

Attention-Deficit/Hyperactivity Disorder: A Life-Span Perspective

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There is increasing scientific recognition that attention-deficit/hyperactivity disorder (ADHD), a heterogeneous disorder that carries a high risk of comorbidity, continues past childhood and adolescence into adulthood in many cases and may be underidentified in girls. The etiology of ADHD is unknown, although evidence from family studies of ADHD suggests a genetic origin for some forms of this disorder. A variety of pharmacologic agents are available in treating ADHD: stimulant medications remain the first-line treatment for noncomorbid ADHD, whereas tricyclic antidepressants and bupropion are recommended for stimulant nonresponders and patients with more than one psychiatric disorder. Complex cases of ADHD, however, may require rational use of combined pharmacotherapy.

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Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder of unknown etiology. It is one of the major clinical and public health problems in the United States because of its associated morbidity and disability in children, adolescents, and adults. Its impact on society is enormous in terms of financial cost, stress to families, interference with academic and vocational activities, as well as negative effects on self-esteem. Data from cross-sectional, retrospective, and follow-up studies indicate that children with ADHD are at risk for developing other psychiatric difficulties in childhood, adolescence, and adulthood including antisocial behaviors, substance use disorders, and mood and anxiety symptoms and disorders.

The name and nosology of ADHD have undergone a number of changes over the last several decades. In the 1960s, in DSM-II, motoric symptoms were stressed and the disorder was called hyperkinetic reaction of childhood. In 1980, DSM-III renamed the disorder as attention deficit disorder and emphasized inattention as its core feature. In 1987 with DSM-III-R, the disorder was renamed attention-deficit hyperactivity disorder (ADHD). Both inattention and hyperactivity were emphasized as equally important core features. Although the name of

ADHD remained the same in DSM-IV, depending on what symptoms predominate, DSM-IV recognizes three subtypes of ADHD: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype.¹

While its underlying neural and pathophysiologic substrate remains unknown, an emerging neuropsychological and neuroimaging literature suggests that abnormalities in frontal networks or fronto-striatal dysfunction is the disorder's underlying neural substrate, and catecholamine dysregulation is its underlying pathophysiologic substrate.²⁻⁸ Data from family-genetic, twin, and adoption studies as well as segregation analysis suggest a genetic origin for some forms of the disorder.⁹⁻¹⁷ However, other etiologies are also likely including psychological adversity, perinatal insults, and perhaps other as yet unknown biological causes.^{18,19}

Although follow-up studies show that ADHD persists into adulthood in 10% to 60% of childhood-onset cases,²⁰⁻²⁴ little scientific attention has been paid to the adult form of this disorder.

DSM-IV SUBTYPES OF ADHD

In contrast to the unitary view of ADHD in DSM-III-R, DSM-IV recognizes three subtypes based on the preponderance of symptoms of inattention, hyperactivity/impulsivity, or both. The switch from DSM-III-R to DSM-IV was primarily based on a literature that suggested that only two dimensions are needed to explain the covariation of ADHD symptoms: inattention and hyperactivity-impulsivity.²⁵⁻²⁷ This was confirmed by the DSM-IV field trials, which led to the decision that ADHD be separated into inattentive, hyperactive-impulsive, and combined subtypes.²⁷ The field trials clearly

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documented very close case identification between DSM-III-R and DSM-IV ADHD. In addition, they also showed differences among the DSM-IV subtypes: the inattentive patients were more likely to be female, and they were also significantly older than combined-type patients who were significantly older than the hyperactive-impulsive patients. The combined-type patients were more impaired on the Children's Global Assessment Scale than the other two types. The combined and inattentive subtypes had high rates of academic impairment that were greater than that reported for the hyperactive-impulsive subtype.

Notably, the hyperactive-impulsive subsample was small in the DSM-IV field trials, accounting for only 15% of the sample. Paternite et al.²⁸ found that only 9% of cases met their criteria for the hyperactive-impulsive subtype, and Morgan et al.²⁹ reported that less than 10% of DSM-IV-diagnosed ADHD cases were the hyperactive-impulsive type. In a study of consecutive admissions to our clinic, we found similar results: only 6% of DSM-IV-defined ADHD children were hyperactive-impulsive.³⁰ The higher rates in the DSM-IV field trials reflect their more extensive sampling of preschool children (the mean ages were 5.7 years for hyperactive-impulsive, 8.5 years for combined, and 9.8 years for inattentive).

