression always persist in their aggressive behavior. A developmental model of aggression is the more reasonable approach. Ratings of subjects' behavior in this study occurred when they were on average 9 years old. Among those classified as having severe and moderate conduct problems will be those who develop both conduct disorders and/or oppositional defiant disorder in adolescence and those with transitory aggressive behavior in childhood whose problems will not persist past adolescence. Grouping subjects into the life-course, transitional, and late-onset types of aggressive behavior will be necessary to provide explanatory evidence for the relationship between types of childhood conduct problems and adult substance use.

This prospective longitudinal study of ADHD and age-mate control subjects, reconfigured according to research diagnostic proxies for severity of DSM-IV ADHD, has provided evidence that childhood use of CNS treatment is significantly and pervasively implicated in the uptake of regular smoking, in daily smoking in adulthood, in cocaine dependence, and in lifetime use of cocaine and stimulants. The severity of ADHD and early onset of tobacco use are significant risk factors for adult use and dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants. Implications for the self-medication and sensitization hypotheses are explored.

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Diversion, Trafficking, and Abuse of Methylphenidate

Gretchen Feussner

Methylphenidate (MPH, Ritalin®) is classified as a Schedule II stimulant under the Federal Controlled Substances Act (CSA). In response to a 1994 petition by Children and Adults With Attention Deficit Disorder (CH.A.D.D.) and the American Academy of Neurology to lower the regulatory controls on MPH, the Drug Enforcement Administration (DEA) conducted an extensive review of the use, abuse liability, actual abuse, diversion, and trafficking of MPH. This presentation will provide a summary of these data with updates where possible.

Since 1990, the DEA has observed a dramatic increase in the production and use of MPH. Each year, the DEA is required by law to establish an aggregate production quota (APQ) for each Schedule I and II controlled substance to meet the legitimate medical, scientific, industrial, and exporting needs for the United States. The MPH quota has increased from 1,768 kg in 1990 to 14,442 kg in 1998 (Figure 1). Before 1991, domestic sales reported by the manufacturers of MPH remained stable at approximately 2,000 kg per year. In 1997, domestic sales reached nearly 10,000 kg. These increases in production and use are even more striking when compared with worldwide data (Figure 2). According to the United Nations, the United States produces and consumes about 90 percent of the world's production of MPH (INCB Report, 1996).

Figure 1.

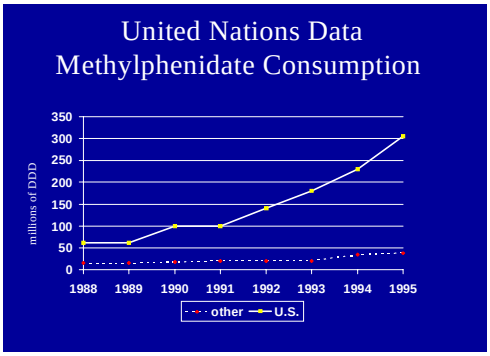

Figure 2.

MPH use can be evaluated using the DEA database ARCOS (Automation of Reports and Consolidated Orders System). This system tracks Schedule II controlled substances from point of manufacture to a location where it will ultimately be distributed to the consumer. Consumption is defined as those quantities received by pharmacies, hospitals/clinics, practitioners, and teaching institutions. Analyzed on a per capita basis by State or zip code area, ARCOS data indicates that there is wide variability in the use of MPH from one State to another, and from one community to another within a State. This variability is consistent with epidemiological studies conducted in Michigan and New York, using actual prescription data, and suggests both over- and under-identification of ADHD (Rappley, 1995; DEA Report, 1996). Those States with the highest levels of MPH use per 10K population are listed in Table 1.

Table 1. 1997 MPH consumption: 10 highest users

Rank	State	Grams per 10K
1	Delaware	373
2	Virginia	350
3	Michigan	334
4	New Hampshire	332
5	Iowa	329
6	Montana	317
7	South Dakota	307
8	Wisconsin	303
9	Ohio	298
10	Minnesota	294

Note: 1997 U.S. average = 223 grams per 10K. Hawaii, Alaska, and California have the lowest (114, 119, 129, respectively).

Abuse Liability

An extensive scientific literature spanning more than 30 years of research unequivocally indicates that MPH has a high abuse liability (for specific citations see DEA Report, 1995):

- MPH is self-administered by laboratory animals and humans;
- MPH produces discriminative stimulus effects similar to d-amphetamine and cocaine in laboratory animals and humans;
- MPH will substitute for d-amphetamine and cocaine in a number of paradigms using both animal and human subjects;
- Like d-amphetamine and cocaine, chronic, high-dose administration of MPH in animals produces psychomotor stimulant toxic effects, including weight loss, stereotypic movements, and death; and
- In clinical studies, MPH produces behavioral, psychological, subjective, and reinforcing effects similar to d-amphetamine and cocaine.

Actual Abuse

A significant body of literature is available that describes the actual abuse of MPH and consequences associated with that abuse (for specific citations see DEA, 1995). Like amphetamine and cocaine, abuse of MPH can lead to marked tolerance and psychic dependence.

MPH can be abused orally, or tablets can be crushed and either snorted or dissolved in water and injected. The pattern of abuse is characterized by an escalation in dose, frequent episodes of binge use followed by severe depression, and an overpowering desire to continue the use of this drug despite serious, adverse medical and social consequences. Typical of other CNS stimulants, high doses of MPH often produce agitation, tremors, euphoria, tachycardia, palpitations, and hypertension. Psychotic episodes, paranoid delusions, hallucinations, and bizarre behavioral characteristics similar to amphetamine-like stimulant toxic effects have been associated with MPH abuse. Severe medical consequences, including death, have been reported. Although the majority of the cases cited in the literature pertain to adults, two case studies profiled adolescents who abused their prescribed MPH medication.

Unlike amphetamine, methamphetamine, and cocaine, where illicit manufacturing and smuggling into the United States account for the vast majority of available drugs for abuse, pharmaceutical products diverted from legitimate channels are the only sources of MPH available for abuse. Diversion of MPH has been identified by drug thefts, illegal sales, prescription forgery, and various scams involving doctor shopping. From January 1990 to May 1995, there were 1,937 incidents of MPH theft reported by DEA registrants. Most reports were generated from pharmacies and most thefts were associated with night break-ins. An analysis of the data entered into the drug theft reporting system from January 1990 to May 1995 indicated that MPH ranked in the top 10 most frequently reported controlled drugs stolen from registrants. From January 1996 to December 1997, about 700,000 DUs of MPH were reported to our drug theft database. Night break-in, armed robbery, and employee theft are the three major sources of this diverted MPH. Also, a significant number of thefts have occurred at unregistered locations, primarily at schools and homes where MPH supplies are kept. It is important to note that many schools have more MPH stored for student daytime dosing than is available in some pharmacies. While State and Federal laws require accountability of controlled substances by licensed handlers, no such regulations are imposed at this level. In addition, a review of practices employed by schools for the handling of medication indicated that most schools did not have a nurse dispensing medication, few schools kept records of drugs given to students, and many schools allowed students to carry or administer their own medication.

Information from DEA case files and State investigative services indicate that MPH is sought after by a wide range of individuals (from street addicts to adolescents). Ohio, for example, has experienced significant diversion of MPH. From March 1979 to January 1994, MPH ranked second among pharmaceutical drugs reported for false or forged prescriptions. The Ohio Board of Pharmacy identified more than 100,000 MPH tablets stolen from Ohio pharmacies (18 cases involving pharmacists) between 1987 and 1994. Numerous States identified "Attention Deficit Scams." (A parent or other adult takes a child who purportedly has ADHD to a number of physicians to obtain MPH prescriptions; the adult obtains the drug for his or her own use or to sell or trade for other drugs.) In the early 1980s, Missouri Medicaid found that about 10,000 tablets per month were being diverted in this manner.

