

# Adults With Attention-Deficit/Hyperactivity Disorder: A Controversial Diagnosis

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The diagnosis of attention-deficit/hyperactivity disorder (ADHD) in adults has remained controversial. This paper reviews the empirical evidence to date as to whether the diagnosis of ADHD in adults is valid and consistent with the childhood syndrome. Evidence of descriptive, divergent, predictive, and concurrent validity were examined. The available literature provides evidence that adult ADHD can be reliably diagnosed and that the diagnosis confers considerable power to forecast complications and treatment response. Studies of genetic transmission, specific treatment responses, and abnormalities in brain structure and function in affected individuals are also consistent with studies in childhood ADHD. There is converging evidence that adult ADHD is a not rare, valid clinical diagnosis. In addition, studies suggest that adult and child patients with ADHD may share a similar treatment-responsive, underlying neurobiological substrate.

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**A**ttention-deficit/hyperactivity disorder (ADHD) is a common disorder that affects at least 5% of children<sup>1,2</sup> and is associated with cognitive, social, and academic impairments. Follow-up studies show ADHD persisting into adulthood in 10% to 60% of childhood-onset cases,<sup>3-6</sup> suggesting that adult ADHD may be a relatively common disorder that may be underidentified in adult psychiatry clinics.<sup>7</sup>

Despite increasing media attention to adult ADHD<sup>8</sup> and its potential public health relevance, the diagnosis has remained controversial. In an influential editorial, Shaffer<sup>9</sup> noted several reasons for skepticism about adult ADHD. The first is practical: because the diagnosis requires childhood onset, adult ADHD requires the recollection of distant childhood events, and such recollections may not be accurate. In addition, because the symptoms of other disorders could lead to the misdiagnosis of ADHD, psychiatric comorbidity complicates the diagnosis of ADHD in adults.<sup>9,10</sup> Apparent comorbidity may indicate that these

adults truly have another disorder, not ADHD. Also, Shaffer argued that the potential efficacy of stimulant treatment for adult ADHD has drawn attention to the disorder, but that the published literature "does not present overwhelming evidence of efficacy." However, recently published controlled studies report a robust response to stimulants<sup>11,12</sup> as well as nonstimulants<sup>13</sup> (see below).

A common cause of skepticism among clinicians is that ADHD in adults is frequently a "self-diagnosed" condition. Clinicians are skeptical about self-diagnoses since troubled individuals may attribute their problems and failures to a psychiatric syndrome that has been discussed in the media. However, self-diagnosis may also indicate a problem with recognition of a valid diagnostic entity by the mental health system. Clinicians who treat adults have not been sensitized to the existence of adult ADHD, whereas clinicians who treat children do not usually follow-up patients into adulthood.

## WHAT ACCOUNTS FOR THE APPARENT DIAGNOSTIC AMBIGUITY OF ADULT ADHD?

The apparent diagnostic ambiguity has been, in part, due to a theoretical debate about the developmental course of the disorder. As reviewed by Cantwell,<sup>14</sup> early researchers suggested that ADHD would disappear with maturation, usually by adolescence. Other researchers postulated that the full syndrome or at least its core symptoms persist into adulthood along with failure, demoralization, and other sequelae of ADHD. A third model conceived of

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ADHD as a precursor of other psychopathologic conditions of later life, mainly antisocial disorders.

Follow-up studies of ADHD children provide evidence supporting all three lines of thought. Although 50% of ADHD children will no longer meet criteria for the disorder by adolescence, the persistence of the disorder in others significantly increases their risk for antisocial and substance use disorders.<sup>3-5</sup> Children with ADHD followed into adulthood have high levels of school failure, poor work histories, poor social interactions, and low self-esteem.<sup>15</sup> Current research strongly indicates that it is associated with high levels of psychiatric morbidity and dysfunction persisting into adulthood in affected individuals.

Another source of confusion pertains to the various approaches to diagnosis. Three different approaches have been taken in making this diagnosis,<sup>16</sup> as typified by the DSM-IV category of ADHD "in partial remission," DSM-III-R, and the Utah criteria<sup>17</sup> or the Brown Attention-Activation Disorder Scale (BAADS).<sup>18</sup> The DSM-IV category of ADHD "in partial remission" includes adults who had the full syndrome as children and a partial syndrome as adults. DSM-III-R did not provide specific rules for diagnosing adult ADHD but did not exclude adults as long as they continue to fulfill the childhood diagnostic requirements. Published guidelines to diagnosing adult ADHD have suggested that ADHD symptomatology should describe a chronic course from childhood to adulthood.<sup>19</sup> For example, if an adult subject, aged 28 years, reports distractibility during the past month, but never in childhood, this distractibility would not be counted toward the six symptoms needed to categorize an adult as currently ill.