Paternite et al.²⁸ assessed the clinical features of DSM-IV subtypes in a sample of 28 inattentive, 9 hyperactive-impulsive, and 59 combined-type ADHD boys. This study used approximated DSM-IV diagnoses based on data gleaned from the DSM-III version of the Diagnostic Interview for Children and Adolescents, Parent Version (DICA-P). The three groups did not differ in age at onset, but, as in the DSM-IV field trials, the inattentive patients were oldest followed by the combined-type and hyperactive-impulsive patients. These latter two groups showed the most problem behavior at home, but the inattentive patients showed a trend for more academic problems and were significantly more likely to use school services. The groups did not differ in Wechsler Intelligence Scale for Children-Revised (WISC-R) verbal and performance IQ or in reading, arithmetic, or spelling ability as measured by the Wide-Range Achievement Test-Revised (WRAT-R), nor were there differences on the Continuous Performance Test or Kagan's Matching Familiar Figures Test. Measures of family functioning did not differentiate the three groups. The inattentive patients showed lower levels of attention, delinquency, aggression, and conduct disorder symptoms, but the groups did not differ in social problems, psychosomatic problems, or symptoms of anxiety or depression. These authors noted that "The most consistent differences were those distinguishing the inattentive group from the hyperactive-impulsive and combined groups, while the hyperactive-impulsive and combined groups tended to be less distinguishable from each other."^{28(p83)} The authors suggested that this finding raised questions about the validity of the hyperactive-impulsive subtype, but noted that

their inferences in this regard were limited by the small subsample of hyperactive-impulsive children.

Owing to the rarity of hyperactive-impulsive patients, Morgan et al.²⁹ provided validity data only on inattentive and combined-type patients. The two types did not differ in gender or age, or in measures of intelligence and academic achievement. There were, however, more cases of mathematical learning disabilities among the inattentive patients. The combined-type patients had higher externalizing, delinquency, and aggression scores on the Child Behavior Checklist (CBCL) and were more likely to have externalizing disorders.

Data collected prior to DSM-IV have focused on the comparison of ADHD subjects with and without hyperactivity. As Morgan et al.²⁹ showed, there is a strong association between this distinction and that between the inattentive and combined-types from DSM-IV. Cantwell and Baker's³¹ review of the pre-DSM-IV literature found systematic differences between ADHD subjects with and without hyperactivity. Hyperactive subjects were more likely to be impulsive, distractible, and aggressive and had higher rates of conduct disorder symptomatology. In contrast, non-hyperactive subjects were more likely to have diagnoses of internalizing disorders such as anxiety and depression. Both groups show social dysfunction, but hyperactive children tend to show higher rates of peer rejection and unpopularity, whereas inattentive children show increased social withdrawal. Hyperactive subjects show more fine motor problems and neurologic abnormalities, but inattentive subjects have higher rates of learning disability. Consistent with the group differences in psychopathology, Barkley et al.³² reported the families of hyperactive children to have higher rates of substance abuse, aggressiveness, and hyperactivity, whereas the families of inattentive ADHD children have higher rates of anxiety and learning disability. The two groups did not differ in familial rates of depression or antisocial behavior.

Cantwell and Baker³¹ also presented data from 40 hyperactive and 40 matched non-hyperactive children. The hyperactive group had higher rates of oppositional and conduct symptoms, but the two groups did not differ in measures of depression, anxiety, peer relationships, social withdrawal, learning disorders, medical disorders, or treatment history. With the exception of more family discord in families of hyperactive children, most measures of psychosocial stress did not differentiate the two groups. This study found significantly more psychiatric illness among relatives of hyperactive subjects, but no specific disorder reached statistical significance. Notably, at a 4-year follow-up, 80% of the hyperactive subjects retained the diagnosis of ADD with hyperactivity; in contrast, all of the non-hyperactive subjects were either well or diagnosed with another disorder. This is consistent with a subsequent report by Hart et al.³³ reporting that the persistence of ADHD at a 4-year follow-up was pre-

dicted by hyperactive-impulsive symptoms, not inattentive symptoms.

PSYCHIATRIC COMORBIDITY

During the past decade, epidemiologic studies have documented high rates of psychiatric comorbidity among children with psychiatric disorders.^{34–36} This is consistent with the adult epidemiologic literature in suggesting that comorbidity is the rule—rather than the exception—for psychiatric disorders.^{37,38} Although ADHD's comorbidity with conduct and antisocial personality disorders is well accepted, its comorbidity with mood disorders has been controversial. However, reviews of ADHD studies³⁹ and reviews of depression studies⁴⁰ agree that ADHD and depression co-occur beyond what one would expect by chance alone. Consistent with this, our review⁴¹ of family studies of ADHD and family studies of depression suggests that the two disorders share familial risk factors. Similarly, several studies have found comorbidity between bipolar disorder and ADHD,^{42–46} and our review⁴⁷ of family studies of ADHD and family studies of bipolar disorder suggests that the two disorders co-aggregate in families.

