

Primary Care Treatment of Attention-Deficit/Hyperactivity Disorder

Larry Culpepper, M.D., M.P.H.

Primary care physicians should consider the role of families of patients with attention-deficit/hyperactivity disorder (ADHD) not just in terms of their genetic relationship but also in terms of the role family can play in assisting in the treatment and management of the disorder. When first encountering a new case of ADHD, primary care physicians should confirm the diagnosis, identify comorbidities and other primary disorders, and develop a comprehensive assessment of the patient with ADHD that includes consideration of family-related influences. Management of multiple medical, mental health, and psychosocial problems over time will often be ineffective if ADHD is not adequately managed. The most effective management should be multimodal, with patients benefiting from caring professionals with special expertise in the treatment of ADHD as well as the primary care physician. Successful management of ADHD begins with establishing a therapeutic alliance with the patient and affected family that includes patient and family education and agreement on patient-specific goals, treatment, follow-up, and monitoring. As pharmacotherapy controls the core symptoms of ADHD, the primary care physician and treatment team should discuss with the patient other supportive interventions.

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For patients with attention-deficit/hyperactivity disorder (ADHD) and their families, the primary care physician can provide care that will dramatically improve functioning and quality of life. Owing to an abnormality between the norepinephrine and dopamine systems resulting in hypofunction of the prefrontal cortex and associated abnormalities in the striatal region, basal ganglia, and related structures, this brain disease impairs attention, alertness, vigilance, and critical executive functions, including abstract reasoning, mental flexibility, planning, and working memory.¹ While ADHD is likely to be a life-long neurologic disorder, symptoms and impairments in functioning vary greatly, particularly during adulthood. Individuals often adapt, for instance, through their choices of job, social, family, and lifestyle patterns. Such adaptations, which might result in part from treatment, may make further treatment unnecessary. This article discusses the various presentations of ADHD in primary care settings and evaluation and management strategies that the primary care physician can use effectively.

PRESENTATION OF ADHD IN PRIMARY CARE SETTINGS

Given the strong genetic basis of ADHD,² primary care physicians, particularly family physicians caring for both parents and children, often encounter families in which parents and children (and grandparents) all suffer from ADHD and for whom the disorder in the adult generations influences and must be considered in management of the children. Twin studies showing as much as 92% concordance in monozygotic twins and 33% in dizygotic twins^{3,4} and molecular studies demonstrating a role for adrenergic genes in ADHD⁵ strongly support a genetic basis for this disease. Environmental influences also very likely play a role; for instance, smoking during pregnancy may have long-lasting effects on the dopaminergic system and number of nicotine receptors.⁶ In early childhood, children may present with symptoms of hyperactivity and impulsivity, although these might not be evident in the controlled environment of the office visit. However, when children are diagnosed with ADHD at 4 to 6 years of age, symptoms persist at least into the elementary school years.⁷ Of note, while most studies have reported a large preponderance of male children and adolescents with ADHD, this might be a function of the various influences leading to the recognition of ADHD by parents and teachers and diagnostic bias by clinicians. In an unselected sample of siblings, boys and girls had very similar rates of ADHD; there was no association of sex and either type of ADHD or level of cognitive, psychosocial, school, or

From the Department of Family Medicine, Boston University, Boston, Mass.

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Corresponding author and reprints: Larry Culpepper, M.D., M.P.H., Professor and Chairman, Department of Family Medicine, Boston University, 1BMC Place, Dowling 5, Boston, MA 02118 (e-mail: larry.culpepper@bmc.org).

family functioning.⁸ The prevalence of ADHD in primary care populations is similar to that in the general community, ranging from 4% to 11% depending on the diagnostic criteria used.^{9,10}

Hyperactivity may manifest during childhood in such behaviors as restlessness or “seeming to be always on the go,” difficulty playing quietly, excessive fidgetiness or talking, and difficulty remaining seated when asked (Table 1). Impulsivity, almost always associated with hyperactivity in younger children, is reflected by intruding or interrupting others’ activities, difficulty waiting turns, blurting out answers inappropriately, disruptive classroom behavior, peer rejection, and unintentional injury. These symptoms typically become evident by the age of 4 years and then increase during the next 3 to 4 years, peaking in severity by 7 to 8 years of age.¹¹ Thereafter, hyperactive behaviors may decrease and by adolescence no longer be problematic. In contrast, impulsivity usually remains a problem throughout the life span.¹²

Inattention usually does not become noticeable until the demands of the school environment lead to its recognition, often when a child is 8 to 9 years old. Inattention is then evidenced by problems such as forgetfulness, being easily distracted, misplacing or losing things, disorganization, poor concentration, poor follow-through with tasks including homework or in-class assignments, poor attention to detail, and underachievement at school. Similar to impulsivity, inattention usually is a lifelong problem.¹²

