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To: **Chris Jennings**

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From: **Elaine Holland**
Assistant Director (x3005)

Date: **March 16, 2000**

Page 1 of

RE: Hey Chris ☺ I thought your question was simple but not so☹

I ran this by a few pediatricians and psychiatrists and the suggestion is that the First Lady may want to say something like:

We don't have a simple term to encompass children with emotional, mental, behavioral and developmental conditions and disorders so for purposes of this meeting, let me refer to these children and adolescents as having ☹emotional and neurobehavioral conditions☺.

NOTE: If you think 'neurobehavioral' is too technical a word you could just say 'behavioral'

Hope this helps... I'm still checking on the First Lady mentioning the AAP clinical guidelines for diagnosis and evaluation of ADHD. I'll let you know ASAP.

Mental health is the year 2000 annual clinical focus of the 89,400 members of the American Academy of Family Physicians. All year long, the Academy will be sponsoring continuing medical education courses and authoring publications to help family physicians more effectively treat patients with mental health problems. Some of the courses will address the problems of children with ADHD and ADD, depression, behavioral disorders, substance abuse patterns, and a propensity to violence. Adults and children make over 200 million visits to family physicians each year. About one-forth of all pediatric patients encounters are with family physicians, so this mental health emphasis is critical to the health of American's children.

Medications Meeting

Children in Special Education Programs: Attention Deficit Hyperactivity Disorder, Use of Services, and Unmet Needs

Regina Bussing, MD, MSHS, Bonnie T. Zima, MD, MPH, Amy R. Perwien, BA, Thomas R. Belin, PhD, and Mel Widawski, MA

Objectives. Attention deficit hyperactivity disorder (ADHD), a common psychiatric condition, may impair a child's ability to learn and to form social relationships, tasks critical to healthy development. This study describes the prevalence of the disorder among children in special education programs and identifies the extent and predictors of unmet service needs.

Methods. A 2-stage screening protocol of a countywide population of second- through fourth-grade students in special education was conducted to (1) screen for ADHD, employing standardized parent and teacher questionnaires, and determine health services use (n = 499) and (2) perform diagnostic assessments of ADHD (n = 318).

Results. Almost half of the children qualified for a diagnosis of ADHD, yet only half of those were reportedly receiving care for the condition, mainly in the general health care sector. Girls were more than 3 times as likely as boys to have unmet service needs; minority status, low income, and health maintenance organization coverage also emerged as possible risk factors for unmet service needs.

Conclusions. ADHD is a common yet often untreated condition among children in special education. Mental health services for children with this disorder should be integrated with general health care and special education programs. (*Am J Public Health.* 1998;88:880-886)

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Title
The extent of drug therapy for attention deficit-hyperactivity disorder among childre schools.

Author
LeFever GB; Dawson KV; Morrow AL

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Source
Am J Public Health, 1999 Sep, 89:9, 1359-64

Abstract
OBJECTIVES: The purpose of this study was to determine the extent of medicatio attention deficit-hyperactivity disorder (ADHD) in southeastern Virginia. METHODS enrolled in grades 2 through 5 in school districts in city A (n = 5767 students) and c 23,967 students) were included. Nurses recorded students who received ADHD m school. RESULTS: The proportion of students receiving ADHD medication was sim cities (8% and 10%) and was 2 to 3 times as high as the expected rate of ADHD. R therapy was associated with social and educational characteristics. Medication wa times as many boys as girls and by twice as many Whites as Blacks. Medication u with years in school, and by fifth grade 18% to 20% of White boys were receiving A medication. Being young for one's grade was positively associated with medication .01). The prevalence of ADHD was 12% in district A, 63% in district B. CONCLUSI findings suggest that criteria for diagnosis of ADHD vary substantially across US p with potential overdiagnosis and overtreatment of ADHD in some groups of childre

Language of Publication
English

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MeSH Heading (Major)
Attention Deficit Disorder with Hyperactivity|DI/*DT/EP; School Health Services|*S Students|*SN

MeSH Heading
Bias (Epidemiology); Blacks|SN; Child; Child, Preschool; Drug Utilization; Educatio

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Title
Methylphenidate patterns among Medicaid youths.

Author
Zito JM; Safer DJ; dosReis S; Magder LS; Riddle MA

Address
Department of Pharmacy Practice and Science, University of Maryland at Baltimor

Source
Psychopharmacol Bull, 1997, 33:1, 143-7

Abstract
Treatment of attentional disorders in America has increased dramatically in recent trend is accounted for partly by lengthening the duration of treatment into adulthoo individuals as well as by increased treatment among girls. Beyond these factors, th economic status, race, and geographic region to explain the variation in methylphe not well understood. Computerized administrative data were used to explore the in several sociodemographic factors on the prevalence of methylphenidate use. The consisted of Maryland Medicaid prescription drug reimbursement claims data for F children ages 5 to 14 years. In effect, the study was restricted to a sample of patien income. The study aims included (1) measuring gender-, age-, race-, and region-sp methylphenidate prevalence for this restricted income population; (2) comparing th Caucasian:African-American (C:A-A) ratio for methylphenidate with the C:A-A ratio drug therapies having non-psychotropic uses, specifically the anti-asthma drug, the and antibiotics for infections; and (3) estimating the average daily dose of methylph prescription claims data. Total drug-specific prevalence among the 5-14 year olds percent for methylphenidate while age-specific prevalence varied from 0.4 percent to 3.4 percent (9 year olds). The gender ratio was 3.7:1 (M:F), confirming the incre girls to receive this medication. Substantial variation across eight defined regions o was observed. Racial differences were pronounced: African-Americans were 2.5 ti to receive methylphenidate than Caucasian youths. As hypothesized, non-psychot was distinctly different from psychotropic drug use in terms of race: theophylline wa more likely to be found for African-Americans than Caucasians, whereas antibiotic were 1.5 times more likely to be prescribed to Caucasian youths. Average daily do methylphenidate was estimated to be 18.7 +/- 10.4 mg for 5-9 year olds and 26.8 + 10-14 year olds. This brief report confirms the typically lower rate among African-A Medicaid youths for most prescription drugs. The dramatic racial disparity for the p agent methylphenidate is a new and compelling finding which should be verified am economic groups. Diagnostic, referral, and cultural bias should be ruled out as pos explanations for the observed differences.

Language of Publication
English

Unique Identifier

February 23, 2000, Wednesday
National Desk

Sharp Rise Found In Psychiatric Drugs For the Very Young

By ERICA GOODE

In a finding that medical experts called "troubling" and "very surprising," researchers reported today that the number of preschoolers taking stimulants, antidepressants and other psychiatric drugs rose drastically from 1991 to 1995.

In the study, researchers found that the use of stimulants -- most commonly methylphenidate, the generic form of **Ritalin** -- increased twofold to threefold for children, ages 2 through 4, who were enrolled in two state Medicaid programs and in a health maintenance organization in the Northwest. Stimulants are commonly used to treat attention disorders.

The number of preschoolers receiving prescriptions for antidepressants doubled in the Medicaid programs.

And the use of clonidine, a blood pressure drug gaining popularity as a treatment for insomnia associated with attention disorders, also jumped.

Although researchers have known for some time that such drugs are increasingly being prescribed for older children, the study, which appears in today's issue of the Journal of the American Medical Association, is the first to document an increase among children younger than 5. Reseachers suspect that the increase has continued.

"This seems to support the anecdotes that more U.S. children are receiving a diagnosis and treatment for attention deficit hyperactivity disorder in the late 1990's than ever before," said Dr. Julie Magno Zito, an associate professor of pharmacy and medicine at the University of Maryland and lead author of the study.

The research was conducted by analyzing prescription records in the five-year period of more than 200,000 preschoolers in the two Medicaid programs and the H.M.O.

Previous studies had shown significant increases in the use of stimulants and antidepressants to treat children between the ages of 5 and 19. In a smaller study of Medicaid enrollees in Michigan in 1998, researchers found that of 223 children younger than 4 who were diagnosed with attention deficit hyperactivity disorder, 57 percent received at least one drug to treat the condition.

Though the total number of very young children in the latest study who received prescriptions for the drugs was small, 1 percent to 1.5 percent, the increase is disturbing, the researchers said, because research on the safety and efficacy of the medications, scant for older children, is virtually nonexistent for preschoolers.

"We don't have any benchmarks to know if this is or is not a problem," Dr. Zito said.

Dr. Zito and her colleagues noted that the findings may not apply to other all medical settings. But she said she suspects that the use of stimulants to treat attention disorders is even more prevalent among children from higher-income families.

Dr. Steven Hyman, director of the National Institute of Mental Health, said that he was "more than shocked" by the findings. The use of psychiatric drugs in young children, he said, is "an area of enormous concern," and one that Dr. Hyman has made a priority in the institute's funding of research.

At the same time, Dr. Hyman said, he is sympathetic "to the intense need to do something for children who really are so terribly sick that other means cannot control their behavior."

Because the researchers did not track the diagnoses given to the children or the training of the professionals who prescribed the drugs, the reasons for the increases were not clear.

But experts speculated that the reasons might include the reluctance of H.M.O.'s and subsidized medical care programs to pay for counseling or other treatments that do not involve drugs, the pressures from parents and schools to diagnose children with attention disorders, the rise of drugs as the preferred mode of treatment and the fact that most prescriptions in subsidized settings are written by primary care doctors rather than specialists.

Few of the drugs, Dr. Zito and other experts pointed out, are approved by the Food and Drug Administration for treating children of preschool age. The package insert for methylphenidate, for example, carries a warning against prescribing the drug to children under 6.

While the prescription of drugs by physicians for purposes not approved by the F.D.A., called off-label prescribing, is both legal and common in the treatment of older patients, the practice raises more difficult issues in young children.

When a physician prescribes a drug off-label for a child, Dr. Zito said, parents "should be aware that they are entering an area of uncertainty."

The symptoms of emotional or behavioral problems displayed by children younger than 5 may be different from those exhibited by older children, and diagnosis of such conditions in preschoolers is at best iffy. As Dr. Joseph Coyle, chairman of psychiatry at Harvard Medical School, commented, the normal behavior of many 2-year-olds and 3-year-olds looks a lot like attention deficit hyperactivity disorder.

Dr. Zito said, "It is not really clear that children this young could meet the diagnostic criteria for either attention deficit hyperactivity disorder or depression, and those are the probable diagnoses given to justify the use of

stimulants, clonidine and antidepressants."

Even more worrisome, experts said, is the fact that little is known about the effects of antidepressants, stimulants and other psychoactive drugs on brain development. Studies in animals indicate that the brain chemicals that are targeted by some such drugs play an important role in the proliferation of nerve cells in the brain.

"These interventions are occurring at a critical time in brain development," said Dr. Coyle, who wrote an editorial accompanying the report, "and we don't know what consequences are."

In the study, methylphenidate was by far the most popular stimulant prescribed for preschoolers, accounting for 90 percent of the prescriptions. In the Midwestern Medicaid group, 11.1 of every 1,000 children age 2 to 5 were prescribed methylphenidate in 1995.

In the H.M.O. and in a mid-Atlantic Medicaid group, the number of girls receiving prescriptions for stimulants increased more in the five years than the number of boys, researchers found, suggesting that girls are increasingly being diagnosed with attention disorders.

"The message is that girls are more likely than in the past to be getting medicated," Dr. Zito said, "where attention deficit disorder used to be more of little boys' disorder."

Among antidepressants, the older generation of "tricyclic" drugs remained the most commonly prescribed, though the number of children receiving newer medications like Prozac and Zoloft increased dramatically in the Medicaid programs over the five years.

In the Midwestern Medicaid group, 3.2 of every 1,000 preschoolers received prescriptions for antidepressants.

Though clonidine was prescribed less frequently than stimulant drugs, the researchers said, its increased use -- was particularly notable, because there are no rigorous studies demonstrating that it is a safe or effective as a treatment for The study found that 2.3 children per 1,000 in the Midwestern Medicaid group received prescriptions for the drug in 1995, compared to 0.1 child per 1,000 in 1991.

Heart problems have been reported in children taking clonidine in combination with other drugs, including **Ritalin**, the researchers said.

In contrast to the increase in other drugs, the use of antipsychotic drugs for preschoolers remained constant over the five-year period at about 0.7 children per 1,000.

Organizations mentioned in this article:
University of Maryland

Related Terms:
Mental Health and Disorders; Children and Youth; Depression (Mental); Drugs (Pharmaceuticals); Health Insurance; Health Maintenance Organizations and Managed Care; Medicaid

NIMH
National Institute of Mental Health

Press Release

National Institute of Mental Health

National Institutes of Health

Collaborative Study Finds Effective Treatments for Attention Deficit Hyperactivity Disorder

EMBARGOED FOR RELEASE:
Tuesday, December 14, 1999
10 A.M., E.S.T.

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National Institute of Mental Health
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The National Institute of Mental Health (NIMH) will join Columbia University to present the results of the collaborative NIMH Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA). The press conference will be held on December 14, 1999 at 10:00 A.M. at the Columbia University College of Physicians and Surgeons, Conference Center, Columbia Presbyterian, East Side, 16 East 60th Street, New York City. Two papers detailing the results of the MTA study will be published in the December issue of the American Medical Association's ***Archives of General Psychiatry***.

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed disorder of children, estimated to effect 3-5% of school age children. On average, at least one child in every classroom in the United States needs help for the disorder. The core symptoms of ADHD include an inability to sustain attention and concentration, developmentally inappropriate levels of activity, distractibility and impulsivity.

"ADHD is a major public health problem of great interest to many parents, teachers, health care providers, and researchers. Up-to-date information concerning the safety and efficacy of treatments over a significant period of time is critical," said Steven E. Hyman, M.D., Director of NIMH. In this landmark study, the first major clinical trial to look at childhood mental illness and the largest NIMH clinical trial to date, the NIMH and the Department of Education tested the leading treatments for ADHD for long-term efficacy at multiple research sites in the U.S. and Canada.

Including nearly 600 elementary school children, ages 7-9, the MTA study randomly assigned them to one of four treatment programs: (1) medication management alone; (2) behavioral treatment alone; (3) a combination of both; or (4) routine community care. "All children tended to improve over the course of the study, but they differed in the relative amount of improvement," said Peter Jensen, M.D., one of the primary NIMH collaborators for the study and Senior Advisor to the Director of the NIMH, on assignment to Columbia University. "Nonetheless, determining what treatment will be most effective for a particular child is an important question that needs to be answered by each family in consultation with their health care professional."

The MTA study has demonstrated, on average, that carefully monitored medication management with monthly follow-up, with input from teachers, is more effective than intensive behavioral treatment for ADHD. The combination of medication management and intensive behavioral treatments was also significantly superior to psychosocial treatments alone in reducing ADHD symptoms. For some outcomes that are important in the daily functioning of these children (e.g., academic performance, familial relations), the combination of behavioral therapy and medication was necessary to produce improvements, and families and teachers reported somewhat higher levels of consumer satisfaction for those treatments that included the behavioral therapy components. Furthermore, the combination program allowed children to be treated over the course of the study with somewhat

lower doses of medication.

The study also found substantial differences between the study-provided medication treatments and those provided in the community, differences mostly related to the quality and intensity of the medication management treatment. During the first month of treatment, special care was taken to find an optimal dose of medication for each child receiving the MTA medication treatment. After this period, the MTA prescribing therapist met with the family for monthly, one-half hour visits with the parent and the child, to assess any concerns that the family might have regarding the medication or the child's ADHD-related difficulties. In addition, the MTA physicians sought input from the teacher on a monthly basis, and used this information to make any necessary adjustments in the child's treatment. If the child was experiencing any difficulties, the MTA physician was encouraged to consider adjustments in the child's medication. In comparison, the community-treatment physician generally saw the children face-to-face only 1-2 times per year, and for shorter periods of time each visit. Furthermore, they did not have any interaction with the teachers, and generally prescribed lower doses of stimulant medication.

"As the first major randomized treatment study, one of the most important results is that these same findings were replicated across 6 sites, located at diverse but representative geographical areas in this country and in Canada, despite substantial differences among sites in their samples' socio-demographic characteristics. This means that the study's overall results are probably applicable and generalizable for the many and diverse children and families in need of treatment services for ADHD," said Laurence Greenhill, M.D., a research psychiatrist at Columbia University, one of the research sites. Other sites include Duke University Medical Center, Durham, N.C.; Western Psychiatric Institute, Pittsburgh, PA; Long Island Jewish Medical Center, New Hyde Park, N.Y.; University of California at Berkeley; and University of California at Irvine; Montreal Children's Hospital, Canada.

The news conference will include presentations by Peter Jensen, M.D. and Stephen P. Hinshaw, Ph.D., the primary investigator for the research site at University of California, Berkeley. Other study investigators will be available for questions, including Howard B. Abikoff, Ph.D., New York University, Jeffrey Newcorn, M.D., Mount Sinai Medical Center, and Lily Hechtman, M.D., McGill University, Canada. Kimberly Hoagwood, Ph.D., Associate Director for Child and Adolescent Research, and Benedetto Vitiello, M.D., Chief of the Child and Adolescent Treatment and Preventive Intervention Branch, both of the NIMH, will also be present.

Other NIMH researchers participating in the study were: Laurence L. Greenhill, M.D., Glen Elliot, M.D., Ph.D., C. Keith Conners, Ph.D., Karen Wells, Ph.D., John S. March, M.D., M.P.H., James Swanson, Ph.D., Dennis P. Cantwell, M.D., William E. Pelham, Ph.D., Betsy Hoza, Ph.D., Helena C. Kraemer, Ph.D. The principal collaborator from the Office of Special Education Programs in the Department of Education (OSEP/DOE) was Ellen Schiller, Ph.D.; the current OSEP/DOE contact is Tom V. Hanley, Ed.D.

The National Institute of Mental Health (NIMH) is part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services. The Office of Special Education Programs (OSEP) is part of the Office of Special Education and Rehabilitative Services (OSERS), a component of the U.S. Department of Education.

NIMH Multimodal Treatment Study of Children with ADHD - Questions and Answers

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NIMH
National Institute of Mental Health

Questions & Answers

National Institute of Mental Health

National Institutes of Health

NIMH MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD

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1. What is the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (ADHD)? The Multimodal Treatment Study of Children with ADHD (MTA) is an ongoing, multisite, cooperative agreement treatment study of children conducted by the National Institute of Mental Health. The first major clinical trial in history to focus on a childhood mental disorder, and the largest clinical trial ever conducted by the NIMH, the MTA has examined the leading treatments for ADHD, including various forms of behavior therapy and medications. The study has included nearly 600 elementary school children, ages 7-9, randomly assigned to one of four treatment modes: (1) medication alone; (2) psychosocial/behavioral treatment alone; (3) a combination of both; or (4) routine community care.

2. Why is this study important? ADHD is a major public health problem of great interest to many parents, teachers, and health care providers. Up-to-date information concerning the long-term safety and comparative effectiveness of its treatments is urgently needed. While previous studies have examined the safety and compared the effectiveness of the two major forms of treatment, medication and behavior therapy, these studies generally have been limited to periods up to 4 months. The MTA study for the first time demonstrates the safety and relative effectiveness of these two treatments (including a behavioral therapy-only group), alone and in combination, for a time period up to 14 months, and compares these treatments to routine community care.

3. What are the major findings of this study? The MTA results indicate that long-term combination treatments as well as medication-management alone are both significantly superior to intensive behavioral treatments and routine community treatments in reducing ADHD symptoms. The longest clinical treatment trial of its kind to date, the study also shows that these differential benefits extend as long as 14 months. In other areas of functioning (specifically anxiety symptoms, academic performance, oppositionality, parent-child relations, and socials skills), the combined treatment approach was consistently superior to routine community care, whereas the single treatments (medication-only or behavioral treatment only) were not. In addition to the advantages proved by the combined treatment for several outcomes, this form of treatment allowed children to be successfully treated over the course of the study with somewhat lower doses of medication, compared to the medication-only group. These same findings were replicated across all six research sites, despite substantial differences among sites in their samples' socio-demographic characteristics. Therefore, the study's overall results appear to be applicable and generalizable to a wide range of children and families in need of treatment services for ADHD.

4. Given the effectiveness of medication management, what is the role and need for behavioral therapy? As noted in the NIH ADHD Consensus Conference in November 1998, several decades of research have amply demonstrated that behavioral therapies are quite effective. What the MTA study has demonstrated is that *on average*, carefully monitored medication management with monthly follow-up is more effective than intensive behavioral treatment for ADHD symptoms, for periods lasting as long as 14 months. All children tended to improve over the course of the study, but they differed in the relative amount of improvement, with the carefully done medication management approaches generally showing the greatest improvement. Nonetheless, children's responses varied enormously, and some children clearly did very well in each of the treatment groups. For some outcomes that are important in the daily functioning of these children (e.g., academic performance, familial relations), the combination of behavioral therapy and medication was necessary to produce improvements better than community care. Of note, families and teachers reported somewhat higher levels of consumer satisfaction for those treatments that included the behavioral therapy components. Therefore, medication alone is not necessarily the best treatment for every child, and families often need to pursue other treatments, either alone or in combination with medication.

5. Which treatment is right for my child? This is a critical question that must be answered by each family in

consultation with their health care professional. For children with ADHD, no single treatment is the answer for every child; a number of factors appear to be involved in which treatments are best for which children. For example, even if a particular treatment might be effective in a given instance, the child may have unacceptable side effects or other life circumstances that might prevent that particular treatment from being used. Furthermore, findings indicate that children with other accompanying problems, such as co-occurring anxiety or high levels of family stressors, may do best with approaches that combine both treatment components, i.e., medication management and intensive behavioral therapy. In developing suitable treatments for ADHD, each child's needs, personal and medical history, research findings, and other relevant factors need to be carefully considered.

6. Why do many social skills improve with medication? This question highlights one of the surprise findings of the study: Although it has long been generally assumed that the development of new abilities in children with ADHD (e.g., social skills, enhanced cooperation with parents) often requires the explicit teaching of such skills, the MTA study findings suggest that many children can often acquire these abilities when given the opportunity. Children treated with effective medication management (either alone or in combination with intensive behavioral therapy) manifested substantially greater improvements in social skills and peer relations 14 months later than children in the community comparison group. This important finding indicates that symptoms of ADHD may interfere with their learning of specific social skills. It appears that medication management may benefit many children in areas not previously well known to be salient medication targets, in part by diminishing symptoms that had previously interfered with the child's social development.

7. Why were the MTA medication treatments more effective than community treatments that also usually included medication? There were substantial differences between the study-provided medication treatments and those provided in the community, differences mostly related to the quality and intensity of the medication management treatment. During the first month of treatment, special care was taken to find an optimal dose of medication for each child receiving the MTA medication treatment. After this period, these children were seen monthly for one-half hour at each visit. During the treatment visits, the MTA prescribing therapist spoke with the parent, met with the child, and sought to determine any concerns that the family might have regarding the medication or the child's ADHD-related difficulties. If the child was experiencing any difficulties, the MTA physician was encouraged to consider adjustments in the child's medication (rather than taking a "wait and see" approach). The goal was always to obtain such substantial benefit that there was "no room for improvement" compared with the functioning of children not suffering from ADHD. Close supervision also fostered early detection and response to any problematic side effects from medication, a process that may have facilitated efforts to help children remain on effective treatment. In addition, the MTA physicians sought input from the teacher on a monthly basis, and used this information to make any necessary adjustments in the child's treatment. While the physicians in the MTA medication-only group did not provide behavioral therapy, they did advise the parents when necessary concerning any problems the child may have been experiencing, and provided reading materials and additional information as requested. Physicians delivering the MTA medication treatments generally used 3 doses per day and somewhat higher doses of stimulant medications. In comparison, the community-treatment physician generally saw the children face-to-face only 1-2 times per year, and for shorter periods of time each visit. Furthermore, they did not have any interaction with the teachers, and prescribed lower doses and twice-daily stimulant medication.