Follow-up studies provide additional evidence for major depression as an outcome of childhood hyperactivity. Mannuzza et al.²³ found that 23% of the hyperkinetic children whom they studied had a lifetime diagnosis of depression in adulthood. This rate is similar to what others reported among ADHD children and adults.^{39,48,49} However, Mannuzza and colleagues' study discounted the high rate of mood disorder because the rate among "normal" controls was equally high—25%, which is nearly twice the lifetime prevalence in young adult males (13%) reported by the National Comorbidity Survey.⁵⁰ The difference is statistically significant ($\chi^2 = 11.6$, $df = 1$, $p = .001$). Because Mannuzza and colleagues' control group had unusually high rates of major depression, the high rate of major depression in the adults with childhood hyperactivity cannot be discounted.

ADHD's comorbidity with bipolar disorder is particularly intriguing. Winokur et al.⁴⁶ showed that traits of hyperactivity in childhood were elevated among bipolar adults and their bipolar relatives. Similarly, many case reports of bipolar children have noted the co-occurrence of mania and ADHD,^{51–55} and case reports of hyperactive children developing manic-depressive illness have been reported.⁵⁶ Prior systematic studies of children and adolescents found rates of ADHD ranging from 57% to 98% in bipolar children^{42–44} and rates of bipolar disorder of 22% in ADHD inpatients.⁴⁵ Moreover, our review of family studies suggested a familial link between ADHD and bipolar disorder. In that review,⁴⁷ pooled data from five studies showed significantly elevated rates of ADHD in children of bipolar parents, and pooled data from six studies showed significantly elevated rates of bipolar disorder

among families of ADHD children. Although the co-aggregation of ADHD and bipolar disorder was statistically significant, its small effect size suggested that it was due to a fraction of ADHD cases. This may explain why prior follow-up studies did not find bipolar disorder in ADHD children followed into adulthood.

Of course, there is much debate about the nosologic status of children meeting criteria for both ADHD and bipolar disorder: is this "severe" ADHD or "true" bipolar disorder? Nevertheless, most clinicians would agree that, although this subgroup accounts for a relatively small proportion of all ADHD children, they exhibit a syndrome of severe, disabling psychopathology and mood dysregulation frequently leading to hospitalization and marked impairment. These children require clinical resources at a level that far exceeds what one might expect given this comorbid condition's relatively low prevalence. As such, they are a serious clinical concern. Our finding that this subgroup has a distinct pattern of familial transmission^{47,57} and predictive validity over a 4-year follow-up⁵⁸ suggests that the comorbid condition of ADHD with bipolar disorder is a valid entity, suitable for further research.

GENETIC EPIDEMIOLOGY OF ADHD

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.^{9,15,59–64} The biological relatives of ADHD boys are at increased risk for ADHD and other psychiatric disorders.⁶¹ 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 compared with dizygotic twins.^{12,65} Notably, twin studies report a high heritability for ADHD. Three studies examined DSM-III or DSM-III-R formulations of ADHD.^{66–68} 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. Adoption studies also implicate genes in the etiology of ADHD. The adoptive relatives of ADHD children are less likely to have ADHD or associated disorders than are the biological relatives of ADHD children.^{69,70} Thus, a growing body of evidence shows that ADHD is a familial disorder and that transmission in families is mediated, at least in part, by genetic factors.

Our segregation analysis of ADHD¹⁴ confirmed the prior work of Deutsch et al.¹⁶ suggesting that a single gene of major effect was involved in the etiology of ADHD. However, the differences in fit between genetic models were modest.¹⁴ Similar results have since been reported in a twin study by Eaves et al.⁷¹ and a pedigree study by Hess et al.⁷² Several interpretations of these results are possible.

If ADHD has more than one genetic cause, then the evidence for any single mode of transmission might be relatively weak. In this regard it is notable that Hauser et al.⁷³ recently demonstrated that a rare familial form of ADHD is associated with generalized resistance to thyroid hormone, a disease caused by mutations in the thyroid receptor- β gene. Also, other studies have implicated the dopamine D₂, D₄, and transporter genes.⁷⁴⁻⁷⁶ These findings are consistent with genetic heterogeneity. The delineation of familial subtypes of ADHD would be beneficial to ADHD treatment and research. These subtypes may differ from other cases of ADHD in clinical phenomenology, intellectual functioning, and treatment response. This information would be useful to clinicians. Researchers would benefit from having a means to reduce the heterogeneity of ADHD in research studies. In particular, a highly familial form of ADHD would be more suitable for molecular genetic studies (i.e., linkage and association studies) than a less familial form.⁷⁷

