REPORT 10 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-07)
Attention Deficit Hyperactivity Disorder
(Reference Committee E)

EXECUTIVE SUMMARY

Objective: To update the 1997 report of this Council on the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD).

Methods: To supplement the literature search from the 1997 Council report, English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1997 to February 2006 using the term "attention deficit disorder," or attention deficit disorder with hyperactivity*" in combination with "diagnosis," "epidemiology," "drug therapy," "genetics," or "psychology." In addition, the Cochrane Central Controlled Trials Register was searched using the terms "ADHD" or "attention deficit disorder" and a manual search of the index for the *Journal of Attention Disorders* was conducted from 1996 to 2007. Web sites of the American Academy of Pediatrics, National Institute of Mental Health, Food and Drug Administration (FDA), American Academy of Child and Adolescent Psychiatry, and the American Psychiatric Association also were searched for documents relevant to ADHD. A total of 596 articles were retrieved for analysis. When high-quality systematic reviews and meta-analyses were identified, they formed the basis for evaluative statements about treatment safety and efficacy. Additional articles were identified by manual review of the references cited in these publications.

Results: Research increasingly points to ADHD as a developmental disorder of probable neurogenetic origin in which environmental factors also play a role, albeit more limited, in disease expression. ADHD remains the most common reason for referral of children for mental health services, but is increasingly recognized as a lifespan disorder. Diagnosis of ADHD in children is based on meeting the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV-TR, but developmentally appropriate criteria for adults are lacking. Stimulants are the most effective treatment for reducing core ADHD symptoms. The addition of psychosocial interventions may be effective in reducing related behavioral and emotional difficulties, with less substantial effects on core ADHD symptoms, compared with stimulant medication. Recent concerns about the cardiovascular risks and potential psychiatric side effects of medications used to treat ADHD have resulted in modifications to the product labeling for medications approved to treat ADHD, and a requirement for the development of medication guides.

Conclusion: Diagnosis of ADHD in children is based on meeting the criteria of the DSM-IV-TR. Because the criteria are subjective and may be interpreted differently by different observers, their use and applicability to general practice settings may vary somewhat. Clinical samples have not been diverse, with an overrepresentation of Caucasian males. Further information is needed to inform treatment of minority populations and those from lower socioeconomic strata. With the recognition that a substantial percentage of children diagnosed with ADHD have symptoms that persist into adulthood, developmentally valid criteria for adults also need to be refined. The treatment of ADHD requires expertise in many different treatment modalities. Stimulant medication offers the most effective treatment for reducing core symptoms. Although the FDA has recently taken actions to strengthen warnings on the product labeling for medications approved to treat ADHD, some disagreement continues about the risks of these medications.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 10 -A-07

Subject: Attention Deficit Hyperactivity Disorder

Presented by: Mohamed K. Khan, MD, PhD, Chair

Referred to: Reference Committee E
(Paul C. Matson, MD, Chair)

Background

Resolution 410, introduced by the American Academy of Child and Adolescent Psychiatry, American Academy of Pediatrics, American Psychiatric Association, and the American Academy of Psychiatry and the Law and adopted by the House of Delegates at the 2006 Annual Meeting, asked that this Council update its 1997 report on the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD). The 1997 Council report addressed the epidemiology and diagnostic criteria for ADHD, the course of the illness, optimal treatments, and issues surrounding the increasing trends of stimulant use.[1] The steep increase in the utilization of stimulants among children aged 18 years and younger that occurred between 1987 and 1996 attenuated in the following years, and has remained relatively stable among younger children since 2002.[2]

Individuals with ADHD experience substantial impairment in peer, family, and academic functioning. Diagnosis of ADHD is associated with significant educational and social impairment, an increased risk of accident and injury, and increased utilization of healthcare resources.[3] Previous studies clearly showed that a diagnosis of ADHD in elementary school predicts continuing symptoms and impairment into adolescence, and in the last decade ADHD has been conceptualized as a lifespan disorder.[4-6] This realization, and recent Food and Drug Administration (FDA)-mandated changes to prescription drug labeling of stimulants highlighting their potential to cause rare but serious side effects, including sudden death, have focused renewed attention on the treatment of this condition.

Methods

To supplement the literature search from the 1997 Council report, English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1997 to February 2006 using the term "attention deficit disorder," or "attention deficit disorder with hyperactivity*" in combination with "diagnosis," "epidemiology," "drug therapy," "genetics," or "psychology." In addition, the Cochrane Central Controlled Trials Register was searched using the terms "ADHD" or "attention deficit disorder" and a manual search of the index for the *Journal of Attention Disorders* was conducted from 1996 to 2007. Web sites of the American Academy of Pediatrics, National Institute of Mental Health, FDA, American Academy of Child and Adolescent Psychiatry, and the American Psychiatric Association also were searched for documents relevant to ADHD. A total of 596 articles were retrieved for analysis. When high-quality systematic reviews and meta-analyses were identified, they formed the basis for evaluative statements about treatment safety and efficacy. Additional articles were identified by manual review of the references cited in these publications.

Introduction

Research increasingly points to ADHD as a developmental disorder of probable neurogenetic origin in which environmental factors also play a role, albeit more limited, in disease expression. Family, twin, and adoption studies provide compelling evidence that genes have a strong influence in mediating susceptibility to ADHD. Twin studies from several countries have estimated the heritability of ADHD to be between 0.6 and 0.9.[7] Molecular genetic studies suggest that the genetic architecture of ADHD is complex; studies have implicated several genes as potentially influencing susceptibility or treatment response, mostly involving the function of neurons using the neurotransmitters dopamine, norepinephrine, or serotonin.[8]

Additionally, children and adolescents with ADHD (as a group) have smaller brain volumes on magnetic resonance imaging (MRI) scanning (~3%) in all regions compared with healthy controls, although considerable overlap occurs. The developmental trajectories for most structures remain roughly parallel for patients and controls during childhood and adolescence, suggesting that genetic and/or early environmental influences on brain development in ADHD are fixed, nonprogressive, and unrelated to stimulant treatment.[9] Functional brain imaging studies in affected children (and adults) show differential activation of frontal cortical and striatal areas during cognitive tasks. Although not specific to ADHD, on neuropsychological testing, some youth with ADHD show impaired performance on tasks requiring vigilance, orienting or attentional alerting, complex problem-solving, impulse control, verbal learning, and memory.