In contrast to the traditional symptom clusters of inattention, hyperactivity, and impulsivity in DSM, the Utah criteria included additional symptoms of affective lability, hot or explosive temper, stress intolerance, impaired interpersonal relationships, and a high rate of "dysphoric disorder."<sup>17</sup> Although developmental changes in the expression of psychiatric disorders are to be expected, if we generate additional criteria for adults, we cannot be certain that the ADHD we are assessing in adults is consistent with the childhood condition (especially if the additional criteria include symptoms observed in other psychiatric disorders).

### IS ADULT ADHD A VALID DIAGNOSIS?

As articulated by Spitzer and Williams,<sup>20</sup> the validity of a clinical diagnostic entity requires documentation of characteristic signs and symptoms (descriptive validity); evidence for a specific course, outcome, and treatment response (predictive validity); as well as evidence regarding etiology and pathophysiology (concurrent validity). In a recent report, we reviewed the available literature for empirical studies of adult ADHD with childhood onset for evidence of diagnostic validity.<sup>21</sup> We identified 56 studies of adult ADHD from 1969 to 1993. There were 32 case-

controlled retrospective studies, 11 family-genetic studies, and 13 prospective follow-up studies of six cohorts. In all, they provided information on over 1700 adults with a history of ADHD; in 663 of these, ADHD persisted into adulthood.

### DO ADULTS EXHIBIT A SYNDROME CONSISTENT WITH CHILDHOOD ADHD (DESCRIPTIVE VALIDITY)?

Many of the initial, retrospective studies of adult ADHD were motivated by clinical observations of inattention, impulsivity, and restlessness in adults who had referred themselves for treatment. These ADHD adults showed the symptoms and characteristic impairments associated with ADHD in childhood. For example, Borland and Heckman<sup>22</sup> reported that 50% of adults with childhood ADHD had a full or partial syndrome characterized by restlessness, impulsivity, and difficulty concentrating. In contrast, they found this syndrome in only 5% of their non-ADHD siblings. Further, the subgroup of adults with persistent ADHD had higher rates of psychosocial dysfunction as manifested by lower socioeconomic status and shorter job tenure. This psychosocial disability occurred in spite of normal intelligence and the same level of education as the non-ADHD siblings. The ADHD adults described their work difficulties and frequent job changes as stemming from dissatisfaction, easy frustration, boredom, and impulsiveness. Morrison<sup>23,24</sup> reported similar findings and noted that adults with ADHD vividly recalled a childhood history of inability to concentrate, multiple failures, disapproval, and demoralization. These descriptions, obtained from the adults, were corroborated by information provided by their parents.

Additional evidence for descriptive validity comes from treatment studies of ADHD adults. Investigators noted that participating subjects reliably met criteria for adult ADHD with childhood onset. These adult self-reports were confirmed by parents or other relatives.<sup>11,17,25-28</sup> In addition to the criteria required for diagnosis, these adults also had associated clinical features commonly found in childhood ADHD: poor academic performance (despite adequate intellectual abilities); stubbornness; chronic conflicts in social relations with peers, spouses, and authorities; absenteeism from work and frequent job changes; and poor frustration tolerance. Moreover, these ADHD adults did have high rates of comorbid psychiatric disorders consistent with child and adolescent ADHD samples, including substance abuse (27%–46%), antisocial personality disorders (12%–27%), and anxiety disorders (50%).

Recently, Murphy and Barkley<sup>29</sup> reported on the prevalence of self-reported DSM-IV ADHD symptoms in a large (N = 720) population of normal adults by soliciting volunteers from applicants for driver license renewal. These normal adults reported current and past symptoms of ADHD

at rates consistent with previous estimates (4.7%); however, the rates of symptom endorsement *decreased* with advancing age. Using the same diagnostic criteria as used for children (> 6/9 symptoms of inattention or hyperactivity/impulsivity) placed qualifying adults as 99+% deviant from peers as opposed to the 93% cutoff defined for children. In addition, rates of endorsed current and past symptoms both correlated with poorer educational and occupational levels in this normal population. Murphy and Barkley interpreted the findings as suggesting that the present criteria are too restrictive for adults and would miss adults with developmentally impaired attention. On the other hand, this study does suggest that the current criteria for adult ADHD are not overly inclusive and that self reports of ADHD become less rather than more common with age.