To examine the familial heterogeneity of ADHD, Biederman et al.^{9,10,78} and Faraone et al.^{47,79} tested competing hypotheses about the association of ADHD with antisocial, mood, and anxiety disorders based on genetic models proposed by Pauls et al.⁸⁰ and Reich et al.⁸¹ Results of these analyses from our studies of DSM-III attention deficit disorder (ADD)¹⁰ and DSM-III-R ADHD⁹ suggested that (1) ADHD and major depression share common familial vulnerabilities,⁷⁸ (2) ADHD with conduct disorder may be a distinct familial subtype of ADHD,⁷⁹ (3) ADHD with bipolar disorder may be a distinct familial subtype of ADHD,⁴⁷ and (4) ADHD is familially independent from anxiety disorders⁸² and learning disabilities.⁶³ Thus, stratification by conduct disorder and bipolar disorder may cleave the universe of ADHD children into more familially homogeneous subgroups. Major depression may be a nonspecific manifestation of different ADHD subforms (and may therefore be a variable manifestation of ADHD genotypes). In contrast, anxiety disorders and learning disabilities do not appear to be good candidates for resolving either variable expression or familial heterogeneity.

GENDER AND ADHD

Although little doubt remains that ADHD affects both genders, an extraordinarily limited literature exists on ADHD in females.⁸³ The limited literature that exists clearly 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, high comorbidity with mood and anxiety disorders and learning disabilities, and high levels of familiality.^{84,85} However, rates of aggressive symptoms and comorbid conduct disorder are far less prevalent in females than in males, perhaps accounting for the up to 10:1

overrepresentation of males to females in clinical samples of children with ADHD.⁸⁶ The preponderance of boys over girls is much less dramatic in epidemiologic and adult samples, in which the ratio of males to females approximates 2:1. This suggests that ADHD may be underidentified in girls. If confirmed, this is a serious problem since the underidentification and undertreatment of females with ADHD may have substantial clinical and educational implications by depriving them of highly effective treatment programs aimed at improving ADHD-associated impairments.

THE PERSISTENCE AND REMISSION OF ADHD

Follow-up studies of ADHD children into adolescence and early adulthood indicate that ADHD frequently persists and is associated with significant psychopathology and dysfunction in later life.^{20,33,87-97} The ADHD adolescent and young adult is at risk for school failure, emotional difficulties, poor peer relationships, and trouble with the law.^{20,98} These well-designed follow-up studies have provided a wealth of data regarding the outcome of ADHD children in adolescence and adulthood. For example, several studies found that aggression or conduct problems in childhood^{20,92,99} predicted persistence of ADHD into adolescence and young adulthood. Hart et al.³³ reported that the persistence of ADHD at a 4-year follow-up was predicted by hyperactive-impulsive symptoms and by comorbid conduct disorder. Although they highlight a significant subgroup of ADHD children who will go on to develop serious psychopathology and dysfunction in adolescence and young adult years,^{20,21,24,98} relatively little is known about the risk factors that determine these poor outcomes.

Prior work also provided limited information regarding the timing of remission of ADHD symptoms. Although some follow-up studies indicated that remission of ADHD symptoms occurred by adolescence, others suggested that—in some cases—remission occurs shortly after diagnosis. For example, in Taylor and colleagues'⁹⁹ study, 37% of ADHD boys no longer satisfied diagnostic criteria 9 months later. These findings suggested that ADHD can remit in either childhood or adolescence. Consistent with this, at our 4-year follow-up,¹⁰⁰ we identified a subsample of ADHD probands characterized by early remission (prior to age 12). The early remitters differed from subjects with persistent cases and later remitting cases by having low levels of comorbidity, low familiality, and low psychosocial risk factors.¹⁰⁰ This raises the possibility that differences exist between those subjects who remit early in childhood and those who remit later in adolescence.

Prospective, longitudinal follow-up studies provide compelling evidence for the continuation of ADHD into adulthood in some cases. Yet the issue of how many cases persist is not yet resolved. Prior longitudinal studies found

variable rates (10% to 60%) of persistence of ADHD symptoms into adolescence¹⁰¹⁻¹⁰³ and adulthood.^{22,23} These studies showed that the persistence of ADHD into adulthood included symptoms of inattention, disorganization, distractibility, and impulsiveness along with academic and occupational failure. Curiously, despite this variability in published rates, DSM-IV still asserts that "in most individuals symptoms attenuate during late adolescence and adulthood, although a minority experience the full complement of symptoms of Attention-Deficit/Hyperactivity Disorder into mid-adulthood."^{1(p82)} Moreover, the idea that ADHD remits in adulthood was recently given more credibility by a recent review of ADHD outcome studies.¹⁰⁴ This review fit a mathematical function to the rates of remission reported by ADHD outcome studies. The model predicted an exponential decline in the rate of ADHD with time. It estimated the rate of adult ADHD to range from about 0.8% at age 20 to 0.05% at age 40.¹⁰⁴ Unfortunately, as the authors of the review noted, this conclusion relied heavily on data from a single outcome study that reported on ADHD diagnoses subsequent to age 20. Moreover, as Barkley¹⁰⁵ details, there are major flaws with the paper by Hill and Schoener.¹⁰⁴ Most importantly, early definitions of hyperkinesis, being vague and subjective, tended to diagnose many mild cases that would not meet modern diagnostic criteria. Additionally, the one study that found a very low rate of ADHD persistence²³ excluded children with significant conduct problems. These excluded children are those who are at highest risk for persistence. Surprisingly, other studies using well-defined methodology were excluded by these same investigators.¹⁰⁵ Thus, until more information becomes available, the conclusions of Hill and Schoener should be viewed as tentative.