The research base to inform clinical decision-making and treatment is well-developed for children, and considerable attention has recently been devoted to problems suffered by adult ADHD patients. Studies involving strictly adolescents have not received as much attention. In general, the discussion that follows reviews the evidence pertaining to children, with relevant additional commentary for adolescent and adult populations.

Current American Medical Association (AMA) Policy H-60.950 (AMA Policy Database) encourages physicians to utilize standardized diagnostic criteria in making the diagnosis of ADHD; the development of practice guidelines for ADHD by appropriate specialty societies; continuing medical education programs to increase physician knowledge about ADHD and its treatment; the use of individualized, multimodal therapeutic approaches for children diagnosed with ADHD; and efforts to improve teachers' abilities to recognize ADHD.

Epidemiology

ADHD is the most common reason for referral of children for mental health services. Over time, the point prevalence of ADHD internationally has ranged from ~2% to 18%. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV-TR, 3% to 5% of school-aged children have ADHD.[10] Estimates have varied according to the sample source (community, school, clinically referred) and because of changing diagnostic criteria.[11,12]

Studies using DSM-III and -III-R criteria estimate a prevalence of 4% to 12% in the elementary school population.[12] Similar rates have been reported in pediatric primary care settings using DSM-IV criteria.[13] Another study using DSM-IV criteria found a prevalence of 6.8% in a school sample of kindergarten through fifth-graders.[14] The cumulative incidence of definite ADHD based on DSM-IV criteria was 7.4% by age 19 years in a population-based birth cohort study.[15] Another longitudinal study involving a community-based sample of children aged 9 to 13 years, found a cumulative prevalence of 4.1% for ADHD by age 16 years, with males outnumbering females ~6:1.[16]

Analysis of data (based on parent reports) from the 2003 National Survey of Children's Health indicated that in 2003 approximately 7.8% of US children (nearly 4.5 million) aged 4 to 17 years had ever had ADHD diagnosed. A diagnosis of ADHD was reported 2.5 times more frequently among males than females.[17] ADHD, regardless of subtype, occurs at higher rates in male school-aged children, and is more prevalent in younger children.[11] Generally, the male to female ratio is substantially higher in clinically referred samples, with less of a difference in community samples, approaching unity among older adolescents and adults.[18-21] A family history, presence of psychosocial adversity, and comorbid conduct, mood, or anxiety disorders (see below) increases the presence and persistence of ADHD symptoms.

As many as 80% of children diagnosed with ADHD have symptoms that persist into adolescence, and ADHD persists into adulthood in 36% to 70% of patients.[18,22-25] It is estimated that 4% to 5% of US adults continue to suffer from symptoms referable to ADHD.[26,27] The diagnosis of ADHD in adults nearly doubled from 1995 to 2002, with equal proportions of women and men seeking treatment.[28]

Diagnosis and Treatment

Several informative clinical reviews and evidence-based guidelines on the diagnosis and treatment of ADHD have been generated by government organizations, medical specialty societies, and other healthcare entities since the previous Council report on ADHD.[29-41]

Diagnosis. Children may be initially referred for evaluation of learning problems, behavioral problems, or specifically ADHD by teachers or other school personnel, parents, or healthcare professionals. Most adolescent patients were initially diagnosed in childhood, and most contemporary adult patients are self-referred.

Diagnosis of ADHD in children is based on meeting the criteria of the DSM-IV-TR.[10] Because the criteria are subjective and may be interpreted differently by different observers, their use and applicability to general practice settings may vary somewhat.

The DSM-IV-TR criteria require evidence of inattention, or hyperactivity and impulsivity, or both (see Appendix 1).[10] These 2 dimensions of impairment comprise 9 symptoms each; at least some of the symptoms must have been present before age 7. Additionally, the child's behavior must be inconsistent with his or her developmental level and intellectual ability, and symptoms must have been present for at least 6 months. Functional impairment is evident in 2 or more settings, with clinically significant impairment in social, academic, or occupational functioning. Three subtypes are distinguished based on the presence or absence of 6 or more symptoms in each dimension: predominately *inattentive*, predominantly *hyperactive-impulsive*, or *combined*; the latter is most common. The number of children who meet the diagnostic criteria for ADHD declines over time, and the subtype assigned to an individual also may change over time.[42]

Assessment typically involves a parent interview to establish the child's developmental and treatment history, the child's current and previous symptoms and resulting impairments, the family history of ADHD and other psychiatric disorders, and to assess the family environment, caregiver-child interactions, family resources, psychosocial stressors, and the parents' beliefs and attributions concerning their child's abilities.[12,38] Information from school personnel also is essential to establishing the core symptoms of ADHD, their duration, and the degree of functional impairment in the school setting. Many specific questionnaires and rating scales also have been developed and validated to review and quantify the behavioral characteristics of ADHD in the home and school setting, although discrepancies may exist between parent and teacher ratings.

In addition to history, physical, and mental status evaluation, clinicians need to assess the child for comorbidities, as well as academic skills/learning, speech, and language disabilities. The diagnosis of ADHD can be complicated by either the presence of another coexisting psychiatric condition or a condition with symptoms that overlap with those of ADHD. At least one-third of children with ADHD have one or more coexisting conditions. As many as two-thirds of children with ADHD referred to psychiatrists have comorbidity, most commonly learning disorders, oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, tic disorder, and adjustment disorder.[38] Based on these results, referral for additional evaluation may be warranted.

