

# Gender Differences in ADHD Adults During Clinical Trials with Atomoxetine

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## ABSTRACT

**Introduction:** Patients with ADHD exhibit several consistent gender differences, a male preponderance and more males with externalizing disorders (conduct and oppositional defiant disorder).

**Objective:** To examine gender differences in a very large clinical trial of adults with ADHD.

**Methods:** Data from two identical placebo-controlled studies of atomoxetine in adult ADHD using 535 subjects at 31 sites were combined<sup>1</sup>. The studies lasted 8 weeks and both showed positive medication-placebo differences. Most current Axis-I diagnoses were exclusionary criteria.

**Results:** The male/female ratio of this self-referred population was 2.4:1, lower than in child studies<sup>2</sup>. In contrast to a predominance of an inattentive ADHD diagnosis subtype in female children, these adult females were more frequently combined type versus the males. Females were rated as more impaired on every measure of ADHD symptoms including total CAARS-INV, total WRAADDS<sup>3</sup>, and subscales of both measures. Females were rated as having more emotional symptoms on the WRAADDS emotional dimension, lifetime SCID-P psychiatric diagnoses, HAM-A, and HAM-D. Females exhibited significantly greater improvement on the WRAADDS emotional dimension but not on similar items in the Psychological Well-Being Scale. There were no significant gender by treatment effects in the CAARS-INV or CGI-S scores.

**Conclusion:** These females with ADHD displayed significantly greater ADHD symptoms and emotional impairment on multiple measures. On the WRAADDS emotional dimension they responded better to treatment, than their male counterparts.

## INTRODUCTION

Past research shows that ADHD is much more common in males particularly in pediatric samples. Children exhibit few gender differences on a consistent basis except in the area of associated symptoms. The present study addresses whether ADHD adults displayed gender differences at screening or in treatment response using data from the largest studies ever conducted in ADHD adults

## METHODS

The data were taken from two identical placebo-controlled studies of atomoxetine in adult ADHD<sup>1</sup>. Patients with depression, anxiety, or other psychiatric diagnoses were excluded from the study. After a placebo washout, 535 subjects at 31 sites completed the 8-week double-blind period. The studies showed positive medication-placebo differences and were the pivotal studies leading the FDA to approve atomoxetine as the first non-stimulant medication for the treatment of ADHD in adults.

The primary analysis of baseline measures was a comparison of gender-defined groups. The student T-test was used for continuous variables, the Mann-Whitney was used for ordinal data, and the Chi Square was used for nominal data.

Improvement on all measures (except the CGI-S) was examined using ANCOVA, controlling for baseline measures and looking for a gender by treatment effect. Improvement on the CGI-S was evaluated using ANOVA.

## RESULTS

There were relatively more women than in studies of ADHD in children. In contrast to a childhood ratio of 3.4:1 in epidemiological studies<sup>2</sup> and 6:1 in clinic-referred populations, the male/female ratio was 2.4:1. Seventy-five percent of females were as having diagnosed combined type ADHD, a significantly higher rate than the males.

**TABLE 1: ADHD DIAGNOSIS CATEGORY**

	Female	Male
Hyperactive/Impulsive	1 (1%)	12 (3%)
Inattentive	46 (24%)	121 (35%)
Combined	141 (75%)	213 (62%)

1) ADHD Diagnosis Category :  $X^2=11.79$ ,  $df=2$ ,  $p=.005$

Females showed more impairment than males in total CAARS-INV and in total WRAADDS, and females showed more symptoms of emotional dysregulation as well as the other sub-scales of these two measures.

**TABLE 2: MEASURES OF ADHD AT BASELINE**

	Female	Male	p Value <sup>1</sup>
Total WRAADDS	18.2±4.4	16.7±5.2	.001
Attention/Disorganization	6.9±1.2	6.5±1.4	.007
Hyperactivity/Impulsivity	5.5±1.6	5.1±1.9	.010
Emotional Dysregulation	5.8±2.8	5.0±2.9	.002
Total CAARS-INV	38.9±6.4	36.3±7.5	.000
Inattention	21.3±3.4	20.4±3.9	.004
Hyperactivity	17.6±4.8	15.9±5.4	.000

Females were more likely than males to have siblings and children with ADHD.