THE CASE FOR AN ADULT ADHD SYNDROME

In recent years, a large number of adults have been referred for evaluation and treatment of ADHD. Although controversial¹⁰⁶ and novel, this is not at all surprising considering that adult ADHD may be a much more common disorder than previously assumed. Yet, the intense controversy surrounding the diagnosis of adult ADHD continues to be a strong impediment for patients trying to access appropriate care. Although the reasons for this situation are multifactorial and complex, several factors stand out. Concerns have been voiced regarding the paucity of scientific knowledge on adult ADHD, the retrospective nature of the diagnosis in adults, and the fact that the mainstay for its treatment is controlled substances like methylphenidate and dextroamphetamine. Other less-discussed reasons include the limited knowledge of the disorder and its treatment by adult psychiatrists and the limited interest of child psychiatrists in treating these adults.

In a series of studies, Biederman et al.^{48,49} document that referred adults, with a retrospectively defined diagnosis of ADHD with a childhood onset of symptoms that have persisted into adulthood, have high levels of familiarity and psychiatric comorbidity. Compared with age- and gender-matched controls without ADHD, adults with ADHD have significantly higher rates of childhood conduct disorder, adult antisocial personality disorder, alcohol and drug dependence, bipolar and non-bipolar mood disorders, and anxiety disorders. Our group also documented in ADHD adults a pattern of neuropsychological, school, and occupational impairments highly consistent with this disorder.¹⁰⁷ This excellent correspondence in clinical correlates from multiple domains in children and adults with ADHD strongly supports the diagnostic continuity of the disorder from childhood into adulthood. Moreover, persistence of *childhood* ADHD has been associated with familiarity and psychiatric comorbidity with conduct, mood, and anxiety disorders, and these are precisely the hallmarks of the disorder in adults with persistent adult ADHD. In addition, considering the strong association identified in long-term follow-up studies between persistent *childhood* ADHD with Psychoactive Substance Use Disorders (PSUD) and antisocial personality disorder, these findings in adult ADHD (*diagnosed retrospectively*) further strengthens the diagnostic continuity between the pediatric and the adult form of the disorder.

PHARMACOTHERAPY

Stimulants are sympathomimetic drugs structurally similar to endogenous catecholamines (e.g., dopamine and norepinephrine). The most commonly used compounds in this class include methylphenidate, dextroamphetamine, and magnesium pemoline. Methylphenidate and dextroamphetamine are both short-acting compounds, with an onset of action within 30 to 60 minutes and a peak clinical effect usually seen between 1 and 3 hours after administration.

Although there are more than 150 controlled studies of stimulants with more than 5000 children, adolescents, and adults, the vast majority of the studies are limited to latency-age, white boys treated for no longer than 2 months. These studies document the short-term efficacy and safety of stimulants in all age groups but more clearly in latency-age children. Despite the findings on efficacy of the stimulants, studies have also reported consistently that, on average, as many as 30% of ADHD children do not respond to these drugs.¹⁰⁸⁻¹¹⁰ Although methylphenidate is by far the most studied stimulant, the literature provides little evidence of differential response to the various available stimulants. However, some patients may respond preferentially to one or another stimulant.¹¹¹

Although the efficacy of stimulants in ADHD is most clearly documented in latency-age children, a more lim-

ited literature reveals a good response in both preschoolers and adolescents. Studies in preschoolers report improvement in structured tasks as well as mother-child interactions.¹¹²⁻¹¹⁶ Similarly, in adolescents, response has been reported as moderate to robust, with no abuse or tolerance noted.¹¹⁷⁻¹²⁴ In contrast, studies in adults with ADHD report a more variable response ranging from 25% to 78% with an average of 54%.¹²⁵⁻¹³⁰ Potential reasons for this variability in adult ADHD studies include a low average daily dose (0.6 mg/kg), diagnostic imprecision,¹²⁵ differing assessment methodology, and effects of psychiatric comorbidity. The largest response in adults was reported by our group in a recent randomized, controlled study of methylphenidate in patients diagnosed with childhood-onset DSM-III-R ADHD. This investigation used standardized instruments for diagnosis; separate assessments of ADHD, depressive, and anxiety symptoms; and a robust daily dose of 1.0 mg/kg/day.¹³⁰ This study found a marked therapeutic response to methylphenidate treatment over placebo (78% vs. 4%) that appeared to be dose dependent. Also, in this study, response to methylphenidate was independent of gender, psychiatric comorbidity, or family history of psychiatric disorders.