Adolescents. Core symptoms related to hyperactivity/impulsivity typically diminish in intensity with age, and teacher reports may be less useful in adolescents. Impairments commonly include inattention, poor impulse control and organizational skills, and difficulties in setting and maintaining priorities.[30,38] Combined with poor problem-solving skills, these traits result in diminished school performance, low self-esteem, and not surprisingly, poor peer relations.

Additional behavioral manifestations in adolescents with ADHD include restlessness, increased risk-taking behaviors, medication noncompliance or diversion, alcohol or drug abuse, increased motor vehicle accidents, loss of motivation and interest in school (including school drop-out), antisocial behavior, and suicidality. Vocational counseling or training is often needed. Additionally, safe driving evaluation assumes increased importance in adolescents with ADHD.

A practice parameter for the assessment and treatment of children and adolescents with ADHD has recently been updated by the American Academy of Child and Adolescent Psychiatry. See Appendix 2 for a list of recommendations.[38]

Adults. ADHD may be unrecognized if the patient was not diagnosed in childhood, if he or she has developed sufficient compensatory skills (including avoidance of certain work environments), or significant comorbidity masks the ADHD.[43]

Diagnosis in adults is hampered by the absence of developmentally appropriate criteria. An early attempt to provide clarity in this area was the so-called Utah criteria proposed by Wender.[44] The Utah criteria required: (1) a retrospective childhood diagnosis; (2) persistent symptoms of inattention and hyperactivity; and (3) the presence of at least 2 symptoms from a group of symptom clusters, some of which (eg, irritability and hot temper, mood lability) are now viewed as problematic. Currently, ADHD is usually diagnosed in adults who exhibit DSM-IV-TR symptoms, and who can provide, either via retrospective self-reports or family input, recollection of the onset of such symptoms in childhood, with onset of some before age 7 years. Evaluation of symptoms; a biopsychosocial assessment that considers work, family, and social stressors; and personal, as well as family psychiatric history, are informative. The shortcomings of many DSM-IV-TR symptoms (which were based on child behaviors) for adults with ADHD are readily apparent, and the basis for establishing 6 symptoms (Criterion A, see Appendix 1) as the appropriate threshold for adult diagnosis has never been validated.[44] The defining characteristic remains a history of ADHD symptoms.

In contrast to pediatric populations, approximately equal numbers of men and women comprise the adults who seek treatment. Corroboration of self- and familial reports is accomplished with a clinical interview and the use of scales designed for ADHD diagnosis (and comorbidities) in adults. Studies of clinically referred adults show that about half have clinically important levels of hyperactivity and impulsivity, and most have persistent problems of inattention and deficits in executive function tasks.[45,46] Such individuals tend to have more problems functioning in the

workplace, impaired career development, lower socioeconomic status, relationship/marital failures, and reckless conduct (eg, driving), thus, there is an increasing need for psychosocial support.[47,48] Common comorbidities include higher rates of substance abuse and anxiety, mood, and antisocial/personality disorders.[47,49]

Treatment Plan for Children and Adolescents With ADHD

It is generally agreed in the empirical literature that 3 treatments are effective on a *short-term* basis for ADHD: (1) psychosocial interventions, primarily behavior modification; (2) central nervous system (CNS) stimulants and certain other psychotropic medications; and (3) combination of these treatments.[50] Less information is available regarding their long-term effectiveness, although a few large trials have provided relevant insight. Pharmacologic treatments for ADHD are far more widely employed in the United States, are considerably less expensive, and exert more potent effects on core symptoms than do psychosocial interventions.

Although stimulants impart substantial beneficial effects on multiple key domains of functioning in children with ADHD, limitations remain[32,50,51]: (1) up to 30% of children do not show clear beneficial responses or cannot tolerate uninterrupted therapy due to side effects; (2) behavior is not completely normalized in most subjects; (3) many older children and adolescents fail to adhere to medication regimes or discontinue medication entirely; (4) evidence is lacking that academic achievement is improved; (5) students with ADHD still may have substantial problems fostering peer relationships; and (6) evidence is lacking that long-term prognosis is significantly improved. Thus, despite substantial evidence of efficacy in controlled studies, the evidence for long-term *effectiveness* in naturalistic settings is more limited, and other types of interventions are needed to foster more normal behavior. Recent actions taken by the FDA to require "black box" and other warnings for stimulants (see below) may further impact long-term use of pharmacotherapy.

Accordingly, most agree that physicians should establish a multimodal approach in treatment planning that recognizes ADHD as a chronic condition guided by measurable target outcomes.[30,33,38,39] ADHD differs from most other chronic conditions in that the educational system plays an indispensable role in implementing treatment and in monitoring its effectiveness. A multimodal approach involves education about ADHD; using medication to reduce the core symptoms of inattention, impulsivity, and hyperactivity; environmental modifications and/or psychosocial interventions to address other behavioral symptoms in the home and school; classroom placement and other educational strategies; and social support and social skills training to help establish the foundation for successful interpersonal relationships. Psychosocial interventions rely on parents and teachers as agents to deliver treatment directly to children. For adolescents, more attention is directed at transitioning to adult life.

Six primary areas of improvement may be targeted by treatment[33]: (1) improvement in relationships with parents, siblings, teachers, and peers; (2) decreased disruptive behaviors; (3) improved academic performance; (4) increased independence in self-care or homework; (5) improved self-esteem; and (6) enhanced safety in the community. A toolkit enabling multimodal treatment involving primary care physicians, school personnel, parents, and children is available from the American Academy of Pediatrics. Ongoing care in children and adolescents requires review and management of medical, psychosocial, educational, and psychological issues; provision of anticipatory guidance; and assistance with transitioning to adulthood.