**TABLE 3: FAMILY HISTORY OF ADHD**

	Female	Male	p Value
Father	14%	14%	ns
Mother	13%	12%	ns
Grandparents	3%	3%	ns
Siblings	31%	22%	.03
Children	61%	46%	.01
Any	66%	52%	.05

Females had higher scores on multiple measures including HAM-A, HAMD-17, Sheehan Social Adjustment Scale, measures of physical symptoms particularly sleep, appetite, and other somatic concerns (mostly headaches and backaches).

Lifetime SCID-P diagnosis, revealed that females were more likely to have been diagnosed with depression, anxiety, substance abuse, and any psychiatry diagnosis.

**TABLE 4: LIFETIME SCID-P DIAGNOSIS, HAM-A AND HAMD-17**

	Female	Male	p Value
N	188	346	
Depression	33 (18%)	34 (10%)	.05
Anxiety	10 (5%)	7 (2%)	ns
Substance Abuse	13 (7%)	23 (7%)	ns
Any Diagnosis	44 (23%)	52 (15%)	.02
Total HAM-A	7.9±5.4	6.6±4.7	.003
Total HAMD-17	5.7±4.1	4.9±3.6	.020

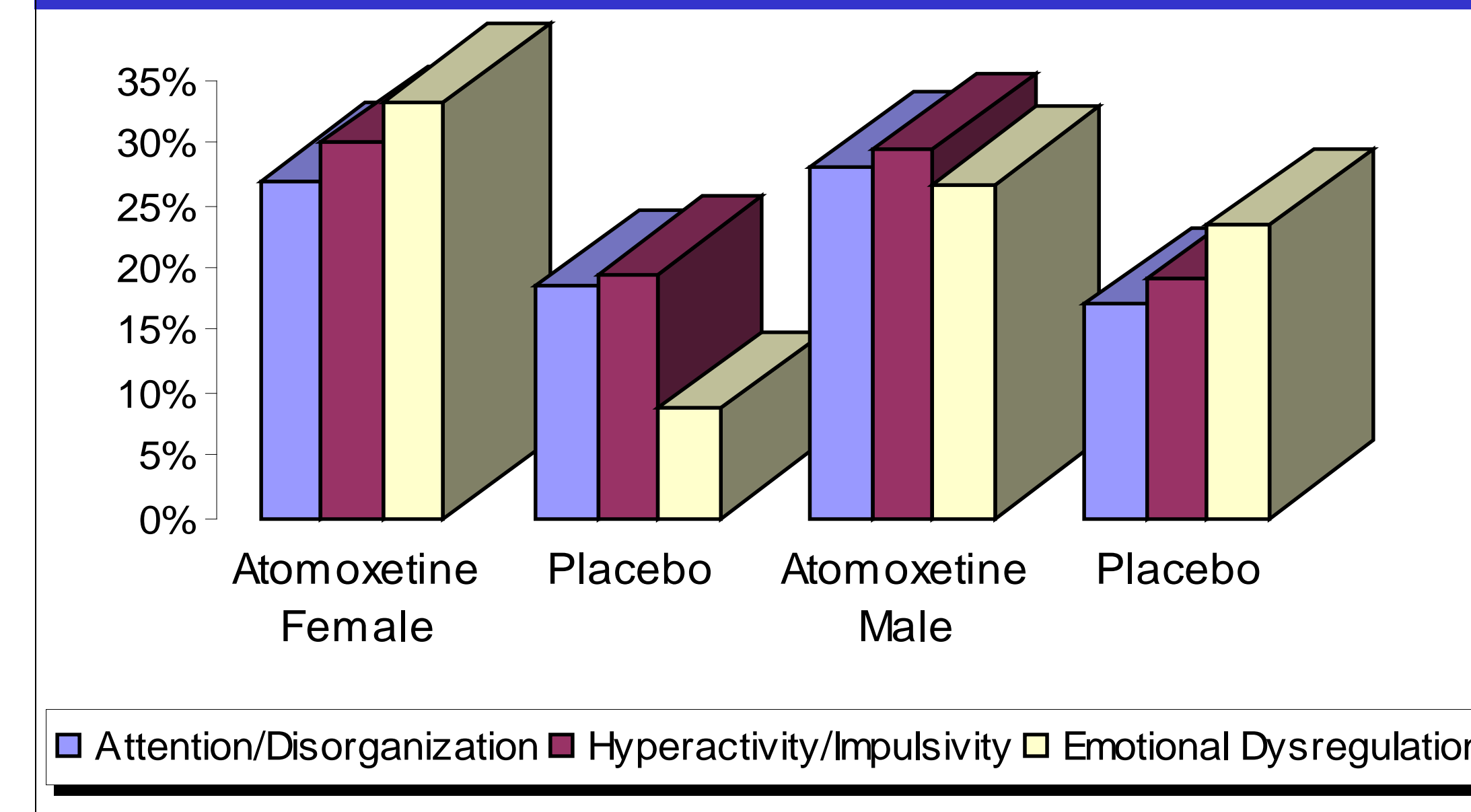
On the Psychological General Well-Being Questionnaire, both males and females showed the highest symptom levels on tension-anxiety and energy-drive, with lesser elevations on mood. The lowest symptom levels were on psychological control, mood, and somatic symptoms.