An area of discrepancy between adult and pediatric samples of ADHD is the differing proportion of males as opposed to females diagnosed. The male preponderance in pediatric samples of ADHD subjects<sup>3,4,30</sup> appears to be less characteristic of adult ADHD samples.<sup>11,13,17,25,27-29,31</sup> One proposed explanation for this discrepancy is that compared with male ADHD subjects, female ADHD subjects are less likely to be severely conduct disordered.<sup>26,31-33</sup> Thus, lower levels of serious behavioral disturbance in girls could have led to gender referral biases that may explain the underrepresentation of girls in pediatric samples of ADHD children.<sup>34,35</sup>

#### **DO ADULTS WITH ADHD HAVE SIMILAR COGNITIVE DEFICITS AND HISTORIES OF SCHOOL FAILURE AS CHILDREN WITH ADHD?**

Neuropsychological performance is not diagnostic of ADHD, but it is an associated clinical feature. Cognitive deficits, particularly impairments in attention and executive functions, are hypothesized to be a core part of ADHD.<sup>36</sup> This pattern of deficits is similar to that found in adults with frontal lobe damage and thus has generally supported the hypothesis that ADHD may be a brain disorder primarily affecting the frontal cortex or the regions projecting to frontal cortex.<sup>37,38</sup> Cognitive deficits and related impairments such as academic underachievement, placement in special classes, need for tutoring, and learning disabilities plague ADHD children throughout childhood and adolescence, creating fertile soil for chronic psychological and social disability in adulthood.<sup>4,28,39,40</sup> Measures of cognitive performance are especially useful in adult ADHD because they do not depend on self-report.

Several studies of childhood ADHD have reported that the underlying neuropsychological deficits endure into adolescence.<sup>41,42</sup> Recently, investigations have focused on neuropsychological impairments in ADHD adults. In a follow-up study, Klein and Mannuzza<sup>43</sup> found that ADHD adults scored worse on standardized achievement tests af-

ter controlling for IQ. Biederman et al.<sup>19</sup> found significantly higher rates of repeated grades, tutoring, placement in special classes, and reading disability in ADHD adults compared with non-ADHD comparisons. The ADHD adults also had lower scores on subscales of the Wide Range Achievement Test (arithmetic and reading scores) and the Wechsler Adult Intelligence Scale-Revised (vocabulary, block design, digit symbol, and estimated "freedom-from-distractibility" IQ).

In a recent study of the neuropsychology of unmedicated ADHD adults, Seidman<sup>44</sup> found that irrespective of age, gender, psychiatric comorbidity, or presence of learning disability, ADHD adults were significantly impaired on auditory vigilance, executive components of verbal learning, and arithmetic ability when compared with controls. In the absence of learning disabilities, ADHD adults were more likely than controls to have repeated at least one grade in school, to have required placement in special classes, to have received extra help or tutoring in school, and to have a lower occupational attainment in adult life than controls. These results support the study hypothesis that ADHD in adults is associated with executive dysfunctions and support the validity of this syndrome in adulthood.

#### **DO ADULTS WITH ADHD HAVE SIMILAR PATTERNS OF PSYCHIATRIC COMORBIDITY AS CHILDREN WITH ADHD?**

Research suggests that high levels of conduct, depressive, and anxiety disorders in ADHD children do not represent spurious comorbidity due to referral and screening artifacts.<sup>45,46</sup> For example, epidemiologic studies report comorbidity in unselected general population samples.<sup>1,2</sup> Our family studies of comorbidity also dispute the notion that artifacts cause comorbidity; instead, they assign a causal role to etiologic relationships among disorders.<sup>47-55</sup> Although the systematic evaluation of patterns of comorbidity in ADHD adults has been limited, the available literature is consistent with findings reported in ADHD children.

The early studies of adult ADHD, employing nonblind, clinical assessments for diagnoses, found consistent comorbidity in their samples. Borland and Heckman<sup>22</sup> reported high rates of antisocial personality, anxiety, and depressive disorders among adults with childhood-only ADHD and with childhood-onset adult ADHD. Morrison<sup>23,24</sup> also reported that adults with childhood-onset ADHD had higher rates of antisocial personality disorder and alcoholism. ADHD adults in treatment studies had high rates of substance abuse (27%–46%), antisocial personality disorders (12%–27%), and anxiety disorders (50%). More recently, Biederman et al.<sup>19,31</sup> reported that adults with ADHD had high rates of antisocial, mood, and anxiety disorders.

Several studies of adults with substance abuse disorders found that compared to adults with substance use disorders alone, adults with substance use disorders who also had a history of childhood ADHD showed characteristics frequently encountered among ADHD children and adolescents: social maladjustment, immaturity, personality disturbance, lower social assets, less ego capacity to regulate drives, impulse control deficits, and school failure.<sup>56-59</sup> These ADHD-type problems persisted into adulthood and led to poor academic and occupational achievement, high rates of separation and divorce, and social impairment.

