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ATTENTION DEFICIT/HYPERACTIVITY DISORDER ACROSS THE LIFESPAN

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■ **Abstract** Attention deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder presenting for treatment in youth. ADHD is often chronic with prominent symptoms and impairment spanning into adulthood. ADHD is often associated with co-occurring anxiety, mood, and disruptive disorders, as well as substance abuse. The diagnosis of ADHD by careful review of symptoms and impairment is both reliable and valid. Recent genetic, imaging, neurochemistry, and neuropsychological data support the biological underpinning of the disorder. All aspects of an individual's life must be considered in the diagnosis and treatment of ADHD. Pharmacotherapy, including stimulants, antidepressants, and antihypertensives, plays a fundamental role in the management of ADHD across the lifespan.

INTRODUCTION AND OVERVIEW

Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most common emotional, cognitive, and behavioral disorder treated in youth (1, 2). (The term ADHD in this report refers to previously used definitions including hyperkinesis, minimal brain dysfunction, and ADD with or without hyperactivity.) Epidemiologic studies indicate that ADHD is a prevalent disorder, affecting 4% to 5 % of children in the United States, New Zealand/Australia, Germany, and Brazil (3). Although it was previously thought to remit largely in adolescence, a growing literature supports the persistence of the disorder and/or associated impairment into adulthood in a majority of cases. It is a major clinical and public health problem because of its associated morbidity and disability in children, adolescents, and adults (2). Data from cross-sectional, retrospective, and follow-up studies indicate that youth with ADHD are at risk for developing other psychiatric difficulties in childhood,

adolescence, and adulthood including delinquent, mood, anxiety, and substance-use disorders (4).

Diagnostic Considerations

The diagnosis of ADHD is made by careful clinical history (5). A child with ADHD is characterized by a considerable degree of inattentiveness, distractibility, impulsivity, and often hyperactivity that is inappropriate for the developmental stage of the child. Other common symptoms include low frustration tolerance, shifting activities frequently, difficulty organizing, and daydreaming. These symptoms are usually pervasive; however, they may not all occur in all settings. Children whose predominant symptom is inattention may have more difficulties in school and in completing homework but not manifest difficulties with peers or family. Conversely, children with excessive hyperactive or impulsive symptoms may do relatively well in school but have difficulties at home or in situations of less guidance and structure.

Adults must have childhood-onset, persistent, and current symptoms of ADHD to be diagnosed with the disorder. Adults with ADHD often present with marked inattention, distractibility, organization difficulties, and poor efficiency reflected in life histories of academic and occupational failure (4, 6).

Rating scales such as the Conners and Brown scales are available for all age groups and can be useful in assessing and monitoring home, academic, and occupational performance (7, 8). Although neuropsychological testing is not relied on to diagnose ADHD, it may serve to identify particular weaknesses within ADHD (9) or specific learning disabilities co-occurring with ADHD (for review see 5).

Our concept of the disorder has undergone a number of changes over the past several decades. Whereas ADHD was initially characterized as a disorder of hyperkinesis or overactivity, both inattention and hyperactivity are now equally emphasized as important core features. Three subtypes of ADHD are currently recognized: predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype (Figure 1). The combined subtype is the most commonly represented subgroup, accounting for 50% to 75% of all ADHD individuals, followed by the inattentive subtype (20% to 30%) and the hyperactive-impulsive subtype (less than 15%) (6, 10–12). Children, adolescents, and adults with the inattentive subtype of ADHD have fewer other emotional or behavioral problems than individuals with the other subtypes. Youth with prominent inattentive problems as part of their ADHD (combined or inattentive subtype) have greater academic impairment than those with predominant hyperactivity/impulsivity. The combined-type ADHD individuals have more co-occurring psychiatric and substance-abuse disorders and are the most impaired overall.