By adolescence, the presentation of ADHD often becomes confusing, as hyperactivity wanes and the consequences of ADHD during childhood become evident, including the development of comorbid problems. Behaviors and attendant primary care presentations related to ADHD during adolescence include alcohol or drug abuse, motor vehicle and other accidents, behavioral impulsivity and risk taking, antisocial behavior and legal difficulties, school problems including failure or dropping out, social failure, low self-esteem, and loss of motivation.¹³ In particular, academic performance often suffers due to memory problems, cognitive fatigue, performance inconsistency, lack of completing tasks and inattention to detail, and ineffective self-monitoring leading to careless errors. Those with inattentive type ADHD often are less disruptive than those with hyperactive type ADHD and thus do not come to adult attention until later; however, they also often have greater social impairment and unhappiness. Recently, functional magnetic resonance imaging findings in adolescents with a history of ADHD during childhood have demonstrated prefrontal and striatal abnormalities consistent with these behaviors.¹⁴

Adult ADHD is a true disorder that can be reliably diagnosed and predicts future functioning and impairment.¹⁵ Childhood ADHD persists as a diagnosable disorder into at least young adulthood in 60% to 70% of cases.¹⁶ Using conservative diagnostic criteria, the U.S. National Comor-

Table 1. Presentation of Attention-Deficit/Hyperactivity Disorder During Childhood and Adolescence, as Reported by the Patient, Parents, or Teachers

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|---|
| By Child or Adolescent: |
| Does not like school or particular subjects or teachers |
| No close or long-term friends |
| Conflict with parents |
| Low self-esteem |
| Always getting in trouble |
| By Parents: |
| Aggression and problems with anger |
| Difficulty completing tasks |
| Disorganized, messy |
| Does not follow directions |
| Impulsive |
| Difficulties with school |
| “Always on the go” |
| Does not make or keep friends |
| Socially or emotionally immature |
| Engages in dangerous activities |
| “Spaced out” or absentminded |
| Loses possessions |
| By Teachers: |
| Hyperactive |
| Inattentive, easily distracted |
| Interferes with others, disrupts class |
| Underachiever, school failure |
| Does not listen |
| Fidgets, will not stay in seat |
| Blurts out answers, does not consider others |
| Frequent behavior problems |

bidity Survey Replication found an adult prevalence of 4.4%.⁹ During adulthood, the presentation in primary care settings is usually one of self-referral, although only one third of adults who believe they have ADHD are found to meet diagnostic criteria.¹⁷

The neurologic disinhibition associated with ADHD during adulthood results in poor self-regulation and difficulty with goal-directed thought and action.¹⁸ Disinhibition results in the inability to prevent immediate responding and deficits in self-monitoring behavior.¹⁹ Affected adults have difficulty prioritizing and instead immediately react to new demands without thinking. Consequently, important tasks are not completed while trivial ones take precedence. Adults with ADHD often appear hectic and are frustrated by their chronic inability to be organized. Inattention often becomes more problematic as responsibilities increase in adulthood: work or school deadlines are missed, and appointments and social commitments forgotten. Lists and notes, both written and on electronic aids, are made but then forgotten.

The impulsivity resulting from ADHD can result in socially inappropriate behavior such as blurting out thoughts that are interpreted as unfeeling or insulting. The hyperactivity evident during an affected adult’s childhood is transformed into restlessness, difficulty relaxing, and feeling chronically “on edge.” Adults may compensate for their impairments through their choices of jobs and living circumstances. While this can lead to their functioning adequately in some areas, often impairments in at least one

other area persist, including impaired social interactions, resulting in painfully diminished quality of life.

EVALUATION OF ADHD IN PRIMARY CARE SETTINGS

The evaluation of a patient with ADHD requires multiple visits and should evolve, along with the education of the patient and family members about the condition and its impact. An adequate evaluation includes eliciting the symptoms required to make the diagnosis and their impact on functioning and quality of life. It also includes assessing whether an immediate crisis exists, whether other primary conditions or comorbidities are present, and what resources are available to aid management.

An initial clinical task is to determine and respond to any crisis that has precipitated the primary care visit and recognition of ADHD symptoms. Depending on the patient's age, these might include threat of suicide, or harm or violence to the affected child or to others. It also might include school- or work-related disruption such as expulsion or termination or threat of arrest or other legal action. Family disruption, including impending divorce or separation of parents or an affected adult, also might bring the patient to the primary care setting. These crises need immediate attention, with the primary care physician returning to the evaluation and management of ADHD once the crises are under control.