**TABLE 5: PSYCHOLOGICAL WELL-BEING AT BASELINE\***

	Female	Male	p Value
N	136	251	
Mood	21 (15%)	46 (18%)	ns
Life Satisfaction	68 (50%)	130 (52%)	ns
Anxiety	65 (48%)	112 (45%)	ns
Control	37 (27%)	61 (24%)	ns
Energy	70 (51%)	111 (44%)	ns
Somatic	21 (15%)	30 (12%)	ns

\*Number of patients who had an average score of greater than 3 in each category on the General Psychological Well-Being Questionnaire. Questions are scored on a scale of 1-6, with 6 being most impaired.

**FIGURE 1: PERCENT IMPROVEMENT IN WRAADDS AFTER TX**



Both genders demonstrated significant atomoxetine/placebo treatment effects. However, on the WRAADDS, emotional dysregulation improved more in females after receiving atomoxetine than in males. In contrast, both genders experienced treatment effects in two Psychological Well-Being Scales - Mood and Anxiety.

**TABLE 6: IMPROVEMENT OF WRAADDS, CAARS-INV & CGI**

	Female		Male		Tx by Gender p Value
	Atomoxetine	Placebo	Atomoxetine	Placebo	
WRAADDS Total	5.6 (30%)	2.8 (16%)	4.8 (28%)	3.1 (19%)	.269
Attention/Disorganization	1.8 (38%)	1.3 (19%)	1.8 (27%)	1.0 (16%)	.548
Hyperactivity/Impulsivity	1.7 (30%)	1.1 (19%)	1.5 (28%)	0.9 (18%)	.896
Emotional Dysregulation	2.1 (34%)	0.4 (7%)	1.5 (28%)	0.7 (14%)	.011
CAARS-INV Total	14.1 (36%)	9.7 (25%)	12.8 (35%)	9.4 (26%)	.433
Inattentiveness	7.2 (34%)	4.6 (22%)	6.8 (33%)	5.1 (25%)	.289
Hyperactivity	6.9 (39%)	5.0 (29%)	6.0 (37%)	4.3 (27%)	.789
CGI-S	3.8±1.2	4.4±1.2	3.9±1.1	4.1±1.0	.134

## CONCLUSIONS

These adults with ADHD displayed multiple significant gender differences. Women usually displayed more impairment than men, especially in symptoms of emotional dysregulation. This discrepancy with many childhood findings may be due to dissimilar referral biases. While children are referred by parents and teachers, often because of conflicts with others, these patients are self-referred. Women with ADHD were also more likely to have a family history of ADHD. These data suggest that women, although often undertreated and underdiagnosed, represent a significant subset of ADHD patients and that adult females with ADHD may benefit substantially from treatment.

## REFERENCES

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