Investigative files and forensic laboratory data indicate that MPH has been involved in the following criminal drug-trafficking activities: street sales as determined by undercover buys, multi-state distribution rings, multi-drug distribution rings (with cocaine, LSD, marijuana, hydromorphone, diazepam, and anabolic steroids), and smuggling from Mexico.

The magnitude and significance of diversion and trafficking of MPH are comparable to those associated with pharmaceutical drugs of similar abuse potential and availability (for example, morphine sulfate). There is little doubt that the lack of clandestine production, Schedule II controls, and predominant use in the treatment of ADHD in children have limited the illegal use of this drug. However, recent reports of MPH misuse/abuse among adolescents and young adults are particularly disturbing, since this group has the freest access to this drug. Reports from numerous States and local municipalities indicate that adolescents are giving and selling their MPH medication to friends and classmates, who frequently crush the tablets and snort the powder like cocaine. Anecdotal reports from students and faculty on college campuses indicate that MPH is being used as a study aid in the same manner that amphetamine was used on campuses in the 1960s.

The extent to which adolescents are abusing MPH is unknown. The following data suggest that the number is small but growing. In 1994, the national high school survey (Monitoring the Future) reported that about 1 percent of all seniors in the United States used Ritalin during the previous year without a doctor's order. In 1997, that percentage increased to 2.8. In 1996, there were 1,725 estimated emergency room mentions for MPH in DAWN (Drug Abuse Warning Network), of which about 27 percent (634 mentions) were for children ages 10 to 17. In 1990, there were 271 mentions for MPH in DAWN. A 1996 phone survey conducted in Georgia found that about 1.1 percent of the adolescent respondents admitted to using Ritalin to get high (DEA Report, 1996). DEA's survey of three States (Wisconsin, South Carolina, and Indiana) found that about 30 to 50 percent of the adolescents in treatment centers were reporting "nonmedical" use of MPH. MPH was not, however, identified as their primary drug of abuse (DEA Report, 1996).

In summary, the DEA review shows that MPH has a high abuse potential and is associated with a degree of diversion, abuse, and trafficking similar to that for other pharmaceutical Schedule II substances. Information from physicians, parents, schools, poison control centers, adolescent treatment centers, surveys, and law enforcement data suggested that a growing number of adolescents were using this drug illicitly, that the primary source was individuals who have been prescribed this drug for ADHD, and that adolescents do not view abuse of this drug as serious. Physicians, parents, and school officials need to be alerted to take the necessary steps to safeguard against the diversion and abuse of this drug.

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Availability of Stimulant Medications: Nature and Extent of Abuse and Associated Harm

James R. Cooper, M.D.

The abuse potential of the stimulants used in the treatment of attention deficit hyperactivity disorder (ADHD) is well documented. Amphetamines and methylphenidate produce reinforcing effects both in populations that abuse multiple drugs and among stimulant-trained laboratory animals in a variety of behavioral paradigms (Martin, Sloan, Sapira, et al., 1971; Ellinwood, Cohen, 1971). Research among abusers of multiple drugs reveals dose-related liking scores for both of these drugs. Although pemoline is reported not to be self-administered in cocaine-dependent rhesus monkeys (Schuster, Woods, Seevers, 1969), it shares common relevant biochemical and behavioral effects with amphetamines (Mueller, Hsiao, 1980; Fuller, Perry, Bymaster, et al., 1978). Moreover, a number of marketed prescription and over-the-counter phenylethylamines and cocaine possess qualitatively similar clinical and preclinical properties albeit varying quantitative differences among individual drugs (Woolverton, English, 1997; Chait, Uhlenhuth, Johanson, 1986a; Chait, Uhlenhuth, Johanson, 1986b; Gawin, Ellinwood, 1988). Reports of actual abuse and illicit diversion of amphetamines and related phenylethylamines, methylphenidate, and pemoline both in the United States and internationally further document the abuse liability of these medications (Willey, 1971; Parran, Jasinski, 1991; Connell, 1968; Cohen, 1975; Pemoline, 1988).

Notwithstanding the preclinical abuse potential and the actual abuse of stimulants among the population that abuses multiple drugs, the nature and extent to which exposure to stimulant medications in children and adolescents with ADHD predicts subsequent stimulant abuse are less well understood and remain controversial. The preclinical and clinical abuse liability studies demonstrate clear individual differences in the reinforcing properties in animals and humans exposed to stimulants (Davidson, Finch, Schenk, 1993; Piazza, Deroche, Rouge-Pont, et al., 1997). Preclinical stimulant abuse liability studies alone do not predict risk of abuse in the general population or within subpopulations of those with medical illnesses, irrespective of reinforcing efficacy data (DeWit, Uhlenhuth, Johanson, 1987). Many patients exposed to stimulant medications never misuse or abuse their medication (Hechtman, Weiss, Perlman, 1984; Spier, 1995; Masand, Tesar, 1996; Lambert, Hartsough, Sassone, et al., 1987). However, subpopulations of patients with ADHD have been identified who are at risk to abuse nicotine (Hughes, 1997; Hartsough, Lambert, 1987) and other stimulants (Schenk, Davidson, 1997) and sedatives, including alcohol (Carroll, Rounsaville, Bryant, 1993). Furthermore, ADHD is overrepresented in adult SUD (substance use disorder) populations. Comorbid conduct disorder, antisocial personality, and bipolar disorder have been identified as mediating factors for substance use disorder (SUD) (Herrero, Hechtman, Weiss, 1994; Carroll, Rounsaville, 1993; Ziedonis, Rayford, Bryant, et al., 1994; Wilens, Prince, Biederman, et al., 1995; Biederman, Wilens, Mick, et al., 1995; Hechtman, Weiss, 1986; Gittelman, Mannuzza, Shenker, et al., 1985; Mannuzza, Klein, Bessler, et al., 1998; Milberger, Biederman, Faraone, 1997; Wilens,

Biederman, Mick, et al., 1997; Biederman, Wilens, Mick, et al., 1997; Ball, Carroll, Rounsaville, 1994). The limitations of this association between ADHD and SUD have been reviewed elsewhere (Wilens, Spencer, Biederman, 1995; Levin, Kleber, 1995).

Over the last 10 years, there has been a significant increase in the annual production quotas of methylphenidate and amphetamine. Media reports (Attention, 1995; Agency, 1996) and law enforcement reports (Drug Enforcement Administration, 1995; Drug Enforcement Administration, Oct. 1995) suggest a proportional increase in morbidity and mortality associated with the increased availability of methylphenidate based primarily on its intrinsic abuse potential and anecdotal reports of methylphenidate abuse, diversion, and public health consequences. However, a causal relationship has not been clearly established. An increase in availability alone does not necessarily predict an increase in abuse and consequences given the existing preclinical and clinical abuse liability research. Although the public health risks associated with stimulant abuse are documented, most reports of abuse and associated consequences occur among the population that abuses multiple drugs (MMWR, 1995; Spensley, Rockwell, 1972; Gunby, 1979; Chillar, Jackson, Alaan, 1982; Zemplenyi, Colman, 1984; Abiuso, 1977). Reports in the literature of abuse, diversion, and consequences among patients with ADHD are anecdotal and uncommon (Garland, 1998; Goyer, Davis, Rapoport, 1979; Jaffe, 1991; Fulton, Yates, 1988). No analysis currently exists with regard to the nature and extent of the abuse and associated consequences of these medications relative to their increased availability or to other licit and illicit stimulants.