Follow-up studies of ADHD children into adolescence and early adulthood indicate that the disorder frequently persists and is associated with significant psychopathology and dysfunction in later life. The ADHD adolescent and young adult is at risk for school failure, emotional difficulties, poor peer relationships,

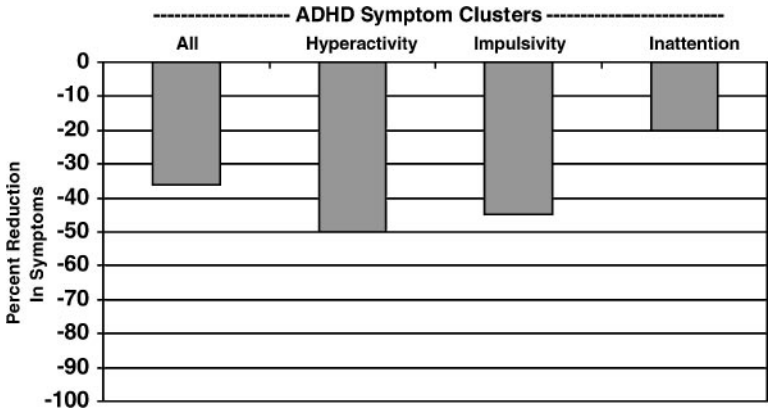

Figure 1 As observed in an ongoing longitudinal study of ADHD youth, assessed off medication, the reduction in ADHD symptom clusters is depicted from age 6 to 19 years (adapted from Reference 12a). A greater reduction in the hyperactive and impulsive symptoms was noted relative to inattentive symptoms from early childhood into young adulthood.

and trouble with the law (13, 14). Factors identifiable in younger youth that predict the persistence of ADHD into adulthood include family history of ADHD and psychiatric comorbidity—particularly aggression or delinquency problems (13, 15–17).

Prospective, longitudinal follow-up studies provide compelling evidence of the continuation of ADHD into adulthood, though the rate at which this occurs remains unclear. Partly because of methodological differences, prior longitudinal studies found highly variable rates of persistence of ADHD symptoms into adolescence (50%–75%) (18–20) and adulthood (4%–60%) (21, 22). More recent studies based in DSM IIIR nomenclature and mindful of the cognitive features of the disorder have indicated higher persistence rates of 75% into young adulthood (23, 24). These studies showed that the persistence of ADHD into adulthood included symptoms of inattention, disorganization, distractibility, and impulsivity, along with academic and occupational failure. In support of this, we reported that over 90% of ADHD adults presenting for treatment endorsed functionally impairing inattentive symptomatology (6).

PSYCHIATRIC COMORBIDITY

During the past decade, epidemiological studies have documented high rates of concurrent psychiatric and learning disorders among individuals with ADHD (25, 26). Most commonly, comorbidity with ADHD in youth includes oppositional, conduct, mood, and anxiety disorders (4).

Conduct Disorder

Conduct disorder is the best-established comorbid condition of childhood ADHD and has been widely reported in epidemiological (26), clinical (28), follow-up (13–15, 29), and family genetic studies. Consistent with childhood studies, recent studies of referred and nonreferred ADHD adults have found high rates of childhood conduct disorder as well as adult antisocial disorders in these subjects (30).

Depression

The comorbidity of ADHD and mood disorders has been controversial. However, reviews of ADHD studies (28) and reviews of depression studies (31) agree that ADHD and depression co-occur beyond what one would expect by chance. Follow-up studies provide additional evidence for major depression as an outcome of childhood hyperactivity. For example, Mannuzza et al. (22) found that 23% of their hyperkinetic children had a lifetime diagnosis of depression in adulthood. This rate is similar to that reported among ADHD children and adults (28, 30). To what extent depression develops as a result of ADHD or independently remains to be seen.

Bipolar Disorder

The overlap of ADHD and bipolar disorder is of recent clinical and scientific interest. Winokur et al. (32) showed that traits of hyperactivity in childhood were elevated among bipolar adults and their bipolar relatives. Similarly, many reports of bipolar children have noted the co-occurrence of mania and ADHD, and there are case reports of hyperactive children developing manic-depressive illness (33). Prior systematic studies of children and adolescents found rates of ADHD ranging from 57% to 98% in bipolar children and rates of bipolar disorder of 22% in ADHD inpatients (34). Family studies suggest a familial link between ADHD and bipolar disorder. Using pooled data from five studies, Faraone et al. (34) showed significantly elevated rates of ADHD in children of bipolar parents and significantly elevated rates of bipolar disorder among families of ADHD children.

