Gender Differences in 2 Clinical Trials of Adults With Attention-Deficit/Hyperactivity Disorder: A Retrospective Data Analysis

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Introduction: Studies show that, in childhood attention-deficit/hyperactivity disorder (ADHD), boys have the combined type with externalizing behaviors more frequently, and girls have the inattentive type with increased internalizing disorders more frequently.

Method: This study explored gender differences in adults with ADHD in 2 large, placebo-controlled, multicenter studies conducted from 2000 to 2001. Information collected included 2 measures of ADHD, multiple psychological measures, general physical symptoms, and treatment response.

Results: Thirty-four percent of the subjects were female. Women were rated as more impaired on every measure of ADHD symptoms including total Conners' Adult ADHD Rating Scale-Investigator Format (CAARS-INV), total Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), and most subscales of both measures. More women (75%) had combined type compared with men (62%). Women showed a more complex presentation, with higher scores on the Hamilton Rating Scale for Anxiety (HAM-A) and the Hamilton Rating Scale for Depression, 17-item version ($HAM\text{-}D_{17}$), more sleep problems, and more past DSM-IV Axis I diagnoses. Both sexes displayed substantial impairment on 3 Psychological General Well-Being Schedule factors: tension-anxiety, life satisfaction, and vitality-drive. Women experienced significantly ($p = .003$) greater rates of emotional dysregulation (37%) versus men (29%) as defined by a cluster of symptoms on the WRAADDS. The emotional dysregulation factor is derived by combining 3 symptoms—temper control, mood lability, and emotional overreactivity—from the Utah Criteria for ADHD in adults. These symptoms are considered associated symptoms in the DSM-IV description of ADHD. Women also experienced greater improvement ($p = .011$) on this symptom factor.

Conclusion: In contrast to the results from childhood studies, women were more impaired than men on ADHD scales in our study. The higher level of emotional symptoms and more complicated presentation in women may obscure the diagnosis of ADHD. Thus, the assessments of adults with ADHD should include an exploration of the emotional dimensions of the illness.

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Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder of childhood, and it is perceived to be a predominately male disorder. This observation is supported by many clinical studies that have reported male to female ratios in children with ADHD ranging from 4:1[1] to 10:1.[2] Conversely, in epidemiological samples, the differences are smaller, ranging from 1.5:1[3,4] to 3:1.[5] These reports lead to the conclusion that many girls with ADHD go undetected,[6] even though the number of girls diagnosed and treated has increased dramatically in recent years.[7,8] In 1994, these concerns and others led a National Institute of Mental Health conference[9] to call for more research in this area.

In the intervening years, reports have consistently identified 3 aspects of ADHD for which there are significant gender-related differences.

First, there are differences in symptom patterns. Girls are reported to be less impulsive,[10,11] while boys are reported to show more discipline problems and externalizing behaviors.[10,12–14]

Second, there are differences in the distribution of ADHD subtypes based on gender. Weiler et al.[15] found that girls with ADHD were more likely to have the inattentive type of ADHD. This predominance of the inattentive subtype in girls was subsequently supported by other reports like Biederman et al.[14] and Weiss et al.[16]

Third, there are gender-related differences in associated conditions in patients with ADHD. Biederman et al.,[14] in a comparison of boys and girls with and without ADHD, found that girls with ADHD were less likely to

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TAKE-HOME POINTS

- Compared with gender distribution in childhood clinical trials, this study of adults with attention-deficit/hyperactivity disorder (ADHD) examined a larger percentage of female patients.
- Unlike results seen in childhood studies, the women in this study had a higher symptom load than the men.
- Women responded to ADHD treatment at a level at least equivalent to that of men.
- Women may have more ADHD symptoms of emotional dysregulation than men, and these symptoms may be reflected in various measures of psychosocial functioning.
- Emotional symptoms in women with ADHD may make it more difficult for a clinician to accurately make the diagnosis.

have a learning disability. In addition, girls with ADHD were at lesser risk for comorbid major depression, conduct disorder (CD), and oppositional defiant disorder than boys with ADHD. Doyle et al.[17] showed that the gender differences in CD reflected the greater prevalence of antisocial disorder among boys in general rather than an effect specific to ADHD. Gender studies of neuropsychological[18] and psychosocial[19] impairment and family-genetic risk[20–23] suggest no differences between boys and girls with ADHD.