Psychosocial Interventions

A large evidence base exists for the short-term efficacy of certain psychosocial interventions, primarily parent training and classroom applications of contingency management techniques, which involve providing rewards for demonstrating the desired behavior or consequences for failure to meet behavioral goals. Such interventions may reduce some behavioral and emotional difficulties, with substantially less effect on core ADHD symptoms, compared with stimulant medication.[30,33,49,50,51] Psychosocial interventions can assist some students in improving social skills, as well as academic performance in specific settings. Cognitive behavioral treatment *per* se does not provide clinically important changes in the behavior and academic performance of children with ADHD.[50]

Behavioral treatments (like medication) must be developmentally sensitive and implemented consistently over the long-term in each setting in which impairment is present.[51] Successful implementation requires sustained effort and energy, and improvements do not generalize to situations other than the ones in which training occurred.

Parent Training. The efficacy of parent training has been evaluated in more than 30 published studies.[50,51] Parent training in child-management skills can modify the child's disruptive behavior, improve parent ratings of problem behavior, and ease negative parent and child interactions. Parents are taught step-by-step approaches to identify and manipulate the antecedents and consequences of child behavior and the environmental conditions that elicit and maintain them, and how to give clear instructions.

Major components include: (1) contingency management to positively reinforce good behavior (ie, contingent positive attention or praise; use of a home token economy or point system for a child's home responsibilities and privileges); (2) ignoring some behaviors (planned ignoring); and (3) using punishment effectively (ie, time-outs, removal of privileges) in order to gradually shape behavior change.[32,49]

School-based Techniques and Management. Many of the difficulties that characterize ADHD interfere with children's classroom behavior and their ability to learn, resulting in lower academic achievement and impaired functioning in the school setting. Meta-analysis of the research literature on school interventions suggests that behavioral and academic interventions in the classroom can produce significant short-term improvement in behavioral problems and academic performance in children with ADHD.[53] As in the home environment, tangible (token-type) reinforcers are more effective than attention or social reinforcers in reducing disruptive behavior and increasing performance. As noted above, improvements from school-based interventions do not generalize to settings outside the school.[52]

Behaviorally based *classroom interventions* typically target task engagement and disruptive behavior, and, similar to home-based programs, teachers are instructed on the use of specific behavioral techniques, including effective commands and class rules, attention to positive behavior, and use of token economies, as well as planned ignoring, time-outs, and response cost programs. The use of a daily report card that provides feedback to parents on the children's school performance, and for which parents provide consequences at home, can enhance the value of interventions.

Academic interventions may involve specific task and instructional modifications such as reducing task length, dividing tasks into subunits and setting goals for the child to achieve in shorter time intervals, minimizing distractibility, and modifying the delivery of instruction. Other

academic interventions such as peer tutoring, computer-assisted instruction, and academic skills training can help individual subjects.

Pharmacotherapy

Drug therapy represents the most effective intervention for core ADHD symptoms. Caucasian male children have been substantially overrepresented in controlled clinical trials for ADHD. FDA-approved drugs used to treat ADHD include stimulants (methylphenidate, amphetamine derivatives) and atomoxetine. The stimulant modafinil, the antidepressants bupropion and nortriptyline, and guanfacine or clonidine are most commonly used off-label. Modafinil was reviewed at the March 2006 meeting of the FDA's Psychopharmacologic Drugs Advisory Committee and the Committee refused to consider approval citing the need for further clinical trials to establish efficacy versus an active comparator, and to address certain safety concerns. Currently, methylphenidate and amphetamine/dextroamphetamine combinations are most commonly prescribed, followed by atomoxetine. In 2005, children and adolescents aged 10 to 19 years accounted for nearly half of the prescriptions for these drugs, with adults aged 20 years and over accounting for nearly one-third.[54]

Stimulants. Methylphenidate and amphetamine derivatives produce CNS stimulation and reduce core symptoms of ADHD by blocking the neuronal dopamine transporter, and to a lesser extent, norepinephrine. These pharmacological effects also can produce reinforcing effects in some individuals. Several systematic reviews and meta-analyses have examined placebo-controlled trials of stimulant medication for core ADHD symptoms in children.[33,55-59] Over the last 30 years, clinical studies have employed a large number of different instruments to measure key outcomes, core symptoms, and/or quality of life, making comparisons across different trials difficult. In general, however, results of these trials support the short-term efficacy of stimulant medications in reducing ADHD core symptoms (attention, hyperactivity, and impulsivity) in approximately 70% of subjects, as well as some observable social and classroom behaviors. Improvement in inattentive symptoms may occur at lower doses.[60] Subjects who do not respond adequately to one stimulant, may respond adequately to another product. However, many children who respond to medication do not demonstrate fully normal behavior and continue to show deficits in certain areas.[33]

Over the last decade, systematic reviews and large clinical trials have examined the overall safety and effectiveness of pharmacologic and nondrug interventions for ADHD, and attempted to determine whether combined interventions are more effective than individual interventions.[61-65] These include reports commissioned by the Agency for Healthcare Research and Quality (AHRQ), the Canadian Coordinating Office for Health Technology Assessment, and the National Institute for Health and Clinical Excellence. These reviews concluded that:

- Stimulants reduce core symptoms as long as they are taken, but academic performance has not been demonstrated to be improved.
- Studies comparing stimulants showed few, if any, differences between methylphenidate and dextroamphetamine.
- Studies comparing drug with nondrug interventions consistently showed that stimulants (mostly methylphenidate) are more effective than nonpharmacological intervention on relieving core symptoms.
- Combination therapies generally yielded no obvious additional benefit on relieving core symptoms.
- Evidence of long-term safety and efficacy is lacking for both types of interventions.

Most of the studies reviewed in these assessments were conducted from 1975 to 2000, and examined the use of immediate-release (short-acting) dosage forms of stimulants. The subsequent development of long-acting stimulant formulations and the development of atomoxetine for ADHD have provided new treatment options.

Methylphenidate. The majority of clinical trials involving stimulant treatment of ADHD have involved methylphenidate, and it is the most commonly prescribed stimulant. Immediate-release methylphenidate (IR-MPH) twice daily is effective in ameliorating core symptoms during the school day; thrice-daily administration (one dose after school) extends efficacy into the home environment, if needed.