Areas of controversy and concern about stimulant use include growth suppression in children,^{131,132} the development of tics,¹³³ drug abuse,¹³⁴ use in adolescents,¹¹⁸ and symptom rebound.¹³⁵ Although stimulants routinely produce anorexia and weight loss, their effect on growth in height is less certain. While initial reports suggested that there was a persistent stimulant-associated decrease in growth in height in children,^{131,132} other reports have failed to substantiate this finding.^{136,137} Ultimate height appears to be unaffected.¹³⁸ However, there are no studies of the effects of stimulants on growth in children treated continually from childhood through adolescence and young adulthood. Moreover, the literature on stimulant-associated growth deficits did not examine the possibility that growth deficits may represent maturational delays related to ADHD itself (i.e., dysmaturity) rather than to stimulant treatment.

In a recent report using data from a longitudinal study of ADHD children, Spencer et al.¹³⁹ suggested that growth deficits in ADHD children may represent a temporary delay in the tempo of growth but that final height is not compromised. They suggested that this effect is mediated by ADHD and not by stimulant treatment.

Although early reports indicated that children with personal or family histories of tic disorders were at greater risk for developing a tic disorder when exposed to stimulants,¹³³ recent work has increasingly challenged this view.¹⁴⁰⁻¹⁴² Similar uncertainties remain about the abuse potential of stimulants in children with ADHD. Despite the concern that ADHD may increase the risk of drug abuse in adolescents and young adults (or their associates), there are no scientific data that stimulant-treated

ADHD children abuse prescribed medication when appropriately administered and monitored. Moreover, recent work has shown that the most commonly abused substance in adolescents and adults with ADHD is marijuana, not stimulants.¹⁴³

ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) include the tertiary amines amitriptyline and imipramine and the secondary amines desipramine and nortriptyline. The mechanism of action of TCAs in ADHD appears to be due to the blocking effects of these drugs on the reuptake of central nervous system neurotransmitters, especially norepinephrine. However, these agents also have variable effects on pre- and postsynaptic neurotransmitter systems, resulting in differing positive and adverse effect profiles. 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 and geriatric populations.

TCAs, especially imipramine and desipramine, are the second most studied compounds in the pharmacotherapy of ADHD after the stimulants. Twenty-nine studies (18 controlled, 11 open) have evaluated TCAs in 1016 children and adolescents and 63 adults with ADHD. Almost all of these studies (93%) report at least moderate improvement. As with the stimulants, however, the majority of studies included primarily latency-age children. Although most studies of TCAs for the treatment of ADHD were relatively brief, lasting several weeks to several months, a few studies extended up to 2 years. Outcomes in both short- and long-term TCA studies have been equally positive. Despite assertion to the contrary, evidence exists that improvement of ADHD symptoms can be maintained when daily doses of TCAs are titrated upward over time.¹⁴⁴⁻¹⁴⁷ For example, studies using aggressive doses of TCAs reported sustained improvement for up to 1 year with desipramine (> 4 mg/kg)^{145,146} and nortriptyline (2.0 mg/kg).¹⁴⁷ Thus, it could be that the apparent short-lived effects reported in previous studies of TCAs in ADHD children could have been due to the use of relatively low (< 3 mg/kg) daily doses.

In the largest controlled study of a TCA in children, our group reported favorable results with desipramine in 62 clinically referred ADHD children, most of whom had previously failed to respond to psychostimulant treatment.¹⁴⁴ The study was a randomized, placebo-controlled, parallel-design, 6-week clinical trial. Clinically and statistically significant differences in behavioral improvement were found for desipramine over placebo, at an average daily dose of 5 mg/kg. Specifically, 68% of desipramine-treated patients were considered very much or much improved,

compared with only 10% of placebo patients ($p < .001$). Our group obtained similar results in a similarly designed controlled clinical trial of desipramine in 41 adults with ADHD.¹⁴⁸ Desipramine, at an average daily dose of 150 mg (average serum level of 113 mg/mL), was statistically and clinically more effective than placebo. Sixty-eight percent of desipramine-treated patients responded compared with none of the placebo-treated patients ($p < .0001$). Moreover, at the end of the study, the average severity of ADHD symptoms was reduced to below the level required to meet diagnostic criteria in patients receiving desipramine. Taken together, available literature suggests that TCAs are as effective as stimulants in controlling abnormal behaviors associated with ADHD, but may be less effective in improving cognitive impairments.^{149–152}