Although many reports have examined the gender-related profiles of children with ADHD, similar characteristics of adults have received less attention. Biederman et al.[24] examined the characteristics of 128 referred adult ADHD cases of both sexes (male/female ratio = 1.6:1). Men had higher rates of CD, a history of repeating grades in school, and lower performance on the digit-symbol subtest of the Wechsler Adult Intelligence Scale.

The goals of the present study were (1) to compare the baseline attributes of men and women in a large, controlled ADHD study and (2) to compare the treatment responsiveness of men and women in the same study.

METHOD

The data for this exploration came from 2 double-blind, placebo-controlled, multicenter studies[25] designed to secure FDA approval for the use of atomoxetine in the treatment of adults with ADHD. Their protocols were identical. The institutional review board for each clinic evaluated and approved the study protocol. Written informed consent was obtained from each subject before administering any study procedures or dispensing medication. The studies were conducted in accordance with the standards of each of the investigative sites' institutional review boards and with the Declaration of Helsinki 1975, as revised in 2000.

The 2 studies produced very similar results and, consequently, the data were combined for this investigation. Adult subjects were required to meet DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by Conners' Adult ADHD Diagnostic Interview for DSM-IV[26] (CAADID). More information on these studies is available.[25]

Adult diagnosis was corroborated by a second reporter, usually the subject's significant other. Childhood diagnosis of ADHD was verified by report from a parent or older sibling. The presence of other DSM-IV disorders, both historic and current, was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Patients with current major depression or anxiety disorder, with current or past psychotic or bipolar disorder, with alcohol dependence, who were actively abusing drugs of abuse at the point of study entry, or with a serious medical illness were excluded from the study.

There was a 1-week, medication-free washout period followed by a 2-week, single-blind phase during which subjects were given placebo. Baseline evaluations occurred during this 3-week period. Subjects then entered a 10-week, double-blind treatment period. All ratings of ADHD symptom levels were performed by raters who were blind to the study design. In total 300 patients were excluded following entry into screening. Of these, 182 were excluded due to failure to maintain entry level of severity and/or to have their diagnosis confirmed by a relative as noted in the previous paragraph.

The following clinical scales were used in the study:

1. Conners' Adult ADHD Rating Scale–Investigator Format (CAARS-INV)[27] is a clinician-administered form, with each item in the CAARS-INV corresponding to one of the DSM criteria for ADHD. It was modified through the addition of examples and probes to improve reliability and to make it more applicable to an adult population. Information regarding these modifications is available.[28]
2. The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)[29] is a clinician-

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administered scale designed to measure 7 areas of adult ADHD functioning: attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. While 4 of the items on the WRAADDS are quite similar to current DSM criteria, 3 (temper, affective lability, and emotional overreactivity) are not. Emotional dysregulation was categorized by using the sum of these 3 items. Scores of 7 or higher (an average of at least moderate impairment) indicated emotional dysregulation, similar to prior analyses.[30]

3. The Clinical Global Impression-Severity of Illness scale (CGI-S)[31]
4. The Hamilton Rating Scale for Depression, 17-item version ($HAM\text{-}D_{17}$)[32]
5. The Hamilton Rating Scale for Anxiety (HAM-A)[33]
6. The Sheehan Disability Scale,[34] which assesses social impairment.
7. The Association for Methodology of Documentation in Psychiatry-Module 5 (AMDP-5)[35,36] is part of a set of scales developed in Europe to assess psychiatric patients. This portion of the AMDP scales provides a self-administered survey of somatic problems in 8 areas (sleep, appetite, gastrointestinal, cardiorespiratory, other autonomic, other somatic, neurologic, and other symptoms). The item ratings are assessed on a scale ranging from absent = 0 to severe = 3.
8. The Psychological General Well-Being Schedule[37] is a 22-item, self-administered schedule, with each item having a unique, 6-point Likert-type scale. The items were organized into 6 scales: anxiety-tension, depressed mood, sense of positive well-being, self-control, general health, and vitality-drive. An average score of moderate or worse was considered evidence of impairment. This scale was selected to provide a broader measure of psychic distress.
9. The Stroop Color and Word Test[38] is a test of executive functioning often used in ADHD research.