Confirming the Diagnosis

The DSM-IV and its primary care adaptation²⁰ provide the criteria currently recognized as important to minimize both overrecognition and underrecognition. The American Academy of Pediatrics (AAP) suggests the following questions as useful for screening during the school years,²¹ given that symptoms may not be apparent during office visits and routine screening has been demonstrated to increase recognition during childhood:

- How is your child doing in school?
- Are there problems with learning that you or the teacher has seen?
- Is your child happy in school?
- Are you concerned with any behavioral problems in school or at home or when your child is playing with friends?
- Is your child having problems completing class-work or homework?

In addition to determining symptoms, the DSM-IV criteria require that onset of some behavioral symptoms occurred before age 7, have persisted at least 6 months, and are present in more than one setting (home, school, play or work, day care). For children and adolescents, obtaining assessment from at least one teacher or other person in direct contact with the child or adolescent

(teacher, day care provider) in addition to parent report and clinician observation is critical to valid diagnosis. The AAP has produced a toolkit (www.nichq.org/resources/toolkit/) to assist in the evaluation of childhood ADHD that includes letters to teachers and parent and teacher questionnaires. These instruments help to determine the ADHD subtype (predominantly inattentive, predominantly hyperactive/impulsive, combined) and degree of impairment. The AAP recommends that only instruments specifically designed to assess ADHD be used, since general child assessment instruments do not provide adequate sensitivity or specificity. Most ADHD-specific instruments have sensitivities and specificities of 94% or better.²¹ The Institute for Clinical Systems Improvement (ICSI) provides an evidence-based guideline for child and adolescent ADHD (accessible at www.icsi.org) and recommends the ADHD-IV Rating Scale and Child Attention Profile.

Parent and teacher reports can be expected to disagree on the diagnosis of ADHD at least one quarter of the time.²² Unfortunately, during adolescence, when symptoms may be most confusing, parent reports can be particularly unreliable regarding school behaviors, and teacher reports may be suboptimal since no one teacher has day long contact with the adolescent. Teacher reports often become more valuable as the school year progresses and are particularly valid regarding academic progress and hyperactive behaviors. Adolescents have been shown to dramatically underreport their symptoms and impairments²³; however, obtaining information directly from them by interviewing and by using self-report scales (Brown Attention-Deficit Disorder Scales for Adolescents or Conners-Wells Adolescent Self-Report Scale) is an important part of the assessment.¹³ When parent- and school-based reports differ, the primary care physician can obtain further insight from other informants such as coaches, former teachers, or other adults with independent relationships with the teen. Supporting parents in requesting (in writing) psychoeducational testing through the local school system is an important primary care role that can help confirm the diagnosis of ADHD. However, the diagnosis is a clinical one, not one based on such testing.

Diagnostic assessment of adults is still somewhat controversial, and 2 diagnostic approaches have been developed, both with limitations and with areas of controversy.¹⁵ Both require a diagnosis of childhood ADHD in retrospect, and both use at least one informant in addition to the patient (such as a parent or significant other). The Wender Utah criteria approach is an empirically based strategy that requires the patient with ADHD to have difficulty in inattention and hyperactivity and at least 2 of 5 additional symptom clusters (mood lability, irritability and hot temper, impaired stress intolerance, disorganization, and impulsivity).²⁴ These have been incorporated into the Wender Utah Rating Scale,²⁵ now available in several languages. Limitations of this approach include the potential ex-

clusion of those with predominately inattentive subtype ADHD, potential misdiagnosis due to inclusion of irritability/hot temper as a criteria, and the exclusion of those with psychiatric comorbidity such as depression and anxiety.

A second approach to diagnosing adults has been developed by Biederman based on the DSM criteria.^{26,27} Controversies exist for this approach in each of the major DSM diagnostic requirements.¹⁵ Requiring 6 symptoms for diagnosing adult ADHD, as is required in the diagnosis of childhood ADHD, might be overly restrictive and exclude individuals with marked impairment who would benefit from treatment. Similarly, requiring confirmation of onset by age 7 is often difficult for adults. Using a threshold of 4 symptoms of hyperactivity or inattention and relaxing the age criteria to demonstration of onset by age 12 have been proposed as more appropriate clinically.

Similarly, the DSM requirements of impairment in 2 settings including home and school (with work a permissible substitute for school) and of impairment in school, academic, or occupational functioning fail to recognize the complexity of the adult world. The requirements ignore other domains such as the larger organized community (driving, legal, citizen obligations), financial management (banking, using credit, contracting), child rearing, and marital roles. Adaptive choices of occupation and lifestyles (e.g., living alone) might limit recognizable impairment to a single domain in an individual who might benefit greatly from treatment. Finally, as with the Wender Utah criteria, the role of psychiatric comorbidities in causing symptoms often leads to diagnostic controversy, given the frequency of such disorders in those with ADHD.