8. How were children selected for this study? In all instances, the child's parents contacted the investigators to learn more about the study, after first hearing about it through local pediatricians, other health care providers, elementary school teachers, or radio/newspaper announcements. Children and parents were then carefully interviewed to learn more about the nature of the child's symptoms, and rule out the presence of other conditions or factors that may have given rise to the child's difficulties. In addition, extensive historical information was gathered and diagnostic interviews were conducted, in order to establish whether or not the child exhibited the long-standing pattern of symptoms characteristic of ADHD across home, school, and peer settings. If children met full criteria for ADHD and study entry (and many did not), informed parental consent with child assent and school permission were received, the children and families were eligible for study entry and randomization. Children who had behavior problems but not ADHD were not eligible for study participation.

9. Where is this study taking place? Research sites include the New York State Psychiatric Institute at Columbia University, New York, N.Y.; Mount Sinai Medical Center, New York, N.Y.; Duke University Medical Center, Durham, N.C.; University of Pittsburgh; Pittsburgh, PA.; Long Island Jewish Medical Center, New Hyde Park, N.Y.; Montreal Children's Hospital, Montreal, Canada; University of California at Berkeley; and University of California at Irvine, CA.

10. How much money has been spent on this study? The study was jointly funded by the NIMH and the Department of Education, with costs totaling just over $11 million dollars.

11. What is Attention Deficit Hyperactivity Disorder (ADHD)? ADHD refers to a family of related chronic neurobiological disorders that interfere with an individual's capacity to regulate activity level (hyperactivity), inhibit behavior (impulsivity), and attend to tasks (inattention) in developmentally appropriate ways. The core symptoms of ADHD include an inability to sustain attention and concentration, developmentally inappropriate levels of activity, distractibility, and impulsivity. Children with ADHD have functional impairment across multiple settings including home, school, and peer relationships. ADHD has also been shown to have long-term adverse effects on academic performance, vocational success, and social-emotional development. Children with ADHD experience an inability to sit still and pay attention in class and the negative consequences of such behavior. They experience peer rejection and engage in a broad array of disruptive behaviors. Their academic and social difficulties have far-reaching and long-term consequences. These children have higher injury rates. As they grow older, children with untreated ADHD, in combination with conduct disorders experience drug abuse, antisocial behavior, and injuries of all sorts. For many individuals, the impact of ADHD continues into adulthood.

12. What are the symptoms of ADHD? (a) Inattention. People who are inattentive have a hard time keeping their mind on one thing and may get bored with a task after only a few minutes. Focusing conscious, deliberate attention to organizing and completing routine tasks may be difficult. (b) Hyperactivity. People who are hyperactive always seem to be in motion. They can't sit still; they may dash around or talk incessantly. Sitting still through a lesson can be an impossible task. They may roam around the room, squirm in their seats, wiggle their feet, touch everything, or noisily tap a pencil. They may also feel intensely restless. (c) Impulsivity. People who are overly impulsive seem unable to curb their immediate reactions or think before they act. As a result, they may blurt out answers to questions or inappropriate comments, or run into the street without looking. Their impulsivity may make it hard for them to wait for things they want or to take their turn in games. They may grab a toy from another child or hit when they are upset.

13. How is ADHD related to ADD? In the early 1980s, DSM-III dubbed the syndrome Attention Deficit Disorder, or ADD, which could be diagnosed with or without hyperactivity. This definition was created to underline the importance of the inattentiveness or attention deficit that is often, but not always, accompanied by hyperactivity. The revised 3rd edition of DSM-III-R, published in 1987, returned the emphasis back to the inclusion of hyperactivity within the diagnosis, with the official name of ADHD. With the publication of DSM-IV, the name ADHD still stands, but there are different subject types within this classification, to include symptoms of both inattention and hyperactivity-impulsivity, signifying that there are some individuals in whom one or another pattern is predominant (for at least the past 6 months). Thus, the term "ADD" (though no longer current) should be understood to be subsumed under the general family of conditions now called ADHD.

14. How is ADHD diagnosed? The diagnosis of ADHD can be made reliably using well-tested diagnostic interview methods. Diagnosis is based on history and observable behaviors in the child's usual settings. Ideally, a health care practitioner making a diagnosis should include input from parents and teachers. The key elements include a thorough history covering the presenting symptoms, differential diagnosis, possible comorbid conditions, as well as medical, developmental, school, psychosocial, and family histories. It is helpful to determine what precipitated the request for evaluation and what approaches had been used in the past. As of yet, there is no independent test for ADHD. This is not unique to ADHD, but applies as well to most psychiatric disorders, including other disabling disorders such as schizophrenia and autism.

15. How many children are diagnosed with ADHD? ADHD is the most commonly diagnosed disorder of childhood, estimated to affect 3 to 5 percent of school-age children, and occurring three times more often in boys than in girls. On average, about one child in every classroom in the United States needs help for this disorder.

16. How are schools involved in diagnosing, assessing, and treating ADHD? Physicians and parents should be aware that schools are federally mandated to perform an appropriate evaluation if a child is suspected of having a disability that impairs academic functioning. This policy was recently strengthened by regulations implementing the 1997 reauthorization of the Individuals with Disabilities Act (IDEA), which guarantees appropriate services and a public education to children with disabilities from ages 3 to 21. For the first time, IDEA specifically lists ADHD as a qualifying condition for special education services. If the assessment performed by the school is inadequate or inappropriate, parents may request that an independent evaluation be conducted at the school's expense. Furthermore, some children with ADHD qualify for special education services within the public schools, under the category of "Other Health Impaired." In these cases, the special education teacher, school psychologist, school administrators, classroom teachers, along with parents, must assess the child's strengths and weaknesses and design an Individualized Education Program. These special education services for children with ADHD are available though IDEA.

17. Aren't there various types of ADHD? According to DSM-IV, while most individuals have symptoms of both

inattention and hyperactivity-impulsivity, there are some individuals in whom one or another pattern is predominant (for at least the past 6 months). The MTA study included only the combined type of ADHD, known as the full syndrome, with symptoms of both inattentiveness and hyperactivity-impulsivity.

18. Is ADHD inherited? Research shows that ADHD tends to run in families, so there are likely to be genetic influences. Children who have ADHD usually have at least one close relative who also has ADHD. And at least one-third of all fathers who had ADHD in their youth have children with ADHD. Even more convincing of a possible genetic link is that when one twin of an identical twin pair has the disorder, the other is likely to have it too.

19. Is ADHD on the increase? If so, why? No one knows for sure whether the prevalence of ADHD per se has risen, but it is very clear that the number of children identified with the disorder who obtain treatment has risen over the past decade. Some of this increased identification and increased treatment-seeking is due in part to greater media interest, heightened consumer awareness, and the availability of effective treatments. A similar pattern is now being observed in other countries. Whether the frequency of the disorder itself has risen remains unknown, and needs to be studied.

20. Can you see ADHD in brain scans of children with the disorder? Neuroimaging research has shown that the brains of children with ADHD differ fairly consistently from those of children without the disorder, in that several brain regions and structures (pre-frontal cortex, striatum, basal ganglia, and cerebellum) tend to be smaller. Overall brain size is generally 5% smaller in affected children than children without ADHD. While this average difference is observed consistently, it is too small to be useful in making the diagnosis of ADHD in a particular individual. In addition, there appears to be a link between a person's ability to pay continued attention and measures that reflect brain activity. In people with ADHD, the brain areas that control attention appear to be less active, suggesting that a lower level of activity in some parts of the brain may be related to difficulties sustaining attention.

21. Can you diagnose a preschool child with ADHD? The diagnosis of ADHD in the preschool child is possible, but can be difficult and should be made cautiously by experts well-trained in childhood neurobehavioral disorders. Developmental problems, especially language delays, and adjustment problems can sometimes imitate ADHD. Treatment should focus on placement in a structured preschool with parent training and support. Stimulants can reduce oppositional behavior and improve mother-child interactions, but they are usually reserved for severe cases or when a child is unresponsive to environmental or behavioral interventions.

22. What is the impact of ADHD on children and their families? Life can be hard for children with ADHD. They're the ones who are so often in trouble at school, can't finish a game, and have trouble making friends. They may spend agonizing hours each night struggling to keep their mind on their homework, then forget to bring it to school. It is not easy coping with these frustrations day after day for children or their families. Family conflict can increase. In addition, problems with peers and friendships are often present in children with ADHD. In adolescence, these children are at increased risk for motor vehicle accidents, tobacco use, early pregnancy, and lower educational attainment. When a child receives a diagnosis of ADHD, parents need to think carefully about treatment choices. And when they pursue treatment for their children, families face high out-of-pocket expenses because treatment for ADHD and other mental illnesses is often not covered by insurance policies. School programs to help children with problems often connected to ADHD (social skills and behavior training) are not available in many schools. In addition, not all children with ADHD qualify for special education services. All of this leads to children who do not receive proper and adequate treatment. To overcome these barriers, parents may want to look for school-based programs that have a team approach involving parents, teachers, school psychologists, other mental health specialists, and physicians.

23. Aren't there nutritional treatments for ADHD? Many parents have exhausted nutritional approaches, such as eliminating sugar from the diet, before they seek medical attention. However, there are no well-established nutritional interventions that have been consistently demonstrated to be efficacious for assisting the great majority of children with ADHD. A small body of research has suggested that *some* children may benefit from these interventions, but delaying the implementation of well-established, effective interventions such as those employed in the MTA study, while engaged in the search for unknown, generally unproven allergens, is likely to be harmful for many children.

24. What are behavioral treatments? There are various forms of behavioral interventions used for children with ADHD, including psychotherapy, cognitive behavioral therapy, social skills training, support groups, and parent and educator skills training. In the MTA study, the behavioral/psychosocial group and the combined group both involved the child's teacher, the family, and participation in an all-day, 8-week summer camp. The consulting therapist worked with teachers to develop behavior management strategies that address behavioral problems

interfering with classroom behavior and academic performance. A trained classroom aide worked with the child for 12 weeks in his or her classroom, to provide support and reinforcement for appropriate, on-task behavior. Parents met with the therapist alone and in small groups to learn approaches for handling problems at home and school. The summer day camp was aimed at improving social behavior, academic work, and sports skills.

25. What medications are currently being used to treat ADHD? Psychostimulant medications, including methylphenidate (Ritalin®) and amphetamine (Dexedrine® and Adderall®), are by far the most widely researched and commonly prescribed treatments for ADHD. Numerous short-term studies have established the safety and efficacy of stimulants and psychosocial treatments for alleviating the symptoms of ADHD. The MTA has concluded that the two most effective treatment modalities for elementary school children with ADHD are a closely monitored medication treatment and a treatment that combines medication with intensive behavioral interventions. Nine out of ten children improved substantially on one of these treatments. Additionally, antidepressant medications may also be used as a second line of treatments for children who show poor response to stimulants, who have unacceptable side effects, or who have comorbid conditions (such as tics, anxiety, or mood disorders). Tricyclic antidepressants have shown clinical efficacy in 60-70% of children with ADHD. Clonidine, a medication used to treat hypertension, may be helpful in people with both ADHD and Tourette's syndrome. While the medications were extremely beneficial to most children, MTA findings indicated that medications alone may not necessarily be the best strategy for many children. For example, children who had accompanying problems (e.g., anxiety, stressful home circumstances, social skills deficits, etc.), over and above the ADHD symptoms, appeared to obtain maximal benefit from the combined treatment.

26. Are there standard doses for these medications? Careful medication management is important in treating a child with ADHD. For methylphenidate (Ritalin®), the usual dosage range is 5 to 20 mg dose given two to three times a day. The dose for dextroamphetamine (Dexedrine® and Dextrostat® and Adderal®) is one-half the methylphenidate dose. Dosage requirements do not always correlate with weight, age or severity of symptoms in an individual patient. Dosages may need to be increased during childhood with increased lean body weight and decreases may be necessary after puberty. Different doctors use these medications in slightly different ways.

27. How long are children on these medications? The expected duration of treatment has lengthened during this past decade as evidence has accumulated that benefits extend into adolescence and adulthood. However, many factors work against continued treatment during adolescence including the partial resolution of the most obvious symptoms, the short-lasting effects of medications, which require multiple doses per day, and the need for regular physician written prescriptions. Additionally, parents often discontinue medication even when benefit has been demonstrated or because they see the child improve and don't think the medication is necessary any longer.

28. How often are stimulant prescriptions used? Data from 1995 show that physicians treating children and adolescents wrote six million prescriptions for stimulants--methylphenidate (Ritalin®), and dextroamphetamine (Dexedrine®). Of all the drugs used to treat psychiatric disorders in children, stimulant medications are the most well-studied.

29. Isn't stimulant use on the increase? Stimulant use in the United States has increased substantially over the last 25 years. A recent study saw a 2.5-fold increase in methylphenidate between 1990 and 1995. This increase appears to be largely related to an increased duration of treatment, and more girls, adolescents, adults, and inattentive individuals (in addition to those individuals with both hyperactivity and inattentiveness/attention deficit) receiving treatment.

30. Why are stimulants used when the problem is overactivity? The answer to this question is not well-established, but one theory suggests that ADHD is related to difficulties in inhibiting responses to internal and external stimuli. Evidence to date suggests that those areas of the brain thought to be involved in planning, foresight, weighing of alternative responses, and inhibiting actions when alternative solutions might be considered, are underaroused in persons with ADHD. Stimulant medication may work on these same areas of the brain, increasing neural activity to more normal levels. More research is needed to firmly establish the mechanisms of action of the stimulants, however.

31. What are the risks of the use of stimulant medication and other treatments? Stimulant drugs, when used with medical supervision, are usually considered quite safe. Although they can be addictive when abused by teenagers and adults, when taken as prescribed for ADHD these medications have not been shown to be addictive nor to lead to substance abuse problems. They seldom make children "high" or jittery, nor do they sedate the child. Although little information exists concerning the long-term effects of psychostimulants, there is no evidence that careful therapeutic use is harmful. When adverse drug reactions do occur, they are usually related to dosage and are always reversable. Effects associated with moderate doses are decreased appetite and

insomnia. These effects occur early in treatment and may decrease with time. There may be negative effects on growth rate, but ultimate height appears not to be affected.

32. Will children taking these medications for ADHD become drug addicts? Actually, it appears to be just the opposite. Although an increased risk of drug abuse and cigarette smoking is associated with childhood ADHD, this risk appears mostly due to the ADHD condition itself, rather than its treatment. In a study jointly funded by the NIMH and the National Institute on Drug Abuse, boys with ADHD who were treated with stimulants were significantly less likely to abuse drugs and alcohol when they got older. Caution is warranted, nonetheless, as the overall evidence suggests that persons with ADHD (particularly untreated ADHD) are indeed at greater risk for later alcohol or substance abuse. Because some studies have come to conflicting conclusions, more research is needed to understand these phenomena. Regardless, in view of the substantial, well-established findings of the harmful effects of inadequate or no treatment for a child with ADHD, parents should not be dissuaded from seeking effective treatments because of misconstrued or exaggerated claims about substance abuse risks.

33. Wasn't there a large conference held at NIH on ADHD recently? In 1998, the NIH held a two-day Consensus Conference on ADHD, bringing together national and international experts, as well as representatives from the public. The Consensus statement is now available at **http://odp.od.nih.gov/consensus/cons/110/110_statement.htm**

34. What is the relationship between ADHD and other disorders, such as learning disabilities, anxiety disorders, bipolar disorder, or depression? Comorbidity occurs in most children clinically treated for ADHD. ADHD can be comorbid with learning disabilities (15-25%), language disorders (30-35%), conduct disorder (15-20%), oppositional defiant disorder (up to 40%), mood disorders (15-20%), and anxiety disorders (20-25%). Up to 60 percent of children with tic disorders also have ADHD. Impairments in memory, cognitive processing, sequencing, motor skills, social skills, modulation of emotional response, and response to discipline are common. Sleep disorders are also more prevalent.

35. What is the history of ADHD? ADHD has assumed many aliases over time from hyperkinesis (the Latin derivative for "superactive") to hyperactivity in the early 1970s. In the 1980s, DSM-III dubbed the syndrome Attention Deficit Disorder, or ADD, which could be diagnosed with or without hyperactivity. This definition was created to underline the importance of the inattentiveness or attention deficit that is often but not always accompanied by hyperactivity. The revised 3rd edition of DSM-III, published in 1987, returned the emphasis back to the inclusion of hyperactivity within the diagnosis, with the official name of ADHD. With the publication of DSM-IV, the name ADHD still stands, but there are varying types within this classification, to include symptoms of both inattention and hyperactivity-impulsivity, signifying that there are some individuals in whom one or another pattern is predominant (for at least the past 6 months). In the International Classification of Diseases (used predominantly in other Western countries), the term "Hyperkinetic Disorder" is used, but the criteria are the same as for ADHD/combined type.

36. What are the future research directions for ADHD? Continued research on ADHD is needed from many perspectives. The societal impact of ADHD needs to be determined. Studies in this regard include (1) strategies for implementing effective medication management or combination therapies in different schools and pediatric healthcare systems (2) the nature and severity of the impact on adults with ADHD beyond the age of 20, as well as their families; and (3) determination of the use of mental health services related to diagnosis and care of persons with ADHD. Additional studies are needed to improve communication across educational and health care settings to ensure more systematized treatment strategies. Basic research is also needed to better define the behavioral and cognitive components that underpin ADHD, not just in children with ADHD, but also in unaffected individuals, with studies to include (1) research on cognitive development, cognitive and attentional processing, impulse control, and attention/inattention; (2) studies of prevention/early intervention strategies that target known risk factors that may lead to later ADHD; and (3) brain imaging studies before the initiation of medication and following the individual through young adulthood and middle age. Finally, further research should be conducted on the comorbid (coexisting) conditions present in both childhood and adult ADHD, and treatment implications.

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NIMH
National Institute of Mental Health

This Child Needs Help

Attention Deficit Hyperactivity Disorder

Many childhood mental illnesses escape notice, but children with attention deficit hyperactivity disorder (ADHD) are often the subject of great concern on the part of parents and teachers. Children with ADHD-the most common of the psychiatric disorders that appear in childhood-can't stay focused on a task, act without thinking, can't sit still, and rarely finish anything. If untreated, the disorder can have long-term effects on a child's ability to make friends or do well at school or work. Over time, children with ADHD may develop depression, lack of self-esteem, and other emotional problems.

- Experts estimate that ADHD affects 3 to 5 percent of school-age children.
- ADHD affects two to three times as many boys as girls.
- Children with untreated ADHD have higher than normal rates of injury.
- ADHD frequently co-occurs with other problems, such as depression and anxiety disorders, conduct disorder, drug abuse, or antisocial behavior.

Treatments

Research has shown that certain medications, stimulants in most cases, and behavioral therapies that help children sit still, pay attention, and focus on tasks are the most beneficial treatments for children with ADHD.

Problems Faced by Families

ADHD can be reliably diagnosed when appropriate guidelines are used. Ideally, a health care practitioner making a diagnosis should include input from parents and teachers. But some health practitioners make a diagnosis without all this information and tend to either overdiagnose the disorder or underdiagnose it. Despite data showing that stimulant medication is safe, there are widespread misunderstandings about the safety and use of these drugs, and some health care practitioners are reluctant to prescribe them. Like all drugs, the medications used to treat ADHD do have side effects and need to be closely monitored.

Given the controversy in the health care community, parents need to think carefully about treatment choices when their child receives a diagnosis of ADHD. And when they pursue treatment for their children, families face high out-of-pocket expenses because treatment for ADHD and other mental illnesses is often not covered by insurance policies. In schools, treatment plans are often poorly integrated. In addition, there are few special education funds directed specifically for ADHD. All this leads to children who do not receive proper and adequate treatment. To overcome these barriers, parents may want to look for school-based programs that have a team approach involving parents, teachers, school psychologists, other mental health specialists, and physicians.

Recent Research Findings

Magnetic resonance imaging research has shown that the brains of children with ADHD differ from those of children without the disorder. In addition, there appears to be a link between a person's ability to pay continued attention and the use of glucose-the body's major fuel-in the brain. In people with ADHD, the brain areas that control attention use less glucose and appear to be less active, suggesting that a lower level of activity in some parts of the brain may cause inattention.

Research shows that ADHD tends to run in families, so there are likely to be genetic influences. Children who have ADHD usually have at least one close relative who also has ADHD. And at least one-third of all fathers

who had ADHD in their youth have children with ADHD. Even more convincing of a possible genetic link is that when one twin of an identical twin pair has the disorder, the other is likely to have it too.

Data from 1995 show that physicians treating children and adolescents wrote six million prescriptions for stimulants-methylphenidate (Ritalin®, dextroamphetamine (Dexedrine®), and pemoline (Cylert®). Of all the drugs used to treat psychiatric disorders in children, stimulant medications are the most well-studied. A 1998 Consensus Development Conference on ADHD sponsored by the National Institutes of Health and a recent, comprehensive scientific report confirmed many earlier studies showing that short-term use of stimulants is safe and effective for children with ADHD. Evidence is mounting that suggests stimulants are more effective than behavioral therapies in controlling the core symptoms of ADHD-inattention, hyperactivity/impulsiveness, and aggression. But the addition of behavioral treatments seems to result in improved functioning, in terms of better social skills and higher academic achievement. More studies are needed to assess the combination of medication and behavioral therapies and to examine the long-term use of stimulant medication.

A two-day consensus conference on ADHD, held at the National Institutes of Health in November 1998, brought together national and international ADHD experts as well as representatives from the public. The Consensus Statement is now available at ***http://odp.od.nih.gov/consensus/cons/110/110_statement.htm***

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NIMH National Institute of Mental Health

Brief Notes on the Mental Health of Children and Adolescents

The future of our country depends on the mental health and strength of our young people. However, many children have mental health problems that interfere with normal development and functioning. In the U.S , 1 in 10 children and adolescents suffer from mental illness severe enough to cause some level of impairment. However, in any given year, it is estimated that fewer than 1 in 5 of these children receives needed treatment. Recent evidence compiled by the World Health Organization indicates that by the year 2020, childhood neuropsychiatric disorders will rise proportionately by over 50 percent, internationally, to become one of the five most common causes of morbidity, mortality, and disability among children. The mental health problems affecting children and adolescents include the following:

Depression

Large-scale research studies have reported that up to 3 percent of children and up to 8 percent of adolescents in the U.S. suffer from depression, a serious mental disorder that adversely affects mood, energy, interest, sleep, appetite, and overall functioning. In contrast to normal emotional experiences of sadness or passing mood states, the symptoms of depression are extreme and persistent and can interfere significantly with the ability to function at home or at school. There is evidence that depression emerging early in life often recurs and continues into adulthood, and that early onset depression may predict more severe illness in adult life Diagnosing and treating children and adolescents with depression is critical in preventing impairment in academic, social, emotional, and behavioral functioning and to allow children to live up to their full potential.