Statistical Methods

The primary analysis of baseline measures was a comparison of gender-defined groups. The independent-samples t test was used for continuous variables, the Mann-Whitney test was used for ordinal data, and the χ^2 test was used for nominal data. Effect size (Cohen's d) was included, when possible. Since baseline ADHD symptoms may have altered non-ADHD measures, a secondary analysis of continuous variables was performed using analysis of covariance (ANCOVA), with gender as a fixed factor and the number of ADHD symptoms noted on the CAADID as a covariate.

Improvement on all measures (except the CGI-S) was evaluated using ANCOVA, with gender and treatment as fixed factors and baseline symptoms as a covariate, and then gender-by-treatment effects were assessed. Improvement on the CGI-S was evaluated using analysis of variance.

Given the large number of statistical comparisons being made, it would not be unusual to report significance using a Bonferroni correction. We have not done so for 2 reasons. First, the gender differences we identified were consistently in the same direction, strongly suggesting that they did not result from random variation. Second, as this study is primarily descriptive of the subject sample, any consequences resulting from a type I error would be minimal.

RESULTS

Baseline Results

While 836 adults were screened, 536 met admission criteria for the study and furnished baseline data. Of these, 515 provided outcome data. The male-female ratio was 1.9:1, or 65% male.

On measures of current ADHD symptoms (Table 1), women were more symptomatic on the WRAADDS total and its factors and CAARS-INV total as well its subscales. These differences are statistically significant and represent small to medium effect sizes. Following previous analyses,[39] we analyzed the WRAADDS as 3 factors: (1) attention + disorganization, (2) hyperactivity + impulsivity, and (3) temper + affective lability + emotional overreactivity. The first 2 are similar to the inattention and hyperactivity subscales in the CAARS-INV. The third, referred to as *emotional dysregulation*, contains items considered associated symptoms in DSM-IV; however, previous analyses of these data suggest that these symptoms are an integral part of ADHD in many adults.[30] Of the 3 factors, emotional dysregulation exhibited the greatest difference between males and females as measured by effect size.

There were significant differences regarding the type of ADHD ($\chi^2 = 11.79$, df = 2, p = .005) based on gender. Women were more often given a combined ADHD diagnosis. Men had a higher frequency of inattentive-type ADHD versus women. To explore the impact of emotional symptoms on ADHD subtype, subjects were redivided into 4 groups. All subjects who met criteria for emotional dysregulation were put into one group, while DSM-IV criteria were used to separate the rest of the subjects into the traditional 3 diagnostic groups. As seen in Table 1, while the statistical significance ($\chi^2 = 9.3$, df = 3, p = .04) diminished somewhat, the relationship between the inattentive diagnosis and gender remained. However, the difference in combined type was no longer present.

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Table 1. Comparison of Baseline ADHD Measures and Diagnoses in Women and Men

Measure	Women (N = 188)	Men (N = 348)	p Value	Cohen's d
WRAADDS, mean ± SD				
Total	18.2 ± 4.4	16.7 ± 5.2	.001	.31
Attention/disorganization[a]	3.4 ± 0.7	3.3 ± 0.8	.004	.23
Hyperactivity/impulsivity[a]	2.8 ± 1.0	2.6 ± 1.1	.010	.23
Emotional dysregulation[a]	2.0 ± 1.3	1.7 ± 1.3	.003	.28
CAARS-Inv, mean ± SD				
Total	35.4 ± 7.6	33.2 ± 7.1	.001	.30
Inattention	19.7 ± 4.3	18.7 ± 4.3	.008	.23
Hyperactivity	15.6 ± 5.4	14.5 ± 5.0	.016	.22
CGI-S, mean ± SD	4.7 ± 0.7	4.7 ± 0.7	NS	.09
DSM-IV ADHD diagnosis category, %[b]				
Hyperactive/impulsive	1	3		
Inattentive	24	35		
Combined	75	62		
Alternative classification of ADHD symptomatology, %[c]				
Hyperactive/impulsive	1	3		
Inattentive	20	28		
Combined	43	40		
Emotional type	37	29		

[a]The 3 WRAADDS factors are expressed as item means to facilitate comparisons.
[b]Diagnostic categories for women and men differed significantly $\chi^2 = 11.79$, df = 2, p = .005.
[c]Alternative classifications for women and men differed significantly $\chi^2 = 9.3$, df = 3, p = .04.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS-Inv = Conners' Adult ADHD Rating Scale-Investigator Format, CGI-S = Clinical Global Impressions-Severity of Illness scale, NS = not significant, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

On the SCID, HAM-A, HAM-D_{17}, AMDP-5, the Psychological General Well-Being Schedule, and the Sheehan Disability Scale, there were a number of significant gender differences (Table 2). Women had more past depressive episodes (p = .05) and higher total scores on the HAM-A and HAM-D_{17}. On the HAM-A, the difference remained significant after using an ANCOVA to control for the number of ADHD symptoms (F = 5.12, df = 1,512; p = .023) but not on the HAM-D_{17} (F = 3.15, df = 1,512; p = .076).