Identifying Comorbidities and Other Primary Disorders

Medical and psychiatric disorders frequently either coexist with ADHD or better explain patients' presenting symptoms, and the initial and periodic reassessment of patients should determine their presence. Table 2 provides an overview of the myriad conditions to be considered as the evaluation of a patient progresses. If present, many of these conditions will be evident or suspected from a primary care physician's longitudinal relationship with a family. A developmentally oriented history and physical examination will uncover other conditions. Information helpful in evaluating a number of other disorders can be gathered from parents and school informants using questionnaires, and a number of helpful instruments for this purpose are available, both general and condition specific. The ICSI guideline provides information about these instruments and further guidance on the evaluation process. There is no required laboratory or psychoeducational testing to establish the diagnosis or rule out other causes; such testing should be guided by the initial clinical assessment.

A number of conditions are highly prevalent among those with ADHD, and these disorders should be sought

Table 2. Conditions That May Be Differentiated From or Comorbid With ADHD

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|--|
| Emotional or psychiatric problems |
| Depression/dysthymia/bipolar disorder ^a |
| Anxiety ^a |
| Oppositional defiant disorder ^a |
| Conduct disorder ^a |
| Substance abuse ^a |
| Obsessive-compulsive disorder |
| Posttraumatic stress disorder |
| Developmental delays, autism |
| Biomedical problems |
| Sensory impairment (hearing or vision) ^a |
| Medication effects (eg, decongestants, β -agonists, anticonvulsants) |
| Asthma |
| Enuresis ^a |
| Encopresis |
| Hypothyroidism |
| Lead toxicity |
| Neurologic (tic disorder, seizure disorder, brain injury) |
| Chromosomal abnormalities (eg, fetal alcohol syndrome, fragile X syndrome, phenylketonuria) |
| Sleep disorders |
| Academic or learning problems |
| Improper learning environment (eg, unsafe, disruptive) |
| Mismatch of school curriculum with child's ability (eg, gifted, learning-disabled) |
| Cognitive impairment |
| Specific learning disability ^a |
| Speech or language problem (expressive/receptive and phonology disorders, dysfluency, apraxia) |
| Other learning disorder or dysfunction |
| Family psychosocial problems |
| Parental psychopathology or chemical dependency ^a |
| Family dysfunction or stressful, disruptive, or chaotic home environment ^a |
| Poor parenting (eg, inappropriate, inconsistent, punitive) ^a |
| Neglect or abuse |
| Family stresses or transitions |
| Social skills deficits |
| Cultural factors |

^aCommon comorbid and associated conditions.

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

both initially and periodically during follow-up care (Table 2). These include psychiatric conditions, academic problems, and family dysfunction. Specifically, mood and anxiety disorders, conduct and oppositional defiant disorders, or substance abuse might already be present or develop over time. Mood and anxiety disorders are more common in those with predominantly inattentive and combined subtypes, while conduct and oppositional defiant disorders are more frequent in those with hyperactive-impulsive and combined subtypes of ADHD. Learning disabilities may already be evident or be identified as children progress through school; adults with ADHD also might have unrecognized learning disabilities.

Mood disorders coexist in about 1 child in 5 with ADHD and increase in frequency during adolescence and adulthood. One study found that 48% of 9- to 16-year-olds with ADHD also had depression or dysthymia, and high rates of depression and dysthymia have been found among adults with ADHD.²⁸ Childhood comorbid depression

conveys increased risk of poor outcomes later in life; for instance, adolescents with comorbid depression are at increased risk of suicidal behaviors. Of note, those with ADHD and comorbid depression frequently have family histories of depression as well. While bipolar disorder is rare compared to ADHD, recent studies indicate that a large portion of those with childhood bipolar disorder have comorbid ADHD.¹³

Anxiety disorders including separation anxiety, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder (PTSD) co-occur in about 25% of children with ADHD, increasing to over one third of adolescents and even higher rates in adults. Those with ADHD are at high risk of PTSD due to their increased risk of both serious accidents and abuse. Adolescents with comorbid anxiety are often complex diagnostically and have been described as “thinking too little (ADHD) and thinking too much (anxiety).”¹³

Conduct and oppositional defiant disorders in childhood and adolescence may be diagnosed as antisocial personality disorder in adulthood. Early signs include negativistic, hostile, and defiant behaviors, including losing temper and being argumentative and deliberately annoying. These may progress to aggression toward animals and people, truancy and running away from home, and serious delinquency. One third of children with ADHD demonstrate such disorders, and these individuals continue to have increasing difficulties in adulthood compared to those with ADHD alone.²¹ Antisocial personality features are highly prevalent in adults with ADHD.²⁹ Inability to cope with the routine frustrations of life may play a major role in these behaviors.