Depression in children and adolescents is associated with an increased risk of suicidal behaviors. Since 1964, the suicide rate among adolescents and young adults has doubled. In 1996, the most recent year for which statistics are available, suicide was the 3rd leading cause of death in 15 to 24 year olds and the 4th leading cause among 10 to 14 year olds.

Antidepressant medications are prescribed to treat children and adolescents with depression. Recent studies indicate that certain selective serotonin reuptake inhibitors (SSRIs) are safe and efficacious treatments for depression in young people. However, care must be used in prescribing and monitoring all medication. Special forms of psychotherapy, such as cognitive-behavioral therapy, have proved effective for adolescents with depression, and current studies are evaluating the effectiveness of individual, family, and group therapies for young people. A current multi-site study of adolescents who are depressed is evaluating the comparative effectiveness of medication, psychosocial, or combined treatments.

Anxiety Disorders

Anxiety disorders are the most common mental health problems that occur in children and adolescents. According to one large-scale study of 9 to 17 year olds, entitled Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA), as many as 13 percent of young people had an anxiety disorder in a year.

Generalized Anxiety Disorder: symptoms include exaggerated worry and tension over everyday events.

Obsessive Compulsive Disorder (OCD): characterized by intrusive, unwanted, repetitive thoughts and rituals performed out of a feeling of urgent need; at least one-third of adult cases begins in childhood.

Panic Disorder: characterized by feelings of extreme fear and dread that strike unexpectedly and repeatedly for no apparent reason, often accompanied by intense physical symptoms, such as chest pain, pounding heart, shortness of breath, dizziness, or abdominal distress.

Post Traumatic Stress Disorder (PTSD): a condition that can occur after exposure to a terrifying event, most often characterized by the repeated re-experience of the ordeal in the form of frightening, intrusive memories, and brings on hypervigilance and deadening of normal emotions.

Phobias: *social phobia*, extreme fear of embarrassment or being scrutinized; *specific phobia,* excessive fear of

an object or situation, such as dogs, heights, loud sounds, flying, costumed characters, enclosed spaces, etc.

Other disorders: *separation anxiety*, excessive anxiety concerning separation from the home or from those to whom the person is most attached; and *selective mutism*, persistent failure to speak in specific social situations.

Various forms of psychotherapy, including cognitive-behavioral therapy and family therapy, as well as certain medications, particularly selective serotonin reuptake inhibitors (SSRIs), are used to treat anxiety disorders in children and adolescents. Research on the safety and efficacy of these treatments is ongoing.

ADHD

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder of childhood, estimated to affect 3 to 5 percent of school-aged children. Research shows that ADHD tends to run in families. Its core symptoms include developmentally inappropriate levels of attention, concentration, activity, distractibility, and impulsivity. Children with ADHD usually have impaired functioning in peer relationships and multiple settings including home and school. ADHD has also been shown to have long-term adverse effects on academic performance, vocational success, and social-emotional development.

Psychostimulant medications, including methylphenidate (Ritalin®), ampheta-mine (Dexedrine ® and Adderall ®), and pemoline (Cylert ®), are by far the most widely researched and commonly prescribed treatments for ADHD. Numerous short-term studies have established the safety and efficacy of stimulants and psychosocial treatments for alleviating the symptoms of ADHD. A multisite study of children with ADHD recently concluded that the two most effective treatment modalities for elementary school children with ADHD are a closely monitored medication treatment and a treatment that combines medication with intensive behavioral interventions. Another study, jointly funded by the NIMH and the National Institute on Drug Abuse, has shown that boys with ADHD who are treated with stimulants are significantly less likely to abuse drugs and alcohol when they get older. In previous studies, these same researchers found that nearly twice as many adults with ADHD (that was generally not diagnosed or treated until much later in life) also abused drugs and/or alcohol at some point in their lives, compared to adults without ADHD.

Eating Disorders

In the U.S., eating disorders are most common among adolescent and young women. In addition to causing various physical health problems, eating disorders are associated with illnesses such as depression, substance abuse, and anxiety disorders. Among adolescent and young adult women in the U.S., it is estimated that between 0.5 and 1.0 percent suffer from anorexia nervosa, 1 to 3 percent have bulimia nervosa, and 0.7 to 4 percent experience binge-eating disorder. There are limited data concerning the prevalence in males.

Similar to other mental disorders, such as obsessive-compulsive disorder and depression, patients with eating disorders have little control over their symptoms, and suffer from often serious and sometimes life-threatening illnesses that require medical and psychiatric attention. Because of their complexity, eating disorders call for a comprehensive treatment plan involving medical care and monitoring, psychotherapy, nutritional counseling, and medication management. Studies are investigating the causes of eating disorders and effectiveness of treatments.

Manic Depressive Illness

Manic-depressive illness causes extreme shifts in mood, energy, and functioning. Overly energized, disruptive, and reckless periods alternate with periods of sadness, withdrawal, hopelessness, and other depressive symptoms. Unlike normal mood states of happiness and sadness, symptoms of manic-depressive illness can interfere with school performance, family relationships, peer interactions, and other everyday activities. Although manic-depressive illness typically emerges in late adolescence or early adulthood, there is increasing evidence that the disorder also can begin in childhood. According to one study, one percent of adolescents ages 14-18 were found to have met criteria for manic-depressive illness or cyclothymia, a milder form of the illness, in their lifetime.

NIMH research efforts are attempting to clarify the diagnosis, course, and treatment of manic-depressive illness in youth. Evidence suggests that manic-depressive illness beginning in childhood or early adolescence may be a different, possibly more severe form of the disorder than older adolescent and adult-onset manic-depressive

illness. When the illness begins before or soon after puberty, it is often characterized by a continuous, rapid-cycling, and mixed symptom state that may co-occur with ADHD or other behavioral disorders, or may have features of these disorders as initial symptoms. In contrast, later onset manic-depressive illness appears to begin suddenly, often with a manic episode, and to have a more episodic pattern with relatively stable periods between episodes.

Various treatments known to be effective in adults with manic-depressive illness also may help relieve the symptoms in young people. The essential treatment for this disorder is the use of appropriate doses of mood stabilizing medications. The most typical is lithium, known to be very effective in adults for controlling mania and preventing recurrences of manic and depressive episodes. Research on the effectiveness of this and other medications in children and adolescents with manic-depressive illness is ongoing. In addition, studies are investigating various forms of psychotherapy to complement medication treatment for this illness in young people.

Autism and Other Pervasive Developmental Disorders

Autism and other pervasive developmental disorders are brain disorders that occurs in as many as 2 in 1,000 Americans. They typically affect the ability to communicate, form relationships with others, and respond appropriately to the outside world. The signs of autism usually develop by 3 years of age. The symptoms and deficits associated with autism may vary among people with the disorder. While some individuals with autism function at a relatively high level, with speech and intelligence intact, others are developmentally delayed, mute, or have serious language difficulty.

Research has made it possible to identify earlier those children who show signs of developing autism and thus initiate early intervention. Both psychosocial and pharmacological interventions can improve the behavioral and cognitive functioning of children with autism. Studies to evaluate medications such as risperidone and valproate are investigating their effects on cognition, behavior, and development, as well as their safety and efficacy. Emerging evidence is suggesting that certain genetic factors may confer susceptibility to the disorder and studies are underway to better understand this process. The prospect of acquiring basic biologic knowledge about autism holds hope for the development of future therapies.

Schizophrenia

Schizophrenia is a chronic, severe, and disabling brain disorder that affects about 1 percent of the population during their lifetime. Symptoms include hallucinations, delusions, disordered thinking, and social withdrawal. Schizophrenia appears to be extremely rare in children; more typically, the illness emerges in late adolescence or early adulthood. However, research studies are revealing that various cognitive and social impairments may be evident early in children who later develop schizophrenia. These and other findings may lead to the development of preventive interventions for children.

Only in this decade have researchers begun to make significant headway in understanding the origins of schizophrenia. In the emerging picture, genetic factors, which confer susceptibility to schizophrenia, appear to combine with other factors early in life to interfere with normal brain development. These developmental disturbances eventually appear as symptoms of schizophrenia many years later, typically during adolescence or young adulthood. A number of new, effective medications for schizophrenia have been introduced during the past decade.

Tourette's Syndrome

Tourette's Syndrome (TS) is characterized by repeated, involuntary movements and uncontrollable vocal sounds, known as tics. Affecting approximately 100,000 Americans in its full-blown form, TS generally emerges during childhood or early adolescence.

Although the basic cause of TS is unknown, current research suggests there is a genetic abnormality affecting certain neurotransmitters in the brain, and that varying environmental factors, possibly including infections, modifies the clinical expression of the disorder. Symptoms of TS are seen in association with some other neurological disorders, particularly OCD. Researchers are investigating the neurological similarities between OCD and TS to determine whether a genetic relationship exists.

In most cases, Tourette's Syndrome is not disabling, symptoms don't impair patients, development proceeds

normally, and there is no need for treatment. However, some effective medications are available in the rare instances when symptoms interfere with functioning. Children with TS can generally function well at home and in the regular classroom. If they have an accompanying learning disability or other disorder, such as ADHD or OCD, they may require tutoring, special classes, psychotherapy, or medication.

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Depression in Children and Adolescents

A Fact Sheet for Physicians

Diagnosis and treatment of depression in children and adolescents is a major challenge. Many children as well as adolescents suffer from depression, a disorder that can have far reaching effects on the functioning and adjustment of young people. Among both children and adolescents, depressive disorders confer an increased risk for illness and interpersonal and psychosocial difficulties that persist long after the depressive episode is over; in adolescents there is also an increased risk for substance abuse and suicidal behavior. Unfortunately, major depressive disorder—also known as unipolar depression—often goes undiagnosed. Studies show that signs of major depressive disorder in young people are frequently viewed as normal mood swings typical of a particular developmental stage. In addition, health care professionals may be reluctant to prematurely "label" a young person with a mental illness diagnosis. Yet early diagnosis and treatment are important; between 80 and 90 percent of people with depression—even the most serious forms—can be helped.

The scientific literature on treatment of children and adolescents with depression is far less extensive than that concerning adults. A handful of large-scale studies—mostly conducted in the last four to five years—has evaluated the short-term efficacy and safety of treatments for depression in children and adolescents. Larger treatment trials are needed to determine which treatments work best for which youth. Studies are also needed on how to best incorporate these treatments into primary care practice.

Given the challenging nature of the problem, it is usually advisable to involve a child psychiatrist or psychologist in the evaluation, diagnosis, and treatment of a child or adolescent in whom depression is suspected.

This fact sheet, prepared by the National Institute of Mental Health (NIMH), the lead Federal agency for research on mental disorders, summarizes some of the latest scientific findings on child and adolescent depression and lists resources where family physicians can obtain more information.

Scope of the Problem

An NIMH-sponsored epidemiological study of 9- to 17-year-olds estimates that the prevalence of any depression is more than 6 percent, with 4.9 percent having major depression.[1] In addition, research has found that depression onset is occurring earlier in life. A study reported in the *Journal of the American Medical Association* suggests that early onset depression often persists, recurs, and continues into adulthood.[3] Depression in childhood may also predict more severe illness in adult life.[4] Depression in young people is often accompanied by psychological or somatic symptoms, behavioral manifestations, or other disorders, such as anxiety disorders. It also often occurs in conjunction with illnesses such as diabetes.

Suicide. Depression in children and adolescents is associated with an increased risk of suicidal behaviors. This risk may rise, particularly among adolescent boys, if the depression is accompanied by conduct disorder and alcohol or other substance abuse.[5] In 1997, suicide was the third leading cause of death in 10- to 24-year-olds.[6] NIMH research indicates that among children and adolescents who develop major depressive disorder, as many as 7 percent may commit suicide in the young adult years.[3] Consequently, it is important for doctors and parents to take all threats of suicide seriously.

NIMH researchers are developing and testing various interventions to prevent suicide in children and adolescents. Early diagnosis and treatment, accurate evaluation of suicidal thinking, and limiting young people's access to lethal agents—including firearms[7] and medications—may hold the greatest suicide prevention value.

Diagnostic Criteria

The diagnostic criteria and key defining features of depression in children and adolescents are the same as

they are for adults. However, recognition and diagnosis of the disorder are more difficult in youth for several reasons. The way symptoms are expressed varies with the developmental stage of the youngster. In addition, depressed children and young adolescents may have difficulty in properly identifying and describing their internal emotional or mood states. For example, young people may not complain about how bad they feel and may instead act moody and cranky, which may be interpreted by others as misbehavior or disobedience. Research also shows that parents are even less likely to identify major depression in their adolescents than are the adolescents themselves.

Symptoms of Major Depressive Disorder Common to Adults, Children, and Adolescents

- Persistent sad or irritable mood
- Loss of interest in activities once enjoyed
- Significant change in appetite or body weight
- Difficulty sleeping or oversleeping
- Psychomotor agitation or retardation
- Loss of energy
- Feelings of worthlessness or inappropriate guilt
- Difficulty concentrating
- Recurrent thoughts of death or suicide

Five or more of these symptoms must persist for 2 or more weeks before a diagnosis of depression is indicated.

Ways Symptoms May Manifest in Children and Adolescents

- Frequent vague, non-specific physical complaints such as headaches, muscle aches, stomachaches or tiredness
- Frequent absences from school or poor performance in school
- Talk of or efforts to run away from home
- Outbursts of shouting, complaining, unexplained irritability, or crying
- Being bored
- Lack of interest in playing with friends
- Among adolescents, alcohol or substance abuse
- Social isolation, poor communication
- Fear of death
- Extreme sensitivity to rejection or failure
- Increased irritability, anger, or hostility
- Reckless behavior
- Difficulty with relationships

Screening

There are several tools that are useful for screening children and adolescents for depression. They include the Children's Depression Inventory (CDI)[9] for ages 7 to 17; and, for adolescents, the Beck Depression Inventory[10] and the Center for Epidemiologic Studies Depression (CES-D) Scale.[11] When these are positive, further evaluation, which may include interviews with the child, parents, and collateral informants, such as teachers and social services personnel, is warranted.

Risk Factors

Among children, boys and girls appear to be at equal risk for developing depression. Adolescent girls, however, may be more at risk than their male counterparts.[13] Children who develop major depression are likely to have a family history of the disorder, often a parent who experienced depression at an early age.[14] Adolescents with depression are also likely to have a family history of depression, though the correlation is not as high as it is for children. In addition, teen cigarette smoking is associated with depression.[15]

Other risk factors include:[16]

- Stress
- A loss of a parent or loved one
- Attentional, conduct or learning disorders
- Chronic illnesses, such as diabetes
- Abuse or neglect
- Other trauma, including natural disasters

Treatment

The last decade has spawned advances in treatment options for young people with depression. Treatment often combines short-term psychotherapy, medication, and targeted interventions involving the home or school environment. There remains, however, a pressing need for additional research on treatments for depression in

children and adolescents, including medications as well as psychotherapies.

In general, to prevent the recurrence of depression, it is recommended that treatment be continued for all patients for at least 6 months after the remission of symptoms.

Psychotherapy. Recent research shows that certain types of short-term psychotherapy, particularly cognitive-behavioral therapy (CBT), can help relieve depression in children and adolescents.[12,18,19] CBT is based on the premise that depressed patients have cognitive distortions in their views of themselves, the world, and the future. CBT, designed to be a time-limited therapy, focuses on changing these distortions. An NIMH-supported study on treating major depression in adolescents, for example, found that CBT resulted in a rate of remission of nearly 65 percent, a higher rate than either supportive therapy or family therapy. CBT also resulted in a more rapid treatment response.[20]

Related forms of focused, problem-solving psychotherapy that target interpersonal features of depression also appear to be effective.[21]

Continuing psychotherapy after remission of symptoms helps patients and families consolidate the skills learned during the acute phase of depression, cope with the after-effects of the depression, effectively address environmental stressors, and understand how the young person's thoughts and behaviors contribute to a relapse. If the patient is taking antidepressants, continued psychotherapy may also help to promote medication compliance.[12]

Medication. Research clearly demonstrates that antidepressant medications, especially when combined with psychotherapy, can be very effective treatments for depressive disorders in adults.[22] Using medication to treat young people, however, has caused controversy. Many doctors have been understandably reluctant to treat depressed children and adolescents with psychotropic medications because, until fairly recently, little evidence was available about the effects of antidepressants on young people.

In the last few years, however, researchers have been able to conduct randomized, placebo-controlled studies on children and adolescents. Some of the newer antidepressant medications, specifically the selective serotonin reuptake inhibitors (SSRIs), have been shown to be safe and effective for the short-term treatment of severe and persistent depression in young people, although large scale studies in clinical populations are still needed. So far, there are controlled studies showing good results for fluoxetine and paroxetine.[23,24]

It is important to note that available studies do not support the efficacy of tricyclic antidepressants (TCAs) for this age group.[25] In addition, a recent review of the role of TCAs in children and adolescents cautions that "the future therapeutic role of TCAs for children and adolescents need to be seriously weighed against lethality of overdose, the unresolved issue of possible sudden unexplained death, and the availability of safer and easier to monitor medications."[26]

Medication as a first-line course of treatment should be considered for children and adolescents with severe symptoms that would prevent effective psychotherapy, those who are unable to undergo psychotherapy, those with psychosis, and those with chronic or recurrent episodes.

To develop more science-based information on the effectiveness of both medication and psychotherapeutic treatments for adolescent depression, NIMH has started a large, controlled clinical trial at 9 sites that is being coordinated by Duke University. The sites, which may be good sources of information for family physicians, are located at New York University/New York State Psychiatric Institute, Wayne State University, University of Chicago, University of Nebraska-Creighton, University of Oregon, University of Pennsylvania, University of Texas Southwestern, Carolinas Medical Center (Charlotte, NC), and The Johns Hopkins University.

Talking With Parents

One of the most important things family physicians can do is to reassure parents that children can be effectively treated for depression. Parents are likely to be asked to be involved in psychotherapeutic treatments to help identify major sources of stress for their child or adolescent and to help the family develop better ways of coping with life situations. Parents may be reluctant to agree to drug treatment when it is needed because of the newness of data on medications to treat the disorder in young people and because of sensational and

erroneous media coverage linking antidepressants to violent activity or suicide. Physicians can calm these fears by informing parents about the latest studies on the effectiveness and safety of current medications. They can also point to the recommendation of the American Academy of Child and Adolescent Psychiatry that medication can be an effective part of the treatment for depression, especially when it is used as part of a comprehensive treatment plan that includes psychotherapy.[12]

Other Types of Depression In Children and Adolescents [BOX]
Bipolar Disorder.

Although rare in young children, bipolar disorder[27]—also known as manic-depressive illness—can appear in both children and teenagers. Bipolar disorder involves unusual shifts in mood, energy, and functioning. It may begin with either manic or depressive symptoms. It is more likely to affect the children of parents who have the disorder.

Unlike adults, whose symptoms are acute and episodic, young children often experience rapid mood swings and cycle from depression to mania several times within a day. Children with mania are more likely to be irritable and prone to destructive tantrums than to be elated or euphoric. Bipolar disorder accounts for a large proportion of children's psychiatric hospitalizations. Some 20 percent of adolescents with major depression develop bipolar disorder within 5 years of the onset of depression.[13]

Teenagers with bipolar disorder display a combination of extremely manic and depressive moods. Highs may alternate with lows, or, for some youths, the moods may change so quickly that the adolescent feels both extremes at almost the same time.

Symptoms of bipolar disorder often can be difficult to distinguish from other problems of childhood and adolescence. For example, while irritability and aggressiveness can indicate bipolar disorder, they can also be symptoms of depression or conduct disorder. Among teenagers, irritability and aggressiveness could indicate more common adolescent problems such as drug abuse, delinquency, attention deficit hyperactivity disorder (ADHD), or a less frequent disorder, schizophrenia. However, any child who appears to be depressed and exhibits ADHD-like symptoms that are very severe, with excessive temper outbursts and mood changes, should be evaluated to rule out bipolar disorder, particularly if there is a family history of bipolar disorder. This evaluation is necessary especially since psychostimulants, often prescribed for ADHD, may worsen manic symptoms. There is also limited evidence suggesting that some of the symptoms of ADHD may be a forerunner of full-blown mania.

Bipolar Disorder: Manic Symptoms[28,8]

- Severe changes in mood; unusual happiness or silliness, or extreme irritability
- Overly-inflated self-esteem
- Great energy increase; ability to go with very little or no sleep for days without tiring
- Increased talking—talks too much, too fast; changes topics too quickly; cannot be interrupted
- Distractibility—attention moves constantly from one thing to the next
- Disregard of risk

Bipolar Disorder: A Warning about Antidepressants

There is some evidence that using antidepressants to treat a child with depression who has bipolar disorder may induce manic symptoms.[27] While it can be hard to determine which young patients will become manic, there is a greater likelihood among children who have a family history of bipolar disorder. Family physicians seeing a child who may be depressed and who has a family history of bipolar disorder may want to consult with a child psychiatrist. Family practitioners should also be aware of the signs and symptoms of mania so that they can educate families on how to recognize these immediately.

***Dysthymic disorder* (or *dysthymia*)**

This less severe yet typically more chronic form of depression is diagnosed when depressed mood persists for at least one year in children or adolescents, and is accompanied by at least two of the symptoms of major depression.[8] Dysthymia often precedes major depressive disorder. Treatment of the child or adolescent with dysthmia may prevent the deterioration to more severe illness.[12]

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Policy Statement

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Medication for Children With Attentional Disorders (RE9627)

AMERICAN ACADEMY OF PEDIATRICS

Committee on Children With Disabilities and Committee on Drugs

*** ABSTRACT. Increasing numbers of children with attentional difficulties have been treated with medication, especially during the last 25 years, and now adolescents and adults are also being recognized with attentional difficulties. This policy statement provides information on the role and the pharmacology of medications used to treat children with attention deficit disorders. Indications and use of medications are discussed and recommended drugs and dose levels are outlined. Information on adverse effects and common side effects is presented.**

Children with attentional difficulties have been described since the turn of the century. The modern era of treatment began with the publication by Bradley[1] regarding the beneficial effect of benzedrine in children with attentional and other behavior problems. Increasing numbers of children have been treated with medication, especially during the past 25 years, and now adolescents and adults are also being recognized with attentional difficulties. More than 700 studies on the effects of drugs on learning or behavior in children had been published by 1973,[2] and many studies and reviews have been published since that time. The American Academy of Pediatrics (AAP) has reviewed this subject several times, beginning with a position paper in 1970; the most recent statement was published in 1987.[3] The nomenclature for these disorders has changed with time, as has the knowledge and use of the medications involved. The role and the pharmacology of medications used to treat children with attention deficit disorders is reviewed in light of current information. In recent years, the term attention deficit disorder has become established as a recognized diagnostic category because of its listing in the *Diagnostic and Statistical Manual of Mental Disorders* compiled by the American Psychiatric Association. The new *Diagnostic and Statistical Manual for Primary Care* for children and adolescents, developed by the AAP in conjunction with the American Psychiatric Association and the Society for Pediatric Psychology, offers a comprehensive, pediatric-oriented definition of attentional disorders. Children with attention deficit/hyperactivity disorder demonstrate a persistent pattern of inattention or hyperactivity and impulsivity that is more frequent and severe than that observed in other children at a similar level of development.[4] Although genetic factors or neurologic insults are sometimes involved, the etiology in many instances is unknown. The primary symptoms of these disorders occur along a continuum of severity and include: (1) difficulties with selective attention, including easy distractibility; (2) difficulty with impulse control; (3) problems with maintaining appropriate task-related activities; (4) disorders of executive function, including planning and organization of cognitive tasks; (5) difficulty recognizing and responding to social cues; (6) difficulty attending to directions; and (7) low frustration tolerance. Commonly associated features include combinations of impairments in learning, memory, sequencing, motor skills, language, modulation of emotional response, compliance with societal demands, sleep patterns, and mood and affect. Although attentional disorders may occur alone, they are more commonly manifested as one of a series of symptoms associated with disorders of higher cortical function, including disturbances in movement, cognition, communication, and social competence.