Despite an emerging literature from convergent sources, there continues to be much controversy about the validity of the concurrent diagnoses of ADHD and bipolar disorder. Overlap of symptoms does not account for spurious diagnosis of either bipolar disorder or ADHD (35). Whereas ADHD is characterized by cognitive and hyperactive/impulsive features, bipolar disorder is characterized by mood instability, pervasive irritability, grandiosity, psychosis, cyclicity, and lack of response to structure. When youth experience both sets of symptoms, they may suffer from both ADHD and bipolar disorder.

Substance-Use Disorders

Combined data from retrospective accounts of adults and prospective observations of youth indicate that juveniles with ADHD are at increased risk for cigarette smoking and substance abuse during adolescence. In particular, ADHD youth

with bipolar or conduct disorder are at risk for very early (i.e., <16 years of age) cigarette use and substance-use disorders, whereas the typical age of risk for the onset of substance use accounted for by ADHD itself is probably between 17 and 22 years of age (36). Recent work suggests that ADHD youth disproportionately become involved with cigarettes, alcohol, and then drugs (37, 38). ADHD adolescents and adults become addicted to cigarette smoking at twice the rate of non-ADHD individuals. Moreover, ADHD substance abusers tend to prefer drugs other than alcohol with no evidence of a preference for a specific type of drug (39): Data indicate that cocaine and stimulant abuse are not overrepresented in ADHD; in fact, as among non-ADHD abusers, marijuana is the most commonly abused agent (39). Individuals with ADHD, independent of comorbidity, tend to maintain their addiction longer than do their non-ADHD peers (40).

Based largely on some preclinical animal studies (41), concerns about the later abuse liability and potential kindling of specific types of drug abuse secondary to early stimulant exposure in ADHD children have been raised. However, the preponderance of clinical data and consensus in the field do not appear to support such concerns. For example, in a prospective study of ADHD youth, a significant reduction in the risk for substance abuse was reported in treated versus untreated ADHD youth followed into midadolescence (42). Moreover, of five studies evaluating substance-use disorder risk in treated and untreated ADHD individuals, both studies with follow-up in adolescents (Figure 2) and two of three studies with follow-up in adults indicated a significant reduction in the risk for substance abuse in the treated ADHD group (T. E. Wilens, unpublished data). Clearly, further work is needed in this important area.

GENDER AND ADHD

Although little doubt remains that ADHD affects both genders, the literature on ADHD in females is limited (43). It indicates that ADHD females share with their male counterparts prototypical features of the disorder (e.g., inattention, impulsivity, and hyperactivity), high rates of school failure, comorbidity, and high levels of familiality (44–46). For instance, in the largest study of girls with ADHD, girls had rates of mood, anxiety, and learning disorders paralleling findings in boys. Girls with ADHD had lower rates of conduct and oppositional disorders than boys, which may account for the up to 10:1 overrepresentation of males over females in clinical samples of children with ADHD. The preponderance of males is much less dramatic in epidemiological and adult samples, in which the ratio approximates 2:1 (6). This suggests that ADHD may be underidentified in girls. If confirmed, the underidentification and undertreatment of females with ADHD would have substantial clinical and educational implications, depriving girls of effective treatment programs aimed at improving ADHD-associated impairments.