On the AMDP-5, these adults had a frequent history of significant sleep problems. Women were statistically more likely to have problems with sleep (p = .006). This difference between genders was significant for 2 items—interrupted sleep and daytime drowsiness. Women also had more other somatic complaints (p = .009), consisting mostly of headaches and backaches. Similarly, both genders reported problems in the Psychological General Well-Being Schedule, particularly in 3 areas. The highest was sense of positive well-being, which measures a sense of frustration or discouragement with life. The next highest was vitality-drive, which measures a sense of being worn out, overwhelmed by life. The last was anxiety-tension. Three of the 6 scales exhibited significant, but small differences—anxiety-tension (p = .046), self-control (p = .04), and general health (p = .01).

These subjects acknowledged problems on the Sheehan Disability Scale. When both sexes were combined, 80% reported at least moderate problems at work, 67% in social functioning, and 84% within their family. While women had higher scores overall than men, indicating more impairment, as displayed in Table 2, the difference was only statistically significant for family (p = .021) and total (p = .015) scores. These statistically significant differences are considered small effect sizes using Cohen's d. When Sheehan scores were reanalyzed, controlling for the number of current ADHD symptoms, neither family (p = .14) nor total (p = .126) scores retained statistical significance.

On the Stroop Color and Word Test, only a minority of subjects had impaired executive functioning. Average t scores for this test (Table 2) were slightly worse than normal. Further, only 8% of subjects had t scores of 40 or less on the critical interference score. There were no gender differences on the Stroop. More complete information on the Stroop Color and Word test in this sample is presented in a recent publication.[40]

Treatment Results

The 2 studies from which these data are taken showed positive treatment effects. A statistically significant change favoring atomoxetine was observed in both studies on the CAARS, the WRAADDS, and the CGI-S.

ANCOVA analyses of the end point total WRAADDS (last-observation-carried-forward analysis, using baseline scores as the covariate) scores showed no significant treatment-by-gender interaction (F = 1.22, df = 1,446; p = .269). Combining the individual WRAADDS items (attention + disorganization; hyperactivity + impulsivity; temper + affective lability + emotional overreactivity) made it possible to treat them as continuous data and perform ANCOVA evaluations similar to those used with the

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Table 2. Associated Psychiatric Measures at Baseline

Measure	Women (N = 188)	Men (N = 348)	p Value	Cohen's d
SCID lifetime diagnosis, %				
Depression (any diagnoses)	18	10	.05	
Anxiety (any diagnoses)	5	2	NS	
Substance abuse (any diagnoses)	7	7	NS	
Any diagnosis	23	15	.02	
Total HAM-D_{17}, mean ± SD	5.7 ± 4.1	4.9 ± 3.6	.020	.21
Total HAM-A, mean ± SD	7.9 ± 5.4	6.6 ± 4.7	.003	.25
AMDP-5, N (%)[a]				
Sleep	69 (37)	88 (25)	.006	
Difficulty falling asleep	29 (15)	38 (11)	NS	
Interrupted sleep	43 (23)	42 (12)	.014	
Shortened sleep	20 (11)	29 (8)	NS	
Early waking	13 (7)	20 (6)	NS	
Drowsiness	35 (19)	36 (10)	.028	
Other somatic[b]	42 (22)	47 (14)	.009	
Psychological General Well-Being Schedule, mean ± SD (%)[c]				
Sense of positive well-being	3.3 ± 0.9 (50)	3.4 ± 1.0 (52)	.395	.09
Vitality-drive	3.2 ± 1.0 (51)	3.1 ± 1.1 (44)	.320	.108
Anxiety-tension	3.2 ± 0.8 (48)	3.0 ± 0.9 (45)	.046	.220
Self-control	2.7 ± 0.8 (27)	2.5 ± 0.9 (24)	.040	.225
Depressed mood	2.3 ± 0.8 (15)	2.3 ± 0.9 (18)	.729	.003
General health	2.4 ± 0.7 (15)	2.2 ± 0.9 (12)	.010	.285
Sheehan Disability Scale, %[d]				
Work	85	76	.064	.21
Social	73	63	.059	.19
Family	87	82	.021	.21
Total	85	77	.015	.23
Stroop test, mean ± SD (%)[e]				
Word	44.6 ± 8.6 (31)	45.1 ± 8.8 (26)	.49	.06
Color	45.1 ± 8.7 (28)	44.8 ± 9.1 (28)	.79	.03
Color-word	49.0 ± 12.2 (26)	49.9 ± 12.5 (25)	.38	.07
Interference	52.7 ± 10.4 (8)	53.6 ± 10.7 (7)	.38	.08