Substance use and abuse is a concern for some of those with ADHD, given the potential for abuse of the stimulants used to treat ADHD.³⁰ Those with ADHD start smoking at a younger age and are more likely to smoke as adults. The influence of treatment of ADHD on smoking is controversial. Attention-deficit/hyperactivity disorder may lead to a 3- to 4-fold increase in non-alcohol-related substance abuse, and those affected constitute 15% to 25% of adults with substance abuse disorders. Conduct disorder is a major risk factor for early-onset substance abuse; however, treatment of ADHD may actually be protective. A meta-analysis demonstrated almost a 2-fold reduction in substance abuse in those treated for ADHD with stimulants compared to those managed with nonpharmacologic interventions,³¹ and the duration of treatment had a linear effect on the reduction of hallucinogen and cocaine use. Treatment of ADHD might improve self-esteem and reduce academic and other failures, thereby reducing the risk of substance abuse; alternatively, treatment might be a marker of greater family investment and resources in responding to childhood and adolescent ADHD.³¹ The diagnosis of ADHD may be difficult in those with ongoing substance abuse; for instance, long-term marijuana or al-

cohol abusers report inattention and poor concentration. A clear history of ADHD symptoms before the initiation of substance use and observation after abstinence for 1 to 3 months are important.

Speech and language disorders are present in over half of children with ADHD and not only affect learning, but also heighten social impairment, leading to difficulty maintaining friends. They are more common in adolescents with antisocial behaviors. If primary care screening or parent or patient history suggests such a problem, evaluation by a speech and language specialist should occur. At least 25% to 30% of children with ADHD will have a learning disorder, and those with ADHD may constitute 40% to 80% of the learning disabled population.³² Any indication of significant problems in the school setting should lead to a written request to the child's school for evaluation. Multidisciplinary evaluation in the school setting is an entitlement under the federal Individuals With Disabilities Education Act. The evaluation must be performed within a specified period of time following the formal request from the parent. Evaluation in the school setting is a requirement to qualify for special education services. Because of biases or conflicts of interest (limited resources or funding), parents may request an independent second opinion evaluation outside the school system. The primary care physician can be of great help in guiding parents through these processes and in working with the school system.

A final area requiring evaluation is that of family psychosocial problems. Families of patients with hyperactive-impulsive subtype ADHD are more likely to have other members with aggression and substance abuse-related problems, while patients with inattentive subtype are more likely to have family histories of anxiety disorders and learning problems.³³ Depression and parental and sibling ADHD also are more common in affected families. These conditions may compound the stress on such families and decrease their coping abilities, resilience, and quality and consistency of caregiving and may result in increased rates of divorce or other major family dysfunction. Not uncommonly, the primary care physician will need to either treat or arrange treatment for other family members as well as for the individual with ADHD. This may improve greatly the functioning and long-term outcomes of all involved.

Developing a Comprehensive Assessment of the Patient With ADHD

The primary care evaluation should culminate in a comprehensive formulation including the subtype of ADHD and comorbid conditions and an understanding of past management strategies used by the family or patient.³⁴ The impact of ADHD and comorbidities, including developmental concerns, academic difficulties, and social, work, and family issues, and an inclusive depiction of the individual's

functioning should be part of the formulation. This also should include the patient's and family's vulnerabilities and strengths. This formulation, possibly developed in consultation with those with special expertise in ADHD, is critical to guiding the successful management of ADHD.

PRIMARY CARE MANAGEMENT OF ADHD

Successful management of ADHD begins with establishing a therapeutic alliance with the patient and affected family members. As noted above, initial care might involve response to a presenting crisis, either directly by the primary care physician or through referral. As the crisis is stabilized, the strategies demonstrated effective in care of chronic disease can be applied to management of ADHD. These strategies begin with patient and family education and agreement on patient-specific goals, treatment, follow-up, and monitoring. Patient and family education should be viewed as a continuing activity, starting with information about ADHD and relevant comorbidities and ways ADHD can affect attention, impulse control and behaviors, learning, social skills, and family relationships and functioning. Demystifying the condition; clarifying misconceptions about ADHD, its treatment options, and barriers to treatment; and discussing realistic expectations of treatment set the basis for involving the patient/family in subsequent decisions about therapy. Several visits may be required before the patient/family understand and accept the diagnosis. Putting them in touch with other patients or support groups may be very helpful. Particularly for those patients with comorbidities or severe symptoms or functional impairments, a key function of the primary care physician is assembling a treatment team involving mental health and education specialists or other specialists appropriate to the patient's age and difficulties faced by the patient.

As the patient/family accepts the diagnosis and need for treatment, a second step suggested by the AAP is setting 3 to 6 specific treatment goals with them.³⁴ For children and adolescents, involvement of school personnel in determining these may be of help. Such goals should be attainable within a reasonable time and measurable and might be school- (or work-) based or related to social or family functioning or self-management activities. These goals should reflect the priorities of the patient/family and can then be used in decisions about treatment and in monitoring treatment response. Communicating these goals to all caring professionals involved will decrease the possibility of conflicting recommendations.