Available national data will be reviewed to determine the extent to which increases in availability of and exposure to these medications have affected morbidity and mortality associated with their use. Where available, these data will be compared with other stimulants with known abuse potential.

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A National Perspective on Treatments and Services for Children With Attention Deficit Hyperactivity Disorder

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Purpose

This review accomplishes four aims: (1) it summarizes available data from national and local studies on trends in services for children with ADHD, (2) it summarizes studies on types of treatments or services provided to children with ADHD, settings in which such care is given, and types of providers, (3) it describes types of barriers preventing access to mental health services for children with ADHD from the perspectives of children, caregivers, and clinicians, and (4) it identifies areas for further research.

Background

Treatment planning depends upon having reliable estimates of the need for and the use of mental health services. Despite rising estimates of childhood mental disorders, before 1989 mental health service use was not assessed in most studies of children's mental health needs (Horwitz, Hoagwood, Stiffman, et al., 1998; Leaf, Alegria, Cohen, et al., 1996), nor were reliable measures of such services available. However, recent population-based studies that include symptoms or diagnoses and service-level data are now available to characterize patterns of care for children with specific disturbances of behavior or affect and to model the relationship between service need and service provision.

Method

Data from two national studies, four community epidemiological studies, and a review of published literature are presented to describe the status of services, treatments, and barriers to care for children with ADHD. In this review, treatments and services are defined broadly to include the following: prescription of psychotropic medications (usually stimulants), outpatient mental health counseling, psychotherapy, health counseling, diagnostic services, referrals, followup visits, and school services (usually counseling or special classes). There are many other kinds of services provided in communities, such as respite care, after-school care, specialized day care, and parent management training, but no data on these services for children with ADHD were located.

National findings presented here are from the National Ambulatory Medical Care Survey (NAMCS),[3] conducted by the National Center for Health Statistics, and the Child Behavior Study (CBS), conducted by two large practice-based primary care research networks. Trends in services are described from analyses of NAMCS, covering the years 1989, 1991, 1993, 1995, and 1996. NAMCS uses a multistage probability design of samples of medical practices within primary sampling units and patient visits within practices. The basic sampling unit is the visit to medical practices engaged in office-based, patient care. For these analyses, a sample was constructed of all children ages 0 to 17 seen by any physician and coded with an ICD-9 diagnosis of attention deficit hyperactivity disorder. All analyses of NAMCS data refer to this sample.

The CBS, conducted by Pediatric Research in Office Settings (PROS) and the Ambulatory Sentinel Practice Network (ASPN), included 401 pediatric and family practice clinicians across 44 States, Puerto Rico, and Canada. A total of 21,150 visits were registered, 9.5 percent of which were children ages 4 to 15 identified by the clinician as having attention deficit hyperactivity problems. This group of 2,007 comprised the study sample for this national dataset.

The four community epidemiological studies include the Great Smoky Mountains Study (GSMS) (Costello, Angold, Burns, et al., 1996), a longitudinal study of psychiatric disorders and service need in rural North Carolina; the Caring for Children in the Community Study (CCCS) (Angold, Costello, 1998), a longitudinal study of young child psychiatric disorders and service use in urban and rural North Carolina; Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA), a four-site study in largely urban settings using epidemiologic household sampling procedures; and the Patterns of Care Study (POC) (Hough, Landsverk, Hurlburt, 1998), a longitudinal study of mental health needs of children in the public service systems in San Diego.

Results

Trends in Types of Services From 1989 to 1996 (NAMCS). Types of services provided to children identified as having ADHD were analyzed in the NAMCS from 1989 to 1996. See Table 1. These included medication management, diagnostic services, mental health counseling, other (health-related) counseling, psychotherapy, and followup services.

Medication Management. Prescriptions of *stimulants* increased from 54.8 percent of visits in 1989 to 75.4 percent in 1996. The largest increase was between 1989 and 1991 but has remained relatively constant since 1991. Prescriptions of other *psychotropics* decreased 50 percent from 15.3 percent in 1989 to 7.5 percent in 1996. The biggest drop occurred between

[3]The assistance of Michael Feil in analyzing data from NAMCS is gratefully acknowledged. I wish also to thank Diane Comer for her assistance in analyzing data from the CBS, Michael Hurlburt for analyses of the POC data, and Adrian Angold for analyses from GSMS and CCCS.

Table 1. Trends in types of services for children with attentional problems (NAMCS, 1989–1996)

Types of Services	1989*	1991*	1993*	1995*	1996*
Medication management					
Stimulants	54.8	77.8	76.3	74.8	75.4
Other psychotropics	15.3	3.5	5.6	4.0	7.5
Other drugs	6.5	2.5	2.6	6.3	4.3
No drugs	23.4	16.2	15.5	14.9	12.8
Diagnostic services	22.3	76.6	43.1	60.6	62.1
Mental health counseling	24.3	59.4	34.3	44.2	39.3
Other counseling	3.5	29.7	4.3	29.9	35.2
Psychotherapy	40.1	38.3	5.6	21.3	25.2
Followup services	91.0	84.5	75.5	83.4	75.1

*Values given in percentages.

1989 and 1991, but there has been a slight trend upward since 1991. Prescriptions of *other drugs* dropped from 6.5 percent in 1989 to 4.3 percent in 1996. There has been a 45 percent decrease in visits where *no drugs* are prescribed, from 23.4 percent in 1989 to 12.8 percent in 1996. In other words, a larger percentage of visits now include prescription of some kind of drug.

Diagnostic Services. There was a threefold increase in diagnostic or screening services for children with attentional problems, from 22.3 percent in 1989 to 62.1 percent in 1996. The largest increase occurred between 1989 and 1991.

Mental Health Counseling. This service increased from 24.3 percent of visits in 1989 to 39.3 percent in 1996.

Other (Health-Related) Counseling. This service had the largest change over time, increasing tenfold from 3.5 percent in 1989 to 35.2 percent in 1996.

Psychotherapy. There was a sizable decrease in the percentage of visits where children received psychotherapy, falling from 40.1 percent of visits in 1989 to 25.2 percent in 1996.

Followup Services. There was a decrease in the number of visits where followup services were recommended, dropping from 91 percent in 1989 to 75.1 percent in 1996.

Trends in Prescription Practices. Safer and colleagues (1985, 1988, 1994, 1996) studied levels of methylphenidate use over time and found increased levels of prescribing for all ages of children. The rate of medication treatment for elementary school students increased from 1.07 percent in 1971 to 5.96 percent in 1987; for middle school students, it increased from .59 percent in 1975 to 2.98 percent in 1993; and for high school students, it increased from .22 percent in 1983 to .70 percent in 1993. Methylphenidate use for adolescents increased 2.5-fold from 1990 to 1995, perhaps due to increases in diagnoses of ADHD among girls, increased duration of medication treatment, and increased public acceptance of stimulants.

Similar trends have been found among Medicaid populations and very young children. Zito and colleagues (1996, 1997) found that from 1987 to 1995, psychotropic prescriptions for youths increased an average of 4.3 percent per year. Polypharmacy (multiple psychotropic prescriptions) increased an average of 7.5 percent per year. Stimulant prescription for very young children has also been on the rise. Zito found an increase of 180 percent between 1991 and 1995 in the number of prescriptions of stimulant drugs for children 5 years old or younger.