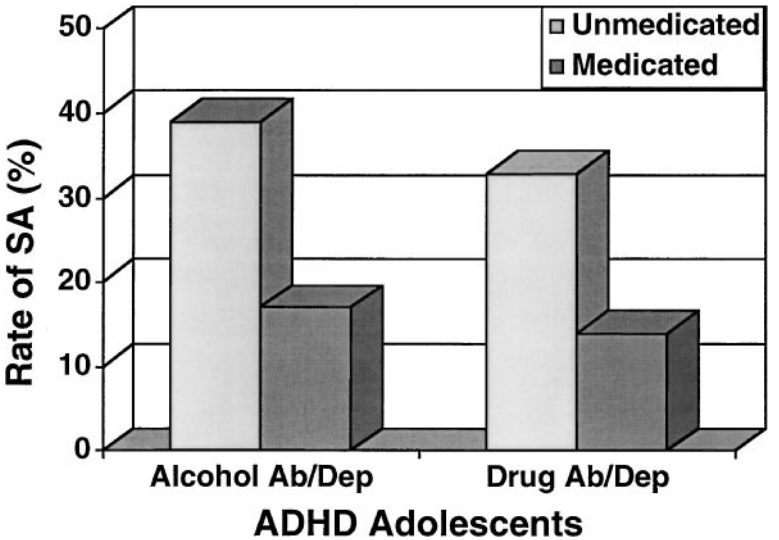

Figure 2 The effect of pharmacotherapy in ADHD children on the development of later substance abuse (SA)—alcohol or drug abuse (Ab) or dependence (Dep). These data represent studies of youth followed for five years (mean age of adolescents is 16 years). ADHD pharmacotherapy (almost ubiquitously with stimulants) was strongly associated with a reduction in the risk for substance abuse. Note that the unmedicated ($N = 198$) and medicated ($N = 118$) groups were similar in severity of ADHD and associated comorbidity at baseline.

PATHOPHYSIOLOGY AND GENETICS

Neurobiology

Although the precise neural and pathophysiological substrate of ADHD remains unknown, an emerging neuropsychological and neuroimaging literature suggests the presence of abnormalities in frontal and/or frontostriatal networks (47–49). As reviewed by Zametkin & Liotta (50), a number of brain structural and functional imaging studies have demonstrated differences between ADHD individuals and matched controls. Structural magnetic resonance imaging (MRI) studies in boys and girls with ADHD have generally shown reduced total brain, corpus callosum, caudate, and/or cerebellar volumes (47, 51, 52). Positron emission tomography (PET) research has demonstrated reduced prefrontal cortex metabolism in ADHD adults and reduced global metabolism in adolescent girls (53). No differences in brain structure related to stimulant exposure have been reported (52). Despite robust changes in behavioral ratings with stimulants, imaging studies have failed to demonstrate reversal in baseline abnormalities in ADHD (54, 55).

More recently, using single photon emission computed tomography (SPECT) scanning, adults with ADHD were found to have increased binding at the dopamine transporter protein (56, 57). In one study (56), the binding of I^{123}-altropane to the dopamine transporter in patients with ADHD did not overlap with, and was twofold higher than, that in age-matched controls, suggesting the potential utility of developing SPECT or related imaging techniques for diagnostic purposes.

Neurochemical studies continue to point to the centrality of catecholamine dysregulation in the pathophysiology of ADHD (50). Dopaminergic dysfunction, in particular, and norepinephrine, indirectly, appear to be important in the underlying pathophysiology of ADHD. Although serotonin and the inhibitory neurotransmitters glycine and GABA are apparently not central to ADHD, reports of alterations of serotonin in aggressive individuals have been reported. Pharmacological agents affecting catecholamine neurotransmission appear useful for ADHD, whereas those affecting serotonin are not (58).

Given the previously mentioned overlap of nicotine use with ADHD, there has been interest in the interface of the cholinergic and catecholaminergic-dopaminergic systems (59). Nicotine is known to improve cognition and heighten attention (59). Data from laboratory studies showed that nicotine stimulates dopaminergic neurotransmission, whereas nicotinic receptor antagonism results in diminished dopamine release (60).

Genetics of ADHD

As recently highlighted in the special issue of *Science* dedicated to the Human Genome Project, ADHD is among the most recognized genetic-based disorders in psychiatry (61). Family studies of ADHD have shown that the relatives of ADHD children are at high risk for ADHD, comorbid psychiatric disorders, school failure, learning disability, and impairments in intellectual functioning (62). Additional lines of evidence from twin, adoption, and segregation analysis studies suggest that the familial aggregation of ADHD has a substantial genetic component. Twin studies find greater similarity for ADHD and components of the syndrome between monozygotic twins than between dizygotic twins (63, 64). Their results suggest that the heritability of ADHD ranges from 0.88 to 1.0, suggesting a substantial role for genetic factors in its etiology.

Molecular genetic studies have implicated the dopamine D4 and the dopamine transporter as candidate genes (65–67). Of these candidate genes, multiple groups have independently reported on associations between ADHD and the postsynaptic D4 receptor in both children and adults with ADHD (67). The occurrence of the postsynaptic D4 polymorphism in ADHD youth is higher than would be expected by chance. In addition, ADHD youth with the polymorphism have more severe symptomatology and impairment than those without it. The D4 polymorphism is related to a deficiency in the third cytoplasmic loop of the receptor resulting in an incomplete receptor coupling to the G-protein system. It is of interest that the D4 receptor has affinity for both dopamine and norepinephrine, and its response

to dopamine appears to be blunted in the affected state. Clearly, more work is necessary to disentangle the relationship of candidate genes to ADHD, as well as patients' response to pharmacological and nonpharmacological treatments.