### **IS ADULT ADHD SECONDARY TO ANOTHER PSYCHIATRIC DIAGNOSIS?**

The high levels of psychiatric comorbidity in adults with ADHD are consistent with findings reported in ADHD children and adolescents. While this consistent pattern of comorbidity strengthens evidence for descriptive validity, skeptics may raise the question of whether the adult form is merely secondary to these (or other) psychiatric disorders. If so, it may be that childhood ADHD is a neurodevelopmental precursor to other disorders; that the childhood symptoms of inattention, impulsivity, and hyperactivity do not represent a distinct disorder with a predictable course but are only a prodrome to a more typical disorder, such as depression, whose characteristic features may not fully emerge until adulthood.

If adult ADHD is secondary to other disorders, it should rarely be present without a comorbid psychiatric disorder. This was not the case in our literature review. In these studies, approximately 40% of adults with ADHD did not have a comorbid psychiatric disorder. For example, in the study by Biederman et al.,<sup>19</sup> 23% of the adults with ADHD had no adult psychiatric disorder yet met full DSM-III-R criteria for ADHD in childhood and had the characteristic symptoms of inattentiveness, distractibility, and impulsivity associated with ADHD. Compared with findings in normal control adults, the condition of uncomplicated ADHD was also associated with significant impairment, consistent with the status of being a meaningful psychiatric disorder. These impairments were evidenced by poorer functioning on the Global Assessment of Functioning scale and poorer cognitive performance, as indicated by histories of school failure and impaired performance on neuropsychological measures.<sup>19</sup>

### **WHAT ARE THE FINDINGS IN CONTROLLED PROSPECTIVE STUDIES OF ADHD CHILDREN?**

Perhaps the most compelling evidence for the validity of adult ADHD derives from prospective, longitudinal follow-up studies that examined the continuity of childhood ADHD symptoms into adulthood. These controlled studies clearly documented the reliability of the diagnosis

of ADHD in adults using blind assessments.<sup>3-5,60</sup> Persistent symptoms of inattention, disorganization, distractibility, and impulsiveness were associated with psychosocial dysfunction, school related problems, work failure, and psychiatric comorbidity (especially substance abuse and antisocial personality).<sup>43,61-63</sup> Weiss et al.<sup>64</sup> reported that employers of these ADHD adults said they had poor levels of work performance, impairment in task completion, lack of independent skills, and poor relationships with supervisors.

### **IS ADULT ADHD RARE?**

Skepticism about adult ADHD also derives from the belief that ADHD should be rare in adulthood. In controlled longitudinal studies, Weiss et al.<sup>3,60</sup> and Gittelman et al.<sup>4,5</sup> found that 31% to 44% of young adults with childhood-onset ADHD had the full syndrome and 9% to 25% had a partial syndrome with at least one disabling symptom. In a further follow-up of their sample, Gittelman and colleagues<sup>6</sup> recently reported a rate of persistence of ADHD symptoms in adulthood (mean age = 26 years) that, although greater than that for controls (11% vs. 1%), was somewhat discrepant with higher rates in earlier reports.<sup>4,5</sup>

The putative scarcity of adult ADHD was given credibility by Hill and Schoener,<sup>65</sup> who reported on a meta-analysis of ADHD outcome studies. However, Barkley has addressed seven methodologic flaws with this analysis.<sup>66</sup> For example, early definitions of hyperkinesis were vague and subjective, tending to diagnose mild cases that would not meet modern diagnostic criteria. While the computations made by Hill and Schoener relied heavily on data from a single outcome study, other studies using well-defined methodology were not consistent with Hill and Schoener's model. For example, one of the other studies reported that two thirds of ADHD children had disabling symptoms of ADHD in young adulthood.<sup>67</sup>

There are other reasons to believe that ADHD is not rare in adulthood. Family studies have estimated that an average of 3.8% of fathers and 2.4% of mothers of *non-ADHD* comparisons had childhood-onset ADHD.<sup>30,68-70</sup> These data are consistent with a report by Murphy and Barkley,<sup>29</sup> who used self-report rating scales to diagnose ADHD in 720 adults applying for or renewing their drivers' licenses in the state of Massachusetts. In this sample, 4.7% of adults met DSM-IV criteria for ADHD. These ADHD cases met full DSM-IV criteria currently and in childhood (based on retrospective reports).