From NAMCS analyses, the percentage of visits by children with ADHD when psychotropic medications were prescribed has risen from 54.8 percent in 1989 to 75.4 percent in 1996. Conversely, prescription of other psychotropic medications has fallen from 15.3 percent in 1989 to 7.5 percent in 1996.

Types of Services Received. When service use is assessed over a 3-year minimum period, between 40 percent and 60 percent of children with ADHD are found to have received specialty mental health services (Angold, Costello, 1998; Kelleher, Comer, Childs, 1998). Over a 1-year period, the rates are lower, generally hovering around 30 percent (Jensen, Kettle, Roper, et al., in press). Approximately 50 percent of children with attentional problems have received medical services (Angold, Costello, 1998), usually involving visits to pediatricians. Rates of school service use vary from 24 percent to 80 percent, depending on whether one uses a 1-year or 3-year timeframe (Angold, Costello, 1998; Jensen, Kettle, Roper, et al., in press).

Rates of stimulant treatments prescribed for children with ADHD differ considerably, depending upon the age of the sample and the time period assessed. Wolraich and colleagues (1996) found that only one-quarter of elementary children who met criteria for ADHD were reported to have received medication, whereas Jensen and colleagues (in press) found that over a 1-year period only 12 percent of children ages 9 to 17 had been treated with stimulants. Over a 3-year period, 72 percent of children ages 9 to 13 meeting criteria had received stimulants (Angold, Costello, 1998). Similarly, findings from a national study of primary care physicians indicate that 72 percent of children ages 4 to 15 have received stimulants over the child's lifetime (Kelleher, Comer, Childs, 1998).

Variations in Use of Services by Sex, Race, or Region. A 3 to 1 ratio of boys to girls has been reported in the assignment of ADHD diagnoses (Angold, Costello, 1998; Wasserman, Kelleher, Bocian, et al., in press; Zito, Safer, dosReis, et al., 1997), and a similar ratio of 2 or 3 to 1 (boys to girls) has been reported for prescription of stimulants (Gardner, Pajer, Kelleher, 1998; Zito, Safer, dosReis, et al., 1997). The GSMS has found that girls are twice as likely to use specialty mental health services as boys, whereas boys are three times as likely to use pediatric services as girls (Angold, Costello, 1998).

Racial differences have also been reported. In the GSMS, Caucasian youth meeting diagnostic criteria for ADHD were significantly more likely to use general medical services and twice as likely to use specialty mental health services than African American youths (Angold, Costello, 1998). Two studies have found that minority youth, primarily African American, are less than half as likely to have been prescribed psychotropic medications as Caucasian youths (Bussing, Zima, Belin, 1998; Zito, Safer, Riddle, et al., 1996; Zito, Safer, dosReis, et al., 1997).

Geographical region has also been associated with differences in prescription rates of methylphenidate. Rappley found a tenfold difference in prescription rates between counties in Michigan (Rappley, Gardiner, Jetton, et al., 1995), and Zito (1997) found fivefold rate differences in Maryland.

Service Mix. Data from the CBS (Kelleher, Comer, Childs, 1998) indicate that on any given day, 27.5 percent of children being seen by primary care physicians for attentional problems receive no counseling, no medications, and no referrals—simply a checkup; another 27 percent receive counseling and medications; 17 percent receive no counseling, but do receive medications; and 11.5 percent receive counseling only and no medications.

Types of Services by Provider Type. Analyses of NAMCS data from 1996 revealed pronounced differences in types of services provided by pediatricians, family practice physicians, and psychiatrists. See Table 2.

Table 2. Types of services received by children with attentional problems by physician

Type of service	Psychiatry*	Pediatrics*	Family Practice*	Other*
Medication management				
Stimulants	74.2	75.4	94.9	43.9
Other psychotropics	14.8	4.3	1.9	9.2
Other drugs	-	10.9	-	-
No drugs	11.0	9.4	3.2	46.9
Diagnostic services	80.6	64.0	32.6	55.6
Mental health counseling	67.3	44.2	7.3	-
Other counseling	15.6	54.1	42.4	7.7
Psychotherapy	44.3	29.7	-	-
Followup services	88.5	79.0	45.7	75.9

*Values given in percentages.

Medication Management. Approximately three-quarters of both psychiatrists and pediatricians (74.2 percent and 75.4 percent, respectively) prescribed *stimulants* to children identified with ADHD, whereas 94.9 percent of family practitioners did so. Prescription of other *psychotropics* had an opposite pattern: most such prescriptions were given by psychiatrists (14.8 percent), whereas pediatricians and family practitioners prescribed far less often (4.3 percent and 1.9 percent). The category of *no drugs* occurred most often among psychiatrists (11 percent) and pediatricians (9.4 percent), and least often among family practice physicians, occurring on only 3.2 percents of the visits.

Diagnostic Services. There were large differences between providers in use of diagnostic services: 80.6 percent of visits to psychiatrists included these, whereas only 32.6 percent of visits to family practice physicians did. Pediatricians used these services on 64 percent of the visits.

Mental Health Counseling. This service followed a pattern similar to that for diagnostic services, with 67.3 percent of visits to psychiatrists including this service and only 7.3 percent of family practitioners doing so. Pediatricians again fell in the middle, using these services on 44.2 percent of the visits.

Other (Health-Related) Counseling. Pediatricians were more likely to provide general health-related counseling than the other physician specialists. Counseling was provided on 54.1 percent of visits to pediatricians, 42.4 percent of visits to family practitioners, and only 15.6 percent of visits to psychiatrists.

Psychotherapy. This service followed a pattern similar to that for mental health counseling and diagnostic services, with psychiatrists using psychotherapy more often than the other specialists. Psychotherapy was included in 44 percent of visits to psychiatrists and 29.7 percent of visits to pediatricians, whereas family practitioners did not use it at all (0%).

Specific Followup. This was most likely to be provided by psychiatrists (88.5 percent) and pediatricians (79 percent), but it was likely to be recommended in fewer than half of the visits to family practitioners (45.7 percent).

Factors accounting for these differences are unknown but may include severity, comorbidity, or case mix seen by different physicians, and training or level of expertise with which service decisions are made.

Barriers to Care. Barriers to services or treatment among children with attentional problems have been identified in three studies (CBS—Kelleher, Comer, Childs, 1998; GSMS and CCCS—Angold, Costello, 1998). In these cases, barriers are defined as events, actions, or inactions that delayed or prevented the use of mental health services.

The five most common child-reported barriers were lack of information, anticipation of being placed out of the home, loss of parental rights, negative reactions, and fear or distrust of professionals. Major barriers reported by caregivers were concerns about costs, lack of information, lack of time, negative experiences with professionals, and services being withheld. As many as 94 percent of parents reported at least one barrier over a 3-year period (Angold, Costello, 1998).

The CBS study of primary care physicians measured barriers from the clinicians' perspective. The major barriers to care for children with mental health problems were lack of pediatric specialists, difficulty in getting appointments, nonacceptance of Medicaid patients, physician panel restrictions, and complex appeals process.

Conclusions and Recommendations for Future Research

Patterns of services for children with ADHD have changed dramatically since 1989. Prescriptions of stimulants have risen from about one-half of all visits to three-quarters of all visits. During the same period, prescriptions of other medications have dropped. Children with ADHD are more likely now to receive diagnostic services, mental health counseling, and general

health counseling than they were in 1989. However, some of the trends are disturbing. Children younger than age 5 are more likely to be prescribed stimulant drugs than in the past, despite the lack of evidence of its safety in this age group. Fewer visits of children now include recommendations for followup visits than in 1989, psychotherapy is provided less often, and the likelihood of a child with ADHD having a visit without a psychotropic medication prescription has diminished. Further, the mix of services children receive depends largely upon the type of physician they see. Family practitioners are more likely than pediatricians or psychiatrists to prescribe stimulants and less likely to prescribe anything else. Family practitioners use diagnostic services and provide mental health counseling less often than other physicians. They are also about one-half as likely to follow up with these children than are psychiatrists. Children with ADHD are more likely to receive general health counseling if they are seen by pediatricians or family practitioners rather than psychiatrists.