Many educators and physicians do not realize that a differential diagnosis exists for these behaviors

much as for any other complex of symptoms. To establish an accurate diagnosis, information must be obtained concerning factors such as: (1) the child's birth, developmental, family, medical, psychosocial, and scholastic history; (2) sensory screening (ie, vision and hearing); and (3) physical, neurologic, and neuromaturational examinations.

As was originally stated by the Council on Child Health:

> The use of drug therapy in the management of the hyperkinetic child does not differ appreciably from drug therapy in other treatable maladies. In both instances, prescription drugs should be prescribed only by appropriately licensed physicians. Although the screening of patients may frequently be done by other disciplines, the ultimate selection of patients to be treated remains the responsibility of the prescribing physician.[5]

INDICATIONS AND USE OF MEDICATION

Medication may be indicated when a child or adolescent manifests signs of an attentional disorder and other related difficulties to a point that these problems interfere with the ability to learn or to develop satisfactory interpersonal relationships. Such symptoms may result in academic failure, inability to fulfill intellectual potential, poor self-esteem, or socially maladaptive behavior.

Drug therapy should not be considered a panacea or cure-all. An appropriate diagnostic evaluation is essential before a child begins any drug therapy for learning or behavior problems, both to establish the diagnosis and to identify commonly associated disorders that may require specific intervention. Such an evaluation often requires that the child be seen by other health professionals, such as psychologists, speech pathologists, and educational diagnosticians. Unfortunately, some children receive drug treatment for long periods without such evaluation and without continuing evaluation during therapy. Medication for children with attentional disorders should never be used as a sole treatment. The treatment team for children who have attentional disorders should consist of a partnership that includes the child, family, school personnel, physician, and other health professionals. Proper classroom placement, behavior modification, counseling, and provision of structure should be used, even if pharmacology is being considered.[6,7] This integrated approach should also continue once the drug therapy has been started. Medication should not be used without clear evidence that a child's attentional difficulties significantly affect school performance, cause difficulties with social adjustment, or are associated with a significant behavioral disorder. Medication should not be continued if clear-cut benefits are not observed.

RECOMMENDED DRUGS AND DOSE LEVELS

The medications used most effectively and frequently in the treatment of attentional disorders are the stimulants methylphenidate hydrochloride, dextroamphetamine sulfate, and pemoline. Therapy with these drugs results in significant improvement in 70% to 80% of properly diagnosed children with attention deficit disorders.[6,8,9]

Any medication that is used to treat an attentional disorder should be started at a low dose, with gradual, small increases. The effects of methylphenidate and dextroamphetamine become evident quickly, but it may take several weeks before maximum effectiveness can be judged. Pemoline has been believed to require 3 to 6 weeks before effectiveness can be judged, but more recent evidence indicates that this drug may show an effect very quickly.[10] The usual dose range for methylphenidate is 0.3 to 0.8 mg/kg per dose given two to three times each day; low doses are recommended for initial treatment.[11] The usual starting doses of methylphenidate for children in the early elementary grades are 5 mg in the morning and 5 mg at noon, with an additional dose after school if needed. Each dose of the standard form of methylphenidate provides improved attentional ability for 3 to 4 hours. The dose can then be increased gradually, if necessary, to obtain optimal response. Doses of methylphenidate greater than 1.0 mg/kg per dose may lead to decreased performance in attention testing and memory.[8] The increased use of methylphenidate in the adolescent and adult population is recent enough that maximum doses have not been established. The manufacturer does not recommend a daily dose larger than 60 mg for children. Changes in attention and behavior should be closely monitored at school and home. The use of a qualitative rating scale as a baseline for behavioral observations is advisable before

treatment is started and should be continued regularly thereafter.[12-14]

Dextroamphetamine and methylphenidate are manufactured as short- and long-acting medications. The recommended dose of dextroamphetamine is half that of methylphenidate. Results with the sustained-release form of methylphenidate have been disappointing, because the duration of effect is highly variable.[14,15] Pemoline is generally administered at a dose of 1 to 2 mg/kg once a day in the morning.

OTHER POTENTIALLY USEFUL DRUGS

Tricyclic antidepressants also ameliorate the symptoms of attentional disorders in children.[16] The most commonly used drugs are imipramine, desipramine, and nortriptyline. Overall, stimulant medications appear to be superior to the tricyclic drugs in the treatment of attentional disorders.[16] Tricyclic drugs, however, represent appropriate drugs of second choice when children do not respond to stimulant drugs, have intolerable side effects of stimulant drugs, or have attentional deficits associated with anxiety, mood disturbances, or depression. Blood levels can be helpful in establishing the proper dose. Many authors recommend various forms of electrocardiographic monitoring during therapy with tricyclic drugs, owing to a very small number of reports of sudden death in children receiving these medications.[17] Several studies have demonstrated electrocardiographic changes during therapy with these drugs, especially prolonged QT intervals.[18,19] On the other hand, no current evidence indicates that such monitoring can help clinicians identify a child at risk, and the value of such monitoring has not been demonstrated. Thus, routine electrocardiographic monitoring is not recommended at this time.

A variety of other medications have helped selected children. The most commonly used alternative medication to the stimulant drugs and tricyclic antidepressants has been clonidine.[20] Although clonidine has not been approved for this purpose, it is particularly useful for treating the hyperactive component of attentional disorders and has been helpful in children with associated conduct disorders. The major side effect is sleepiness. Clonidine can be used alone or in combination with the stimulant medications. A bedtime dose of clonidine may benefit those children who respond well to the stimulant medications but who develop insomnia.

The use of alternative drugs such as tricyclics and clondine must be approached with caution, because they have the potential for causing death when ingested intentionally by emotionally fragile children or accidentally by their siblings (and other household members). When the decision is made to use potentially toxic medications for a behavior disorder, the care givers should be informed about the risks. Pediatricians should help assure that families take precautions to avert toxic ingestion of these drugs.

ADVERSE EFFECTS

The most common side effects of stimulant medications are decreased appetite, insomnia, stomachaches, and headaches.[21] There had been concern that stimulant medications lead to growth retardation. Recent studies indicate, however, that no growth suppression occurred with doses of methylphenidate up to 0.8 mg/kg taken for a prolonged period.[22] On rare occasions, pemoline has been linked to a hypersensitivity reaction, which may result in jaundice and elevation in laboratory tests of liver function. Overt hepatic dysfunction is rare.

Stimulant drugs can also help alleviate the attentional deficits that may accompany other developmental problems, such as tic disorders, pervasive developmental disorders, and mental retardation. Occasionally, however, children with these disorders experience worsening of their symptoms. For this reason, such drugs must be used with added caution in children whose attentional difficulties are part of broader developmental problems. There is no conclusive evidence that the stimulant medications precipitate tic disorders, such as Tourette syndrome, except when a genetic predisposition already exists.[23]

Drug holidays on weekends and during summer vacations have been suggested by some physicians. This suggestion is based on the unproved hypothesis that sensitivity to the effects of stimulant drugs is heightened if they are given intermittently. This recommendation also reflects the concern that continuous administration leads to growth suppression. For many patients the symptoms of attentional disorders may not disappear during vacations or weekends. For these patients, drugs should be given

continuously. Medication should be administered continuously when the child's impulsiveness, activity, and other traits result in significant maladaptive behaviors toward family and peers.

RECOMMENDATIONS

Drug therapy should not be used as a part of the overall treatment program for children and adolescents without clear evidence that their attentional disorders have led to social, behavioral, and learning difficulties, and such therapy should not be continued if clear-cut benefits are not observed. Careful evaluation of patients is essential before drug treatment is initiated. Monitoring and follow-up both at school and home are vital. Pediatricians must work in concert with parents, principals, teachers, special educators, and school nurses to combine drug therapy with appropriate management of the child's environment and curriculum. In view of requests from other professionals and from school personnel to prescribe medication for children with attentional disorders, pediatricians should be cautious of becoming surrogate prescribers of medication. Although the overall management of social and school failure is a multidisciplinary venture, it is important to remember that the ultimate responsibility for the use of medication is the physician's.[24] The decision to use medication must always consider the overall needs of the child and family, and medication should never be considered the complete treatment program.

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Section on Anesthesiology
Stanley J. Szefler, MD
Section on Allergy and Immunology

REFERENCES

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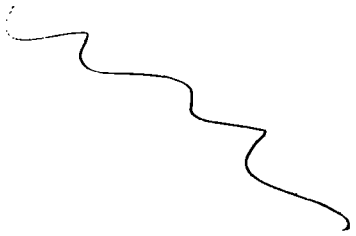
Children & adults
with ADD



Karin
Nana
Aunt Janet

March 1, 2000, Wednesday
Editorial Desk

The Role For Pills in Preschool

By Harold S. Koplewicz

The outcry over a recent report showing a dramatic increase in the use of medications like **Ritalin** for preschoolers reminded me of a patient of mine named Christopher.

In the early 1980's, when I was researching the efficacy of **Ritalin** in young children, Christopher was 3 1/2. He still slept in a crib to discourage his getting up in the middle of the night and wandering around the house. It didn't work: he often escaped, going to the kitchen and playing with the stove. Babysitters came only once. Nursery schools kept him for just a few days.

We observed Christopher and his mother in our clinic. She kept running after him to catch his attention; he played with 61 toys in one five-minute span. Then we put Christopher on **Ritalin**. In his mother's words: "He became a different child. He will sit and let me read a book to him. I can take him to a puppet show. We now can enjoy each other."

Christopher is now 20, a high school graduate who describes himself as well adjusted and happy. He also still takes **Ritalin** twice a day.

I guess I shouldn't be surprised that attention deficit hyperactivity disorder is still so frequently dismissed as childhood exuberance or "just a phase." Most adults do not realize how it differs from behavior that is simply on the active end of normal. Children with the disorder are 10 times as likely as the average child to drop out of high school. They have a higher incidence of drug abuse. This is a real psychiatric disorder and requires treatment.

The latest study, published in the Journal of the American Medical Association, found that between 1991 and 1995, there was a twofold to threefold increase in the use of **Ritalin** and similar drugs in children aged 2 to 4. About 1 in 100 children received **Ritalin** in 1995. Is 1 percent of children taking such medications too high?

Unfortunately, we have no information about the percentage of very young children who meet the criteria for an accurate diagnosis of A.D.H.D. For those who do, medications like **Ritalin** are the best treatment we have.

Understandably, there is concern that medications may affect brain development. Encouragingly, the evidence we have, although limited and crude, does not suggest that development is compromised by **Ritalin**.

Critics are also concerned that some medications for psychiatric illness are prescribed for preschoolers without approval by the Food and Drug Administration for use in that age group. But this practice holds true in other areas of medical care. One asthma medication, for example, is frequently given to young kids even though the F.D.A. has not approved it for children. There is ample evidence of **Ritalin**'s effectiveness for school-aged children with A.D.H.D., and some evidence that it helps younger children.

What should be at issue is not the clinical wisdom of giving **Ritalin** to young children, but who gives it and how the decision is made. Unfortunately, pediatricians and general practitioners are usually not trained to undertake the necessary clinical evaluations to make psychiatric diagnoses and monitor treatment.

Increasing use of **Ritalin** is not necessarily cause for alarm. The real outrage is that an estimated 20 percent of the nearly 10 million American children and teenagers who suffer from diagnosable psychiatric illnesses ever receive help.

Organizations mentioned in this article:

Related Terms:
Attention Deficit Hyperactivity Disorder; **Ritalin** (Drug); Children and Youth; Drugs (Pharmaceuticals)

NIMH National Institute of Mental Health

NIH BACKGROUNDER

NATIONAL INSTITUTES OF HEALTH NATIONAL INSTITUTE OF MENTAL HEALTH

DRAFT FOR WHITE HOUSE STAFF
March 15, 2000

Contact: Clarissa Wittenberg
301-443-4536

Prescription of Psychotropic Medications to Preschoolers

Introduction

The major news media have seized upon the topic of young children being given psychotropic drugs as an important story in our national life. NIMH stresses that each child merits a comprehensive evaluation--physical, mental and social--and an individualized treatment plan. Behavioral therapies and other psychosocial interventions should be employed as a first line option, and medication should be prescribed only in this context. The key question is how can we improve our treatment practices? If medications are needed, how should they be followed up to see if they are effective. Are we helping families to understand the potential risks and side effects of these medication as well as the potential benefits? Taking the medicine as prescribed is important and a close working relationship between the family and the doctor is needed to protect the child's well being. Today we are focused on overmedication, but under-medication is also a serious problem.

The discussion today, however, has many troubling aspects: are these young children mentally ill; is medication the answer or is it being used inappropriately? There are reports of stimulant medication (Ritalin®) being used for children under age 1. There are other questions being asked in this discussion: Why haven't psychotropic medications in general been studied and approved for children? When are specific drugs appropriate for young children? Why are these medications being used? For bedwetting? Or to control serious aggressive or self-injurious behavior? What effect do such medications have on the rapidly developing brains of young children? Even if appropriate and helpful, are these the right medications to use? Is the trend toward pharmaceutical management the right path for treating young children? Were the groups studied atypical in their use of these medications for small children? What needs to be done immediately to gather this crucial information? Little research has been done and it is important

to ask if the one described below actually is representative of the broader pediatric practice across the United States.

The Article

The article, "Trends in the Prescribing of Psychotropic Medication to Preschoolers," that sparked the attention was published in *The Journal of the American Medical Association* on February 23, 2000, Vol. 283, No. 8. The article reported research responsive to concerns about the uses of psychotropic medications for preschool-aged children with behavioral or emotional disorders. The article suggests that 1% to 1.5% of all children ages 2 to 4 enrolled in the groups studied received stimulants, antidepressants, or antipsychotic medications. The article states that the use of these medications has increased during the past decade.

The study by Julie Magno Zito, PhD; Daniel J. Safer, MD; Susan dos Reis, PhD; James F. Gardner, ScM; Myde Boles, PhD and Frances Lynch, PhD was designed to find the prevalence use of these medications in preschool children and to show 5-year trends.

Ambulatory care prescription records from two state Medicaid programs and an HMO were reviewed. The Medicaid populations were almost entirely eligible for care under Aid to Families with Dependent Children. A small proportion were qualified because of disability status (Supplemental Security Income) or foster care status. The HMO data represented a predominantly employed population in the northwest region. Three major psychotropic drug classes (stimulants, antidepressants, and neuroleptics) and two leading psychotherapeutic medications (methylphenidate and clonidine) were studied.

Sizeable increases in prevalence of drug prescriptions were noted between 1991 and 1995. Use of psychotropic medication is relatively small compared to that of use in older groups. The predominance of medications were prescribed "off-label."

Off-Label Use of Medication in Children

Drugs approved by the U.S. Food and Drug Administration (FDA) carry indications for use as established by research and carry warnings about possible side effects, derived from the research population. However, once a drug is approved, physicians may prescribe drugs as they think appropriate. At times, second level indications for drug use are established at a later date as a result of more research.

Drugs are often used "off-label" for children for the treatment of all kinds of medical conditions. This is due to a historical pattern of not testing drugs in children and not establishing pediatric use during FDA approval process. This is true for the use of drugs to treat children with mental illness as well. Effective October 1, 1998, NIH has established guidelines on the inclusion of children in research involving human subjects. This requirement grew out of a workshop with the National Institute of Child Health and Human Development (NICHD) and the American Academy of Pediatrics (AAP) held in June 1996 to address the inclusion of children in clinical research.

The AAP has reported that only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients.

The FDA has moved to suggest changes in testing of drugs to ensure that manufacturers specifically examine the drugs' effects on children if the medications are to have clinically significant pediatric use. In November 1998, a law was passed to extend patent exclusivity of drugs with potential value for children as a way to encourage studies in children. In 1999, Congress allowed the FDA to request studies in children using an expedited process.

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NIH NEWS ADVISORY

NATIONAL INSTITUTES OF HEALTH — National Institute of Mental Health

EMBARGOED for release 5:00 PM (EST) April 23, 1999

Constance Burr
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Ensuring Safe and Effective Psychotropic Medications for Children

Up-to-date information on the safety and efficacy of medications for children and adolescents with mental disorders is now available to parents, clinicians, researchers, and policymakers. Presented in a comprehensive series of articles in the May issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*, new studies show that the most widely prescribed psychotropic medications for children, stimulants and selective serotonin reuptake inhibitors (SSRIs), are safe and effective in the short term for specific conditions, such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder. Research results and consensus opinions from leaders who have clinical experience in pediatric psychopharmacology will enable people to make more informed decisions about the safety of these drugs and how they are used.

Until now there have been no systematic studies on the extent of use of all the major classes of psychoactive medications for children and adolescents. Previous studies were limited to specific locations or single institutions, or they focused on a single medication, such as methylphenidate (Ritalin). Addressing this gap, a team from the National Institute of Mental Health (NIMH) analyzed prescribing patterns and drug safety for children younger than 18 years by examining data from the National Ambulatory Medical Care Survey, a survey conducted annually by the National Center for Health Statistics, and the National Disease and Therapeutic Index, a pharmaceutical marketing database, for the year 1995.

"For the first time ever," said Peter S. Jensen, M.D., NIMH Associate Director for Child and Adolescent Research, "we have assembled the latest information on the actual level of all psychoactive medication prescriptions for children, combined these data with current evidence of safety and efficacy, and identified mismatches between clinical practices and scientific evidence." Expert investigators around the country worked together to compile evidence on the safety and efficacy of the entire range of psychoactive medications prescribed for U.S. children and adolescents and to make recommendations for future studies.

The data focused on children's visits to physicians for psychiatric reasons that involved prescribing a psychotropic medication. Results from the consensus review show good support for the safety and short-term efficacy of stimulants, which were prescribed most to treat ADHD, and for SSRIs, the second most prescribed group of agents, to treat major depression and obsessive compulsive disorder. Tricyclic antidepressants (TCAs) were the third most frequently mentioned, and central adrenergic agonists, such as clonidine, ranked fourth. Jensen and associates contrasted the estimated current use of psychotropics with the scientific evidence. Because many pediatric psychiatric disorders tend to be chronic and require long-term treatment, the study has also helped identify research needs on the long-term effects of these medications.

To advance knowledge of treatment information, NIMH established 7 Research Units on Pediatric Psychopharmacology (RUPPs), a network where clinical studies focus on the effects and safety of psychotropic medications in children. They are: Columbia University, Johns Hopkins University, University of Pittsburgh, Yale University, University of California Los Angeles, Indiana University, and Ohio State University. Through RUPPs, NIMH is studying SSRIs for anxiety in children and adolescents. Also, NIMH will host a conference this summer on the long-term safety of stimulants for ADHD.

"Gathering safety data on psychotropic medications for children is a public health imperative," Dr. Jensen said. The NIMH team's research results encourage optimism for children with mental illness, their parents, physicians, and all who have a stake in the future of the nation's children. Recommendations for future research include:

- When possible, practitioners and professional associations should encourage the enrollment of children in responsibly conducted rigorous clinical trials, rather than prescribing medications that have been studied only in adults.

- NIH institutes should target the development of short-term safety and efficacy studies of medications where knowledge is limited, levels of prescribing are highest, and potential for toxicities with long-term exposure are most prominent.
- For companies that voluntarily develop medications for children and adolescents, extension of patent life may help offset the costs of such studies.
- Responsible federal government agencies (FDA, NIH) should ensure that issues related to long-term safety and efficacy of psychotropic agents are systematically examined.

The articles below appear in a special section of the *Journal of the American Academy of Child and Adolescent Psychiatry,* 38:5, May 1999:

"Introduction—Current Knowledge and Unmet Needs in Pediatric Psychopharmacology." Guest Editors: Benedetto Vitiello, M.D., Vinod S. Bhatara, M.D., and Peter S. Jensen, M.D.

"Psychoactive Medication Prescribing Practices for U.S. Children: Gaps Between Research and Clinical Practice," by Peter S. Jensen, M.D., Vinod S. Bhatara, M.D., Benedetto Vitiello, M.D., Kimberly Hoagwood, Ph.D., Michael Feil, M.S., and Laurie B. Burke, R.Ph., M.P.H.

"Critical Review of Tricyclic Antidepressant Use in Children and Adolescents," by Barbara Geller, M.D., Daniel Reising, M.D., Henrietta Leonard, M.D., Mark Riddle, M.D., and B. Timothy Walsh, M.D.

"Nontricyclic Antidepressants: Current Trends in Children and Adolescents," by Graham J. Emslie, M.D., John T. Walkup, M.D., Steven R. Pliszka, M.D., and Monique Ernst, M.D., Ph.D.

"Stimulant Medications," by Laurence L. Greenhill, M.D., Jeffrey M. Halperin, Ph.D., and Howard Abikoff, Ph.D.

"Mood Stabilizers in Children and Adolescents," by Neal D. Ryan, M.D., Vinod S. Bhatara, M.D., and James M. Perel, Ph.D.

"Antipsychotics in Children and Adolescents," by Magda Campbell, M.D., Judith L. Rapoport, M.D., and George M. Simpson, M.D.

"Anxiolytics, Adrenergic Agents, and Naltrexone," by Mark A. Riddle, M.D., Gail A. Bernstein, M.D., Edwin H. Cook, M.D., Henrietta Leonard, M.D., John S. March, M.D., and James M. Swanson, Ph.D.

The National Institute of Mental Health (NIMH) is part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services.

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This page was last updated: Apeil 23, 1999.

Ritlin

United States Senate

WASHINGTON, DC 20510

March 3, 2000

Jane E. Henney, M.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane, Room 14-71
Rockville, MD 20857

Dear Dr. Henney:

We were troubled to learn of a study recently published in the *Journal of the American Medical Association (JAMA)* which found a rapidly increasing use of stimulants and anti-depressants by preschoolers, despite a lack of information about the safety of these products for young children. As you know, the dangerous shortage of medicines labeled for children has been a long-standing concern of ours. That is why we authored the Better Pharmaceuticals for Children Act, which was enacted into law as part of the Food and Drug Administration Modernization Act (FDAMA) of 1997.

The Better Pharmaceuticals for Children Act provides a market incentive for drug companies to make the extra effort needed to test their products for children. By all accounts, this incentive approach is beginning to close the dangerous gap in knowledge about how drugs work in children. In just the 18 months since the initiation of the incentive program, research has been completed on 19 drugs that were previously used for children without adequate information about safety. These studies have already resulted in new safety information being added to six drugs, with labeling changes expected for the other 13 in the near future. In addition, pediatric studies of more than 125 additional drugs are currently underway. In contrast, in the five years prior to enactment of the legislation, only 11 studies to gather additional safety information about drugs already on the market were conducted.