Managing Medication

A substantial literature is consistent in demonstrating that pharmacotherapy has beneficial effects on attention, hyperactivity, and impulsiveness and on social and classroom behaviors. Studies of medication treatment in children with ADHD have shown that the drugs that are most

effective target dopamine and/or norepinephrine receptors. Other drugs that are being investigated for their efficacy in treating the symptoms of ADHD include the wake-promoting agent modafinil and the antihypertensive agent guanfacine. As the etiology of ADHD is better understood, new and more selective medications will be developed for ADHD.

Stimulants. Stimulants, such as methylphenidate, dextroamphetamine, and the combination of amphetamine and dextroamphetamine, are considered first-line treatment for ADHD. Long-acting formulations of stimulants appear to be safe and effective. The therapeutic benefit may be the result of stimulants' affecting dopamine and norepinephrine levels in the central nervous system.³⁵ Although stimulants have been shown to be generally safe and well tolerated,³⁶ not all patients respond to these drugs. Common side effects include weight loss, stomachaches, headaches, and initial insomnia.³⁶ Stimulants may also raise blood pressure and pulse.

One of the difficulties of treating ADHD in children has been dosing during school or extracurricular activities. A new methylphenidate patch that uses transdermal technology to deliver continuous medication release throughout the day is under review by the FDA. Trials^{37,38} have found that application time does not appear to have a substantial effect on total daily functioning, and low doses of methylphenidate yielded enhanced response, particularly when combined with behavior modification. This new formulation of methylphenidate was well tolerated and shows promise as an alternative to oral dosing.

Atomoxetine. Recently, atomoxetine became the only nonstimulant medication approved by the FDA for the treatment of ADHD in children, adolescents, and adults. Atomoxetine inhibits the presynaptic norepinephrine transporter; this action is believed to improve efficiency in the norepinephrine system and is associated with improved ADHD symptoms.³⁹

Modafinil. Modafinil has been approved by the FDA to improve wakefulness in patients with excessive sleepiness. The alerting effects of this drug may help to improve attention in patients with ADHD. The pharmacologic profile and structure of modafinil is notably different from those of the stimulants. There is no demonstrated abuse potential. Modafinil appears to selectively activate the cortex without generalized effects on the central nervous system. Recent studies^{40,41} of a new film-coated modafinil tablet administered once daily to children and adolescents with ADHD have shown improvements in the full spectrum of symptoms of ADHD. These tablets were well tolerated, and the most common adverse events were insomnia, headache, and decreased appetite. No clinically meaningful effects on measures of cardiovascular function, including heart rate and blood pressure, were noted. Modafinil film-coated tablets may provide a novel therapeutic option for the management of ADHD in pediatric and adolescent patients.

Tricyclic antidepressants. Of the nonstimulant medications used in ADHD, tricyclic antidepressants (TCAs), particularly desipramine and imipramine, have been the most studied.⁴² TCAs inhibit norepinephrine reuptake, which makes them a viable candidate for ADHD treatment, but their use in children has declined because of their possible cardiac side effects and associated need for monitoring.⁴³ Mild side effects include dry mouth, constipation, sedation, and weight gain; however, because TCAs affect cardiac conduction and repolarization, the primary care physician must clearly explain to families the risk of death associated with overdose and carefully monitor symptoms referable to the cardiovascular system.

Bupropion. This antidepressant blocks the reuptake of norepinephrine and dopamine. It has more stimulant properties than do the TCAs but is of only modest efficacy in decreasing hyperactivity and aggressive behavior.⁴⁴ Its adverse effects include motor tics and a decreased seizure threshold.

Antihypertensive agents. Antihypertensive drugs, such as the α_2 -adrenergic agonists clonidine and guanfacine, may work in ADHD by affecting norepinephrine discharge rates in the locus ceruleus, and this action may indirectly affect dopamine firing rates.⁴⁵ Guanfacine, in particular, has come under investigation for its use as a treatment alternative in patients with ADHD who are vulnerable to the abuse liability of stimulants.