The potential benefits of TCAs in the treatment of juvenile ADHD have been clouded by rising concerns about their safety stemming from reports of sudden unexplained death in four ADHD children treated with desipramine.¹⁵³ However, the causal link between desipramine and these deaths remains uncertain. A recent report estimated that the magnitude of desipramine-associated risk of sudden death in children may not be much larger than the baseline risk of sudden death in this age group.¹⁵⁴ Moreover, these deaths have been difficult to reconcile with the rather extensive literature evaluating cardiovascular parameters in TCA-exposed patients of all ages and the magnitude of worldwide use of TCAs in all age groups. In most studies of children and adolescents, TCA treatment has been associated with asymptomatic, minor, but statistically significant increases in heart rate and ECG measures of cardiac conduction times consistent with the adult literature.¹⁵⁵ Because of this uncertainty, prudence mandates that until more is known, TCAs should be used as second-line treatments to stimulants for ADHD in juveniles and only after carefully weighing the risks and benefits of treating or not treating an affected child.

Bupropion hydrochloride is a novel aminoketone antidepressant related to the phenylisopropylamines, but pharmacologically distinct from available antidepressants.¹⁵⁶ Although bupropion possesses both indirect dopamine and noradrenergic agonist effects, its specific site or mechanism of action remains unknown. Bupropion has been reported to be superior to placebo in reducing ADHD symptoms in two controlled studies in children, including a four-center multisite study ($N = 72$).^{156–158} Bupropion also reduced ADHD symptoms in a comparison with methylphenidate ($N = 15$).¹⁵⁹ In an open study of 19 adults treated with an average of 360 mg of bupropion for 6 to 8 weeks, Wender and Reimherr¹⁶⁰ reported a moderate-to-marked response in 74% of adults, with sustained improvement at 1 year noted in 10 subjects. The response of ADHD to bupropion appears to be rapid and sustained. Dosing of bupropion is similar for ADHD to that recommended for de-

pression, with a suggested maximum dose of 450 mg/day in adults, divided into three daily doses.

Preliminary studies suggest that monoamine oxidase inhibitors (MAOIs) are effective in juvenile and adult ADHD. In a recent open study,¹⁶¹ selegiline (*L*-deprenyl, a specific MAOI-B at low dose) was evaluated in 29 children with both ADHD and tics. Results showed that ADHD symptoms improved in 90% of the children with no serious adverse effects and only two patients showing an exacerbation of tics. In a 12-week double-blind, crossover trial, using two MAOIs in 14 hyperactive children, Zametkin et al.¹⁶² reported significant and rapid reduction in ADHD symptoms with minimal adverse effects. These investigators used clorgiline (a specific MAOI-A) and tranylcypromine sulfate (a mixed MAOI-A/B). In open studies in adult ADHD, moderate improvements were reported in studies with pargyline and selegiline (selective MAOI-Bs) with associated adverse effects.^{163,164} A major limitation to the use of MAOIs is the potential for hypertensive crisis (treatable with phentolamine) associated with dietetic transgressions (tyramine-containing foods, i.e., most cheeses) and drug interactions (pressor amines, most cold medicines, and amphetamines).

Serotonin selective reuptake inhibitors (SSRIs) have not been systematically evaluated in the treatment of ADHD. Although a small open study¹⁶⁵ suggested that fluoxetine may be beneficial in the treatment of children with ADHD, extensive clinical experience at our center with children, adolescents, and adults does not support the usefulness of these compounds in the treatment of core ADHD symptoms. Recently, two open studies of venlafaxine in ADHD adults with prominent mood symptoms reported preliminary results of moderate improvement; however, 11 of 34 adults could not tolerate the adverse effects.^{166,167}

Clonidine is an imidazoline derivative with α -adrenergic agonist properties that has been primarily used in the treatment of hypertension. Beneficial effects of clonidine in the treatment of childhood ADHD have been reported in a total of 122 patients in four studies: one open study,¹⁶⁸ one retrospective review,¹⁶⁹ and two controlled studies^{170,171} with daily doses of up to 4 to 5 μ g/kg (average dose = 0.2 mg/day). All studies reported a positive behavioral response, with 50%–70% of subjects displaying at least moderate improvement; however, beneficial effects on cognition were less clear. There is one open study ($N = 13$) of a longer acting, more selective α_2A agonist, guanfacine, in children and adolescents with ADHD. Beneficial effects on hyperactive behaviors and attentional abilities were reported.¹⁷²