### **WHAT ARE THE RELIABILITY AND VALIDITY OF THE RETROSPECTIVE DIAGNOSIS OF ADULT ADHD?**

Another source of uncertainty pertains to the retrospective nature of the assessment of a childhood-onset disorder

such as ADHD in adults. However, retrospective assessments of psychopathology are the rule rather than the exception in adult psychiatry, and ADHD is a chronic, disabling disorder that is not likely to be forgotten. Several studies have demonstrated that rating scales, self-endorsed by adults with ADHD, correlate both with the Parental Rating Scale<sup>71</sup> and methylphenidate response.<sup>71,72</sup> Moreover, the other studies we reviewed in this paper indicate that a reliable and valid retrospective diagnosis of childhood-onset ADHD can be made. The clinical and cognitive characteristics of retrospectively diagnosed adults with ADHD revealed a pattern of demographic, psychosocial, psychiatric, and cognitive features identical to those of ADHD children.<sup>19,73</sup> Furthermore, Zametkin et al.<sup>74</sup> showed that even never-diagnosed, never-treated ADHD parents of children with ADHD had evidence of PET-assessed brain dysfunction during attentional tasks (see below). It is highly unlikely that this pattern of results could be due to the psychological consequences of living with an ADHD child.

#### **WHAT ARE THE SPECIFIC COURSE, OUTCOME, AND TREATMENT RESPONSE OF ADULT ADHD (PREDICTIVE VALIDITY)?**

Ideally, longitudinal studies of adults would show that an adult diagnosis predicts future outcome. Unfortunately, no long-term outcome studies of adults are available. However, there are studies that show the predictive validity of adult ADHD in the context of psychopharmacologic treatment trials.

We recently reported on three controlled studies of adult ADHD<sup>11,13,83</sup> using similar methodology. Subjects were outpatient ADHD adults of both sexes between 18 and 60 years of age. Diagnoses were established using standardized instruments and confirmed by clinical interview. All subjects met full criteria for a DSM-III-R diagnosis of ADHD with at least 8 of 14 symptoms (DSM-III-R) and an onset of the clinical picture in childhood by the age of 7 years. In all cases, the disorder was continuous until the time of assessment and associated with significant distress and disability. Careful attention was paid to comorbidity with separate assessments of ADHD, depressive, and anxiety symptoms using standardized instruments. Subjects were not excluded with psychiatric comorbidity unless they were judged to have clinically unstable psychiatric conditions (i.e., suicidal behaviors, psychosis, current [within the past 6 months] drug or alcohol abuse or dependence) or currently used psychotropics.

#### **PHARMACOTHERAPY OF ADULT ADHD**

##### **Methylphenidate in the Treatment of Adult ADHD**

Stimulant drugs, the mainstay treatment of childhood ADHD, have been evaluated previously in the treatment of

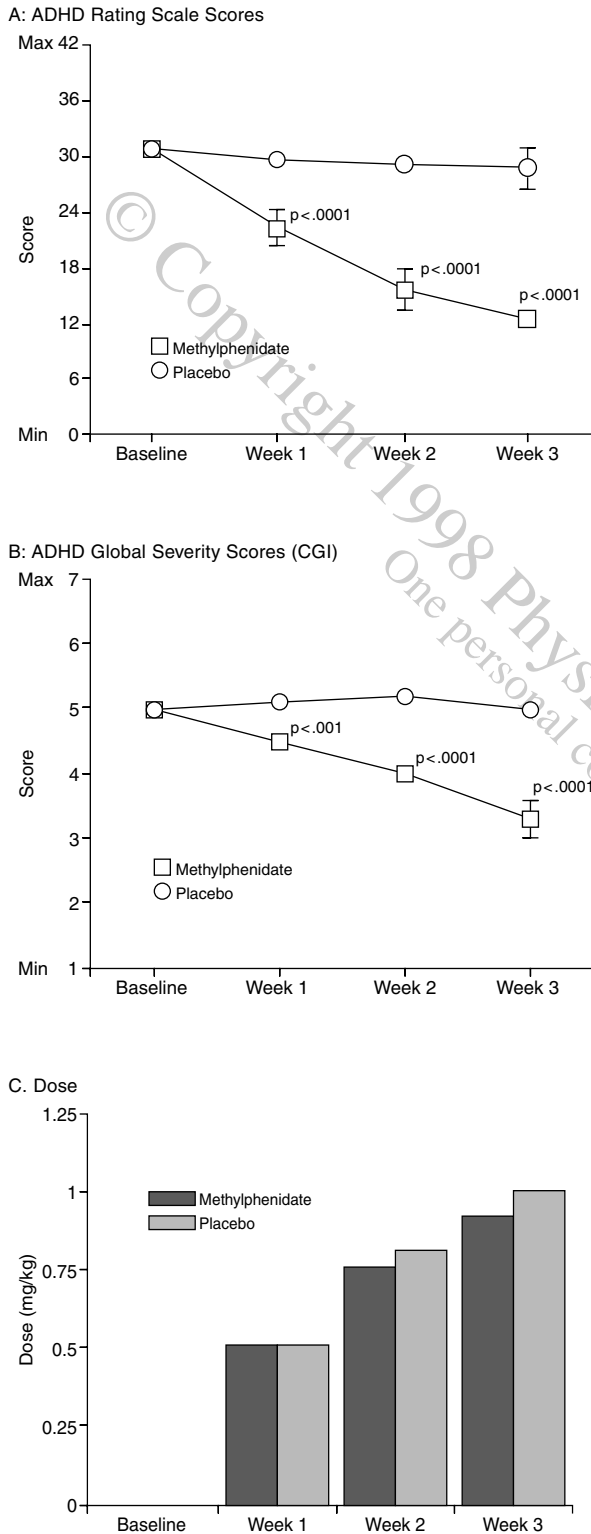
adults with ADHD. Of the five previous controlled studies evaluating the efficacy of stimulants (methylphenidate and pemoline) in adults with ADHD, the levels of response ranged from 25%<sup>27</sup> to 73%.<sup>25</sup> These response rates are more inconsistent than the 70% rate of response among children and adolescents.<sup>75</sup> This discrepancy could be due to various methodological differences between the studies such as diagnostic methods, sample characteristics, psychiatric comorbidity, and differences in daily doses. For example, the estimated mean daily weight-corrected dose of methylphenidate in the available studies of adult ADHD patients was 0.6 mg/kg/day. Recently, we reported on a treatment study by our group<sup>11</sup> of adults with ADHD, which employed an average daily dose of methylphenidate of 1.0 mg/kg, consistent with that commonly used in the treatment of children with this disorder.