With respect to the question of service need versus service use, it appears that the majority of children with attentional problems do receive either specialty mental health services, medical services, or school services at some point during their childhood. Well over half of children with ADHD symptoms will receive mental health services over a 3-year period. The picture on stimulant treatment is uneven, but there may be a time lag as to when stimulants are received versus when they may be needed. Approximately three-quarters of children with diagnosable ADHD will receive stimulants at some point in their childhood, but over a 12-month period, only one in eight will have received this treatment. Further, there are significant variations in prescriptions of stimulants by race and by sex, with African American youths and girls being less likely to receive these treatments than Caucasians and boys, respectively.

Significant barriers to services and treatments are reported by families, children, and clinicians. Ninety-four percent of caregivers report at least one and usually multiple significant barriers to care for their children with ADHD. These barriers include lack of information, concerns about costs, and time constraints. Primary care clinicians report significant barriers to care for their patients' mental health problems, including unavailability of pediatric specialists, cumbersome authorization or appeal procedures, and long waiting lists for services.

Several major gaps in knowledge about treatments and services can be identified from this review. First, although it appears that most children with ADHD do receive some form of service at some point, it is not clear whether these services are appropriate or whether they are meeting even minimal standards of quality. One study (Angold, Costello, 1998) has found that more than twice as many children received stimulants as received a full diagnosis of ADHD. The issue of the appropriate use of stimulants and the appropriate match between services and specific treatment needs has not been adequately studied in community settings. The movement of treatment efficacy studies into service delivery settings where issues of effectiveness can be investigated is one important effort to address this research gap.

Second, the question of how to remove barriers to care for families and children deserves immediate attention. Lack of information was listed as a major barrier by both caregivers and children, and other identified barriers were either attitudinal (fear, distrust, or negative anticipation) or pragmatic (costs and time-related). However, most of the studies reviewed for this paper did not even ask about barriers to care. Studies that address optimal ways of engaging

families in the treatment process as a means of identifying and removing barriers are greatly needed. Studies that investigate the effects of cultural mistrust on either access or barriers to care are nonexistent, but they are necessary if removal of barriers is to occur equitably. Additionally, it is not known how racial identity or acculturation affects attitudes toward mental health services or influences help-seeking patterns, but this kind of knowledge is essential to improving service delivery.

Finally, unevenness in the kinds of services received by children who are seen by different providers leads to troubling questions. Why are children receiving a different mix of services and what factors predict variation in quality of services provided to children and families? It is not clear whether the findings about differences in service mix can be explained by differences in severity of disorder, provider training, or factors such as race, sex, income, or geographic variation. Research on issues of service quality, appropriateness, and equity of care will be a high priority for the next generation of studies on services for children with ADHD.

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Current Assessment and Treatment Practices

Mark L. Wolraich, M.D.

Three medical disciplines have had a primary interest in attention deficit hyperactivity disorder (ADHD): psychiatry, neurology, and pediatrics. Which clinicians treat these children has depended on parental preference; the severity and nature of the disorder, in part reflected by the extent of co-morbid conditions; and a community's standards and referral patterns. Historically, pediatricians have played a significant role in the condition going back to the time when it was called minimal brain dysfunction or hyperactive child syndrome (Laufer, Denhoff, 1957). In recent years, studies of stimulant medication prescriptions substantiate that the majority of treatment with stimulant medication takes place in primary care, where primary care pediatricians, in particular, provide the majority of the prescriptions (Sherman, Hertzig, 1991; Rappley, Gardiner, Jetton, et al., 1995; Ruel, Hickey, 1992).

Pediatric participation in the care of children with this disorder stems from the historical perception of ADHD as a "biologic" rather than "emotional" condition, but more importantly because of the high prevalence rates of this condition, ranging from 1 percent to 14 percent (Szatmari, Offord, Boyle, 1989), although usually quoted as 3 to 5 percent (American Psychiatric Association, 1994). There are simply not a sufficient number of mental health clinicians to provide the necessary care. This is not likely to change in the future; in fact, the prevalence of children with ADHD may even increase further with the recent changes in diagnostic criteria. Within the same samples, the prevalence rates of ADHD increased from 2.6 percent for DSM-III to 6.1 percent for DSM-IIIR (Lindgren, Wolraich, Stromquist, et al., 1990) and from 9.6 percent to 17.8 percent (Baumgaertel, Wolraich, Dietrich, 1995) and 7.2 percent to 11.4 percent (Wolraich, Hannah, Pinnock, 1996) from DSM-IIIR to DSM-IV. (Caution must be taken in the last two studies because the new criteria require a degree of pervasiveness and impairment not determined in those studies.) With such high prevalence rates, the limited number of child psychiatrists, and more restrictions placed on mental health services in managed care, the treatment of children with ADHD will continue to require significant participation by primary care physicians. The children seen in primary care compared with psychiatry appear to be younger and more learning disabled and have fewer comorbidities (Wolraich, Lindgren, Stromquist, et al., 1990; Zarin, Suarez, Pincus, et al., pending).

Diagnosis

Given the significant role played by primary care physicians, it is important to explore further how these physicians diagnose and treat children with ADHD. Previous studies (Costello, Edelbrock, Costello, et al., 1988; Lindgren, Wolraich, Stromquist, et al., 1989) have found that primary care physicians underdiagnose ADHD and conditions such as conduct or oppositional defiant disorder that are frequently comorbid with ADHD (Biederman, Newcorn, Sprich, 1991). Currently, to make the diagnosis of ADHD requires reports of specific behaviors

by those individuals who have the most contact with the children, most commonly their parents and teachers. While direct observation, particularly in the child's natural setting, can provide additional objective information, it is limited to a small sample of time. In the case of physician observation, observations usually occur in settings that do not necessarily correlate with home or school behaviors (Sleator, Ullman, 1981). Although information about behavior in other than school settings, particularly the home, and additional information, such as family functioning, are essential to the diagnosis of ADHD, teacher input and consideration of the school environment continue to be critical elements.

Parents remain the most commonly used source of information for both primary care physicians and psychiatrists. Teacher or school reports are reported to be utilized by almost all primary care physicians and three-quarters of psychiatrists (Kwasman, Tinsley, Lepper, 1995; Wolraich, Lindgren, Stromquist, et al., 1990; Zarin, Suarez, Pincus, et al., pending). However, anecdotal reports describe communication problems in both directions. In addition, by examining the agreement of physician diagnosis with the diagnosis based on teacher behavior rating scales or parent information, one of the studies (Wolraich, Lindgren, Stromquist, et al., 1990) found agreement to be no more than 50 percent with teachers and 70 percent with parents. This suggests that physicians are more influenced by information provided by parents than by that provided by teachers in their consideration of the diagnosis. The issues of sources of information are problematic because of disagreements between teachers and parents (Fergusson, Horwood, 1993; Sandberg, Weiselberg, Shaffer, 1980). While diagnostic criteria now require the presence of symptoms and impairment in more than one setting (American Psychiatric Association, 1994), there is no clarification about how to address the discrepancies between multiple informants. Standardized teacher rating scales are reported to be used by 53 percent of family practitioners, 64 percent of psychiatrists, and 74 percent of pediatricians (Wolraich, Lindgren, Stromquist, et al., 1990; Zarin, Suarez, Pincus, et al., pending), and psychoeducational testing is obtained by one-half to more than three-quarters of the physicians. The problem of physicians having adequate information about their patients' performance in school remains and requires further study to determine its impact on establishing the diagnosis.