[a]Subjects with moderate problems on any question within each category.
[b]Mostly headaches and backaches.
[c]Percentage at least moderately impaired.
[d]Percentage moderately impaired.
[e]Percentage scoring ≤ 40; scores of 40 are 1 SD below the standardized average of 50.
Abbreviations: AMDP-5 = Association for Methodology of Documentation in Psychiatry-Module 5, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, NS = not significant, SCID = Structured Clinical Interview for DSM-IV Axis I Disorders.

total WRAADDS. The 3 symptoms measuring emotional dysregulation displayed a significant treatment-by-gender interaction for emotional dysregulation (p = .011). The 2 groupings that mimic the traditional DSM categories did not show a treatment-by-gender interaction.

A similar ANCOVA on the CAARS-INV total score found no significant treatment-by-gender interaction (F = .617, df = 1,511; p = .433). The same is true of its 2 subscales, CAARS-INV inattentiveness (F = 1.125, df = 1,511; p = .289) and CAARS-INV hyperactivity/impulsivity (F = .072, df = 1,446; p = .789). Table 3 displays both the average and the percentage improvement for men and women under both treatment conditions. Atomoxetine produced a significant positive treatment effect for each measure within genders (p value < .05, not shown in the table). While women consistently exhibited larger atomoxetine/placebo treatment effects, only on the WRAADDS emotional dysregulation factor was this difference significant.

There was a significant gender-by-treatment effect for Sheehan Disability Scale social life subscale scores (p = .042). Women showed a stronger treatment effect than men. There was no treatment-by-gender interaction using the Sheehan disability total score or 2 of its individual measures (work and family functioning). There were no treatment-by-gender effects on the CGI-S, HAM-D_{17}, or HAM-A.

DISCUSSION

The goals of the present study were to compare the attributes of adult men and women in a large clinical trial of ADHD and to compare the treatment responsiveness of men and women.

There were many significant gender differences in this sample. In contrast to childhood studies, women showed more ADHD symptoms at baseline. This difference was detected on both the WRAADDS and CAARS-INV and on subscales/factors of these measures. Even though

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Table 3. Improvement of ADHD Symptoms as a Function of Gender and Treatment Compared With Baseline Values

	Women		Men		
Measure	Atomoxetine (N = 88), Mean ± SD (%)	Placebo (N = 91), Mean ± SD (%)	Atomoxetine (N = 169), Mean ± SD (%)	Placebo (N = 167), Mean ± SD (%)	p Value[a]
WRAADDS					
Total	5.7 ± 6.9 (30)	2.8 ± 6.3 (16)	4.6 ± 5.9 (28)	2.9 ± 4.6 (19)	.269
Attention/disorganization	1.8 ± 2.2 (27)	1.1 ± 2.5 (19)	1.7 ± 2.3 (28)	1.0 ± 1.8 (17)	.548
Hyperactivity/impulsivity	1.7 ± 2.4 (30)	1.1 ± 2.0 (19)	1.4 ± 2.1 (29)	0.9 ± 1.7 (19)	.896
Emotional dysregulation	2.1 ± 3.5 (31)	0.4 ± 2.9 (11)	1.3 ± 2.9 (29)	1.0 ± 2.2 (16)	.011
CAARS-Inv					
Total	10.8 ± 13.1 (31)	5.9 ± 11.5 (17)	9.4 ± 11.7 (28)	6.5 ± 10.1 (20)	.433
Inattentiveness	5.8 ± 7.2 (29)	2.8 ± 6.3 (14)	5.1 ± 6.5 (27)	3.5 ± 5.9 (19)	.289
Hyperactivity	5.1 ± 6.5 (32)	3.0 ± 6.0 (20)	4.3 ± 6.2 (30%)	3.0 ± 5.3 (21)	.789
CGI-S	0.9 ± 1.3	0.4 ± 1.1	0.9 ± 1.1	0.5 ± 0.9	.134
Sheehan Disability Scale					
Total	5.3 ± 7.6 (31)	4.0 ± 7.7 (22)	3.9 ± 8.3 (24)	3.0 ± 7.1 (19)	.319
Work	1.9 ± 3.1 (31)	1.4 ± 3.1 (22)	1.6 ± 3.0 (27)	0.9 ± 3.1 (16)	.739
Social	1.8 ± 2.9 (36)	1.2 ± 2.9 (21)	1.0 ± 3.1 (21)	0.9 ± 2.9 (20)	.042
Family	1.6 ± 2.8 (26)	1.4 ± 2.8 (22)	1.3 ± 3.2 (23)	1.2 ± 2.7 (20)	.634