We conducted a randomized, placebo-controlled crossover study of methylphenidate in 23 adult patients with DSM-III-R ADHD.<sup>11</sup> Each patient participated in a balanced 7-week, double-blind, placebo-controlled, crossover study design. The study consisted of two 3-week treatment periods with 1 week of washout (no drug) in between. Medication (methylphenidate or placebo) was titrated from an initial, t.i.d. dose of 0.5 mg/kg/day at Week 1 to 0.75 mg/kg/day at Week 2 to 1.0 mg/kg/day at Week 3, as tolerated.

Of 25 subjects enrolled in the study, 23 (92%) completed it. The one man and one woman who dropped out were both taking methylphenidate. One had an episode of chest pain in the third week of the trial while on a dose of 1 mg/kg/day of methylphenidate. Although dropped from the study, he elected to have further treatment with methylphenidate after consultation with his internist. The second patient dropped out in the first week because of agitation, irritability, and general unease. The final sample consisted of 13 women and 10 men who ranged in age from 19 to 56 years (mean  $\pm$  SE = 40  $\pm$  2 years). Only one subject had been diagnosed in childhood with ADHD and none had been previously treated. Seventy-four percent (N = 17) of ADHD subjects had at least one past comorbid psychiatric disorder, and for 59% (13/22), the comorbid disorder was current. The average number of comorbid diagnoses was 2.6  $\pm$  0.3 per subject. Baseline ratings of depression (Hamilton Rating Scale for Depression [HAM-D] = 5.6  $\pm$  1.1 and Beck Depression Inventory = 8.6  $\pm$  1.6) and anxiety (HAM-A = 5.7  $\pm$  1.0) symptoms were relatively low. On the basis of standard cutoff points for moderate severity on ratings of depression (HAM-D > 16; Beck Depression Inventory > 19) and anxiety (HAM-A > 21), only 9% of subjects had scores of depression or anxiety above those cutoff points.

While methylphenidate treatment was more effective than placebo after the first week of treatment, improvement was increasingly robust in subsequent weeks with increases in daily doses (Figure 1). There was a very sig-

**Figure 1. ADHD Rating Scale and Global Severity Scores by Week and Dose in 23 Adults\***



\*Adapted from reference 11, with permission.

nificant drug by time interaction for ADHD symptoms ( $p = .0001$ ) as well as significant main effects of drug (methylphenidate or placebo,  $p = .0001$ ) and time (Weeks 0, 1, 2, 3,  $p = .0002$ ). In addition, there were no significant order effects (methylphenidate first vs. placebo first). Our analyses of the ADHD severity score produced a similar pattern of results.

In contrast to the significant findings for ADHD, none were found for depression or anxiety by any of the study measures. To evaluate further the absolute rate of improvement in this sample, we analyzed end of treatment results using our preestablished definition of improvement, defined as the attainment of a score of 2 or better (much or very much improved) on the Clinical Global Improvement (CGI) scale and a reduction of at least 30% in individual rating scales. Because of the scarcity of subjects with severe depressive or anxiety pictures, we could not evaluate the impact of treatment on these domains by this method of comparison. Seventy-eight percent (18/23) of patients had meaningful improvement in ADHD symptoms while taking methylphenidate compared with only 4% (1/23) taking placebo ( $p < .0001$ ). Further analysis showed highly significant differences between methylphenidate and placebo for reduction of each of the 14 symptoms of ADHD ( $p < .001$ ).