Treatment

Stimulant medications, methylphenidate in particular, remain the most frequent and efficacious treatment for children with ADHD (Greenhill, 1995; Swanson, McBurnett, Wigal, et al., 1993). In fact, stimulant medications are the primary interventions employed by primary care physicians (Wolraich, Lindgren, Stromquist, et al., 1990; Kwasman, Tinsley, Lepper, 1995). This is also true of psychiatrists, although they also frequently use other psychotropic medications, particularly antidepressant and alpha-adrenergic agonists (Zarin, Suarez, Pincus, et al., pending). Despite the known efficacy of stimulant medications, their use remains controversial (Diller, 1996). Since the main concern is that too many children are being medicated, the real issue is diagnostic, namely, who gets treated. The decisions about diagnosis and the determination of the effect of stimulant medications on a given child, again, depend on physician-teacher communication, since the major effect of stimulant medication is to improve the behavior and function of children in school. Unless there is direct communication between teachers and physicians, the clinician must depend on secondhand, and therefore less accurate,

information in deciding about the effects of treatment. As with the diagnostic process, the situation is particularly difficult when discrepancies exist between parents' and teachers' assessments of the effect of medication.

Despite the problem of assessing drug effects, preliminary data so far suggest that although there may be inappropriate use of stimulant medication, there is not necessarily overuse. In surveying all the elementary school-age children in a suburban Tennessee county, we found that among those meeting the criteria for ADHD combined type, only about one-third were reported by teachers to have been diagnosed, and only one-quarter had been treated with medication (Wolraich, Hannah, Pinnock, 1996; Wolraich, Hannah, Baumgaertel, 1998).

Although other therapies for treating ADHD exist, primary care physicians utilize few of them. In a survey (Wolraich, Lindgren, Stromquist, et al., 1990), primary care physicians reported utilizing behavior modification; parents of a sample of their patients with ADHD did not report receiving the intervention. This is particularly important for interventions dealing with parent training. Schools, however, play an important role in providing interventions other than medications. School systems must provide services that frequently include classroom adaptations and classroom behavioral programs. These are not always included when considering what interventions a child is receiving. Social skills training, a frequent deficit in children with ADHD, lends itself best to a school-based intervention because it needs to occur in group settings where children better generalize the training to be effective.

Lastly, there are no systematic methods of providing services to the spectrum of children with ADHD of varying severity. This creates both referral and reimbursement problems. In terms of referrals, there are no clear guidelines indicating to whom children should be referred for mental health services. In the past, pediatricians tended to refer children with ADHD to child psychiatrists infrequently (Fritz, Bergman, 1985; Wolraich, Lindgren, Stromquist, et al., 1990), and psychiatrists report that only 14 percent of their referrals are from nonpsychiatric physicians (Zarin, Suarez, Pincus, et al., pending). This has been further complicated by the use of behavioral health carve-outs, many now using central screening programs to determine the type of service approved for treatment. A major issue for reimbursements is that both the health and educational systems provide some of the care and in some cases are obligated to provide services, yet there is no mechanism to allocate those responsibilities. Families are caught between health maintenance organizations identifying services as "developmental or educational" and therefore not their responsibility and school systems identifying services as "health-related" and not their responsibility.

In summary, primary care physicians play a significant role in the diagnosis and treatment of children with ADHD, but problems remain with their ability to diagnose the disorder and common comorbid conditions as well as to monitor treatment. Communication between schools and health care providers is an important link in this process which requires further study and intervention through a systems conceptualization of the process and examining individual physician's practices. Further, there is a need to develop a more systematic method for organizing the broad array of services available to develop a seamless system of care.

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Educational Policy: Educating Children With Attention Deficit Disorders

Louis Danielson, Kelly Henderson, Thomas Hehir, Ed.D., and Ellen Schiller, Ph.D.

In 1991 Congress charged the U.S. Department of Education's Office of Special Education Programs (OSEP) with synthesizing and communicating research on educating children with attention deficit disorders (ADD). OSEP led several initiatives. First, OSEP responded by working with researchers and teacher educators to move this information off their shelves and into the hands of teachers, parents, and families who could use it.

Second, the U.S. Department of Education clarified the provisions under which children with ADD could be educated in the public schools. Children with ADD may qualify for accommodations or other assistance in general education settings under Section 504 of the 1973 Rehabilitation Act, or for special education and related services under the Individuals with Disabilities Education Act (IDEA). Under IDEA, children with ADD can be served under the category of "other health impaired." Finally, OSEP collaborated with the National Institute of Mental Health to conduct a treatment study on effective interventions for children with ADD.

Given these initiatives, the purpose of this paper is to report on the changes in State policies since 1991. The paper reports the results of a survey of State departments of education regarding the policies guiding the practices for educating children with ADD. The survey findings include definitions of ADD, identification criteria, assessment procedures, and intervention practices required by States of schools as well as the number of students identified as ADD by the States. Last, the paper addresses the issues and implications for educational policy.

Use of Services and Costs for Youth With Attention Deficit Hyperactivity Disorder and Related Conditions

Kelly J. Kelleher, M.D., M.P.H.

Attention deficit hyperactivity disorder (ADHD) is both the most common of the behavioral and emotional disorders and the most common of chronic medical conditions diagnosed in primary care settings among school-age children. Identification and treatment rates among primary care clinicians are growing rapidly. Among school-age children, ADHD and related problems are identified by primary care clinicians more often than any other chronic medical disorder, making them the most commonly diagnosed chronic condition in this age group.

Table 1. Prevalence of ADHD* by structured diagnostic interview and clinician diagnosis in primary care samples

	N	Diagnosed	Age Range
Structured diagnostic interview			
Costello (1984-85)	789	12 (1.5%)	7-11
Horwitz (1988-89)	1,540	135 (8.8%)	5-9
Clinician diagnosis			
Goldberg† (1979)	9,612	136 (1.4%)	4-15
Horwitz‡ (1987-88)	1,886	175 (9.3%)	4-8
Kelleher (1994-97)	21,151	2,007 (9.5%)	4-15

*ADHD and related conditions.
†Children <4 and >15 excluded.
‡Includes mental retardation, learning disabilities, language delay, speech problems, overactivity, gross motor delay, and fine motor delay.

Although ADHD is frequently diagnosed, almost nothing is known about the use or costs of care for ADHD. To provide some insight into these questions, we (1) examine the use of care by children and youth with ADHD, (2) compare direct treatment costs between ADHD and asthma, another common illness of childhood, and (3) identify areas for further research exploring the impact of ADHD on the health care system.

Use of Services

Children with psychosocial problems use more medical and mental health services than do those without psychosocial problems. Youth with ADHD are no exception. Use of outpatient

medical services by youth with ADHD compared with control groups is greater. A recent study of pediatric visits to a nationally representative sample of primary care clinicians found that children with ADHD averaged 0.15 more outpatient visits compared with children with other psychosocial problems and 1.85 more visits than youth without any identified psychosocial problems over a 6-month period (Table 2). Most of the increase in use was related to mental health services, although the number of primary care visits also increased among those with ADHD. How psychosocial conditions induce or are associated with increased use is not clear. However, family distress, teacher frustration, and the discovery of unmet medical needs during behavioral care (onset effect) may play a role.