[a]All p values report the gender-by-treatment interaction and result from analyses of covariance.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS-Inv = Conners' Adult ADHD Rating Scale-Investigator Format, CGI-S = Clinical Global Impressions-Severity of Illness scale, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

gender differences produced effect sizes only in the small to medium range, this higher symptom load in women was reflected in the type of ADHD diagnosis. While a majority of both men and women were given a combined ADHD diagnosis, the women were more likely than the men to have a diagnosis of ADHD combined type and less likely to have a diagnosis of ADHD inattentive type. This finding stands in contrast to those of childhood studies. For example, Baumgaertel et al.[41] and Weiler et al.[15] both found that a majority of girls were diagnosed with the ADHD inattentive type. Additionally, Biederman and Faraone[42] found that girls were more frequently diagnosed as having the ADHD inattentive type compared with boys, although a majority of girls were diagnosed with the combined type. The difference in diagnostic categories between men and women was partly related to the higher emotional dysregulation symptom load of women. When subjects with emotional dysregulation were put into a separate category, the percentage of men with a combined diagnosis became closer to the percentage of women with this diagnosis.

Women's higher impairment on the HAM-D_{17} and Sheehan Disability Scale family functioning subscale was associated with more ADHD symptoms. ADHD severity level did not explain gender differences in the HAM-A, sleep problems, and other somatic measures. No attempt was made to assess the impact of this higher ADHD symptom load on categorical data like the Psychological General Well-Being Schedule, historical SCID diagnosis, or family ADHD history.

The most consistent finding in this study was the greater symptom load for women on a variety of emotional measures. On the WRAADDS, the greatest gender difference was on the factor of emotional dysregulation. Thirty-seven percent of female subjects in this study had substantial elevations on symptoms of emotional dysregulation (temper, affective lability, and emotional overreactivity, as defined in a previous study[30]) in the WRAADDS compared with 29% of male subjects ($\chi^2 = 9.3$, df = 3, p = .04). We have previously reported on this complex of emotional symptoms frequently found in patients with ADHD.[30] The concept is derived from the Utah Criteria for adult ADHD and fits within Barkley's conceptualization[2] of ADHD. These symptoms have also been recognized as associated symptoms of ADHD in the DSM-IV.

The symptoms assessed by the WRAADDS were identified prior to DSM-III, when most clinicians believed that ADHD, then called *minimal brain dysfunction*, gradually disappeared during adolescence. Nor was it seen as a precursor or complicating factor for later adult psychiatric conditions. We had noted clinically that, in treating ADHD children, often one of the parents reported having problems similar to their child's. The WRAADDS was subsequently developed through interviews with these parents, their spouses, and other family members. In contrast with the DSM criteria, the WRAADDS items are age-appropriate and focus on symptoms, not behaviors. Previous factor analysis has shown all 7 symptom areas to be closely related, although they separate into 3 factors: symptoms of emotional dysregulation, attentional/organizational symptoms, and hyperactive/impulsive symptoms. While 4 of the symptoms in the WRAADDS are similar to DSM criteria, 3 (temper, affective lability, and emotional overreactivity) are not. Temper presents as irritability and frequent outbursts, usually of short duration. Patients experiencing affective lability often undergo definite shifts from normal mood to de-

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pression or mild excitement. Patients experiencing emotional overreactivity demonstrate a diminished ability to handle typical life stresses, resulting in feeling overwhelmed. Past analyses have demonstrated that symptoms of emotional dysregulation respond to ADHD treatment in parallel with inattention and hyperactivity/impulsivity, even when measures of depression (HAM-D) and anxiety (HAM-A) do not improve.[30] Furthermore, symptoms of emotional dysregulation affect significant numbers of adults with ADHD who do not meet DSM criteria for other Axis I DSM-IV disorders.