A twice-daily dosing regimen of IR-MPH for ADHD requires in-school dosing, leading to issues surrounding dispensing and storage of controlled substances by school personnel, privacy and confidentiality concerns, and potential embarrassment or peer ridicule associated with taking medications in public at school. Therefore, alternate dosage forms designed to provide for once-daily dosing have been developed. Thus, in addition to immediate-release formulations of racemic methylphenidate (Ritalin®; Methylin®), intermediate-acting (Ritalin SR®; Metadate ER; Methylin ER®) and long-acting (Ritalin LA®; Concerta®; Metadate CD®) formulations are available, as well as immediate- and extended-release formulations of the purified *d*-isomer (Focalin®; Focalin-XR®). The pure *d*-isomer is twice as potent as racemic methylphenidate, but otherwise provides about the same benefits and risks.[66] Additionally, a transdermal formulation (Daytrana™) was approved in 2006. Generic versions of immediate- and intermediate-release racemic methylphenidate are available.

Single morning doses of extended-release formulations provide benefits similar to IR-MPH administered 3 time daily (every 4 hours) for the treatment of core symptoms at a similar total dosage.[67,68] Symptoms in children with the combined subtype respond to increasing dosages, whereas children without hyperactivity (inattentive subtype) often respond at lower dosages.[69] Based on parent ratings, extended-release formulations (compared with usual care with IR-MPH) provide more profound remission of core symptoms.[70] In one randomized, controlled, multicenter trial, extended-release methylphenidate provided greater ADHD symptom improvement than atomoxetine.[71]

Amphetamine Salts. These include short (Dexedrine®) and long-acting (Dexedrine Spansules®) formulations of *d*-amphetamine, racemic formulations of mixed amphetamine salts (Adderall®; Adderall XR®), and a recently-approved lysine-based prodrug formulation of *d*-amphetamine (Vyvanse™).

Dextroamphetamine is as effective as methylphenidate in decreasing core symptoms in children with ADHD. Some children who are unresponsive to methylphenidate may respond to dextroamphetamine, and vice versa.[59,61,64] Adderall® is a mixture of neutral sulfate salts of *d*-amphetamine, amphetamine sulfate, *d*-amphetamine saccharate, and *d*,*l*-amphetamine aspartate. The combination of salts and isomers results in a 3:1 ratio of *d* to *l*-amphetamine. Comparative trials indicate Adderall® is at least as efficacious as standard IR-MPH dosing.[72-75] A single morning dose of Adderall® is comparable to the behavioral effects of standard twice-daily IR-MPH dosing.[72-74,76] In one small study, splitting the recommended 20-mg dose into a twice daily regimen improved afternoon control of attention and behavior.[77] Overall response rates (at weight-based dosing) were smaller in adolescents.[78] Adderall XR® is a formulation containing a 50:50 mix of immediate- and controlled-release portions. A single morning dose of Adderall XR® provides significant improvement through the late afternoon in both naturalistic and

laboratory settings.[79,80] Significant improvements have been noted with long-term (2 years) treatment at ~20 mg/daily.

Lisdexamphetamine (Vyvanse™) is a prodrug in which lysine is conjugated to *d*-amphetamine. During first-pass metabolism through the liver, the lysine is removed and *d*-amphetamine is generated. Theoretically, this product may have a reduced potential for parenteral abuse because of the need for metabolic activation.

Atomoxetine. Atomoxetine (Strattera™) is a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD. It is not a CNS stimulant or controlled substance, and has a different pattern of adverse effects. Atomoxetine once or twice daily improves core symptoms of ADHD in children, adolescents, and adults.[81-87] Randomized, controlled trials comparing atomoxetine with stimulants are not available. The most common adverse effects include sedation, appetite suppression, nausea, vomiting, and headaches. In children and adolescents after ≥2 years of treatment, weight and height were close to predicted values based on baseline measurements, with no decrement detected in those subjects in the lowest quartile.[88] Long-term use in adults is associated with increases in heart rate and blood pressure, and a slight decrease in weight.[89]

Atomoxetine is characterized by 3 other differences.[90] It is primarily metabolized by CYP2D6, a cytochrome P450 isoform that is lacking in 5% to 10% of Caucasians; thus, elimination kinetics and risk of toxicity may be substantially higher in such individuals, or in those receiving a drug that inhibits CYP2D6. Additionally, the product labeling for this drug contains warnings about the potential for 2 specific adverse reactions—increased suicidal ideation and severe liver toxicity.

Other Medications. Medications from virtually every psychotropic class have been investigated for efficacy in ADHD over the past 35 years.[91] The antidepressants bupropion, nortriptyline, and desipramine/imipramine, and to a lesser extent, the adrenergic α_2 receptor agonists, clonidine and guanfacine, reduce core symptoms in patients with ADHD, and have been used off-label in patients who do not respond adequately or cannot tolerate stimulants.[38] Approved for the treatment of narcolepsy, modafinil (Provigil®) also has been used off-label for ADHD.[92-96] However, in not considering modafinil for approval for use in children, the FDA's Psychopharmacologic Drugs Advisory Committee expressed concerns about its safety.[97]

Bupropion is significantly more effective than placebo in reducing ADHD symptoms in children, but in comparison trials versus methylphenidate it was less effective in reducing core symptoms than methylphenidate, and caused more side effects.[98,99]