But, while progress has been made, we still have a long way to go to make sure that children are not an afterthought when it comes to drug research – as the *JAMA* article so clearly highlights. As reported in *JAMA*, doctors are prescribing powerful psychiatric drugs like Ritalin and Prozac for preschoolers at rates that have doubled or even tripled from 1991 to 1995. Given all that we know about the astonishing pace of brain development in young children, it is extremely troubling that the effect of the drugs on children's long-term cognitive, social, and emotional development are largely unknown.

We are pleased with the progress you have made in implementing the Better Pharmaceuticals for Children legislation. However, major work remains to be done, particularly with regard to psychiatric drugs. We understand that Clonidine, an adult blood pressure medication that is being used for attention deficit disorder in children, is on the list of products that your agency has identified as needing better pediatric information, but that no request for studies has yet been made of the manufacturer. We also understand that Prozac is now being

studied under our incentive program for children aged seven and older, but even when these studies are completed, we will still lack information about its safety in pre-school age children.

Therefore, we urge you to make the pediatric testing of psychiatric drugs a high priority for your agency. We strongly encourage you to work with pharmaceutical manufacturers to complete the pediatric research they have begun and to initiate research for those products not yet being studied. We also urge you to work with the National Institute of Child Health and Human Development to facilitate research on off-patent drugs such as Ritalin, for which the market exclusivity incentive is not appropriate.

Thank you again for your continued support of our efforts to secure better information about the safety and effectiveness of prescription drugs for children. In the absence of this much-needed information, the continuation of current prescribing practices holds too dear a price: the safety of our children.

Sincerely,

CHRISTOPHER J. DODD
United States Senator

MIKE DEWINE
United States Senator

7572104

26775

① Cross professional org. support.

② agreement on Conference admin → broader group target period to plan upon.

studies underway 125

studies rq 250

previous 11 54 vs final

labels as result of studies

Office of the Assistant Secretary for Health
and
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FAX TRANSMISSION COVER SHEET

Date: 3-15-2000

To: Chris Jennings

Fax: 456-5557

Re: (As discussed)

From: Beverly Malone

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Surgeon General's Mental Health Report

more children and families in the system of care group received case management and home visits than those in the comparison group. Findings indicate no differences in clinical or functional status 12 months after intake. These results are similar to those of the Fort Bragg study and suggest that attention should be paid to the effectiveness of services delivered *within* systems of care rather than only to the organization of these systems.

Summary: Effectiveness of Systems of Care

Collectively, the results of the evaluations of systems of care suggest that they are effective in achieving important system improvements, such as reducing use of residential placements, and out-of-state placements, and in achieving improvements in functional behavior. There also are indications that parents are more satisfied in systems of care than in more traditional service delivery systems. The effect of systems of care on cost is not yet clear, however. Nor has it yet been demonstrated that services delivered within a system of care will result in better clinical outcomes than services delivered within more traditional systems. There is clearly a need for more attention to be paid to the relationship between changes at the system level and changes at the practice level.

Conclusions

1. Childhood is characterized by periods of transition and reorganization, making it critical to assess the mental health of children and adolescents in the context of familial, social, and cultural expectations about age-appropriate thoughts, emotions, and behavior.
2. The range of what is considered "normal" is wide; still, children and adolescents can and do develop mental disorders that are more severe than the "ups and downs" in the usual course of development.
3. Approximately one in five children and adolescents experiences the signs and symptoms of a DSM-IV disorder during the course of a year, but only about 5 percent of all children experience what professionals term "extreme functional impairment."
4. Mental disorders and mental health problems appear in families of all social classes and of all backgrounds. No one is immune. Yet there are children who are at greatest risk by virtue of a broad array of factors. These include physical problems; intellectual disabilities (retardation); low birth weight; family history of mental and addictive disorders; multigenerational poverty; and caregiver separation or abuse and neglect.
5. Preventive interventions have been shown to be effective in reducing the impact of risk factors for mental disorders and improving social and emotional development by providing, for example, educational programs for young children, parent-education programs, and nurse home visits.
6. A range of efficacious psychosocial and pharmacologic treatments exists for many mental disorders in children, including attention-deficit/hyperactivity disorder, depression, and the disruptive disorders.
7. Research is under way to demonstrate the effectiveness of most treatments for children in actual practice settings (as opposed to evidence of "efficacy" in controlled research settings), and significant barriers exist to receipt of treatment.
8. Primary care and the schools are major settings for the potential recognition of mental disorders in children and adolescents, yet trained staff are limited, as are options for referral to specialty care.
9. The multiple problems associated with "serious emotional disturbance" in children and adolescents are best addressed with a "systems" approach in which multiple service sectors work in an organized, collaborative way. Research on the effectiveness of systems of care shows positive results for system outcomes and functional outcomes for children; however, the relationship between changes at the system level and clinical outcomes is still unclear.
10. Families have become essential partners in the delivery of mental health services for children and adolescents.
11. Cultural differences exacerbate the general problems of access to appropriate mental health

gap between research and clinical practice is discussed in greater depth elsewhere in this chapter and in Chapter 2.

Psychotherapy

The major types of psychotherapy for children are supportive, psychodynamic, cognitive-behavioral, interpersonal, and family systemic. With the exception of the latter, these therapies originally were developed for adults and then tailored for use in children.

Most psychotherapies are deemed effective for children and adolescents because they improve more than with no treatment, as discussed later in this chapter under Treatment Interventions (Casey & Berman, 1985; Hazelrigg et al., 1987; Weisz et al., 1987; Kazdin et al., 1990; Baer & Nietzel, 1991; Grossman & Hughes, 1992; Shadish et al., 1993; Weisz & Weiss, 1993; Weisz et al., 1995). But despite this strong body of research on children comparing treatment with no treatment, far less attention has been paid to, and guidance provided about, the efficacy of a given psychotherapy for a specific diagnosis (Lonigan et al., 1998). In other words, it is not clear which therapies are best for which conditions. The American Psychological Association sought to rectify this problem by convening two task forces, the second of which exhaustively reviewed the professional literature to evaluate the strength of the evidence for treating individual disorders in children. The second task force refined two sets of criteria against which to evaluate the evidence: the first, and more rigorous, set of criteria was for *Well-Established Psychosocial Interventions*, while the other was for *Probably Efficacious Psychosocial Interventions* (Lonigan et al., 1998). The findings of the task force's comprehensive evaluation were published, disorder by disorder, in an entire issue of the *Journal of Clinical Child Psychology* in June 1998. While findings relating to individual disorders are presented in the next section of this chapter, this was the overarching conclusion: ". . . the majority of these [psychosocial] interventions do not meet criteria for the highest level of empirical support, the well-established criteria" (Lonigan et al., 1998). The problem, according to these authors, is that too few well-controlled studies have been performed for each disorder. To meet the criteria for a *Well-Established Psychosocial Intervention*, there must be at least two well-conducted group-design studies conducted by different teams of researchers, among other criteria.[4] Hereafter, these criteria are referred to as the American Psychological Association Task Force Criteria.

Some other general points are warranted about the value of psychotherapies for children. Psychotherapies are especially important alternatives for those children who are unable to tolerate, or whose parents prefer them not to take, medications. They also are important for conditions for which there are no medications with well-documented efficacy. They also are pivotal for families under stress from a child's mental disorder. Therapies can serve to reduce stress in parents and siblings and teach parents strategies for managing symptoms of the mental disorder in their child (see later sections on Disruptive Disorders and Home-Based Services).

Psychopharmacology

Dramatic increases have occurred over the past decade in the use of pharmacological therapies for children and adolescents with mental disorders, but research has lagged behind the surge in their use (Jensen et al., 1999). Our gaps in knowledge span three areas in particular. First, for most prescribed medications, there are no studies of safety and efficacy for children and adolescents. This is true for medications for mental disorders as well as for somatic disorders. Depending on the specific medication, evidence may be lacking for short-term, or most commonly, for long-term safety and efficacy. The problem is even more pronounced with newer medications, most of which have been introduced into the market for adults. Only in the case of psychostimulants for ADHD is there an adequate body of research on their safety and efficacy in children and adolescents, albeit short-term information only (Greenhill et al., 1998) (see later section on ADHD). Second, there is often limited information about pharmacokinetics, that is, drug concentrations in body

[4] The criteria are listed in Chapter 1.

fluids and tissues over time (Clein & Riddle, 1996). Most of what is known about pharmacokinetics comes from studies of adults. But pediatric pharmacokinetic studies are crucial to identifying the appropriate dose and dose frequency for children of different ages and body sizes. Third, the combined effectiveness of pharmacological and psychosocial treatments, that is, multimodal treatments, is seldom studied. Multimodal treatments have the potential to yield dose reductions in pharmacological treatments, thereby improving the side-effect profile, parental acceptance, and patient compliance.

The dearth of research on children and adolescents has allowed for widespread "off-label" use of medications. This means that, for this population, physicians who are prescribing a given drug do not have the benefit of research and drug labeling information developed by the sponsor and approved by the Food and Drug Administration (FDA). Under U.S. food and drug law, a drug is approved by the FDA only for a defined population. Yet after its approval and market availability, physicians are at liberty to prescribe it for anyone, even though the sponsor only is allowed to *market* the drug for the approved population (which typically is adults) (FDA, 1998). Fortunately, there is a large body of clinical experience with children and adolescents to guide prescribing practices, despite few controlled studies (Green, 1996).

There are several reasons for the paucity of research on medications for children and adolescents. One is greater caution on the part of both the medical profession and parents to experiment with children or to prescribe drugs with potentially serious side effects. Another reason is the need for compliance with dosing requirements of the clinical trial protocol. When children are research subjects, enforcing compliance is generally perceived to be more difficult. Researchers must rely on parents to assess the degree of compliance. A final reason is the cost of research. Once drugs have reached the market for adults, pharmaceutical companies have fewer financial incentives to conduct expensive and methodologically demanding studies with children, to whom drugs may be given through off-label prescribing. The problem has been significant enough to have galvanized Congress into passing legislation, the FDA Modernization Act of 1997, to create financial incentives for drug sponsors to conduct research with pediatric subjects [FDA, 1999 Title 21 USC 505A(g)]. The FDA Modernization Act may help alleviate this problem, but it is too early to tell.

Despite the relative lack of information concerning safety and efficacy of psychotropic agents in children, six scientific reviews have been completed recently; these reviews comprehensively surveyed all available published research concerning the safety and efficacy of psychotropic medication, focusing on six general classes of medication: the psychostimulants (Greenhill et al., 1998), the mood stabilizers and antimanic agents (Ryan et al., 1999), the selective serotonin reuptake inhibitors (SSRIs) (Emslie et al., 1999), antidepressants (Geller et al., 1998), antipsychotic agents (Campbell et al., 1999), and other miscellaneous agents (Riddle et al., 1998).

Review of this comprehensive body of research evidence indicates strong support for the safety and efficacy of several classes of agents for several conditions, specifically, SSRIs for childhood/adolescent obsessive-compulsive disorder, and the psychostimulants for ADHD. For many other disorders and medications, however, information from rigorously controlled trials is sparse or altogether absent (see Figure 3-2). Further, only in the area of ADHD is information now emerging on longer term safety and efficacy, as well as on the merits of combining psychopharmacologic and psychotherapeutic treatments.

Given the inadequacy of efficacy data for most nonstimulant psychotropics, studies are needed for the majority of agents. However, efficacy data appear to be most urgently needed for SSRIs, mood stabilizers, and novel antipsychotics, since the level of usage of these medications appears to be highest among the growing list of psychotropic medications used in youth (Fisher & Fisher, 1996). In contrast to adult psychopharmacology that is focusing on differential efficacy and speed of onset of these categories of psychotropics,

Figure 3-2. Grading the Level of Evidence for Efficacy of Psychotropic Drugs in Children

Category	Indication	Level of Supporting Data: Short-Term Efficacy	Long-Term Efficacy	Short-Term Safety	Long-Term Safety	Estimated Frequency of Use: Rank
Stimulants	ADHD	A	B	A	A	1
Selective Serotonin Reuptake Inhibitors	Major depression	B	C	A	C	2
	OCD	A	C	A	C	
	Anxiety disorders	C	C	C	C	
Central Adrenergic Agonists	Tourette syndrome	B	C	B	C	3
	ADHD	C	C	C	C	
Valproate and Carbamazepine	Bipolar disorders	C	C	A	A	4
	Aggressive conduct	C	C	A	A	
Tricyclic Antidepressants	Major depression	C	C	B	B	5
	ADHD	B	C	B	B	
Benzodiazepines	Anxiety disorders	C	C	C	C	6
Antipsychotics	Childhood schizophrenia and psychoses	B	C	C	B	7
	Tourette syndrome	A	C	B	B	
Lithium	Bipolar disorders	B	C	B	C	8
	Aggressive conduct	B	C	C	C	

Key: A = ≥ 2 randomized controlled trials (RCTs).
B = At least 1 RCT.
C = Clinical opinion, case reports, and uncontrolled trials.

Source: Jensen et al., 1999

pediatric psychopharmacology needs basic studies of efficacy.

Additional information on specific medication treatment is presented in the succeeding sections, providing more detailed discussion of particular disorders. Indepth information is presented on two disorders where a great deal of research has been done, namely, ADHD and major depressive disorder, followed by briefer discussions of other childhood mental disorders.

Attention-Defi it/Hypera tivity Disorder

As its name implies, attention-deficit/hyperactivity disorder (ADHD) is characterized by two distinct sets of symptoms: inattention and hyperactivity-impulsivity (see Table 3-3). Although these problems usually occur together, one may be present without the other to qualify for a diagnosis (DSM-IV). Inattention or attention deficit may not become apparent until a child enters the challenging environment of elementary school. Such children then have difficulty paying attention to details and are easily distracted by other events that are occurring at the same time; they find it difficult and unpleasant to finish their schoolwork; they put off anything that requires a sustained mental effort; they are prone to make careless mistakes, and are disorganized, losing their school books and assignments; they appear not to listen when spoken to and often fail to follow through on tasks (DSM-IV; Waslick & Greenhill, 1997).

Table 3-3. DSM-IV criteria for Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

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

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that cause impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

The symptoms of hyperactivity may be apparent in very young preschoolers and are nearly always present before the age of 7 (Halperin et al., 1993; Waslick & Greenhill, 1997). Such symptoms include fidgeting, squirming around when seated, and having to get up frequently to walk or run around. Hyperactive children have difficulty playing quietly, and they may talk excessively. They often behave in an inappropriate and uninhibited way, blurting out answers in class before the teacher's question has been completed, not waiting their turn, and interrupting often or intruding on others' conversations or games (Waslick & Greenhill, 1997).

Many of these symptoms occur from time to time in normal children. However, in children with ADHD they occur very frequently and in several settings, at home and at school, or when visiting with friends, and they interfere with the child's functioning. Children suffering from ADHD may perform poorly at school; they may be unpopular with their peers, if other children perceive them as being unusual or a nuisance; and their behavior can present significant challenges for parents, leading some to be overly harsh (DSM-IV).

Inattention tends to persist through childhood and adolescence into adulthood, while the symptoms of motor hyperactivity and impulsivity tend to diminish with age. Many children with ADHD develop learning difficulties that may not improve with treatment (Mannuzza et al., 1993). Hyperactive behavior is often associated with the development of other disruptive disorders, particularly conduct and oppositional-defiant disorder (see Disruptive Disorders). The reason for the relationship is not known. Some believe that the impulsivity and heedlessness associated with ADHD interfere with social learning or with close social bonds with parents in a way that predisposes to the development of behavior disorders (Barkley, 1998).

Even though a great many children with this disorder ultimately adjust (Mannuzza et al., 1998), some—especially those with an associated conduct or oppositional-defiant disorder—are more likely to drop out of school and fare more poorly in their later careers than children without ADHD. As they grow older, some teens who have had severe ADHD since middle childhood experience periods of anxiety or depression. This seems to be especially common in children whose predominant symptom is inattention (Morgan et al., 1996). Excellent reviews of ADHD can be found in DSM-IV and other sources.[5]

Prevalence

ADHD, which is the most commonly diagnosed behavioral disorder of childhood, occurs in 3 to 5 percent of school-age children in a 6-month period (Anderson et al., 1987; Bird et al., 1988; Esser et al., 1990; Pelham et al., 1992; Shaffer et al., 1996c; Wolraich et al., 1996). Pediatricians report that approximately 4 percent of their patients have ADHD (Wolraich et al., 1990), but in practice the diagnosis is often made in children who meet some, but not all, of the criteria recommended in DSM-IV (Wolraich et al., 1990) (see also Treatment later in this section). Boys are four times more likely to have the illness than girls are (Ross & Ross, 1982). The disorder is found in all cultures, although prevalences differ; differences are thought to stem more from differences in diagnostic criteria than from differences in presentation (DSM-IV).

Causes

The exact etiology of ADHD is unknown, although neurotransmitter deficits, genetics, and perinatal complications have been implicated. In the early post-World War II years, a number of pediatricians, neurologists, and child psychiatrists noted that brain-damaged children were often hyperactive (Strauss & Lehtinen, 1947; Eisenberg, 1957; Laufer & Denhoff, 1957). These observations led to the diagnostic concept of "minimal brain damage" (Wender, 1971), which was thought to be characterized by hyperactivity, inattention, learning difficulties, and a wide variety of behavior problems. However, large epidemiological studies (Rutter & Quinton, 1977) of grossly brain-damaged children with cerebral palsy, epilepsy, and so

[5] Taylor, 1994; Cantwell, 1996; Waslick & Greenhill, 1997; Barkley, 1998; and NIH Consensus Statement 110, 1998.

forth, did not find an excess of hyperactivity, and more recent imaging studies have found no evidence of gross brain damage in children with ADHD (Swanson et al., 1998). The past view that ADHD is a form of minimal brain damage has therefore been abandoned by experts. Many brain-damaged children are, if anything, significantly underactive.

In the late 1970s, it was postulated that the core problem in hyperkinetic children was one of inattention (Douglas & Peters, 1979). This view led, in 1980, to the adoption, in the official DSM-III (American Psychiatric Association, 1980) nomenclature, of the new diagnostic label *attention-deficit disorder*.

Because the symptoms of ADHD respond well to treatment with stimulants, and because stimulants increase the availability of the neurotransmitter dopamine, the "dopamine hypothesis" has gained a wide following. The dopamine hypothesis posits that ADHD is due to inadequate availability of dopamine in the central nervous system. The neurotransmitter dopamine plays a key role in initiating purposive movement, increasing motivation and alertness, reducing appetite, and inducing insomnia, effects that are often seen when a child responds well to methylphenidate. The dopamine hypothesis has thus driven much of the recent research into the causes of ADHD.

The fact that ADHD runs in families suggests that inheritance is an important risk factor. Between 10 and 35 percent of children with ADHD have a first-degree relative with past or present ADHD. Approximately one-half of parents who had ADHD have a child with the disorder (Biederman et al., 1995). Over the past decade, a large number of twin studies have shown that, when ADHD is present in one twin, it is significantly more likely also to be present in an identical twin than in a fraternal twin (Goodman & Stevenson, 1989). These findings have led geneticists to estimate that genes are important in a high proportion of children with ADHD.

Research to pinpoint abnormal genes is honing in on two genes: a dopamine-receptor (DRD) gene on chromosome 11 and the dopamine-transporter gene (DAT1) on chromosome 5 (Cook et al., 1995; Smalley et al., 1998). Several studies have found evidence that children with ADHD have genetic variations in one of the dopamine-receptor genes (DRD4), although the largest of these studies suggests that the presence of such a variation is associated with only a modest increase in the risk of developing ADHD (Smalley et al., 1998). Several other studies have found evidence for abnormalities of the dopamine-transporter gene (DAT1) in children with very severe forms of ADHD (Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998).

Yet for most children with ADHD, the overall effects of these gene abnormalities appear small, suggesting that nongenetic factors also are important. Although none of the many imaging studies have found evidence of gross brain damage, some investigators have suggested that exposure to toxins, such as lead, or episodes of oxygen deprivation for the fetus, as may occur during some complications of pregnancy, may adversely affect dopamine-rich areas of the brain. These theories support observations that hyperactivity and inattention are more common in children whose mothers smoked during pregnancy (Nichols & Chen, 1981), in children who have been exposed to high quantities of lead (Needleman et al., 1990), and in children who had a lack of oxygen in the neonatal period (Whittaker et al., 1997).

Some investigators have noted that the parents of hyperactive children are often overintrusive and overcontrolling (Carlson et al., 1995). It has therefore been suggested that such parental behavior is another possible risk factor for ADHD. However, others have noted that, when children are treated with methylphenidate, there is a reduction in parental negativity and intrusiveness. This suggests that the observed overintrusive and overcontrolling behavior of the parent is a response to the child's behavior rather than the cause (Barkley et al., 1985).

Treatment

The American Academy of Child and Adolescent Psychiatry (AACAP) published "practice parameters" (i.e., guidelines for clinical practice) on the diagnosis and treatment of ADHD. The AACAP parameters include an extensive literature review, detailed descriptions of the clinical presentation of the disorder, and recommendations for treatment. The practice parameters state that "the cornerstones of treatment are support and education of parents, appropriate school placement, and pharmacology" (AACAP, 1991). These practice parameters evolved out of research relating to two major types of treatment: pharmacological treatment and psychosocial treatment, particularly behavioral modification, as well as multimodal treatment, the combination of psychosocial and pharmacological treatments.

Pharmacological Treatment

Psychostimulants

Pharmacological treatment with psychostimulants is the most widely studied treatment for ADHD. Stimulant treatment has been used for childhood behavioral disorders since the 1930s (Bradley, 1937). Psychostimulants are highly effective for 75 to 90 percent of children with ADHD. At least four separate psychostimulant medications consistently reduce the core features of ADHD in literally hundreds of randomized controlled trials: methylphenidate, dextroamphetamine, pemoline, and a mixture of amphetamine salts (Spencer et al., 1995; Greenhill, 1998a, 1998b; Greenhill et al., 1998).

These medications are metabolized, leave the body fairly quickly, and work for 1 to 4 hours. Administration is timed to meet the child's school schedule, to help the child pay attention and meet his or her academic demands, and to mitigate side effects. These medications have their greatest effects on symptoms of hyperactivity, impulsivity, and inattention and the associated features of defiance, aggression, and oppositionality. They also improve classroom performance and behavior and promote increased interaction with teachers, parents, and peers. Small effects were found on learning and school achievement (see reviews by Barkley, 1990; Pelham, 1993; Swanson et al.,1993, 1995b; Greenhill et al., 1998; Cantwell, 1996a; Spencer et al., 1996.) However, psychostimulants do not appear to achieve long-term changes in outcomes such as peer relationships, social or academic skills, or school achievement (Pelham et al., 1998).

Children who do not respond to one stimulant may respond to another (Elia et al., 1991; Elia & Rapoport, 1991). Children should be reevaluated without the medication to see if stimulant treatment is still indicated. Many families choose to have their child take a "drug holiday" on weekends and vacations to reduce overall exposure, but the utility of this strategy has not been demonstrated (AACAP, 1991).