TREATMENT

The management of ADHD includes consideration of two major areas: nonpharmacological therapy (educational remediation, individual and family psychotherapy) and pharmacotherapy.

Nonpharmacological Therapy

Support groups for ADHD are a valuable and inexpensive manner for families to learn about ADHD and resources available for their children or themselves. Support groups can be accessed through a large organization such as Children and Adults with ADD (CHADD, http://www.chadd.org) or the National Alliance for the Mentally Ill (NAMI, http://www.nami.org).

Specialized educational planning based on the child's difficulties is necessary in most cases (68). Because learning disorders co-occur in one third of ADHD youth, ADHD individuals should be screened and appropriate remediation plans developed. Parents should be encouraged to work closely with the child's school guidance counselor, who can provide direct contact with the child and serve as a valuable liaison with teachers and school administration. The school's psychologist can provide cognitive testing and assist in the development and implementation of the individualized education plan, commonly referred to as an IEP. Educational adjustments should be considered in ADHD youth with difficulties in behavioral or academic performance. Increased structure, predictable routine, learning aids, resource room time, and checked homework are among typical educational considerations in these youth. Similar modifications in the home environment should be undertaken to optimize the child's ability to complete homework. Frequent parental communication with the school about the child's progress is essential.

Focused therapies incorporating cognitive-behavioral features have been reportedly effective in children, adolescents, and adults with ADHD (68); however, the benefit of these treatments independent of pharmacotherapy has yet to be determined (69, 70). Behavioral modification for the child and parents is useful in cases of co-occurring disruptive behaviors, inflexibility, anxiety, or outbursts. More traditional insight-oriented psychotherapy should be considered in ADHD cases with evidence of self-esteem issues, adjustment problems, or depression. Social-skills remediation for improving interpersonal interactions, and coaching for improving organization and study skills, are useful adjuncts to treatment.

Pharmacotherapy

Medications remain a mainstay of treatment for children, adolescents, and adults with ADHD (Table 1). In fact, recent multisite studies suggest that medication

TABLE 1 Medications used in the treatment of ADHD

Generic class (Brand name)	Daily dose (mg/kg)	Daily dosage schedule	Typical dosing schedule**	Common adverse effects
Stimulants				
Amphetamine	0.3–1.5			Insomnia
Short-acting (Dexedrine tablets)		Twice or three times	5–30 mg BID to TID	Decreased appetite, weight loss Tic exacerbation Depression, anxiety
Intermediate-acting (Adderall, Dexedrine spansules)		Once or twice	5–30 mg BID	Rebound phenomena (short-acting preparations only)
Extended-release (Adderall-LA)		Once	10–30 mg QD	
Methylphenidate	0.5.0–2.0			
Short-acting (Ritalin, Metadate, Ritadex)		Twice to four times	5–40 mg BID to QID	Insomnia Decreased appetite, weight loss Tic exacerbation
Intermediate-acting (Ritalin SR, Metadate SR)		Once or twice	10–60 mg QD to BID	Depression, anxiety Rebound phenomena (short-acting preparations only)
Extended-release (Concerta, Ritalin LA,* Metadate CD)		Once	18–108 mg QD	
Magnesium Pemoline (Cylert)	1.0–3.0	Once	37.5–150 mg QD	Same as other stimulants Hepatitis
Antidepressants				
Tricyclics (TCAs) e.g., Imipramine, Desipramine, Nortriptyline (NT)	2.0–5.0 (1.0–3.0 for NT)	Once or twice	25–300 mg QD (25–150 mg QD for NT)	Dry mouth, constipation Weight change Vital sign and ECG changes
Bupropion (Wellbutrin, short-acting and sustained-release—SR)	1.0–6.0	Once to three times	75–100 mg TID (short) 150–200 BID (SR)	Irritability, insomnia Risk of seizures Contraindicated in bulimics
Venlafaxine (Effexor)	0.5–3	Twice	75–150 mg BID	Nausea, GI distress Agitation
Antihypertensives				
Clonidine (Catapress)	3–10 mcg/kg	Twice or three times	0.05–0.1 mg TID	Sedation, dry mouth, depression Confusion (with high dose) Rebound hypertension
Guanfacine (Tenex)	30–100 mcg/kg	Twice	0.5–1 mg TID	Similar to clonidine but less sedation Insomnia, irritability reported

* Not FDA approved at time of publication.