Several tricyclic antidepressants, primarily imipramine, desipramine, and nortriptyline, have been studied in ADHD beginning in the 1970s.[91] Desipramine or nortriptyline are generally regarded as providing the best balance between efficacy and tolerability. However, desipramine was associated with reports of sudden death in 4 children in the 1990s, and thus is viewed as an alternative to other tricyclics, which are viewed as third-line agents.[100] The American Heart Association recommends specific pretreatment parameters for resting heart rate, PR interval, and ventricular repolarization, and monitoring for cardiac symptoms such as palpitations, syncope, or near syncope in pediatric patients with ADHD who may be candidates for receiving tricyclics.[101] Desipramine has demonstrated efficacy in both children and adolescents, and has been used as an alternative in patients with Tourette's syndrome or tic disorder, and in patients with comorbid anxiety or depression.[91,102] Clonidine also has been used in children with tics, but its efficacy for reducing ADHD symptoms is less substantial than other medications; sedation, dry mouth, depression, confusion, and cardiovascular side effects also limits its usefulness.[103]

Combination of Psychotherapy and Pharmacotherapy

Because virtually all studies conducted on the efficacy of pharmacotherapy and behavior therapy up to the 1990s were short-term, the National Institutes of Mental Health and the Department of Education cosponsored a 14-month clinical trial (the MTA Study) involving children aged 7 to 9.9 years with the combined subtype of ADHD (and a wide range of comorbid conditions) randomized to 4 treatment groups: (1) carefully crafted medication management, mostly using thrice-daily methylphenidate with a half-dose in the afternoon; (2) intensive behavioral treatment, including parent training, summertime child-focused treatment, and school-based interventions; (3) combined pharmaco- and behavioral therapy; or (4) standard community care. This trial examined the effects of treatment on a wide variety of dependent measures of daily life functioning, as well as ADHD symptoms.[62]

In this trial, medication management and combination treatment were substantially superior to behavioral and community care interventions for ADHD core symptoms; more than 85% of subjects receiving medication management, either singly or in combination treatment, no longer met full criteria for ADHD at study endpoint. High-quality medication treatment characterized by careful yet adequate dosing with methylphenidate, monthly follow-up visits, and communication with schools conveyed substantial benefits to those children who received it. Other randomized and open-label follow-up studies have confirmed the benefit of long-term stimulant use in relieving core symptoms.[104,105] Somewhat surprisingly, combined treatment did not differ significantly from medication management for core ADHD symptoms, although lower doses of medication were able to be used in conjunction with behavior management. Combined treatment was superior to behavioral management on some and to community care on all non-ADHD domains of functioning (parent-reported oppositional/aggressive behaviors, internalizing symptoms, teacher-reported social skills, parent-child relations, and reading achievement scores), with slight advantages over medication management alone. Benefits of combined treatment were most evident in patients with comorbid anxiety or learning disorders, and in families of lower socioeconomic strata.

Another 2-year study that examined the relative value of multimodal psychosocial treatment (parent training family therapy; academic skills training and assistance; social skills training, and individual psychotherapy) in methylphenidate-responsive children aged 7 to 9.9 years also found no significant additional benefits of multimodal psychosocial treatment added to medication.[106]

Taken together, these two long-term trials failed to find obvious additional benefits from multimodal treatment over medication alone in reducing ADHD symptoms. Nevertheless, the behavioral treatment arm of the MTA study demonstrated significant improvements, and children afflicted with the inattentive subtype were excluded from the MTA trial. Additionally, combined treatment was more acceptable to parents, allowed lower doses of medication, and typically fared better than medication alone with regard to many areas of functional improvement. Although combined treatment was rated as more acceptable by the parents, families were likely attracted to the MTA study by the possibility of receiving free and intensive behavioral therapy, including a therapeutic summer day camp of 8 weeks' duration. Consequently, these findings cannot be generalized from the MTA sample to the population at large.

Secondary analyses also supported the conclusion that combined treatment was somewhat more effective than medication management alone in normalizing behavior.[107] The question is how multimodal treatment can be effectively applied across populations in the community, and whether the incremental value derived from such treatment is justified on a broad scale, given the cost and labor intensive techniques that are required.

Safety of Pharmacotherapy

Common Side Effects of Stimulants. The report commissioned by AHRQ evaluated 29 studies containing data on the adverse effects of drug therapy.[61] Most side effects were relatively mild and of short duration, including nervousness, headache, gastrointestinal distress, appetite suppression, weight loss, and sleep disturbances. These are all expected extensions of the pharmacology of CNS stimulants. However, in one study, severe appetite suppression and sleep disturbances were reported by more than 25% of subjects receiving the largest daily doses of extended-release methylphenidate.[108]

Weight and Growth. The use of stimulants in children causes acute weight loss and/or attenuation of weight gain on continued administration. This has generally been viewed as not clinically significant, as weight gain eventually is accomplished. A more controversial aspect is the effect of stimulant medication on skeletal growth and height. A recent systematic review of 22 studies involving children found disparate results.[109] Higher quality studies, particularly those using a longitudinal design and companion control group, estimated that a height deficit amounting to ~1 cm/yr manifested during the first few years of treatment. Another long-term study of stimulants found that the losses in expected weight and body mass index (BMI) were greatest for the heaviest children, and the losses in expected height were greatest for the tallest children.[110] For weight, height, and BMI, nearly all of the growth deficits occurred in the first year. The loss in expected growth was not significant in the second year of treatment, but the reductions in expected height and weight were not fully rectified over the course of treatment. Similar results were found in the MTA study.[62]

Tics. A significant fraction of children with Tourette's syndrome have comorbid ADHD. Reports surfaced in the early 1980s that stimulants such as methylphenidate exacerbated tics in these subjects.[111] This conclusion has been questioned, and others concluded that stimulants are effective in treating ADHD in patients with tics, and that the benefits outweigh the risks.[112,113] One controlled trial and long-term open study found that methylphenidate is effective in treating ADHD symptoms in children with Tourette's syndrome or tics, and that tic frequency is not increased, and in fact, may be decreased in some patients. Another controlled trial concluded that a substantial minority of comorbid subjects had consistent worsening of tics on stimulants, although the majority experienced improvement in ADHD symptoms with "acceptable" effects on tics.[114-116] Clonidine (or desipramine) is an alternative in patients with ADHD whose tics are markedly worsened by stimulants.[102]