**Desipramine in the Treatment of Adult ADHD**

To follow up on our studies showing the efficacy of desipramine in treating symptoms of ADHD in ADHD children, we completed a double-blind, parallel clinical trial of desipramine in 41 adults with ADHD.<sup>13</sup> Within the past two decades, the tricyclic antidepressants (TCAs) have been used increasingly as alternative or adjunctive treatments to the stimulants for ADHD in children and adolescents.<sup>76-81</sup> While stimulants are effective for approximately 70% of individuals with ADHD, alternative treatments are necessary for the remaining 30%. In addition, TCAs may be particularly helpful for ADHD adults with concurrent anxiety and depressive symptoms for which the TCAs have been extensively employed<sup>82</sup> and for adults in whom the use of controlled substances would be problematic.

Thus, we conducted a randomized, 6-week, placebo-controlled, parallel-design study of desipramine in 48 adult patients with DSM-III-R ADHD at a target desipramine dose of 200 mg/day.<sup>13</sup> The study consisted of one 6-week treatment period in which subjects received either placebo or desipramine (parallel design). They were rated on symptomatology at baseline and subsequently at 2-week intervals. We found a significant reduction in ADHD symptomatology over the 6 weeks for desipramine-treated but not placebo-treated patients ( $z = 6.9, p < .001$ ). The response rate at the end of the protocol was 68% for the desipramine group and 0% for the placebo group ( $p < .001$ ).

### Tomoxetine in the Treatment of Adult ADHD

Another potentially useful medication for the treatment of adult ADHD is the experimental compound tomoxetine. Tomoxetine has a novel cyclic structure that is dissimilar to that in all other available psychotropics. It has a selective high affinity for noradrenergic function and little affinity for other neurotransmitter systems; it therefore has fewer side effects than other noradrenergic modulators such as the available antidepressants. Tomoxetine has been subject to extensive preclinical and clinical testing. Because of its high noradrenergic activity and its modest rate of side effects (including limited cardiac effects and the absence of abuse potential), we believe that tomoxetine offers potential benefit for the treatment of adults with ADHD.

We conducted a 7-week, double-blind placebo-controlled crossover study of tomoxetine using the same assessment methodology for our other treatment studies of adult ADHD.<sup>83</sup> Treatment with tomoxetine at an average oral daily dose of 76 mg/day was consistently more effective than placebo. The overall response rate for ADHD symptoms was clinically and statistically higher during tomoxetine treatment than during placebo (53% vs. 10.5%;  $p < .05$ ). There was a highly significant ( $p = .001$ ) reduction of ADHD symptoms over time for the tomoxetine group, but not for the placebo group, that was robust enough to be detectable in a parallel groups comparison during the first 3 weeks of the protocol ( $p = .002$ ). This preliminary study has shown that tomoxetine significantly improved ADHD symptoms and was well tolerated. These promising results provide support for a further study of tomoxetine employing robust dosage and an extended period of treatment in a parallel design.

### Summary of Pharmacotherapy Trials of Adult ADHD

While medication responses may be nonspecific, the high level of positive response in these studies indicates that the adult form of the ADHD may also respond to the same stimulant and nonstimulant treatments as used in children with ADHD. These adults, diagnosed retrospectively with ADHD, showed a high rate of response of their self-reported attentional symptoms to standard treatments. These findings provide guidelines for clinical care and support the predictive validity of adult ADHD.

### WHAT IS THE EVIDENCE REGARDING THE ETIOLOGY AND PATHOPHYSIOLOGY OF ADULT ADHD (CONCURRENT VALIDITY)?

Although a valid syndrome need not be familial, the demonstration of familial transmission supports the hypothesis that a syndrome is a discrete disease entity. Numerous studies have documented that the biological relatives of ADHD boys are at increased risk for ADHD and other psychiatric disorders.<sup>23,30,48,49,69,84-89</sup> Recently, the familial-

ity of ADHD was also demonstrated in an epidemiologic sample.<sup>90</sup> Additional lines of evidence from twin,<sup>91-93</sup> adoption,<sup>94,95</sup> and segregation analysis studies<sup>70,96-98</sup> suggest that the familial aggregation of ADHD has a substantial genetic component. Twin studies report a greater concordance of ADHD symptoms between monozygotic twins than between dizygotic twins.<sup>91,92,99</sup> Furthermore, the adoptive relatives of ADHD children are less likely to have ADHD or associated disorders than are the biological relatives of ADHD children.<sup>94,95</sup> Thus, a growing body of evidence shows that ADHD is a familial disorder and that transmission in families is mediated in part by genetic factors.