Dosing

Stimulants are usually started at a low dose and adjusted weekly (AACAP, 1991). A recent study demonstrated that the practice of dosing methylphenidate on the basis of body weight fails to predict the optimal dose of medication (Rapport & Denney, 1997). One of the goals of the recently completed NIMH Multimodal Treatment Study of ADHD (described more fully below) was to develop medication strategies to guide "best dose," dose changes, management of side effects, and integration with other treatments (Greenhill et al., 1996).

Side Effects

Common stimulant side effects include insomnia, decreased appetite, stomach aches, headaches, and jitteriness. Some children may develop tics, but a recent study suggests that they disappear with continued treatment (Gadow et al., 1995). Rebound activation (i.e., a sudden increase in attention deficit and hyperactivity) has been noted anecdotally after the child's last dose of medication wears off (Johnston et al., 1988). Most of the side effects are mild, recede over time, and respond to dose changes. Children rarely experience cognitive impairment, which, if it does occur, can be resolved with reduction or cessation of the drug (Cantwell, 1996). A few cases of psychosis have been reported. Pemoline has been associated with hepatotoxicity, so monitoring of liver function is

necessary. Two studies have shown no long-term effects of stimulants on later height or weight (Klein & Mannuzza, 1988; Vincent et al., 1990). Nonetheless, regular precautionary monitoring of weight and height for children on stimulants is recommended.

Other Medications

For children with ADHD who do not respond to stimulants (10 to 30 percent) or cannot tolerate the side effects, there are other useful medications. The antidepressant bupropion has been found to be superior to placebo, although the response is not as strong as that found with stimulants (Cantwell, 1998). Bupropion can also be used as an adjunct to augment stimulant treatment. Well-controlled trials have shown tricyclic antidepressants to be superior to placebo but less effective than stimulants (Elia et al., 1991; Elia & Rapoport, 1991). Reports of sudden death of a few children in the early 1990s on the tricyclic compound desipramine led to great caution with the use of tricyclics in children (Riddle et al., 1991).

Considerable controversy surrounds the use of central alpha-adrenergic blocking drugs, such as clonidine and guanfacine, to treat ADHD. There is some evidence that clonidine is effective for ADHD when it occurs with a tic disorder (Hunt, 1987; Hunt et al., 1990, 1995). Caution is warranted in view of the four cases of sudden death that have been reported in children taking methylphenidate and clonidine together and of a number of reports of nonfatal cardiac side effects in children taking clonidine alone or in combination (Swanson et al., 1995a).

Neuroleptics have been found to be occasionally effective (Green, 1995), yet the risk of movements disorders, such as tardive dyskinesia, makes their use problematic. Lithium, fenfluramine, or benzodiazapines have not been found to be effective treatments for ADHD (Cantwell, 1996a; Green, 1995), nor have SSRIs, such as fluoxetine (Goldman et al., 1998). Furthermore, more than 20 studies have shown that dietary manipulation (e.g., the Feingold diet) is not efficacious (Mattes & Gittelman, 1981), and controlled studies failed to demonstrate that sugar exacerbates the symptoms of children with ADHD (Milich & Pelham, 1986).

Psychosocial Treatment

Important options for the management of ADHD are psychosocial treatments, particularly in the form of training in behavioral techniques for parents and teachers. Behavioral techniques, which are described more fully below, typically employ "time-out," point systems and contingent attention (adults reinforcing appropriate behavior by paying attention to it). Psychosocial treatments are useful for the child who does not respond to medication at all or for whom the therapeutic benefits of the medication have worn off and for the child who responds only partially to medication or cannot tolerate medication. In addition, some families express a strong preference not to use medication. Even children who are receiving medication may continue to have residual ADHD symptoms or symptoms from other disorders, such as oppositional defiant disorder or depression, which make specialized child management skills necessary and helpful (see next section, Multimodal Treatments). Furthermore, children with ADHD can present a challenge that puts significant stress on the family. Skills training for parents can help reduce this stress on parents and siblings.

Behavioral Approaches

The main psychosocial treatments for ADHD are behavioral training for parent and teacher, as well as systematic programs of contingency management (this behavioral technique is described in more detail in the Treatment section later in this chapter). Of these options, systematic programs of intensive contingency management conducted in specialized classrooms or summer camps with the setting controlled by highly trained individuals is the most effective (Abramowitz et al., 1992; Carlson et al., 1992; Pelham & Hoza, 1996). The efficacy of behavioral training of teachers is *well-established*, while the evidence for parent training is less solid, according to the criteria, noted earlier, promulgated by the American Psychological

Association Task Force (Pelham et al., 1998). There is, however, indirect support for the effectiveness of parent training in the literature, demonstrating the efficacy of parent training for children with oppositional defiant disorder who share many characteristics with children who have ADHD (see section on Disruptive Disorders).

A number of studies have compared parent training (Gittelman et al., 1980; Firestone et al., 1986; Horn et al., 1987, 1990, 1991; Pelham et al., 1988) or school-based behavioral modification (Gittelman et al., 1980; Pelham et al., 1988) with the use of stimulants. Most of the studies are of outpatient behavioral therapy programs in which parents meet in groups and are taught behavioral techniques such as time out, point systems, and contingent attention. Teachers are taught similar classroom strategies, as well as the use of a daily report card for parents that evaluates the child's in-school behavior. The improvements in the symptoms of ADHD achieved with psychosocial treatments are not as large as those found with psychostimulants (Pelham et al., 1998). Behavioral interventions tend to improve targeted behaviors or skills but are not as helpful in reducing the core symptoms of inattention, hyperactivity, or impulsivity. Questions remain about the effectiveness of these treatments in other settings. To be fully effective, treatments for ADHD need to be conducted across settings (school, home, community) and by different people (e.g., parents, teachers, therapists)—a consistency and comprehensiveness that can be hard to achieve.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT), primarily training in problem solving and social skills, has not been shown to provide clinically important changes in behavior and academic performance of children with ADHD (Pelham et al., 1998). However, CBT might be helpful in treating symptoms of accompanying disorders such as oppositional defiant disorder, depression, or anxiety disorders (Abikoff, 1985; Hinshaw & Ehardt, 1991; Lochman, 1992).

Psychoeducation

Although there are no studies evaluating the efficacy of psychoeducation as a treatment modality for ADHD, providing information to parents, children, and teachers about ADHD and treatment options is considered critical in the development of a comprehensive treatment plan (AACAP, 1991). Educational accommodations for children with ADHD are federally mandated, and mental health providers are required to ensure that patients and families have access to adequate and appropriate educational resources. Organizations such as Children and Adults with Attention Deficit Disorder (CHADD) and the National Attention Deficit Disorder Association can be helpful sources of information and support for families.

Multimodal Treatments

Many researchers and families have long suspected that multimodal treatment—medication used together with multiple psychosocial interventions in multiple settings—should be more effective than medication alone. Multimodal treatment has thus been used in the absence of empirical support (Hechtman, 1993). To determine whether multimodal treatment is indeed effective, the recent NIMH Multimodal Treatment Study of ADHD (called the MTA Study) examined three experimental conditions: medication management alone, behavioral treatment alone, or a combination of medication and behavioral treatments. The study compared the effectiveness of these three treatment modes with each other and with standard care provided in the community (the control group). The behavioral treatment condition consisted of parent training, a school intervention, and a summer treatment program. The MTA Study was also designed to determine the relative benefits of these treatments over time (Richters et al., 1995). All subjects were treated for 14 months and then followed for an additional 22 months.

Results of the MTA Study comparing the 14-month outcomes of 579 children randomly assigned to one of the four treatment conditions were presented in the fall of 1998 (MTA Cooperative Group, 1998). At 14 months, medication and the combination treatment were generally more effective than the behavioral

treatment alone or the control treatment. Notably, the combined treatment resulted in significant improvement over the control condition in six outcome areas—social skills, parent child relations, internalizing (e.g., anxiety) symptoms, reading achievement, oppositional and/or aggressive symptoms, and parent and/or consumer satisfaction—whereas the single forms of treatment (medication *or* behavior therapy) were each superior to the control condition in only one to two of these domains. The conclusions from this major study are that carefully managed and monitored stimulant medication, alone or combined with behavioral treatment, is effective for ADHD over a period of 14 months. Addition of behavioral treatment yields no additional benefits for core ADHD symptoms but appears to provide some additional benefits for non-ADHD-symptom outcomes.

Treatment Controversies

Overprescription of Stimulants

Concerns have been raised that children, particularly active boys, are being overdiagnosed with ADHD and thus are receiving psychostimulants unnecessarily. However, recent reports found little evidence of overdiagnosis of ADHD or overprescription of stimulant medications (Goldman et al., 1998; Jensen et al., 1999). Indeed, fewer children (2 to 3 percent of school-aged children) are being treated for ADHD than suffer from it. Treatment rates are much lower for selected groups such as girls, minorities, and children receiving care though public service systems (Bussing et al., 1998a, 1998b). However, there have been major increases in the number of stimulant prescriptions since 1989 (Hoagwood et al., 1998), and methylphenidate is being manufactured at 2.5 times the rate of a decade ago (Goldman et al., 1998). Most researchers believe that much of the increased use of stimulants reflects better diagnosis and more effective treatment of a prevalent disorder. Medical and public awareness of the problem of ADHD has grown considerably, leading to longer treatment, fewer interruptions in treatment, and increased treatment of adults. Adolescents and younger girls with ADHD, who were underdiagnosed in the past, are being identified and treated.

Nonetheless, some of the increase in use may reflect inappropriate diagnosis and treatment. In one study, the rate of stimulant treatment was twice the rate of parent-reported ADHD, based on a standardized psychiatric interview (Angold & Costello, 1998). While many children who do meet the full criteria for ADHD are not being treated, the majority of children and adolescents who are receiving stimulants did not fully meet the criteria. These findings may reflect a failure of proper, comprehensive evaluation and diagnosis rather than a failure of the diagnostic criteria, which are clear and validated by research (Angold & Costello, 1998). A diagnosis of ADHD requires the presence of impairing ADHD symptoms in *multiple* settings for at least 6 months. Although fidgeting and not paying attention are normal, common childhood behaviors, DSM-IV criteria reserve a diagnosis of ADHD for children in whom such frequent behavior produces persistent and pervasive dysfunction. An adequate diagnostic evaluation requires histories to be taken from multiple sources (parents, child, teachers), a medical evaluation of general and neurological health, a full cognitive assessment including school history, use of parent and teacher rating scales, and all necessary adjunct evaluation (such as assessment of speech, language). These evaluations take time and require multiple clinical skills. Regrettably, there is a dearth of appropriately trained professionals.

Family practitioners are more likely than either pediatricians or psychiatrists to prescribe stimulants and less likely to use diagnostic services, provide mental health counseling, or provide followup care (Hoagwood et al., 1998). The American Academy of Pediatrics published a policy statement in 1996 on the use of medication for children with attentional disorders, concluding that use of medication should not be considered the complete treatment program for children with ADHD and should be prescribed only after a careful evaluation (American Academy of Pediatrics Committee on Children With Disabilities and Committee on Drugs, 1996).

Safety of Long-Term Stimulant Use

Even though the MTA Study found no safety issues over a 14-month period (Greenhill et al., 1998), concerns have been raised about the longer term safety of stimulant treatment. Since ADHD has an early onset and requires an extended course of treatment, research is needed to examine the long-term safety of treatment and to investigate whether other forms of treatment could be combined with psychostimulants to lower their dose as well as to reduce other problem behaviors found with ADHD. Such combined treatments could be targeted for symptoms of disorders that often accompany ADHD, such as conduct disorder, substance abuse, and learning disabilities, and could be targeted to improve overall functioning (Laufer, 1971; Gittelman et al., 1985).

Because stimulants are also drugs of abuse and because children with ADHD are at increased risk for a substance abuse disorder, concerns have also been raised about the potential for abuse of stimulants by children taking the medication or diversion of the drug to others. While stimulants clearly have abuse potential, the rate of lifetime nonmedical methylphenidate use has not significantly increased since methylphenidate was introduced as a treatment for ADHD, suggesting that abuse is not a major problem (Goldman et al., 1998). Case reports describing abuse by children prescribed stimulants for ADHD are rare (Hechtman, 1985).

Depression and Sui ide in Children and Adoles ents

In children and adolescents, the most frequently diagnosed mood disorders are major depressive disorder, dysthymic disorder, and bipolar disorder. Because mood disorders such as depression substantially increase the risk of suicide, suicidal behavior is a matter of serious concern for clinicians who deal with the mental health problems of children and adolescents. The incidence of suicide attempts reaches a peak during the midadolescent years, and mortality from suicide, which increases steadily through the teens, is the third leading cause of death at that age (CDC, 1999; Hoyert et al., 1999). Although suicide cannot be defined as a mental disorder, the various risk factors—especially the presence of mood disorders—that predispose young people to such behavior are given special emphasis in this section, as is a discussion of the effectiveness of various forms of treatment. The evidence is strong that over 90 percent of children and adolescents who commit suicide have a mental disorder, as explained later in this section.

Major depressive disorder is a serious condition characterized by one or more major depressive episodes. In children and adolescents, an episode lasts on average from 7 to 9 months (Birmaher et al., 1996a, 1996b) and has many clinical features similar to those in adults. Depressed children are sad, they lose interest in activities that used to please them, and they criticize themselves and feel that others criticize them. They feel unloved, pessimistic, or even hopeless about the future; they think that life is not worth living, and thoughts of suicide may be present. Depressed children and adolescents are often irritable, and their irritability may lead to aggressive behavior. They are indecisive, have problems concentrating, and may lack energy or motivation; they may neglect their appearance and hygiene; and their normal sleep patterns are disturbed (DSM-IV).

Despite some similarities, childhood depression differs in important ways from adult depression. Psychotic features do not occur as often in depressed children and adolescents, and when they occur, auditory hallucinations are more common than delusions (Ryan et al., 1987; Birmaher et al., 1996a, 1996b). Associated anxiety symptoms, such as fears of separation or reluctance to meet people, and somatic symptoms, such as general aches and pains, stomachaches, and headaches, are more common in depressed children and adolescents than in adults with depression (Kolvin et al., 1991; Birmaher et al., 1996a, 1996b).

Dysthymic disorder is a mood disorder like major depressive disorder, but it has fewer symptoms and is more chronic. Because of its persistent nature, the disorder is especially likely to interfere with normal adjustment. The onset of dysthymic disorder (also called dysthymia) is usually in childhood or

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release August 13, 1997

REMARKS BY THE PRESIDENT
AT EVENT ON PEDIATRIC DOSAGE

Room 450
Old Executive Office Building

2:19 P.M. EDT

THE PRESIDENT: You know, one of the most important rules about being President is to never go on after the star of the show. (Laughter.) I would like to thank all of you for being here today. The Vice President, the First Lady, and Secretary Shalala have spoken about what we're trying to do and acknowledged the work of many individuals and groups. But I want to thank Dr. David Kessler, who as the Vice President said, used to work at the FDA; Dr. Friedman, the Acting Commissioner of the FDA. I also want to thank Dr. Koop, who wrote us a letter in support yesterday. And Hillary mentioned our good friend, Elizabeth Glaser. I got a wonderful letter today from her husband, Paul, about how much this would mean to their son, Jake. And so, all of you who have been in this situation, I thank you for helping this day come to pass.

And I thank Reagan Ralph for her eloquent speech under some duress. (Laughter.) I thank her spouse for doing what I think is a noble duty there. (Laughter and applause.) And next time we'll let you give the speech. (Laughter.) And the rest of us will handle Sam. (Laughter.)

I'm glad Sam came up here today and showed us what childhood should be like. It's what kids that are a year and a half old should be doing, and they should be able to do it. They should be able to do it. And according to the American Academy of Pediatrics, more than 50 percent of the medicines that have proved helpful for children have not been adequately tested for children's use. That is not acceptable.

The executive action that I take today simply is designed to ensure that parents and pediatricians have the safety information they need. Doctors have known for a long time that children respond differently than adults to many drugs. In cases -- many cases -- children can only tolerate vastly scaled-down doses. In some cases, their bodies simply haven't developed enough to take any dosage of a medicine that has been perfectly safe for adults.

Moreover, we still don't even have good information about medication for some of the most common childhood illnesses that Hillary mentioned, like asthma, allergic reactions, ear infections. And we certainly don't know enough about medications for treating life-threatening diseases.

Less than half the drugs used to help the estimated 12,000 children with HIV infection in our country have been tested for use

in children. Information is especially sparse for children under two, the time when the medication may be most needed.

Without clear guidance, pediatricians sometimes decide not to prescribe for children drugs used successfully by adults, and this means that the children may well be being deprived of what may be the very best treatment available. And as the Vice President said, the pediatrician's other alternative is to guess -- with potentially grave consequences.

Some time ago, for example, doctors gave infants small doses of a crucial antibiotic commonly used by adults, but it turned out that the infants were unable to clear the drug from their bodies and large amounts built up in their livers and, because of needed dosage studies which had not been done, 23 infants died.

The rule I announce today will put an end to this guesswork. It will require manufacturers of all medicines needed by children to study the drug's effects on children. The results will then be displayed on drug labels to help pediatricians and other health care professionals make good decisions about how to treat their young patients. Groups representing patients, physicians, nurses, pharmacists, and drug manufacturers all have indicated their willingness to help us implement this new rule, and we appreciate their willingness to do so.

I also want to applaud Senators Dodd and DeWine and Congressman Greenwood and Congressman Waxman, all of whom have introduced legislation that would provide additional incentives for drug manufacturers to perform the needed dosage studies in children. Their approach is compatible with the rule we're announcing today, and I look forward to working with them on this issue as Congress continues our bipartisan efforts to pass comprehensive FDA reform this fall.

And I know Congressman Greenwood and his children are here -- I'd like to ask him to stand. Thank you, sir, for being here. We appreciate your work. (Applause.) In your new position in the Congress you may have many more controversial issues to deal with, but few that will do more good. And we thank you for your leadership.

Today we take one more significant step toward assuring quality health care for our children, building on our historic commitment in the balanced budget to extend health care coverage to five million of them who don't have it today.

Again, let me say when something like this happens the President gets to give a speech, but the credit goes to all the people who worked on it -- to all the parents, to those who kept working for this even after their children suffered terrible injury and sometimes even death; to all the members of the professional groups. You deserve the credit. And I am very grateful to you for bringing this matter to my attention and giving me the power to use what the law has given me as President to do what you know and to do what you have long known is the right thing to do. This is your day.

As the First Lady has often said, children are not rugged individuals. They depend upon us to give them love and guidance, discipline and the benefit of good medical care. Today, their dependence has been justified. Their future and ours depends upon how well we continue to do this important work.

Thank you very much. (Applause.)

END 2:26 P.M. EDT

NIH BACKGROUNDER

NATIONAL INSTITUTES OF HEALTH NATIONAL INSTITUTE OF MENTAL HEALTH

DRAFT FOR WHITE HOUSE STAFF

March 15, 2000

Contact: Clarissa Wittenberg
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Prescription of Psychotropic Medications to Preschoolers

Introduction

The major news media have seized upon the topic of young children being given psychotropic drugs as an important story in our national life. NIMH stresses that each child merits a comprehensive evaluation--physical, mental and social--and an individualized treatment plan. Behavioral therapies and other psychosocial interventions should be employed as a first line option, and medication should be prescribed only in this context. The key question is how can we improve our treatment practices? If medications are needed, how should they be followed up to see if they are effective. Are we helping families to understand the potential risks and side effects of these medication as well as the potential benefits? Taking the medicine as prescribed is important and a close working relationship between the family and the doctor is needed to protect the child's well being. Today we are focused on overmedication, but under-medication is also a serious problem.

The discussion today, however, has many troubling aspects: are these young children mentally ill; is medication the answer or is it being used inappropriately? There are reports of stimulant medication (Ritalin®) being used for children under age 1. There are other questions being asked in this discussion: Why haven't psychotropic medications in general been studied and approved for children? When are specific drugs appropriate for young children? Why are these medications being used? For bedwetting? Or to control serious aggressive or self-injurious behavior? What effect do such medications have on the rapidly developing brains of young children? Even if appropriate and helpful, are these the right medications to use? Is the trend toward pharmaceutical management the right path for treating young children? Were the groups studied atypical in their use of these medications for small children? What needs to be done immediately to gather this crucial information? Little research has been done and it is important

to ask if the one described below actually is representative of the broader pediatric practice across the United States.

The Article

The article, "Trends in the Prescribing of Psychotropic Medication to Preschoolers," that sparked the attention was published in *The Journal of the American Medical Association* on February 23, 2000, Vol. 283, No. 8. The article reported research responsive to concerns about the uses of psychotropic medications for preschool-aged children with behavioral or emotional disorders. The article suggests that 1% to 1.5% of all children ages 2 to 4 enrolled in the groups studied received stimulants, antidepressants, or antipsychotic medications. The article states that the use of these medications has increased during the past decade.

The study by Julie Magno Zito, PhD; Daniel J. Safer, MD; Susan dos Reis, PhD; James F. Gardner, ScM; Myde Boles, PhD and Frances Lynch, PhD was designed to find the prevalence use of these medications in preschool children and to show 5-year trends.

Ambulatory care prescription records from two state Medicaid programs and an HMO were reviewed. The Medicaid populations were almost entirely eligible for care under Aid to Families with Dependent Children. A small proportion were qualified because of disability status (Supplemental Security Income) or foster care status. The HMO data represented a predominantly employed population in the northwest region. Three major psychotropic drug classes (stimulants, antidepressants, and neuroleptics) and two leading psychotherapeutic medications (methylphenidate and clonidine) were studied.

Sizeable increases in prevalence of drug prescriptions were noted between 1991 and 1995. Use of psychotropic medication is relatively small compared to that of use in older groups. The predominance of medications were prescribed "off-label."

Off-Label Use of Medication in Children

Drugs approved by the U.S. Food and Drug Administration (FDA) carry indications for use as established by research and carry warnings about possible side effects, derived from the research population. However, once a drug is approved, physicians may prescribe drugs as they think appropriate. At times, second level indications for drug use are established at a later date as a result of more research.

Drugs are often used "off-label" for children for the treatment of all kinds of medical conditions. This is due to a historical pattern of not testing drugs in children and not establishing pediatric use during FDA approval process. This is true for the use of drugs to treat children with mental illness as well. Effective October 1, 1998, NIH has established guidelines on the inclusion of children in research involving human subjects. This requirement grew out of a workshop with the National Institute of Child Health and Human Development (NICHD) and the American Academy of Pediatrics (AAP) held in June 1996 to address the inclusion of children in clinical research.

The AAP has reported that only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients.

The FDA has moved to suggest changes in testing of drugs to ensure that manufacturers specifically examine the drugs' effects on children if the medications are to have clinically significant pediatric use. In November 1998, a law was passed to extend patent exclusivity of drugs with potential value for children as a way to encourage studies in children. In 1999, Congress allowed the FDA to request studies in children using an expedited process.

DRAFT FOR PARENTS

Questions and Answers:
Treatment of Children with Mental Disorders

A Note to Parents

There has been recent public concern over reports that very young children are being prescribed psychotropic medications. Some parents are criticized for giving their children these medications, while others are criticized for not doing so. The studies to date are incomplete, and much more needs to be learned about young children who are treated with medications for all kinds of illnesses. In the field of mental health, new studies are needed to tell us what the best treatments are for children with emotional and behavioral disturbances. For medications, we must also make sure that there are no negative consequences for the developing brain.