Substance Abuse. CNS stimulants, such as methylphenidate and amphetamine derivatives, are controlled substances with reinforcing properties. Because children and adolescents with ADHD are at increased risk for various psychiatric disorders, including conduct disorder and substance abuse, a concern has existed about the potential for abuse and addiction with these drugs. Virtually all studies have found no evidence that stimulant treatment of children with ADHD leads to an increased risk of substance use, dependence, or abuse by adulthood. A 13-year longitudinal study of a clinically referred sample of children with ADHD confirmed this viewpoint.[117] Meta-analysis of studies that examined childhood exposure to stimulants with follow-up into adolescence or adulthood actually found a reduction in the risk for subsequent drug and alcohol use disorders.[118]

Cardiovascular Effects. Case reports of sudden death in children receiving desipramine or stimulants +/- clonidine have been noted periodically over the last 25 years. Safety concerns about stimulants in ADHD are based on their effects to increase blood pressure and heart rate, and longstanding precautions against their use in patients with known cardiovascular risk factors

(coronary artery disease, structural cardiac abnormalities). Additionally, other sympathomimetic drugs (eg, phenylpropanolamine, ephedrine) are known to increase the risk of heart attack and stroke. Renewed safety concerns about stimulants have emerged in part because drug treatment of ADHD has increased in all age groups, treatment potentially may be life-long, and elevated blood pressure is strongly and directly correlated with vascular and overall mortality in adults. For example, statistically significant increases in heart rate and blood pressure occur in adults treated with methylphenidate on a short-term basis for ADHD.[119] Long-term treatment of otherwise healthy adults with amphetamine mixed salts found increases in blood pressure, heart rate, and QT_c; 3% of subjects discontinued treatment due to hypertension or tachycardia.[120] Likewise, stimulants increase blood pressure and heart rate in children, but few long-term studies have been conducted. Clinical trials involving atomoxetine also detected modest increases in heart rate and blood pressure compared with placebo. Signals generated from the FDA's Adverse Events Reporting System suggest the potential for rare fatal and nonfatal cardiovascular events associated with stimulant treatment of ADHD; however, the calculated reporting rates of sudden death do not exceed estimated background rates.

In February 2006, the FDA's Drug Safety and Risk Management Advisory Committee voted 8 to 7 to recommend adding a black box warning to the labeling of stimulants used to treat ADHD to alert prescribers about cardiovascular risks associated with the use of these drugs.[121] This recommendation was surprising since the agenda for the meeting was not devoted to this question. This action was based on the known relationship between elevated blood pressure and cardiovascular risk in adults, and the fact that prescribing of stimulants for ADHD has increased significantly over the last 15 years, and is now being extended into the adult population.

In March 2006, the FDA's Pediatric Advisory Committee met to consider information on the potential psychiatric and cardiovascular adverse events associated with drugs to treat ADHD in children. This committee, in recognizing that the evidence for the efficacy of these medications in pediatric patients is quite strong, was not impressed with the level of cardiovascular risk to children and opposed requiring a black box warning to the labeling of stimulants. The committee instead recommended that the FDA use changes in other sections of the product labeling to accomplish the intended purpose. The FDA agreed and chose this course.

Thus, additional language in the "Warnings" section of product labeling for stimulants used for ADHD now caution on: (1) use in patients with structural cardiac abnormalities or other serious heart problems; (2) the potential for increasing blood pressure and exacerbating pre-existing conditions such as hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia; (3) the need to conduct a careful history (including assessment for a family history of sudden death or ventricular arrhythmia); (4) a physical examination to assess for the presence of cardiac disease, and further cardiac evaluation if warranted; (5) the potential for causing or exacerbating psychotic, manic, or "aggressive" symptoms or seizures; (6) the potential for growth suppression in continuously medicated youth; and (7) the potential for visual disturbances.

On February 21, 2007, the FDA also directed the manufacturers of all drug products approved for the treatment of ADHD to develop Patient Medication Guides to alert patients to possible cardiovascular risks, and risks of adverse psychiatric symptoms associated with these medicines, and to advise them of precautions that can be taken.

<u>Treatment of Adolescents—Additional Comments</u>

Although the findings from the treatment of children with ADHD are commonly applied to adolescents, numerous developmental and environmental changes characterizing the transition

from childhood to adolescence may impact treatment and outcomes. Adolescents must actively participate in treatment, and there is a greater need for vocational evaluation, counseling or training, and evaluation of safe driving practices. Problems in school tend to be the most common complaint by parents. Relatively less research has been conducted on psychosocial interventions for adolescents with ADHD.

Nevertheless, the beneficial and adverse effects of stimulants and atomoxetine appear to be comparable in children and adolescents. However, adolescents frequently discontinue psychotropic medication for ADHD or have poor treatment adherence.[30,38,122-124] Additionally, some adolescents participate in the diversion of immediate-release stimulants.

Although tricyclic antidepressants such as desiprmaine and nortriptyline reduce core symptoms of ADHD in adolescents, they are not as effective as stimulants, and are viewed as second-line agents because of toxicity concerns.[125,126] Bupropion and clonidine also have been studied in a limited fashion, the latter in adolescents with ADHD and prominent hyperactivity or aggressiveness.[127-29]

Treatment of Adults—Additional Comments

Atomoxetine is FDA-approved for treating adult ADHD. Although atomoxetine is significantly more effective than placebo in adults, effects on core symptoms are relatively modest and some adults do not tolerate the drug well.[130]

Until recently, relatively little high-quality research had been conducted on the use of stimulants for the treatment of adult ADHD. Initial reviews found conflicting evidence for the efficacy of methylphenidate in adults, and response rates were substantially less than the 70% typically observed in pediatric clinical trials.[61] However, many early trials in adults lacked adequate dosing (compared with pediatric trials) and did not use validated rating scales for diagnosis and symptom improvement.[131] More recent clinical trials using larger doses in adults have found significant improvement on stimulants that are more comparable to the effect sizes and response rates observed in younger patients.[132-136]