Tailoring Treatment

The diverse alternatives available, the effects of and potential for interactions with other medications, and the need for repeated adjustments based on seasonal needs, daily schedules, and growth if the patient is a child or adolescent, are among the factors to be considered in managing pharmacotherapy of ADHD. Consequently, the mental health professional and primary care physician should be in close communication about treatment decisions, and the mental health professional may be in the best position to recommend pharmacotherapy. For example, adults might require control of symptoms not only during working hours but also during evening hours to support their attainment of family and social goals.⁴⁶ Atomoxetine might be particularly appropriate for those with a history of substance abuse, those in college or other settings where medication diversion is a concern, or those averse to amphetamine-related treatment options.³⁰ If the patient does not respond adequately to the initial medication, a second (or third) stimulant should be tried; most patients will be successfully treated by an alternative stimulant.⁴⁷

As pharmacotherapy controls the core symptoms of ADHD, the primary care physician and treatment team should discuss other supportive interventions with the patient. These interventions can help to increase symptom control and help the patient/family adapt to the illness and alter dysfunctional patterns of behaviors, relationships,

and life choices that they have engaged in prior to treatment. For children and adolescents, a variety of behavioral therapies have been demonstrated to be effective.³⁴ These involve training parents and teachers in specific techniques to improve behaviors and environmental management strategies to reduce distractions, increase structure of activities, and support improved patient functioning. Cognitive-behavioral therapy and other psychotherapeutic approaches might be of particular help to the adolescent or adult who has developed long-standing dysfunctional behaviors, especially when pharmacotherapy is providing relief from core symptoms and improving cognitive processes.⁴⁸

As patients and their families progress from initial diagnosis to a stable treatment plan, the primary care physician's role will change, but will remain critical to optimizing long-term success. Patient education should be ongoing, focused on helping patients evolve their understanding of the disorder and its management and promoting competent self-monitoring and self-management. A life and family stage approach can be of help in anticipating and helping the patient prepare for developmental tasks and challenges. For example, during adolescence, the development of greater independence and the challenges of expanded social expectations, driving, and alcohol use are areas in which counseling, either directly by the primary care physician or through referral, is likely to be beneficial. For the young adult with ADHD, further education and training, adapting to the work environment, decisions related to starting a family, and childrearing all provide major challenges.⁴⁶ The primary care physician can be helpful through not only counseling the patient, but also educating significant others, brief problem solving, and modifying medication regimens in keeping with evolving needs.

The primary care physician also has a major role in assuring preventive care and recognizing and treating acute and chronic illnesses as they develop over time. These might be the comorbidities known to be associated with ADHD as discussed above or other medical conditions. Monitoring side effects and treatment effectiveness when new medications are introduced and helping with strategies to maintain treatment adherence can be of great help.

Given the high prevalence of ADHD, its pervasive effects on patients and families, and its long-term course, primary care physicians can expect to have multiple patients with ADHD in their practice. Such patients present to the office setting with multiple medical, mental health, and psychosocial problems over time. Management of these will often be ineffective if their ADHD is not adequately managed. To be most effective, such management will be multimodal, with patients benefiting from caring professionals with special expertise in the treatment of ADHD as well as the primary care physician. However, a long-term therapeutic alliance with the primary care

physician can be invaluable to helping patients with ADHD improve their and their families' quality of life.

Drug names: amphetamine/dextroamphetamine (Adderall), atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), guanfacine (Tenex and others), imipramine (Tofranil and others), methylphenidate (Ritalin, Concerta, and others), modafinil (Provigil).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, clonidine, desipramine, guanfacine, imipramine, methylphenidate transdermal system, and modafinil are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