Women were twice (12%) as likely to have a lifetime history of major depression as men (6%). The incidence of current anxiety and depressive symptoms was low, but again, the women were rated as more symptomatic. In the Psychological General Well-Being Schedule, half of subjects experienced problems in 3 areas: vitality-drive, sense of positive well-being, and anxiety-tension. Women experienced significantly more symptoms than men in 3 subscales (anxiety-tension, self-control, and general health). The WRAADDS and the Psychological General Well-Being Schedule were more sensitive in detecting emotional symptoms in this sample than the HAM-D_{17} or HAM-A.

Three facts must be noted when considering these data. First, exclusionary criteria for this study included most current DSM-IV diagnoses. Second, depression and anxiety diagnoses are more prevalent in women than men in the general population. Third, many more men develop substance abuse and/or conduct problems as adults than women.[43] Many of these subjects would have past and/or current ADHD possibly with emotional symptoms such as we have described. Given the fact that most ADHD studies do not assess emotional dysregulation, it is possible that these symptoms have been misinterpreted as anxiety and/or depressive symptoms. For example, one third of the children in the Multimodal Treatment Study of Children with ADHD (MTA)[44] met criteria for a comorbid anxiety or depressive diagnosis. However, in describing these symptoms, March et al.[45] stated, "Anxiety is more strongly associated with negative affectivity and disruptive behavior than with fearfulness/phobic symptoms,"[45(p537)] and "The MTA sample is not 'anxious' in the same sense as would be expected in a clinical sample of children in this age group with primary anxiety disorders."[45(p537)] A report by Greenhill et al.,[1] in this same sample, documented that anger was not a side effect of treatment but instead responded positively to treatment by the stimulants.

In contrast to clinical trials of adults with ADHD, there has been interest in affective or emotional symptoms in psychotherapeutic studies of ADHD. For example, McDermott[46] adapted Beck's cognitive therapy for use with ADHD. Stevenson et al.[47,48] developed a similar cognitive remediation program that included segments addressing organization and anger management. In an effort that seems to view adult ADHD in a manner very close to our approach, Hesslinger et al.[49] developed a structured skill-training program which included segments addressing emotions (emotional instability and brief recurrent depressive states), stress intolerance (including subsequent disorganization), and difficulty controlling anger. These authors didn't address whether the emotional symptoms are part of ADHD or a comorbid disorder. However, they found that the emotional symptoms were an important element in treating adults with ADHD.

Both men and women showed a greater treatment response to atomoxetine than placebo on the CGI-S, total WRAADDS, and total CAARS-INV, as well as most subscales within each test. In general, women had a numerically superior treatment response. However, only on the emotional dysregulation factor of the WRAADDS was this gender-related treatment effect significant.

There was 1 statistically significant gender-by-treatment interaction in our measure of social functioning. Women showed a significantly greater treatment effect in the Sheehan Disability Scale social functioning subscale compared with men. Men and women showed similar positive treatment effects for the subscales of family and work, as well as the total Sheehan Disability Scale. However, it is possible that the 10-week study period was too short to allow for full response to treatment. In an unpublished study of methylphenidate, 2 of the authors (F.W.R. and B.K.M., 1997) found that improvements in psychosocial functioning were maximized by 6 months. Thus, continued treatment may lead to more improvement and alternative gender effects.

The sample used in this analysis is representative of many adult women with ADHD and certainly is similar to those in most adult ADHD clinical trials. The degree to which our findings are applicable to highly comorbid ADHD samples is a very interesting question. This clinical sample showed gender differences across many measures. Women consistently displayed more ADHD impairment than men, with effect sizes in the small to medium range. This was especially true of the ADHD factor of emotional dysregulation. The complex emotional symptoms in these ADHD women are of concern, since their presence could lead to a clinician's missing the ADHD diagnosis. Given the very favorable treatment response of these women, that failure could be unfortunate. Conversely, the hypothesis that emotional symptoms in ADHD women can lead to a clinician's missing a diagnosis of ADHD is a theory that needs supporting empirical data.

Drug name: atomoxetine (Strattera).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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