Table 2. Use of services in prior 6 months by parent report*

	N	Mental Health	Primary Care	Emergency Room	Total Outpatient	Hospital
ADHD visits	2,007	1.47	2.37	0.19	4.02	0.05
Non-ADHD psychosocial problem visits	2,005	1.25	2.39	0.22	3.87	0.07
Nonpsychosocial problem visits	17,139	0.13	1.90	0.15	2.17	0.03

*Mean number of visits is reported in each category.
Ref.: Child Behavior Study (NIMH 50629; PI: Kelleher).

Regardless of the mechanism, it appears that youth with ADHD are comparable with youth with other psychosocial problems in their increased use of many types of health services. The fact that there appears to be little difference in utilization between children and adolescents with ADHD and those with other psychosocial problems suggests that the specific aspects of ADHD symptoms (hyperactivity) or treatment (stimulant prescriptions and behavior modification) do not account for the increased use of services but that other family, patient, or community characteristics explain why children with psychosocial problems use more services.

In addition to increased use of outpatient and physician services, children and adolescents with ADHD also are prescribed the bulk of psychotropic drugs in primary care settings as noted in Figure 1. The majority of the psychotropic drugs prescribed are stimulants, but antidepressants make up a growing proportion of the drugs employed. Drug treatment is described further in Dr. Hoagwood's paper.

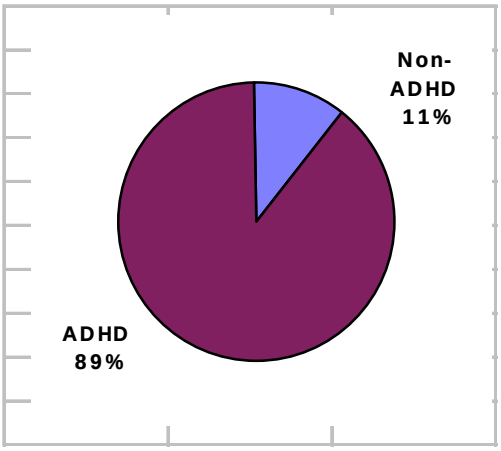

Figure 1. Percentages for those treated with drugs in primary care.

Costs of Care

As noted by others, the child psychiatric literature is bereft of economic studies on mental health services, particularly for specific disorders. These deficiencies have precluded careful comparative analyses of the benefits of different treatment strategies, providers, settings, or financing systems. It is hoped that this Conference will focus attention on inadequacies in the area.

To initiate some discussion on the costs of treatment for ADHD, we compared direct treatment costs for ADHD with another common childhood condition, asthma. We employed a payor perspective, focusing on children publicly insured through Medicaid in southwestern Pennsylvania. Claims and eligibility data were obtained from the State Department of Public Welfare.

Children and adolescents ages 7 to 20 were identified as being continuously enrolled in the traditional Medicaid (MA) fee-for-service (FFS) plan for fiscal year 1994-95 from the demographic and eligibility files for seven counties in southwestern Pennsylvania. Using the MA claims file for that year, we identified 1,602 children and adolescents as having ADHD who had either one or more ADHD diagnoses (ICD-9 code 314), primary or secondary, or at least three filled prescriptions for stimulant medications. Those with at least one asthma diagnosis (ICD-9 code 493), primary or secondary, in the MA claims file for that year or at least three filled prescriptions for asthma medications (NDC Class 1940) were designated as having asthma (N = 1,411). Children or adolescents enrolled in managed care during the year were excluded from the study group because their full claims for the year are not reported.

For each condition, payments for all services were summed and averaged over pharmacy and nonpharmacy claims to calculate total costs for all of a patient's services during the 1994-95 fiscal year. In addition, a separate measure for the costs of all psychiatric services (including

both pharmacy and nonpharmacy reimbursements) was calculated. As noted in Table 3, ADHD and asthma bear remarkable similarities to each other, with regard to both their frequency in the eligible population and their cost structure. Children with ADHD and asthma have similar distributions of pharmacy and nonpharmacy services, although children with ADHD receive most services in the mental health arena whereas those with asthma receive them almost exclusively in the general health arena. Outpatient visits and inpatient days were also examined between the two groups. Children with ADHD had nine more total outpatient visits on average than those with asthma, but 0.4 fewer inpatient days. These were not separated by type of service. Any comparison between these utilization figures for a Medicaid population and those from Kelleher's national primary care population using parental 6-month recall should note that these figures use 12 months of administrative data.

Table 3. Comparison of reimbursements and services for children and adolescents with ADHD or asthma in southwestern Pennsylvania: Fiscal year 1994–1995[*]

	Mean	Standard Deviation	Median	99th Percentile
ADHD[†] ***N = 1,602***				
All services—payments	$1,795	$2,069	$1,041	$9,442
Pharmaceuticals	$ 508	$ 554	$ 375	$2,352
All other services	$1,287	$1,956	$ 553	$8,788
All psychiatric services	$1,134	$1,807	$ 100	$8,313
Outpatient visits[‡]	28.8	21.7	23	107
Inpatient days	0.1	1.3	0	5
Asthma ***N = 1,411***				
All services—payments	$1,666	$1,863	$942	$8,858
Pharmaceuticals	$ 413	$ 566	$243	$2,676
Other services	$1,252	$1,681	$586	$7,844
All psychiatric services	$ 110	$ 652	$ 0	$3,003
Outpatient visits	19.6	15.7	15	74
Inpatient days	0.5	1.8	0	8

[*]The sample is limited to those aged 7 to 20 years whose total reimbursements did not exceed $10,000 and who were continuously enrolled in Medicaid FFS during the fiscal year in Allegheny, Armstrong, Beaver, Butler, Greene, Washington, and Westmoreland counties.
[†]The 76 children who received both types of services during the fiscal year were placed in the ADHD group.
[‡]Outpatient visits include visits to hospital clinics and ER visits that did not lead to a hospitalization. Multiple visits on the same day were counted as one visit.

A small percentage of children with ADHD services also received asthma services and were classified as having ADHD. One difference in sample selection, which is probably partly the result of Medicaid reimbursement rules, is the percentage of children identified as having ADHD or asthma through pharmacy claims alone. Few of the children (10 percent) identified with asthma had only pharmacy services, whereas the majority of children with ADHD were identified through filled stimulant prescriptions.

Although a number of limitations exist in these data, cost-of-illness or burden studies are important first steps in the recognition of a condition's relevance to different settings and payors. They also establish methods for conducting later comparative analyses. In particular, cost-of-illness studies that examine the impact of ADHD on particular groups in the health care arena, such as insurance companies and State Medicaid agencies, are likely to raise the profile of ADHD and identify deficiencies in current cost measurements related to this unique condition. Such comparisons are essential, especially for payor perspectives in providing benefits.

Further studies including cost-benefit analyses are necessary in order to compare costs and benefits in the same units. Such comparisons are essential decision-making tools, especially for payor perspectives in providing benefits. A complete cost-effectiveness analysis would allow comparative decisions to be made among two or more alternative courses of treatment in order to optimally use limited resources. Such an analysis typically requires an evaluation of both the improvements in outcomes and complete societal costs of the different treatment strategies or interventions being implemented. In most cases, a prospective study is conducted to compare a specific intervention with the current standard of care, ideally measuring outcomes in quality adjusted life years (QALY) to allow for universal comparisons with other studies.

Unfortunately, we lack even basic cost-benefit studies of mental health services for youth with ADHD. In conducting these analyses, a central goal will be to obtain different perspectives on costs. Although societal costs for ADHD and its treatment are important in the context of taxpayer-funded schools and health care, payor and family/community costs are also critical to provide the fullest picture of how ADHD affects the health care system.