REFERENCES

1. Arnsten AFT. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *J Clin Psychiatry* 2006;67(suppl 8):7-12
2. Faraone SV, Khan SA. Candidate gene studies of attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2006;67(suppl 8):13-20
3. Neuman RJ, Heath A, Reich W, et al. Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins. *J Child Psychol Psychiatry* 2001;42:933-942
4. Volk HE, Neuman RJ, Todd RD. A systematic evaluation of ADHD and comorbid psychopathology in a population-based twin sample. *J Am Acad Child Adolesc Psychiatry* 2005;44:768-775
5. Bobb AJ, Castellanos FX, Addington AM, et al. Molecular genetic studies of ADHD: 1991 to 2004. *Am J Med Genet B Neuropsychiatr Genet* 2005;132:109-125
6. Linnert KM, Dalsgaard S, Obel C, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003;160:1028-1040
7. Lahey BB, Pelham WE, Loney J, et al. Three-year predictive validity of DSM-IV attention deficit hyperactivity disorder in children diagnosed at 4-6 years of age. *Am J Psychiatry* 2004;161:2014-2020
8. Biederman J, Kwon A, Aleardi M, et al. Absence of gender effects on attention deficit hyperactivity disorder: findings in nonreferred subjects. *Am J Psychiatry* 2005;162:1083-1089
9. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:617-627
10. Brown RT, Freeman WS, Perrin JM, et al. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. *Pediatrics* 2001;107:E43
11. Byrne JM, Bawden HN, Beattie TL, et al. Preschoolers classified as having attention-deficit hyperactivity disorder (ADHD): DSM-IV symptom endorsement pattern. *J Child Neurol* 2000;15:533-538
12. Mannuzza S, Klein RG. Long-term prognosis in attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2000;9:711-726
13. Wolraich ML, Wibbelsman CJ, Brown TE, et al. Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. *Pediatrics* 2005;115:1734-1746
14. Schulz KP, Fan J, Tang CY, et al. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related fMRI study. *Am J Psychiatry* 2004;161:1650-1657
15. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. *Am J Psychiatry* 2004;161:1948-1956
16. Barkley RA, Fischer M, Smallish L, et al. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *J Abnorm Psychol* 2002;111:279-289
17. Roy-Byrne P, Scheele L, Brinkley J, et al. Adult attention-deficit hyperactivity disorder: assessment guidelines based on clinical presentation to a specialty clinic. *Compr Psychiatry* 1997;38:133-140
18. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 1997;121:65-94
19. Ossmann JM, Mulligan NW. Inhibition and attention deficit hyperactivity disorder in adults. *Am J Psychol* 2003;116:35-50
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: Primary Care Version (DSM-IV-PC). Washington, DC: American Psychiatric Association; 1994
21. American Academy of Pediatrics. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics* 2000;105:1158-1170
22. Mitsis EM, McKay KE, Schulz KP, et al. Parent-teacher concordance for DSM-IV attention-deficit/hyperactivity disorder in a clinic-referred sample. *J Am Acad Child Adolesc Psychiatry* 2000;39:308-313
23. Smith BH, Pelham WE Jr, Gnagy E, et al. The reliability, validity, and unique contributions of self-report by adolescents receiving treatment for attention-deficit/hyperactivity disorder. *J Consult Clin Psychol* 2000;68:489-499
24. Murphy KR, Adler LA. Assessing attention-deficit/hyperactivity disorder in adults: focus on rating scales. *J Clin Psychiatry* 2004;65(suppl 3):12-17
25. Wender PH. Attention-Deficit Hyperactivity Disorder in Adults. New York, NY: Oxford University Press; 1995
26. Biederman J, Faraone SV, Kneed D, et al. Retrospective assessment of DSM-III attention deficit disorder in nonreferred individuals. *J Clin Psychiatry* 1990;51:102-106
27. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 1993;150:1792-1798
28. Bird HR, Gould MS, Staghezza BM. Patterns of diagnostic comorbidity in a community sample of children aged 9 through 16 years. *J Am Acad Child Adolesc Psychiatry* 1993;32:361-368
29. Biederman J. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2004;65(suppl 3):3-7
30. Wilens TE. Impact of ADHD and its treatment on substance abuse in adults. *J Clin Psychiatry* 2004;65(suppl 3):38-45
31. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? a meta-analytic review of the literature. *Pediatrics* 2003;111:179-185
32. DeLong R. Medical and pharmacologic treatment of learning disabilities. *J Child Neurol* 1995;10(suppl 1):S92-S95
33. Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am J Psychiatry* 1991;148:564-577
34. American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics* 2001;108:1033-1044
35. Stevenson RD, Wolraich ML. Stimulant medication therapy in the treatment of children with attention deficit hyperactivity disorder. *Pediatr Clin North Am* 1989;36:1183-1197
36. Greenhill LL. Attention-deficit hyperactivity disorder: the stimulants. *Child Adolesc Psychiatr Clin North Am* 1995;4:123-168
37. Pelham WE, Burrows-Maclean L, Gnagy EM, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. *Exp Clin Psychopharmacol* 2005;13:111-126
38. Pelham WE Jr, Manos MH, Ezzell CE, et al. A dose-ranging study of methylphenidate transdermal system in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 2005;44:522-529
39. Pliszka SR, McCracken JT, Maas JW. Catecholamines in attention-deficit hyperactivity disorder: current perspectives. *J Am Acad Child Adolesc Psychiatry* 1996;35:264-272
40. Swanson JM, Greenhill LL, Lopez FA, et al. Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. *J Clin Psychiatry* 2006;67:137-147
41. Biederman J, Swanson JM, Wigal B, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible dose study. *Pediatrics* 2005;116:777-784
42. Stahl SM. Essential Psychopharmacology. New York, NY: Cambridge University Press; 1996
43. Spencer TJ, Biederman J, Wilens TE, et al. Novel treatments for attention-deficit/hyperactivity disorder in children. *J Clin Psychiatry* 2002;63(suppl 12):17-22
44. Conners CK, Casat CD, Gualtieri CT, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 1996;35:1314-1321
45. Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol* 2001;21:223-228
46. Weiss MD, Weiss JR. A guide to the treatment of adults with ADHD. *J Clin Psychiatry* 2004;65(suppl 3):27-37
47. Weiss MD, Gadow K, Wasdell MB. Effectiveness outcomes in attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2006;67(suppl 8):38-45
48. Safren SA. Cognitive-behavioral approaches to ADHD treatment in adulthood. *J Clin Psychiatry* 2006;67(suppl 8):46-50