IMPACT OF PSYCHIATRIC COMORBIDITY IN THE PHARMACOTHERAPY OF ADHD

Several controlled studies reported improvement in ADHD and aggressive symptoms in ADHD subjects

treated with stimulants.^{173–190} Stimulants suppressed physical and nonphysical aggression in these children both at home and in school in a dose-dependent fashion.^{173,183,184} Stimulants also reduced negative social interactions¹⁸⁰ and covert antisocial behavior (stealing, destroying property, but not cheating).¹⁸⁶ Four studies of antidepressants for ADHD children with comorbid conduct disorder also indicate improvement of ADHD^{147,177,191,192} and aggressive symptoms in these subjects.^{177,191}

Although stimulants historically have been contraindicated in the treatment of patients with tics and ADHD, a recent literature has challenged the absolute contraindication of stimulants in patients with ADHD and tics. Although a recent controlled study, comprising 49 subjects, reported no exacerbation of tics,^{142,193,194} previous studies report worsening of tics in 31% (95/306 patients, N = 10 studies) of comorbid ADHD/ tic patients.^{141,195–203} While many children with this comorbidity respond to stimulants without worsening of tics, until more is known, caution should be exercised in the use of stimulants in this population.

Little is known about the pharmacotherapy of children, adolescents, and adults with ADHD and comorbid anxiety or mood disorders. Of nine stimulant studies in ADHD children with comorbid anxiety or depression, the majority of studies reported a diminished response to stimulants in these patients.^{179,181,204–207} Since stimulants are thought to be anxiogenic and depressogenic, caution should be used in the treatment of individuals with ADHD and comorbid anxiety and mood disorders. In contrast, in the TCA studies that examined the effect of medication on comorbid depressive symptoms, TCA treatment improved both ADHD and depressive symptoms.^{192,208}

Despite increasing recognition of the co-occurrence of ADHD and bipolarity,^{42,43} little is known about the pharmacotherapy of the combined condition. Considering the potential for activation of individuals with ADHD and mania with TCAs and stimulants, caution should be used in treating ADHD and mania with stimulants and antidepressants in the absence of mood stabilizers.²⁰⁹

COMBINED PHARMACOTHERAPY

Although in clinical practice many ADHD patients receive multiple treatments, the literature on combined pharmacotherapy is very sparse, not permitting the development of clear therapeutic guidelines. In contrast to polypharmacy, rational combined pharmacologic 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 of the rational use of combined treatment include the use of an antidepressant plus a stimulant for ADHD and comorbid depression, the use of clonidine to ameliorate stimulant-

induced insomnia, and the use of a mood stabilizer plus an anti-ADHD agent to treat ADHD comorbid with bipolar disorder.²¹⁰

TREATMENT-REFRACTORY PATIENTS

Despite the availability of various agents for ADHD, there appear to be a number of individuals who either do not respond to or are intolerant of the adverse effects of medications used to treat their ADHD. In managing apparent medication nonresponders, several therapeutic strategies are available. If adverse psychiatric effects develop concurrent with a poor medication response, alternate treatments should be pursued. Severe psychiatric symptoms that emerge during the acute phase can be problematic, irrespective of the efficacy of the medications for ADHD. These symptoms may require reconsideration of the diagnosis of ADHD and careful reassessment of the presence of comorbid disorders. If reduction of dose or change in preparation (i.e., regular vs. slow-release stimulants) does not resolve the problem, consideration should be given to alternative treatments. Concurrent non-pharmacologic interventions such as behavioral or cognitive therapies may assist with symptom reduction.

CONCLUSIONS

There is increasing recognition that ADHD is a heterogeneous disorder with considerable and varied comorbidity that persists in a substantial number of cases into adult years. The scope of comorbidity has expanded to include not only conduct and oppositional defiant disorder but mood and anxiety disorders as well. If not recognized and attended to, the combination of comorbid symptoms and ADHD may lead to high morbidity and disability with poor long-term prognosis. Pharmacologic treatment leads to improvement not only in core behavioral symptoms of ADHD but also in associated impairments including cognition, social skills, and family function. The armament of anti-ADHD compounds includes not only the stimulants, but also several antidepressants, and other medications such as clonidine and guanfacine. Effective pharmacologic treatments for ADHD seem to share noradrenergic and dopaminergic mechanisms of action. Stimulant medications continue to be the first-line drug of choice for uncomplicated ADHD in individuals of all ages, with TCAs and bupropion recommended for nonresponders or patients with concurrent psychiatric disorders. Current clinical experience suggests that multiple agents may be necessary in the successful treatment of some complex ADHD patients who have partial responses or psychiatric comorbidity.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), clonidine (Catapres), desipramine (Norpramin and others), dextroam-

phetamine (Dexedrine and others), fluoxetine (Prozac), guanfacine (Tenex), imipramine (Tofranil and others), pemoline (Cylert), methylphenidate (Ritalin), nortriptyline (Pamelor and others), pargyline (Eutonyl), phentolamine (Regitine), selegiline (Eldepryl), tranlycypromine (Parnate), venlafaxine (Effexor).

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