While there has been progress made in diagnosing the mental illnesses that begin in childhood, children are in a state of rapid change and growth, and diagnosis and treatment of mental disorders must be viewed with this in mind. While some problems are short lived, others are persistent and very serious, and parents should seek ways to help their children.

Not long ago, it was thought that many brain disorders such as anxiety disorders, depression, and bipolar disorder began only later in life. We now know they can begin in childhood. An estimated 6 to 9 million children and adolescents in the United States suffer from a serious behavioral or emotional disturbance. Perhaps the most studied, diagnosed, and treated childhood-onset mental disorder is attention deficit hyperactivity disorder (ADHD), but even with this disorder there is a need for further research in very young children. Every decision about treatment should be weighed for risk and benefit, and each child should be viewed individually.

Questions and Answers

Q: What should I do if I am concerned about mental, behavioral, or emotional symptoms in my young child?

A: Talk to your child's doctor. Ask questions and find out everything you can about the behavior or symptoms that worry you. Every child is different and even normal development varies from child to child. Sensory processing, language, and motor skills are developing during early childhood, as well as the ability to relate to parents and to socialize with caregivers and other children. If your child is in daycare or preschool, ask the caretaker or teacher if your child has been showing any worrisome changes in behavior, and discuss this with the doctor. Always bring extreme symptoms, such as self-injury, impulsive or aggressive behavior, persistent sadness, hyperactivity, or social withdrawal, to the attention of the doctor.

Q: How do I know if my child's problems are serious?

A: Many everyday stresses cause changes in behavior. The birth of a sibling may cause a child to temporarily act much younger. It is important to recognize such behavior changes, but also to differentiate them from signs of more serious problems. Problems deserve attention when they are severe, persistent, and impact on daily activities. Seek help for your child if you observe persistent problems such as sleep disturbances, changes in appetite, social withdrawal, or fearfulness; behavior that slips back to an earlier phase such as bed wetting; signs of distress such as sadness or tearfulness; self-destructive behavior such as head banging; or a tendency to have frequent injuries. In addition, it is essential to review the development of your child, any important medical problem he/she might have had, family history of mental disorders, physical and psychological traumas or situations that may cause stress.

Q: Whom should I consult to help my child?

A: First, consult your child's pediatrician. Ask for a complete health examination of

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your child. Describe the behaviors that worry you. Ask whether your child needs further evaluation by a specialist in child behavioral problems. Parents may be faced with a patchwork of providers. Ultimately, a variety of specialists including physicians, behavioral therapists, and educators may be needed to help your child.

Q: How are mental disorders diagnosed in young children?

A: Most disorders are diagnosed by observing signs and symptoms. A skilled clinician will consider these signs and symptoms in the context of the child's developmental level, social and physical environment, and reports from parents and other caretakers or teachers. Very young children often cannot express their thoughts and feelings, which makes diagnosis a challenging task. The signs of a mental disorder in a young child may be quite different from those of an older child or an adult.

Q: Won't my child just grow out of such problems?

A: Sometimes yes, but in other cases children need help. Problems that are severe, persistent, and impact on daily activities should be brought to the attention of the child's doctor. Great care should be taken to help a child who is suffering, because mental, behavioral, or emotional disorders can affect the way the child grows up.

Q: Are there situations in which it is advisable to use psychotropic medications in young children?

A: Psychotropic medications may be prescribed for young children with mental, behavioral, or emotional symptoms when the potential benefits of treatment outweigh the risks. Some problems are so severe and persistent that they would have serious negative consequences for the child if untreated, and psychosocial interventions may not always be effective by themselves. The more extreme the problems, the more likely it is that medication will be prescribed. However, the safety and efficacy of most psychotropic medications have not yet been studied in young children. As a parent, you will want to ask many questions and evaluate with your doctor the risks of starting and continuing your child on these medications. Learn everything you can about the medications prescribed for your child, including potential side effects. Learn which side effects are bothersome but tolerable, and which ones are threatening. In addition, learn and keep in mind the goals of treatment (e.g., change in specific behaviors). Although it has become common practice, combining multiple psychotropic medications should be avoided in very young children unless absolutely necessary. Any medication treatment should proceed with careful monitoring of benefits and adverse effects.

Q: Does medication affect young children differently from older children or adults?

A: Yes. Young children's bodies handle medications differently than older individuals and this has implications for dosage. The brains of young children are in a state of very rapid development, and animal studies have shown that the developing neurotransmitter systems can be very sensitive to medications. A great deal of research is needed to determine the effects and benefits of medications in children of all ages. It is important to remember that serious untreated mental disorders themselves negatively impact brain development.

Q: If my preschool child receives a diagnosis of a psychiatric disorder, does this mean that medications have to be used?

A: No. Psychotropic medications are not generally the first option for a preschool child with a psychiatric disorder. The first goal is to understand (and if possible, to remediate) the factors that may be contributing to the condition. The child's own physical and emotional state is key, but many other factors such as parental stress or a changing family environment may influence the child's symptoms.

Q: How should medication be included in an overall treatment plan?

A: When medication is used, it should not be the only strategy. There are many services that you may want to investigate to develop a complete treatment plan for your child. Family support services, educational classes on parenting strategies, behavior management techniques, as well as family therapy and other approaches should be considered. If medication is prescribed, it should be monitored and evaluated closely and regularly.

Q: Which mental disorders are seen in children?

A: Mental disorders with possible onset in childhood include: anxiety disorders;

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attention deficit and disruptive behavior disorders; autism and other pervasive developmental disorders; eating disorders (e.g., anorexia nervosa); mood disorders (e.g. major depression, bipolar disorder); schizophrenia; and tic disorders. Enuresis and encopresis may be symptoms of a mental disorder.

Q: Can family events such as a death in the family, illness in a parent, onset of poverty, or divorce cause symptoms?

A: Yes. When a tragedy occurs or some extreme stress hits, every member of a family is affected, even the youngest ones. This should also be considered when evaluating mental, emotional, or behavioral symptoms in a child.

Q: What difference does it make if a medication is specifically approved for use in children or not?

A: The approval of a medication by the U.S. Food and Drug Administration (FDA) allows for doctors to prescribe the medication as they feel appropriate. In some cases there is extensive clinical experience in using medications for children or adolescents. However, everyone agrees that studies in children would be valuable for finding appropriate dosages and learning the effects of medications.

Q: What does "off-label" use of a medication mean?

A: Based on clinical experience and medication knowledge, a physician may prescribe to children a medication that has been FDA-approved for use only in adults. This use of the medication is called "off label." Most medications prescribed for child mental disorders, including many of the newer medications that are proving helpful, are prescribed off label, because only a few of them have been systematically studied for safety and efficacy in children. Medications that have not undergone such testing are dispensed with the statement that "safety and efficacy have not been established in children."

Q: Why haven't many medications been tested in children?

A: In the past, medications were not studied in children because of ethical concerns about involving children in clinical trials. However, this created a new ethnical problem: lack of knowledge about the best treatments for children. But in clinical settings, medications are being prescribed for children at increasingly early ages. The NIH and the FDA have begun examining the issue of research on medications in young children. New research approaches are being considered, and progress is being made to require such studies when a medication is undergoing FDA approval.

Q: Does the FDA approve medications for different age groups among children?

A: Yes. For example, Ritalin® is approved for children age 6 and older, whereas Dexedrine® is approved for children as young as 3. The lowest age for which the FDA approves a given medication is a function of the policies in effect at the time of initial approval and the specific requests of the drug manufacturer. Dexedrine® is an older medication than Ritalin®. When Ritalin® was tested for efficacy by the pharmaceutical company that developed it, only children age 6 and above were involved; therefore, age 6 was established as the lower age limit for Ritalin®. There is no reason to believe that one medication is safer than the other based on differences in FDA approval.

Q: What medications are used for which kinds of childhood mental disorders?

A: There are several major categories of psychotropic medications: stimulants, antidepressants, antianxiety agents, antipsychotics, and mood stabilizers. For medications approved by the FDA for use in children, dosages depend on body weight and age.

- *Stimulant Medications:* There are four stimulant medications that are approved for use in the treatment of attention deficit hyperactivity disorder (ADHD), the most common behavioral disorder of childhood. These medications have all been extensively studied and are specifically labeled for pediatric use. Children with ADHD exhibit such symptoms as short attention span, excessive activity, and impulsivity that cause substantial impairment in functioning. Stimulant medication should be prescribed only after a careful evaluation to establish the diagnosis of ADHD and to rule out other disorders or conditions. Medication treatment should be administered and monitored in the context of the overall needs of the child and family, and consideration should be given to combining it with behavioral therapy. If the child is of school age, collaboration with teachers is essential.

Stimulant Medications

Brand Name	Generic Name	Approved Age (children)
Adderal	amphetamines	3 and older
Cylert	pemoline	6 and older
Dexedrine	dextro-amphetamine	3 and older
Ritalin	methylphenidate	6 and older

▪ *Antidepressant and Antianxiety Medications:* These medications follow the stimulant medications in prevalence among children and adolescents. They are used for depression, a disorder recognized only in the last twenty years as a problem for children, and for the anxiety disorders, including obsessive-compulsive disorder (OCD). The medications most widely prescribed for these disorders are the selective serotonin reuptake inhibitors (the SSRIs).

In the human brain, there are many "neurotransmitters" that affect the way we think, feel, and act. Three of these neurotransmitters that antidepressants influence are serotonin, dopamine, and norepinephrine. SSRIs affect mainly serotonin and have been found to be effective in treating depression and anxiety without as many side effects as some older antidepressants. The following are the most commonly prescribed medications for children with depression or anxiety disorders (including OCD).

Antidepressant and Antianxiety Medications

Brand Name	Generic Name	Approved Age (children)
Anafranil	clomipramine	10 and older (for OCD)
Effexor	venlafaxine	
Luvox (SSRI)	fluvoxamine	8 and older (for OCD)
Paxil (SSRI)	paroxetine	
Prozac (SSRI)	fluoxetine	
Serzone (SSRI)	nefazodone	
Sinequan	doxepin	12 and older
Tofranil	imipramine	6 and older (for bedwetting)
Wellbutrin	bupropion	
Zoloft (SSRI)	sertraline	6 and older (for OCD)

- *Antipsychotic Medications:* These medications are used to treat children with schizophrenia, bipolar disorder, autism, Tourette's syndrome, and severe conduct disorders. Some of the older antipsychotic medications have specific indications and dose guidelines for children. Some of the newer "atypical" antipsychotics, which have fewer side effects, are also being used for children. Such use requires close monitoring for side effects.

Antipsychotic Medications

Brand Name	Generic Name	Approved Age (children)
Clozaril (atypical)	clozapine	
Haldol	haloperidol	3 and older
Risperdal (atypical)	risperidone	
Seroquel (atypical)	quetiapine	
(generic only)	thioridazine	2 and older
Zyprexa (atypical)	olanzapine	
Orap	pimozide	12 and older (for Tourette's syndrome). Data for age 2 and older indicate similar safety profile.

- *Mood Stabilizing Medications:* These medications are used to treat bipolar disorder (manic depressive illness). However, because there is very limited data on the safety and efficacy of most mood stabilizers in youth, treatment of children and adolescents is based mainly on experience with adults. The most typically used mood stabilizers are lithium and valproate (Depakote®), which are often very effective for controlling mania and preventing recurrences of manic and depressive episodes in adults. Research on the effectiveness of these and other medications in children and adolescents with bipolar disorder is ongoing. In addition, studies are investigating various forms of psychotherapy, including cognitive-behavioral therapy, to complement medication treatment for this illness in young people.

Effective treatment depends on appropriate diagnosis of bipolar disorder in children and adolescents. There is some evidence that using antidepressant medication to treat depression in a person who has bipolar disorder may induce manic symptoms if it is taken without a mood stabilizer. In addition, using stimulant medications to treat co-occurring ADHD or ADHD-like symptoms in a child with bipolar disorder may worsen manic symptoms. While it can be hard to determine which young patients will become manic, there is a greater likelihood among children and adolescents who have a family history of bipolar disorder. If manic symptoms develop or markedly worsen during antidepressant or stimulant use, a physician should be consulted immediately, and diagnosis and treatment for bipolar disorder should be considered.

Mood Stabilizing Medications

Brand Name	Generic Name	Approved Age (children)
Cibalith-S	lithium citrate	12 and older
Depakote	divalproex sodium	2 and older (for seizures)
Eskalith	lithium carbonate	12 and older
Lamictal*	lamotrigine	16 and older (for seizures)
Lithobid	lithium carbonate	12 and older
Neurontin*	gabapentin	12 and older (for seizures)
Tegretol	carbamazepine	any age (for seizures)

* Putative mood stabilizers

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Evidence Report/Technology Assessment: Number 11

Treatment of Attention-Deficit/Hyperactivity Disorder

Summary

Under its Evidence-Based Practice Program, the Agency for Health Care Policy and Research (AHCPR) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools. Contractor institutions review all relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities.

Overview

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common disorders diagnosed in children and adolescents. The American Psychiatric Association (APA) describes the essential feature as "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."

Terms that have been used to describe children with "distractability, impulsivity, and usually overactivity" include minimal brain dysfunction/damage (MBD), hyperkinetic reaction, and hyperkinesis.

ADHD has been surrounded by great controversy involving clinicians, teachers, policymakers, parents, and the media. The range of opinion regarding the validity of ADHD extends from those who do not believe it exists and regard it as a myth, to those who believe that there is genetic and physiological evidence supporting its existence.

Prevalence estimates of ADHD vary according to the methods of ascertainment, diagnostic criteria, informants, and population sampled. According to the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV), the prevalence of ADHD in school-age children is 3 to 5 percent. However, prevalence studies using the two previous versions of the DSM (DSM-III and DSM-III-R) in the United States, Canada, United Kingdom, Germany, and New Zealand have shown rates that vary from 1.7 to 16.1 percent.

Although it was previously thought that ADHD remitted before or during adolescence, it has been estimated that more than 70 percent of hyperactive children continue to meet criteria for ADHD as adolescents and up to 65 percent as adults.

Problems with the diagnosis and treatment of this condition can also arise because approximately 65 percent of ADHD patients may have at least one comorbid disorder in the form of:

- Anxiety, communication, mood, conduct, oppositional defiant, and learning disorders.
- Tourette's syndrome.
- Subnormal intelligence.

ADHD has been associated with impaired academic achievement, rejection by peers, and family resentment and antagonism. The rich terminology may reflect the broad spectrum and the high frequency with which it is described with other comorbid conditions.

There is also variation and controversy around the treatment of ADHD, which often includes stimulant medication. To reduce inappropriate variation in treatment, major organizations in North America have developed, or are in the process of developing, practice parameters or clinical practice guidelines to guide treatment decisions.

In 1997, the Agency for Health Care Policy and Research (AHCPR) charged the McMaster University Evidence-based Practice Center (MU-EPC) with producing an evidence report on the treatment of ADHD. The objectives of this work were to:

- Conduct a comprehensive systematic review of the literature on the treatment of ADHD, with input from different groups of stakeholders.
- Support guideline development initiatives, while building on existing work and focusing on answerable, clinically relevant questions.

Reporting the Evidence

A multidisciplinary research team was assembled, with participation of members of the nominating organizations, the American Academy of Pediatrics (AAP) and the APA, local experts, and research staff. After multiple consultations and the evaluation of published systematic reviews and meta-analyses, the following general questions were selected as the focus of the evidence report:

- What is the evidence from comparative studies on the effectiveness and safety, both short and long term, of pharmacological and nonpharmacological interventions for ADHD in children and adults?
- Are combined interventions more effective than individual interventions?

To answer these questions, while avoiding the duplication of work, making efficient use of the resources available, and ensuring maximum added value, the scope of the evidence report focused on the following seven categories of research studies:

- Studies with drug-to-drug comparisons of pharmacological interventions.
- Placebo-controlled studies evaluating the effect of tricyclic antidepressants.
- Studies comparing pharmacological with nonpharmacological interventions (drug vs. nondrug studies).
- Studies evaluating the effect of long-term therapies ($\geq$ 12 weeks).
- Studies evaluating therapies for ADHD in adults (> 18 years of age).
- Studies evaluating therapies given in combination.
- Studies evaluating adverse effects of pharmacological interventions.

Numerous systematic reviews and meta-analyses have examined placebo-controlled trials of stimulant medication and have established consistently the short-term efficacy of these agents for core symptoms. Consequently, placebo-controlled trials evaluating stimulant medication were reviewed in this report only if they met the criteria for inclusion in any of the other six categories. In addition, the report focuses on head-to-head comparisons of pharmacological interventions; and on head-to-head comparisons of pharmacological and nonpharmacological interventions. This was identified as the area of prime interest to clinicians rather than effectiveness of stand-alone interventions—either pharmacological or nonpharmacological.

Methodology

Inclusion and Exclusion Criteria

In preparing the Report, we followed current standards for assessing and distilling research evidence. Citations of individual studies were regarded as potentially eligible and selected for further evaluation if:

- They were randomized controlled trials (RCTs) that focused on the treatment of ADHD in humans.
- They were published in peer-reviewed journals, in any language, as a full report.

If the studies included conditions other than ADHD, they were included only if they provided separate analyses for patients with ADHD. We acknowledge that randomized controlled trials are imperfect tools, but so far they are our best probe to evaluate health care interventions. Non-RCTs were included if they provided data on adverse effects of interest collected over more than 16 weeks. More refined inclusion and exclusion criteria defined within each of the seven categories of research studies are described in the body of the report.

Inclusion of a study in the evidence report was decided by two members of the research team, by consensus, and on the basis of the information available in the full published articles.

Literature Search

Citations of potentially eligible studies were identified through a systematic search of:

- MEDLINE (from 1966), CINAHL (from 1982) and HEALTHStar (from 1975), PsycINFO (from 1984), and EMBASE (from 1984) using the search strategy described below. The searches were completed in November of 1997 using the following terms: *behavioral symptoms*, *attention-deficit disorder with hyperactivity*, *attention-deficit*, *hyperactivity*, *cognition disorders*, *minimal brain damage*, *minimal brain dysfunction*, *hyperkinetic syndrome*, *hyperkinetic reaction*, *impulsivity or inattention*, and *random*, *clinical trial*, *comparative*, *case control*, or *cohort*.
- The Cochrane Library (issue 4, 1997).
- The reference lists of any eligible article identified in any of the above sources.
- Web sites of organizations funding research on the treatment of ADHD.
- Files of members of the research team and partner organizations.

Data Extraction

Data extraction forms were especially developed and tested for this project. The local research team, partner organizations, and the Task Order Officer (TOO) were consulted and the forms approved for content. More than 41 different variables describing the general characteristics of the study were recorded. In addition, detailed information on interventions, outcomes, and tests were extracted from each of the full reports, independently by two reviewers, with differences resolved by consensus or by a third member of the research team.

Data Synthesis

Descriptive statistics were calculated for all the variables. Evidence tables were constructed to summarize, globally and question by question, all the information extracted from the study reports. The local research team, in consultation with members of the partner organizations and the TOO, evaluated the overall quantity and quality of the data available and decided that meta-analysis would be inappropriate to summarize the evidence on each of the research questions and for each of the main categories of interest. The main reasons for this decision were:

- Substantial clinical heterogeneity across the studies (e.g., therapies evaluated, patient populations, duration).
- Inconsistency in outcome measurements.
- Low methodological quality.
- Incomplete data reporting (see detailed descriptions within each category).

Therefore, this report represents a systematic qualitative review of the existing evidence, emphasizing the implications for clinical practice and the opportunities for future research to fill existing knowledge gaps.

Findings

- A total of 2,405 citations were identified by the search strategies. Ninety-two reports, describing 78 different studies, met all the inclusion criteria.
- Overall, numerous deficiencies in the reporting of available RCTs limit the assessment of their validity, relevance, precision, and, therefore, their clinical application. Most studies did not clearly describe clinically important information such as the primary outcomes of interest, the presence of comorbid disorders, the characteristics of the patients' families, compliance with treatment, and baseline measurement of outcomes of interest. There was little information on the treatment of ADHD in minority groups.
- The small sample size of most studies limited their power to detect meaningful clinically important differences among the interventions.
- Ninety-seven percent of the reports of RCTs did not describe the method of randomization. Ninety-five percent did not describe efforts to conceal allocation from the investigators who recruited the patients into the study (e.g., allocation codes were obtained by telephone after a patient accepted to enter the study). Eighty-seven percent did not describe the number of withdrawals and dropouts and the reasons for such in each of the groups. These limitations increased the likelihood of biased results.
- Comparison or synthesis of data across studies was limited by the low quality of reporting and by the large number and heterogeneity of outcome measures and tests used in the studies. Researchers often used modified versions of the same tests (e.g., Conners) across studies but did not provide enough information on the modifications. This led to the conclusion in many instances that there is a lack of evidence on the effectiveness of clinically important interventions. It is important to recognize that this is different from finding evidence of the lack of effectiveness of the same interventions.

The following is a description of the main conclusions from each of the seven categories of interest:

- **Drug vs. drug comparisons:** The limited evidence available from studies comparing different stimulants suggests that there are few, if any, short-term differences in effectiveness among methylphenidate (MPH), dextroamphetamine, and pemoline. The studies comparing stimulants to tricyclic antidepressants had many limitations and presented conflicting results.
- **Drug vs. nondrug comparisons:** Despite the limitations in the individual studies, the results indicate consistently that stimulants are more effective than nonpharmacological interventions when compared head-to-head.
- **Combination therapies:** There is a lack of evidence supporting the superiority of combination therapy over stimulant alone or superiority of combination therapy over nondrug intervention alone. A recent large trial found that combined treatment offers modest additional benefits over single-component treatments for non-ADHD areas of functioning.
- **Tricyclic antidepressants vs. placebo:** The studies on desipramine, despite their heterogeneous designs, small sample sizes, and variable quality, suggest that desipramine is more effective than placebo. The studies evaluating imipramine show inconsistent results.
- **Long-term therapy:** All but one of the studies available were restricted to school-age children. Few studies followed children for a period of time equivalent to the length of time children typically remain on

these treatments or reported side effects or used outcome measures that are situation specific (e.g., measure outcomes at home and at school). These studies show a trend to general improvement over time regardless of treatment and support the need for long-term placebo-controlled studies. MPH appears to reduce behavioral disturbance in ADHD children as long as it is taken. However, there is no information on the reasons so many children discontinue medication. The studies available provide little evidence for improvement in academic performance with stimulants, even though MPH treatment appears to produce consistent behavior improvement.

The largest and most comprehensive study to date (the Multimodal Treatment Study of Children With Attention Deficit/Hyperactivity Disorder—the MTA Cooperative Group study) indicates that intensive behavior therapy, comprising child, family, and school-based interventions, adds little to the effects of long-term stimulant therapy. The MTA study also identified that the quality of supervision of medication may be an important factor in optimizing long-term therapeutic benefit. Lithium does not appear to be an effective alternative in patients who do not respond to stimulants.