Summary

ADHD is an important condition not only for its impact on families and children, but also because youth with ADHD are major consumers of primary care services, mental health care, and psychotropic drugs. Although the diagnosis is common, little is known about the use of services by children and adolescents with ADHD, patterns of use over time, or any type of cost analyses. Specific questions to be prioritized include:

- How is use of services for ADHD initiated? What factors predict help-seeking for ADHD specifically, and are these different from those for other psychosocial problems in childhood? Are some systems more accessible for ADHD care?

- What burden or costs for ADHD and related treatment are borne by families and communities? What out-of-pocket costs are incurred by families whose children have

ADHD? What are the costs to communities in loss of productivity and diverted resources?

- How effective are alternative modes of treatment in community and school settings? Do services provided in the school or home provide better outcomes at lower costs than medical services? What combinations work best?

- How do families, employers, and communities value various outcomes? Is better control in the classroom an acceptable outcome for communities with high rates of ADHD treatment? What benefit limits are reasonable for employers and payors faced with increased costs?

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Individual and Family Barriers

Sheila Anderson

Attention deficit hyperactivity disorder (ADHD) is an increasingly common referral problem for children, adolescents, and adults. Its presentation to the primary care physician may range from straightforward to very complex, with diagnosis and treatment often predicated on a patient's health care coverage.

Children and Adults With Attention Deficit Disorders (CH.A.D.D.) is currently active in conducting research into the barriers to treatment of ADHD in the health care system. This research is needed because of increasing nationwide reports of negative individual experiences with various health care plans and coverages. CH.A.D.D.'s constituent concerns are varied and numerous, including diagnostic and treatment process or lack of process, preexisiting condition exclusion, refusal to accept adult diagnosis, and inconsistent or complete lack of coverage.

Whereas anecdotal information stimulates an immediate emotional response, the collection of data will assist CH.A.D.D. in demonstrating statistically the true scope of presently perceived barriers. The information will also serve as reference and substantiating data for legislative advocacy to improve health care coverage of ADHD.

Methodology

A survey comprising 43 questions was mailed to approximately 35,000 CH.A.D.D. constituents in *Attention* magazine, a quarterly publication, and posted to the CH.A.D.D. Web site, which is visited approximately 100,000 times per month.

Respondents were asked to indicate whether the survey was being completed for an adult or a child and to give their State of residence. Questions were divided into two general categories, diagnosis and treatment. Diagnosis questions related to type of insurance coverage, possible reluctance to identification and implications of that reluctance, selection of diagnostician, waiting periods, apparent knowledge of diagnostician, diagnostic process, coexisting condition diagnosis, and cost coverage. Treatment questions focused on treatment planning, options, inclusion in the process, effectiveness, cost coverage, and satisfaction. The survey included three types of questions: those with a yes or no response, those offering a list of answers to select from, and a limited number requesting written information. Questions that encouraged selection from a number of choices also included "other" as a possible choice, and written information could be entered. Responses are being tabulated and analyzed using SPSS PC.

The purpose of the research is threefold:

- to identify issues that may be barriers to treatment of ADHD,
- to investigate nationwide coverage of diagnosis and treatment of ADHD in respondents' health care plans, and
- to identify the type of health care professionals who are making the diagnosis of ADHD.

Preliminary Results

Approximately 2,000 surveys were completed, with a majority via the CH.A.D.D. Web site. This level of participation and response indicates a high level of concern surrounding health care coverage of ADHD. The total number of mail-in or faxed surveys was 284, representing both adults and children. Respondents reflect participation of constituents from most States.

Initial analysis of approximately 10 percent of the data noted that of those completing the survey, 92 percent indicated they did have health care coverage. The following frequencies in type of health care plans were identified: 15 percent indemnity, 31.2 percent preferred provider organization (PPO) with options, 10.7 percent PPO only, 25 percent health maintenance organization, 4.4 percent public, and 4.4 percent other.

When respondents were asked whether the diagnosis of ADHD is covered under their current health care plan, 76 percent answered yes, 17 percent answered no, and 6 percent indicated they had no plan. The amount of time used to make the diagnosis is particularly important in the managed care system. The following diagnostic times are reported:

1 hour	42.4%	more than one visit	34.1%
30 minutes	3.9%	other	17.6%
15 minutes	1.5%		

A pre-diagnostic questionnaire was completed before the initial physician visit by 75 percent of the respondents. When asked under what category ADHD is covered in their current plan, 38.3 percent checked "mental health," 13.4 percent checked "medical condition," 11 percent checked "not covered," and 36.8 percent checked "don't know."

To identify the frequency of coexisting conditions, respondents were given a selection menu that included the following: anxiety, panic attack, dyslexia, motor tic, eating disorder, depression or bipolar illness, obsessive/compulsive disorder, learning disability, migraine headaches, and other. Many respondents selected multiple conditions, usually more than two. When asked whether treatment was adequate for coexisting conditions, 51.7 percent answered "yes" and 48.3 percent answered "no."

When respondents were asked to indicate whether they were reluctant to seek a diagnosis of ADHD because of social stigma, 36 percent answered "yes" and 64 percent answered "no." When asked whether they had a diagnosis of ADHD, 88.3 percent answered "yes" and 11.7 percent answered "no."

In an effort to identify which professionals most often make the diagnosis of ADHD, respondents were asked to select from a menu of professionals. The results were as follows: 7.3 percent, family doctor; 17.6 percent, pediatrician; 36.6 percent, psychologist; 7.3 percent, school psychologist; 15.1 percent, ADHD specialist; 5.4 percent, social worker; and 41 percent, psychiatrist. (Note: these percentages do not add up to 100 percent because in some cases more that one professional was selected.)

When respondents were asked whether their health care plan offered adequate access to professionals with the necessary level of expertise and experience to treat ADHD, 56 percent answered "yes" and 44 percent answered "no." However, when asked whether they had ever gone outside their health care plan and paid out-of-pocket to gain access to professionals with particular expertise in the diagnosis and treatment of ADHD, 63.4 percent answered "yes" and 36.1 percent answered "no."

Of those completing questionnaires, 89.8 percent indicated that medications were prescribed as part of their treatment, with the following medications written with frequency noted:

Adderall, 21.5%	Dexedrine, 14.6%	Tofranel, 2%
Antidepressant, 94.1%	Imipramine, 2.4%	Wellbutrin, 7.8%
Clonidine, 5.4%	Prozac, 5.4%	Other, 15.6%
Cylert, 7.3%	Ritalin, 53.7%	

When asked whether they were happy with the medications prescribed, 78 percent answered "yes" and 22 percent answered "no."

Selection was made from a menu to identify cost coverage of medications by the health care plan, and the following frequencies were noted:

23.4% = 100%	1.5% = 20%
21.5% = 80%	41% = minimal copay
3.4% = 50%	8.8% = not covered

A rating of their current health care plan coverage under the categories of diagnosis, treatment, and "overall" revealed that 47.3 percent felt their coverage for the diagnostic process was average, 25.9 percent thought it poor, and 19.5 percent rated it good. Coverage for treatment was rated similarly: 48.3 percent, average; 25.4 percent, poor; and 19.5 percent, good. For overall coverage, 52.7 percent rated it average, 24.9 percent rated it poor, and 17.1 percent rated it good.

Please note that this information is based on a 10 percent random selection of the total data collected. The remaining data are currently being entered and tabulated and will be analyzed for presentation to the consensus panel.