In two studies, bupropion was significantly more effective than placebo in adults with ADHD, but overall response rates are relatively modest compared with stimulants.[137,138] Similarly, there is some evidence that tricyclic antidepressants are effective.[61]

Summary/Conclusion

ADHD is now believed to represent a disease of neurogenetic origin, whose expression is modified by environmental influences. As such, it is a disorder encompassing the lifespan of many individuals who are at risk. Diagnosis of ADHD in children is based on meeting the criteria of the DSM-IV-TR. Because the criteria are subjective and may be interpreted differently by different observers, their use and applicability to general practice settings may vary somewhat. Clinical samples have not been diverse, with an overrepresentation of Caucasian males. Further information is needed to inform treatment of minority populations and those from lower socioeconomic strata. With the recognition that a substantial percentage of children diagnosed with ADHD have symptoms that persist into adulthood, developmentally valid criteria for adults also need to be refined.

The treatment of ADHD requires expertise in many different treatment modalities, no single one of which can address all of the difficulties likely to be experienced by these individuals.

Stimulant medication offers the most effective treatment for reducing core ADHD symptoms. Psychosocial interventions may be effective in reducing defiance, as well as other related behavioral and emotional difficulties, with less substantial effects on core ADHD symptoms, compared with stimulant medication.

Although the FDA has recently taken actions to strengthen warnings on the product labeling for medications approved to treat ADHD some disagreement continues about the risks of medications used to treat this disorder. With the additional requirement for Patient Medication Guides, it will be important to monitor the impact of such changes on access to treatment, as well as prescribing habits.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted and the remainder of the report be filed:

> That Policy H-60.950—Diagnosis and Treatment of Attention Deficit/Hyperactivity Disorder in School-Age Children, be amended by insertion and deletion to read as follows:
>
> The AMA: (1) encourages physicians to utilize standardized diagnostic criteria in making the diagnosis of ADHD, such as the American Psychiatric Association's DSM-IV, as part of a comprehensive evaluation of children and adolescents presenting with attentional or hyperactivity complaints; (2) urges that attention be directed toward establishing developmentally appropriate criteria for the diagnosis and treatment of ADHD in adults; (~~2~~3) encourages the creation and dissemination of practice guidelines for ADHD by appropriate specialty societies and their use by practicing physicians and assist in making physicians aware of their availability; (~~3~~4) encourages efforts by medical schools, residency programs, medical societies, and continuing medical education programs to increase physician knowledge about ADHD and its treatment; (~~4~~5) encourages the use of individualized therapeutic approaches for ~~children~~ patients diagnosed with ADHD, which may include pharmacotherapy, psycho-education, behavioral therapy, school-based and other environmental interventions, and psychotherapy as indicated by clinical circumstances and family preferences; (~~5~~6) encourages physicians and medical groups to work with schools to improve teachers' abilities to recognize ADHD and appropriately recommend that parents seek medical evaluation of potentially affected children; and (7) encourages further research on the relative risks and benefits of medication used to treat ADHD, including evaluation of the impact of labeling changes on access to treatment and physician prescribing. (Modify HOD Policy)

Fiscal Note: Staff costs estimated at less than $500 to implement.

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APPENDIX 1.
DSM-IV-TR Criteria for Diagnosis of ADHD in Children

Criterion A

Inattention

A1) 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

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 (eg, toys, school assignments, pencils, books, or tools)

h) Is often easily distracted by extraneous stimuli

i) Is often forgetful in daily activities

Hyperactivity and Impulsivity

A2) 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 (eg, butts into conversations or games)

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

Criterion C. Some impairment from the symptoms is present in 2 or more settings (eg, at school [or work] or at home).

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

Criterion 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 (eg, mood disorder, anxiety disorder, dissociative disorder, or personality disorder).

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if criterion A1 is met but criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive, Impulsive Type: if criterion A2 is met but criterion A1 is not met for the past 6 months

314.9 Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified

APPENDIX 2.

Recommendations from the American Academy of Child and Adolescent Psychiatry[38]

1. Screening for ADHD should be part of every patient's mental health assessment

2. Evaluation of the preschooler, child, or adolescent for ADHD should consist of clinical interviews with the parent and patient, obtaining information about the patient's school or day-care functioning, evaluation for comorbid psychiatric disorders, and review of the patient's medical, social, and family history

3. If the patient's medical history is unremarkable, laboratory or neurological testing is not indicated

4. Psychological and neuropsychological tests are not mandatory for the diagnosis for ADHD, but should be performed if the patient's history suggests low general cognitive ability or low achievement in language or mathematics relative to the patient's intellectual ability

5. The clinician must evaluate the patient with ADHD for the presence of comorbid psychiatric disorders

6. A well thought-out and comprehensive treatment plan should be developed for the patient with ADHD

7. The initial psychopharmacological treatment of ADHD should be a trial with an agent approved by the Food and Drug Administration (FDA) for the treatment of ADHD

8. If none of the above agents results in satisfactory treatment of the patient with ADHD, the clinician should undertake a careful review of the diagnosis and then consider behavior therapy and/or the use of medications not approved by the FDA for the treatment of ADHD

9. During a psychopharmacological intervention for ADHD, the patient should be monitored for treatment-emergent side effects

10. If a patient with ADHD has a robust response to psychopharmacological treatment and subsequently shows normative functioning in academic, family, and social functioning, then psychopharmacological treatment of the ADHD alone is satisfactory

11. If a patient with ADHD has a less than optimal response to medication, has a comorbid disorder, or experiences stressors in family life, then psychosocial treatment in conjunction with medication treatment is often beneficial

12. Patients should be assessed periodically to determine if there is continued need for treatment or if symptoms have remitted. Treatment of ADHD should continue as long as symptoms remain present and cause impairment

13. Patients treated with medication for ADHD should have their height and weight monitored throughout treatment