- **Treatment of ADHD in adults:** The few studies evaluating MPH vs. placebo show contradictory results. The study with the highest methodological scores suggests that MPH may be effective for the treatment of ADHD in adults. Antidepressants may be effective in adults. Studies (one each) comparing pemoline, nicotine, or phenylalanine with placebo did not produce evidence in favor of these medications. There were no studies designed to determine the proportion of adults with ADHD who will use and benefit from other interventions.
- **Adverse effects:** Many of the side effects associated with stimulant use appear to be relatively mild and of short duration and respond to dosing or timing adjustments. However, data are inadequate on the long-term effects and severity of the adverse effects of most interventions. No comparative studies were identified with data on important adverse effects of interest, including potential for abuse of stimulants, liver toxicity due to pemoline, or major arrhythmia with tricyclic antidepressants in patients with ADHD.

Future Research

Areas needing further research include the following:

- Effective strategies are needed to improve the quality of the study designs and reports. Journals that publish articles on the treatment of ADHD could benefit by the endorsement of criteria such as those included in the Consolidation of the Standards of Reporting Trials (CONSORT) statement, which has been adopted by over 70 leading peer-reviewed journals.
- Larger studies with more rigorous design and longer term followup are needed to establish the effectiveness and adverse effects of most interventions in both children and adults.
- The field would benefit from empirical methodological research evidence indicating the added value of nonrandomized within-subject and single-subject research designs for direct head-to-head comparisons between psychosocial interventions and other treatments.
- Research groups should make efforts to select a core set of validated and clinically relevant outcomes to be measured in all the studies in addition to any other outcomes of interest to the specific groups of researchers.
- More rigorous studies are clearly needed to establish the relative effectiveness of stimulants and tricyclic antidepressants and to compare the effects of stimulants with clonidine, buproprion, or selective serotonin-reuptake inhibitors.
- More definitive studies are needed to determine the added value of nondrug interventions when patients are already receiving stimulants, as well as the value of adding stimulants when nondrug interventions fail to achieve the desired outcomes. These studies, however, will require complex designs, substantial amounts of resources, and efficient collaboration among research groups. The MTA study is an example of this type of collaborative effort.
- Studies are also needed to determine whether comorbid factors (e.g., anxiety and depressive disorders) influence response to treatment.

- Studies are required to assess the severity of most adverse effects associated with stimulant medication and to evaluate, explicitly, the tradeoff between improvement in ADHD symptoms and signs and adverse effects. However, such a study is only worthwhile if the perspectives of all interested parties (parents, teachers, and patients) are included in the exercise.
- Reports of effectiveness and adverse effects almost always come from parents and/or teachers. One study (of adolescents) showed some important differences between parents and adolescents in the side-effects profile reported by each group. Data need to be collected from children on effectiveness and adverse side effects in order to gain a better understanding of the implications of treatment from the patients' perspective.
- A better understanding of the distinctions between "adverse effects" of therapy and concomitant characteristics of ADHD is needed. A number of reports discuss the high prevalence of "side effects" reported on placebo. Many of these may be associated with problem behaviors. Including such behaviors distorts the context for evaluating the importance of side effects.
- There were very few female patients in the available studies. A possibility exists that effectiveness and adverse effects vary by gender. This is an issue that needs to be examined or at least discussed.
- RCTs are of limited power to evaluate adverse effects, particularly rare ones or those that appear during long-term therapy. Only one comparative non-RCT with adequate data was found and it provided limited information. More observational studies are required (particularly case-control or cohort studies). Knowledge of adverse effects may also improve through more creative use of existing drug databases.
- Few studies have been supported financially by sources other than the Government or pharmaceutical companies. There is a great opportunity for consumer groups to support more research activities, given the number of important questions that remain unanswered and the implications of the results of research on the public.
- Conducting research on the treatment of ADHD is not easy, given the complexity of the disorder, the frequent presence of comorbidity, and the variety of interventions and outcomes available. Future research efforts will require commitment among different groups of stakeholders.

In summary, this report includes seven systematic reviews that incorporate state-of-the-art methodology, represent the most rigorous systematic review conducted to date, and are ready for incorporation into evidence-based clinical practice guidelines or performance measures. The report also provides a detailed description of the many limitations of the evidence available and provides recommendations to fill existing knowledge gaps. Filling such gaps will not be easy and will require highly innovative efforts and collaboration among different groups of decisionmakers. The MTA study confirms that large-scale, long-term collaboration among researchers is possible. If this field continues to produce small, incompletely reported studies with heterogeneous designs, instead of the high-quality collaborative efforts required, research in this area will continue to be abundant but will be of little value to guide most clinically relevant decisions.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared by McMaster University, an AHCPR Evidence-based Practice Center, Ontario, Canada, under Contract No. 290-97-0017. It is expected to be available by winter 2000. At that time, printed copies may be obtained free of charge from the AHCPR Publications Clearinghouse by calling 1-800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No.11, *Treatment of Attention-Deficit/Hyperactivity Disorder* (AHCPR Publication No. 99-E018). When available online, the Evidence Report will be at: http://www.ahrq.gov/clinic/index.html#evidence.

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Technical Review: Number 3

Diagnosis of Attention-Deficit/Hyperactivity Disorder

Summary

The Agency for Health Care Policy and Research (AHCPR) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools, under the Agency's Evidence-Based Practice Initiative, which was launched in the fall of 1996. This technical review summarizes current scientific evidence on the prevalence of attention-deficit/hyperactivity disorder and on the value of various evaluation methods.

Overview

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood-onset psychiatric disorders. It is distinguished by symptoms of inattention, hyperactivity, and impulsivity. ADHD may be accompanied by learning disabilities, depression, anxiety, conduct disorder, and oppositional defiant disorder. The etiology of ADHD is unknown, and the disorder may have several different causes. Investigators have studied, for example, the relation of ADHD to elevated lead levels, abnormal thyroid function, morphologic brain differences, and electroencephalograph (EEG) patterns.

With current public awareness of ADHD, pediatricians and health care providers are reporting increases in referral rates of children with suspected ADHD. Numerous rating scales and medical tests for evaluation and diagnosis of ADHD are available, with mixed expert opinion on their usefulness.

The Agency for Health Care Policy and Research (AHCPR) sponsored the development of this technical review to summarize current scientific evidence from the literature on the prevalence of ADHD and on the value of various evaluation methods. The following questions provided a framework for the analysis:

1. What percentage of the U.S. general population ages 6 to 12 years has ADHD? Of those with ADHD, what percentage has one or more of the following comorbidities: learning disabilities, depression, anxiety, conduct disorder, and oppositional defiant disorder?
2. What percentage of children ages 6 to 12 years presenting at pediatricians' or family physicians' offices in the United States meets diagnostic criteria for ADHD? Of those with ADHD, what percentage has one or more of the following comorbidities: learning disabilities, depression, anxiety, conduct disorder, and oppositional defiant disorder?
3. What is the accuracy (i.e., sensitivity, specificity, positive predictive value) and reliability (i.e., inter/intra-rater agreement) of behavioral rating screening tests for ADHD compared with a reference standard?
4. What is the prevalence of abnormal findings on selected medical screening tests commonly recommended as standard components of an evaluation of a child with suspected ADHD?

Diagnostic screening tests, as analyzed under questions 3 and 4, were of two types: behavioral rating scales and medical screening tests. The behavior rating scales selected for consideration consisted of both ADHD-specific

scales and "broad-band" scales designed to screen for various symptoms (including ADHD symptoms). The medical screening tests considered included commonly recommended tests that are standard components of an evaluation of a child with suspected ADHD: electroencephalography, lead concentration level testing, thyroid hormone level testing, hearing and vision screening, imaging tests, neurological screening, and continuous performance tests (CPTs).

Reporting the Evidence

The evidence on ADHD prevalence and diagnosis reported here was gathered from 87 published articles and 10 behavioral scale manuals. Studies must have been peer reviewed and published in the English language between 1980 and 1997. These 97 sources were identified during searches of the databases MEDLINE and PsycINFO and from reference lists in review articles, research study articles, and a draft guideline on ADHD obtained from the American Academy of Child and Adolescent Psychiatry (currently in development), recent journal publications, citations suggested by members of the American Academy of Pediatricians, and a database of bibliographies on studies that used or evaluated the Child Behavior Checklists (CBCL). Abstracts of more than 4,000 identified citations were reviewed, from which 507 articles and 10 manuals were retrieved and subjected to further consideration. The published studies had to be soundly designed and conform to specified inclusion and exclusion criteria to qualify for consideration.

Methodology

Data from the 97 accepted articles/manuals were abstracted, tabulated systematically, and subjected to statistical analysis. A multiple logistic regression model with random effects was used to analyze simultaneously for the effect of age, gender, diagnostic tool, and setting. This model accommodates the fact that each study estimated ADHD rates under slightly different conditions. The analysis was done using the EGRET software.

Findings

The significant findings derived from the analysis are summarized below.

Prevalence of ADHD in General Population

- Gender, diagnostic tool (DSM-III or DSM-III-R), and setting (community or school setting) are significant contributors to the ADHD rate, but age (5 to 9 years versus 10 to 12 years) is not a significant factor.
- ADHD prevalence is much higher when academic and behavioral functioning impairment criteria are not considered (16.1 percent without impairment criteria versus 6.8 percent with). Boys have higher rates of ADHD than do girls.

Prevalence of Comorbid ADHD in General Population

- One-third of children diagnosed with ADHD also qualify for a diagnosis of oppositional defiant disorder (ODD).
- One-fourth of children diagnosed with ADHD also qualify for a diagnosis of conduct disorder (CD).
- Less than one-fifth of children with ADHD also have a depressive disorder.
- More than one-fourth of children with ADHD qualify for a diagnosis of anxiety disorder.
- Almost one-third of children with ADHD also have more than one comorbid condition.
- Overall, the prevalence rates of comorbid ADHD are high. Estimates of the prevalence rates of various comorbid conditions in children with ADHD range from 12.36 percent (learning disorders) to 35.15 percent (conduct disorder).

Prevalence of Comorbid ADHD in General Population

- Results on prevalence of ADHD in a pediatric clinic setting are varied. A 1997 study finds prevalence conforms to that of the general population; a 1988 study shows much smaller prevalence.

Prevalence of Comorbid ADHD in Pediatric Clinic Setting

- Results on prevalence of comorbid ADHD in a pediatric clinic setting are varied. A 1997 study finds a high prevalence, similar to that in the general population; a 1988 study gives much lower rates.

Behavior Rating Scales, ADHD Specific

- The Conners Rating Scales, 1997 Revision, contain two highly effective indices for discriminating between ADHD children and normal controls. The Barkley School Situations Questionnaire is less effective. These results are based on studies conducted under ideal conditions; actual performance of the scales in physicians' offices is expected to be poorer.
- Hyperactivity subscales that effectively discriminate between ADHD children and normal controls include DSM-III-R SNAP and Conners Abbreviated Teacher Questionnaire (CATQ, HI). The ACTeRS scale performed poorly. These results are based on studies conducted under ideal conditions; actual performance of the scales in physicians' offices is expected to be poorer.
- An inattention subscale that effectively discriminates between ADHD children and normal controls is the DSM-III-R SNAP checklist. The ACTeRS scale performed poorly. These results are based on studies conducted under ideal conditions; actual performance of the scales in physicians' offices is expected to be poorer.
- An impulsivity subscale that effectively discriminates between ADHD children and normal controls is the DSM-III-R SNAP checklist.

Broad-Band Behavioral Rating Scales

- None of the broad-band scales analyzed—the CPCL/4-18-R Total Problem Scale, DSMD Total Problem Scale, CPRS-R:L Global Problem Index, and CTRS-R:L Global Problem Index—effectively discriminate between referred and nonreferred children. Thus, they are not useful as tools to detect clinical-level problems in children presenting at a pediatrician's office.
- Externalizing, internalizing, and adaptive functioning scales did not effectively detect referred versus nonreferred children.

Medical Screening Tests

- Analysis of six studies on the relation between elevated lead levels and ADHD showed that lead levels are not useful as a general diagnostic tool for ADHD. This is strengthened by the fact that ADHD prevalence appears to be increasing even as lead levels in the population appear to be decreasing.
- Analysis of four studies showed no relation between abnormal thyroid function and ADHD. Thus, the evidence does not support the use of tests of thyroid function to screen for ADHD.
- Analysis of seven imaging studies of the brain (computed tomography [CT], computerized axial tomography [CAT], and magnetic resonance imaging [MRI]) that were performed to detect morphologic differences in brain structures of children with ADHD yielded sparse and diverse evidence. Thus, none of the imaging procedures analyzed are considered useful as a screening or diagnostic tool for ADHD.
- Eight studies of electroencephalogram (EEG) patterns and ADHD found no serious EEG abnormalities in ADHD children, although many studies found significant differences in brain wave activity between ADHD children and normal controls. The heterogeneity of results across studies indicates that the EEG should not be routinely used as a screening tool for ADHD.

- Evidence from studies of neurological screening tests did not yield any clues to the etiology of ADHD. Thus, these tests are not deemed effective for screening ADHD.
- Continuous performance tests measure impulsivity, inattention, and vigilance. Statistical analysis of studies using these tests indicated that CPTs would not serve as useful screening tools for ADHD.

Future Research

- There is a need for continued work to gather data on prevalence of ADHD using the following factors, which are lacking in much of the work already done: DSM-IV, use of both genders as subjects, rates of ADHD—Primarily Inattentive Type, and wider-scale studies across regions of the country or across countries using the same criteria.
- Comparison studies are needed to assess the ability of broad-band behavior checklists to discriminate between clinical and nonclinical samples (the studies available at this time have only presented results of the ability of these tests to discriminate between referred and nonreferred samples). Clinically severe problems are present in both of these groups, as are subclinical problems.
- Continued work is needed in the area of magnetic resonance imaging and PET, when possible, to continue to explore structural and functional differences in the brains of children diagnosed with ADHD and each of the types of ADHD.

Availability of the Full Report

The full technical review from which this summary was taken was prepared by Technical Resources International, Inc., located in Rockville, Maryland. It was developed for AHCPR under contract No. 290-94-2024, and is expected to be available in late 1999.

When the technical review is available, printed copies may be obtained free of charge from the AHCPR Publications Clearinghouse by calling 1-800-358-9295. Requestors should ask for Technical Review No. 3, *Diagnosis of Attention-Deficit/Hyperactivity Disorder* (AHCPR Publication No. 99-0050). Internet users will be able to access the review online at: http://www.ahcpr.gov/clinic/index.html#evidence.

For more information on AHCPR's Evidence-Based Practice Initiative or the development of this report, contact the Center for Practice and Technology Assessment, Agency for Health Care Policy and Research, 6000 Executive Boulevard, Suite 310, Rockville, MD 20852; phone (301) 594-4015; fax (301) 594-4027.

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American Academy of Pediatrics

Policy Statement

Pediatrics Volume 98, Number 1 July, 1996, pp.143-145

Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration: Subject Review (RE9622)

AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

*** ABSTRACT. Physicians who prescribe a new drug that has not been approved for a specific indication or a specific age group frequently find themselves in a quandary. Physicians who prescribe "old," time-honored drugs usually do not consult the package insert or search for US Food and Drug Administration (FDA) approval. This statement was written to clarify the legal and informational status of the package insert and the role of the FDA in approving or not approving drugs for specific indications or specific age groups. The unapproved use of approved drugs, or so-called "off-label" use, is extremely prevalent among physicians who care for children. It is important that such use of compounds be brought up to date with current FDA policies and to emphasize the responsibility of the prescribing physician in the use of these compounds.**

THE FDA AND FEDERAL LAW

FDA approval of a new drug is based on the data submitted by the manufacturer. The Federal Food, Drug, and Cosmetic Act requires that "substantial evidence" resulting from "adequate and well-controlled investigations" demonstrating that a new drug "will have the effect it purports or is represented to have under the conditions or use prescribed, recommended or suggested in the proposed labeling" be submitted to the FDA and reviewed and approved by the FDA before the drug is marketed in interstate commerce. The manufacturer can advertise or otherwise promote the drug only for the indications for which FDA approval is obtained, and all promotion must be based on information that is approved by the FDA for inclusion in the labeling of the drug. Labeling includes the package insert and is intended to provide all of the information known to be necessary for the drug to be used safely and effectively for the approved indication(s). Special groups, however, such as children and pregnant women, for whom substantial evidence of safety and efficacy has not been submitted to the FDA but for whom such an implication might otherwise be drawn, are excluded by disclaimers. FDA regulations pertaining to the specific content and format of prescription drug labeling stipulate that pediatric labeling be based on adequate, well-controlled studies involving children (*Federal Register,* June 26, 1979). The intention of these regulations was to encourage drug labeling that would regularly provide adequate information about the use of drugs in children. However, the result was not more adequately labeled drugs; labels now simply state that the drug's safety and effectiveness in children have not been established. Three fourths of the prescription drugs currently marketed in the United States lack full pediatric approval and are labeled with such disclaimers. Consequently, the FDA published regulations that recognize several methods of establishing substantial evidence to support pediatric labeling claims, including relying in certain cases on studies performed in adults and in other cases permitting sponsors

to characterize the available data on pediatric use of the drug or to indicate that no data are available (*Federal Register,* December 13, 1994). The regulations respond to concerns that current prescription drug labeling too often does not contain adequate information about the use of drugs in children and are meant to allow inclusion of more and better information to promote the safe and effective use of prescription drugs in children.

UNAPPROVED USE OF APPROVED DRUGS

An unapproved use of an approved drug refers to a use that is not included or that is disclaimed in the approved labeling. Unapproved use does not imply an improper use and certainly does not imply an illegal use. The word unapproved is used merely to indicate lack of approval, not to imply disapproval or contraindication based on positive evidence of a lack of safety or efficacy. The distinction between the lack of FDA approval of a use or dosage regimen and positive or explicit warnings or contraindications is important medically and legally.

PRESCRIPTION RESPONSIBILITY

The physician who prescribes a drug is responsible for the decision as to which drug and dosage his or her patient will receive and for what purposes. This decision is made in light of either the information contained in the drug's labeling or other data available to the prescriber. New uses, doses, or indications will not be approved by the FDA until "substantial" evidence of safety and efficacy for that indication or age group is submitted to the FDA. This may take years or may never occur, because there is little incentive to gather and submit data for new uses after a drug has been approved for marketing. Physicians and hospitals are understandably concerned that the unapproved use of an approved drug may invite a variety of legal actions. The unapproved use of a drug, however, if based on reasonable medical evidence, done in good faith in the best interests of the patient, and done without fraudulent intent, requires only that the same judgment and prudence be exercised in its use as exercised in medical practice in general for it to conform to accepted professional standards.

A physician may be accountable for the negligent use of any drug in a civil action whether or not the drug has been approved. Labeling is intended neither to preclude the physician from using his or her best medical judgment in the interest of patients nor to impose liability for failure to comply with labeling restrictions. Indeed, a physician could be subject to a claim of malpractice if he or she denied a patient potentially the best treatment solely because the use was not included in the official labeling of the drug.

EXPERIMENTATION AND RESEARCH

One frequently raised question is whether an unapproved use of an approved drug should be viewed as experimentation requiring formalized institutional review and special consent. This question reflects a misunderstanding of what constitutes research and the status and meaning of the drug approval process. The FDA approval process regulates industry, not physicians; it does not determine per se whether treatment constitutes experimentation. The principal determinant of what is research seems to be the purpose or intent of the procedure, ie, whether it is entirely or partially in the interest of other persons compared with being solely used to meet the medical needs of the individual patient. Any medical intervention is based on consent, albeit implied in many instances. Whether institutional review, consultation, or written consent is required for a given intervention depends on the degree of risk or deviation from standard practices and the extent to which research rather than individual patient care is involved. The administration of an approved drug in a way that is not approved by the FDA is not research and does not call for special consent or review if it is given solely in the patient's interest. However, information about the approval status of the drug for the indication prescribed may be a part of the full disclosure to which the patient or parents are entitled, just as its degree of acceptance among physicians generally may be an important issue to discuss with the patient or family.

There also seems to be confusion about whether an unapproved use requires FDA approval of an investigational new drug (IND) application. Neither an IND application nor a report to the FDA is

required for a physician to use a noninvestigational drug that is already available. An IND application exempts a drug from approval requirements and permits interstate shipment of the drug for investigation of an unapproved use(s) in humans; it is not a license to perform drug research. An IND application requires prior FDA approval of the study plan, labeling of the drug (if not approved) as experimental, submission of drug and investigator information, and an agreement to obtain the consent of subjects (and/or parents), to submit reports of efficacy and adverse effects, and to account for the disposal of any unused drug after the study. Investigational trials involving approved drugs do not require IND applications if all of the following apply: (1) the investigation is not intended to be reported to the FDA as a well-controlled study to support a new indication or to support any other substantial change in the labeling; (2) the investigation is not intended to support a substantial change in the product's advertising; (3) the investigation does not involve a route of administration, dose level, or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug; (4) the investigation is conducted in compliance with the requirements for institutional review and informed consent; and (5) the investigation is conducted in compliance with the requirements concerning promotion and charging for investigational drugs. An example of this would be studying the effect of carbamazepine (an anticonvulsant) on behavioral symptoms in children.

DEVELOPMENT OF DRUG INFORMATION

It seems reasonable to suggest that the physician who chooses to prescribe a relatively untried medication of potential importance has both a public and a professional responsibility to assist in the development of information about that drug for the benefit of other patients. Physicians are encouraged to report experiences that result from the use of drugs for unapproved uses or from clinical studies. It is especially important that information about adverse events be reported to the drug manufacturer or directly to the FDA. The law requires manufacturers to report all adverse experience reports they receive or are aware of (ie, published literature) to the FDA. Promising new uses for approved drugs might best be reported to the drug sponsor to encourage formal investigation and ultimate approval of the new indication. The full and ultimate role of a drug is rarely evident at the time of its initial approval, and many of the most important uses emerge from postmarketing clinical experience. Although these uses usually require confirmation or proof in formalized studies, they are frequently discovered through unapproved therapeutic use. In clinical practice, new uses or dosages frequently become widespread and well accepted long before they are reflected in the labeling. Manufacturers are not permitted to promote a drug for uses not approved for labeling, but after a drug is approved and available in a local pharmacy, the medical profession determines its reasonable use. Expanded indications and new dosage regimens may eventually be supportable by objective data that are acceptable to the FDA and may be incorporated into the approved labeling (eg, postapproval changes in labeling to include imipramine for enuresis, lidocaine for arrhythmias, furosemide in children, and naloxone in infants). Some approved uses ultimately may be shown to be unjustified, or even dangerous, by newer data and may be deleted from the labeling. Information about the dosage, metabolism, half-life, and side effects of some drugs in pediatric patients frequently is not available when the drugs are initially approved. A physician who prescribes such a drug for unapproved pediatric indications can best serve the pediatric population at large while still using the drug primarily for the benefit of the patient by consulting with appropriate physicians experienced in the use of such a drug to obtain important data about the drug.

USE OF AVAILABLE DRUGS

Lack of approval for a specific use should not prevent physicians from prescribing an available drug in the best interests of their patients. The decision to prescribe a drug rests with the physician; he or she must weigh the risks and benefits of the drug in question whether or not it has full approval. The decision to prescribe an approved drug for an unapproved use should be based on all available data and should be made with the knowledge that lack of a wider approval status is usually based on the fact that the FDA has not received sufficient data from the drug's sponsor, according to its statutory mandate, to approve labeling for such a use.

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---------- *The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.*

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