Although the adult diagnosis of ADHD may be somewhat controversial, the childhood diagnosis is not. The finding of unequivocal diagnoses of ADHD among the children of adult ADHD probands strengthens the hypothesis that the adult probands are truly suffering from ADHD. To this end, two family studies of adult ADHD suggest that the adult form of the disorder may be highly familial. Manshadi et al.<sup>100</sup> studied the siblings of 22 alcoholic adult psychiatric patients who met DSM-III criteria for ADD, residual type. The authors compared these patients with 20 patients matched for age and comorbid psychiatric diagnoses. Forty-one percent of the siblings of the adult ADHD probands were diagnosed with ADHD compared with 0% of the non-ADHD comparison siblings. Biederman et al.<sup>101</sup> showed a 57% rate of ADHD among children of ADHD adults that was much higher than the more modest 15% risk for ADHD in siblings of referred children with this disorder.<sup>70</sup> These results suggest that the adult form of this disorder may have stronger familial etiologic risk factors than its pediatric form. The high familial loading of adult ADHD suggests that nonfamilial cases are more likely to go into remission during adolescence. This idea finds some support in a 4-year follow-up of ADHD children and adolescents.<sup>102</sup> That study found that having a family history of ADHD predicted persistence of the disorder during the follow-up period.

Segregation analyses of ADHD<sup>70,96-98</sup> suggest that a single gene with incomplete penetrance is involved in the etiology of ADHD. A mathematic model of genetic transmission would be unlikely if reports were due to recall bias. In this regard, it is notable that Hauser et al.<sup>103</sup> 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- $\beta$  gene. Also, other studies have implicated the dopamine D<sub>2</sub> and D<sub>4</sub> receptor genes and the dopamine transporter gene.<sup>104-106</sup> These findings are consistent with genetic heterogeneity.

### DO CHILDHOOD AND ADULT ADHD SHARE NEUROBIOLOGICAL FEATURES?

Childhood and adult ADHD are both familial, but do they share other neurobiological features that suggest they

are the same disorder? Magnetic resonance imaging studies of the brain in childhood ADHD indicate that there are subtle anomalies in caudate<sup>107-109</sup> and corpus callosum size and shape<sup>110,111</sup> or possible reductions in right frontal area<sup>112</sup> in ADHD. These data are consistent with a positron emission tomography (PET) study of adult ADHD and suggest that a neurobiological link between childhood and adult ADHD may eventually be found.<sup>74</sup> The subjects in this study were adult fathers of children diagnosed with ADHD. These adults had never before been diagnosed or treated. The investigators found reduced global and regional glucose metabolism in the premotor cortex and the superior prefrontal cortex—areas of the brain associated with control of attention and motor activity.<sup>74</sup> While these findings have not been fully replicated in a similar PET scan study of adolescents,<sup>113</sup> they are consistent with preliminary results of brain SPECT imaging in adolescents with ADHD.<sup>114</sup>

The results of Zametkin et al.<sup>74</sup> provide a milestone in the study of adult ADHD for several reasons. First, the PET scan abnormalities cannot be attributed to the types of bias that might compromise psychiatric interviews of adults. Second, by showing these neurobiological abnormalities in the ADHD parents of ADHD children, this work lends support to the hypothesis that the familial (and possibly) genetic substrate of ADHD leads to dysfunction in the central nervous system that persists into adulthood.

## CONCLUSION

Despite controversy regarding the validity of ADHD in adults, our review finds multiple reports describing adults with clinical features highly reminiscent of childhood ADHD. These adults, who are impulsive, inattentive, and restless, have the clinical “look and feel” of ADHD children. Like their childhood counterparts, many adults with ADHD suffer from antisocial, depressive, and anxiety disorders. They also show evidence of occupational failure and intellectual performance deficits. Moreover, longitudinal follow-up studies show that documented cases of childhood ADHD often continue to express the ADHD syndrome as adults.

Although there are few studies of predictive validity, psychopharmacologic treatment trials show that the adult diagnosis of ADHD predicts a positive response to the same stimulant and nonstimulant treatments as used in ADHD children. Finally, family-genetic studies and a brain imaging study suggest that adult ADHD has neurobiological and familial correlates implicating a genetic link with childhood ADHD. Taken together, these findings support the validity of adult ADHD.

*Drug names:* desipramine (Norpramin and others), methylphenidate (Ritalin), pemoline (Cylert).

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