**Denotes typical clinical dosing of these compounds; not reflective of FDA-approved indications or dosing.

management of ADHD is the most important variable in outcome in the context of multimodal treatment (70, 71). For example, in the largest prospective and randomized long-term study of ADHD youth, those receiving stimulants alone showed similar improvement in multiple domains at 14 months follow-up compared to those receiving stimulants plus behavior modification (70). Both medicated groups had a better overall outcome than those receiving extensive behavior modification without stimulants.

Stimulants, antidepressants, and antihypertensives comprise the available agents for ADHD. Stimulants and antidepressants have been demonstrated to have similar pharmacological responsivity across the lifespan, including school-aged children, adolescents, and adult groups with ADHD.

STIMULANTS The stimulants are considered first-line agents for children and adults with ADHD based on their extensive efficacy and safety data (72). Although there are more than 250 controlled studies of stimulants with more than 6000 children, adolescents, and adults, the vast majority of the studies are limited to latency-age, Caucasian boys treated for no longer than two months (73). The most commonly used compounds for this class include methylphenidate (Ritalin, Concerta, Metadate, and others), amphetamine (Dexedrine, Adderall), and pemoline (Cylert). Stimulants are sympathomimetic drugs that increase intrasynaptic catecholamines (mainly dopamine) by inhibiting the presynaptic reuptake mechanism and releasing presynaptic catecholamines (74). Whereas methylphenidate and pemoline are specific for blockade of the dopamine transporter protein, amphetamines, in addition to blocking the dopamine transporter protein, also release dopamine stores and cytoplasmic dopamine directly into the synaptic cleft (for review see 75). Moreover, amphetamines release serotonin and norepinephrine to a greater extent than other stimulants. Recent data suggest that acute tolerance to stimulants may develop rapidly (76).

Methylphenidate and D-amphetamine are both short-acting compounds, with an onset of action within 30 to 60 min and a peak clinical effect usually seen between 1 and 2 h after administration lasting 2 to 5 h. The amphetamine compounds (e.g., Adderall) and sustained-release preparations of methylphenidate and dextroamphetamine are intermediate-acting compounds, with an onset of action within 60 min and duration of 6 to 8 h (72, 77).

Given the need to additionally treat ADHD outside of school (e.g., social settings and homework) and to reduce the need for in-school dosage and likelihood for diversion, there has been great interest in extended-release preparations of the stimulants. Extended-release preparations greatly reduce untoward peak adverse effects of stimulants, such as headaches and moodiness, as well as essentially eliminating afternoon wearoff and rebound. Recently released preparations of methylphenidate, Concerta and Metadate CD, have an immediate onset of action with a duration of 8 to 10 h (78). Other preparations of methylphenidate (Ritalin LA as well as a pure D-isomer, Ritadex) and amphetamine (Adderall long-acting) are soon to be released with an extended-release profile of 8 to 12 h.

Although methylphenidate is by far the best-studied stimulant (72, 77), the literature suggests more similarities than differences in response to the various available stimulants. However, based on marginally different mechanisms of action, some patients who lack a satisfactory response or manifest adverse effects to one stimulant may respond favorably to another. Stimulants should be initiated at the lowest available dose once daily and increased every three to four days until a response is noted or adverse effects emerge. Typically, parameters for upward daily dosage of the stimulants are 1 mg/kg/day for the amphetamines, 2 mg/kg/day for methylphenidate, and 3 mg/kg/day for pemoline (77).

Stimulants appear to work in all age groups. Seven studies in preschoolers report improvement in structured tasks as well as mother-child interaction; however, the response is less robust with a higher side-effect burden than in other age groups (for review see 77, 79). In adolescents, response has been reported as moderate to robust, with no abuse or tolerance noted (80). There has been a great interest in the use of stimulant treatment in adults with ADHD. Fourteen studies of stimulants have demonstrated moderate reductions in ADHD symptoms with associated overall improvement in ADHD and general functioning, particularly when aggressive dosing (i.e., 20 mg TID of methylphenidate or 30 mg BID of Adderall) is employed (81).

Predictable short-term adverse effects include reduced appetite, insomnia, edginess, and gastrointestinal upset (82). In adults, elevated vital signs may emerge, necessitating baseline and on-drug monitoring. Stimulant-induced hypertension appears particularly problematic in adults with baseline borderline hypertension (i.e., $\geq$140/80). Pemoline may rarely cause hepatitis; hence, patient education about the symptoms of early hepatic dysfunction and frequent liver function tests are advised.

There are several controversial issues related to chronic stimulant use. Although stimulants may produce anorexia and weight loss, their effect on ultimate height remains less certain. Although initial reports suggested a persistent stimulant-associated decrease in growth in height in children (83), other reports have failed to substantiate this finding (84), and still others raise the possibility that growth deficits may represent maturational delays related to ADHD itself rather than to stimulant treatment (85). Stimulants may precipitate or exacerbate tic symptoms in ADHD children. Recent work suggests that the majority of ADHD youth with tics can tolerate stimulant medications (86); however, up to one third of children with tics may have worsening of their tics with stimulant exposure (87). In those cases, alternative medications for ADHD should be considered. Current consensus suggests that stimulants can be used in youth with comorbid ADHD plus tics with careful monitoring for stimulant-induced tic exacerbation.

Despite case reports of stimulant misuse (88), there is a paucity of scientific evidence that stimulant-treated ADHD individuals abuse their medication (42); however, data suggest that diversion of stimulants to non-ADHD youth continues to be a concern. Families should closely monitor stimulant medication, and college students receiving stimulants should be advised to store their medication carefully.

Despite the findings on efficacy of the stimulants, studies have also reported consistently that typically one third of ADHD individuals do not respond to or cannot tolerate this class of agents.

ANTIDEPRESSANTS The antidepressants are generally considered second-line drugs of choice for ADHD. The tricyclic antidepressants (TCAs)—imipramine (Tofranil), desipramine (Norpramine), and nortriptyline (Pamelor, Aventyl)—block the reuptake of neurotransmitters, including norepinephrine. TCAs are effective in controlling abnormal behaviors and improving cognitive impairments associated with ADHD, but less so than the stimulants (73). The TCAs are particularly useful in stimulant failures, or when oppositionality, anxiety, tics, or depressive symptoms co-occur within ADHD. Doses of the TCAs start with 25 mg daily and are titrated upward slowly to a maximum of 5 mg/kg/day (2 mg/kg/day for nortriptyline) (89). Although relief can be immediate, a lag of two to four weeks to maximal effect is common (73).

Unwanted side effects may emerge from activity at histaminic sites (sedation, weight gain), cholinergic sites (dry mouth, constipation), α-adrenergic sites (postural hypotension), and serotonergic sites (sexual dysfunction). In general, the secondary amines are more selective (noradrenergic) and have fewer side effects, an important consideration in sensitive juvenile populations. Four deaths of ADHD children treated with desipramine have been reported (90); however, independent evaluation of these cases has failed to support a causal link. Because minor increases in heart rate and electrocardiogram (ECG) intervals are predictable with TCAs, ECG monitoring at baseline and at therapeutic dose is suggested, but not mandatory.

Bupropion (Wellbutrin, Zyban) is an antidepressant with indirect dopamine and noradrenergic effects. Bupropion has been shown effective for ADHD in controlled trials of children (91) and adults (92) and in open trials in adults with ADHD and bipolar disorder. Given its utility in reducing cigarette smoking and improving mood, its lack of monitoring requirements, and its paucity of adverse effects, bupropion is often used as an initial agent for complex ADHD patients with substance abuse or a mood disorder. For example, a recent open report suggested the utility of bupropion in adolescents with comorbid ADHD and depression (93). Based on anecdotal reports of anti-ADHD effectiveness at low doses in a minority of patients, it is recommended that the treatment be initiated at 37.5 mg and titrated upward every three to four days up to 300 mg in younger children and 450 mg in older children or adults. Adverse events include activation, irritability, insomnia, and (rarely) seizures.

Although the serotonin reuptake inhibitors (e.g., Prozac) are not useful for ADHD, venlafaxine (Effexor), because of its noradrenergic reuptake inhibition, may have mild efficacy for ADHD (94). Monoamine oxidase inhibitors (MAOIs) have been shown effective in juvenile and adult ADHD. The response to treatment is rapid, and standard antidepressant doses are often necessary. A major limitation to the use of MAOIs is the potential for hypertensive crisis associated with dietetic

transgressions with tyramine-containing foods, such as most cheeses, and interactions with prescribed, illicit, and over-the-counter drugs (pressor amines, most cold medicines, and amphetamines).

ANTIHYPERTENSIVES The antihypertensives clonidine (Catapress) and guanfacine (Tenex) are α-adrenergic agonists that have been primarily used in the treatment of hypertension. These compounds are typically used to treat the hyperactive-impulsive symptoms of ADHD. Clonidine is a relatively short-acting compound with a plasma half-life ranging from $\sim$6 h (in children) to 9 h (in adults) (95). Usual daily doses range from 0.05 mg to 0.4 mg. Guanfacine is longer-acting and less potent than clonidine, with usual daily doses ranging from 0.5 mg to 3 mg. The antihypertensives have been used for the treatment of ADHD as well as associated tics, aggression, and sleep disturbances, particularly in younger children.

Although sedation is more commonly seen with clonidine, both agents may cause depression and rebound hypertension. Recent reports have implicated the combination of clonidine plus methylphenidate in the deaths of four children; however, the presence of many mitigating and extenuating circumstances makes these cases uninterpretable (96). Cardiovascular monitoring (vital signs, ECG) remains optional.

TREATMENT-REFRACTORY AND COMPLEX CASES A number of individuals either do not respond to or are intolerant of the adverse effects of medications used to treat their ADHD. Youth who are nonresponders to one stimulant should be considered for another stimulant trial. If two stimulant trials are unsuccessful, bupropion and the TCAs are reasonable second-line agents. Antihypertensives may be useful for younger children or those with prominent hyperactivity, impulsivity, and aggressiveness. MAOIs and cognitive activators such as donepezil (Aricept) may be considered for refractory youth.

Combined pharmacological approaches can be used for the treatment of comorbid ADHD, as augmentation strategies for patients with insufficient response to a single agent, and for the management of treatment-emergent adverse effects. Examples include the use of an antidepressant plus a stimulant for ADHD and comorbid depression [fluoxetine (Prozac) plus methylphenidate] (97), bupropion plus a stimulant for ADHD individuals with moodiness, clonidine to ameliorate stimulant-induced insomnia (98), and a mood stabilizer plus an anti-ADHD agent to treat ADHD comorbid with bipolar disorder (99).

SUMMARY

ADHD is a prevalent, worldwide, heterogeneous disorder that frequently persists into adulthood. The diagnosis of ADHD is made by careful history; neuropsychological testing is helpful in confirming the diagnosis or mapping out co-occurring learning problems. The scope of co-occurring disorders has expanded to include

not only conduct and oppositional defiant disorders but also mood, anxiety, and substance-use disorders as well. ADHD is increasingly being recognized in girls and in those with the inattentive subtype of the disorder. ADHD in adults entails significant impairment in occupational, academic, social, and intrapersonal domains, necessitating treatment. Converging data strongly support a neurobiological and genetic basis for ADHD, with catecholaminergic dysfunction as a central finding.

Psychosocial interventions such as educational remediation, structure/routine, and cognitive-behavioral therapy should be considered in the management of ADHD. An extensive literature supports the effectiveness of pharmacotherapy, not only for the core behavioral symptoms of ADHD but also for linked impairments including cognition, social skills, and family function. ADHD treatment may translate into reduced risk for the development of sequelae such as substance abuse. Data suggest a similar positive response of individuals with ADHD to treatment from age 6 to 60 years. The stimulant medications are the most effective agents for ADHD with ~80% of individuals responding favorably, followed by the TCAs (65%), bupropion (55%), and antihypertensives (55%). Similarities between juveniles and adults in the presentation, characteristics, neurobiology, and pharmacological responsivity of ADHD support the continuity of the disorder across the lifespan.

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