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# Atomoxetine for the Treatment of Attention-Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder

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## ABSTRACT

**OBJECTIVE.** In this study we examined the effectiveness of atomoxetine for the treatment of oppositional defiant disorder comorbid with attention-deficit/hyperactivity disorder.

**METHODS.** Patients were aged 6 to 12 years and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnostic criteria for attention-deficit/hyperactivity disorder with a Swanson, Nolan, and Pelham Rating Scale-Revised attention-deficit/hyperactivity disorder subscale score above age and gender norms; Clinical Global Impressions-Severity Scale score of  $\geq 4$ ; and Swanson, Nolan, and Pelham Rating Scale-Revised oppositional defiant disorder subscale score of  $\geq 15$ . Patients were randomly assigned in a 2:1 ratio to receive 1.2 mg/kg per day of atomoxetine ( $n = 156$ ) or placebo ( $n = 70$ ) for 8 weeks. Treatment effect on oppositional defiant disorder and attention-deficit/hyperactivity disorder symptoms was measured by using the investigator-rated Swanson, Nolan, and Pelham Rating Scale-Revised.

**RESULTS.** Repeated-measures analysis demonstrated a statistically significant difference favoring atomoxetine over placebo in the reduction of Swanson, Nolan, and Pelham Rating Scale-Revised oppositional defiant disorder total scores. There were significant pairwise treatment differences at weeks 2 and 5 but not at week 8 postbaseline. A last-observation-carried-forward analysis showed Swanson, Nolan, and Pelham Rating Scale-Revised scores at endpoint for the atomoxetine and placebo groups were significantly different for attention-deficit/hyperactivity disorder symptoms but not for oppositional defiant disorder symptoms. Atomoxetine was superior to placebo in a last-observation-carried-forward analysis of Clinical Global Impression-Improvement and Clinical Global Impression-Severity scores.

**CONCLUSIONS.** This study confirms previous findings that patients with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder show statistically and clinically significant improvement in attention-deficit/hyperactivity disorder symptoms and global clinical functioning when treated with atomoxetine. It remains uncertain, however, whether atomoxetine exerts a specific and enduring effect on oppositional defiant disorder symptoms.

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### Key Words

ADHD, adolescents, atomoxetine

### Abbreviations

ODD—oppositional defiant disorder

ADHD—attention-deficit/hyperactivity disorder

DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

SNAP-IV—Swanson, Nolan, and Pelham Rating Scale-Revised

CGI-S—Clinical Global Impressions-Severity Scale

CGI-I—Clinical Global Impressions-Improvement Scale

CGI-P—Conners' Global Index-Parent Version

AIM—Attention-Deficit/Hyperactivity Disorder Impact Module

atomoxetine 1.2—atomoxetine at 1.2 mg/kg per day

atomoxetine 2.4—atomoxetine at 2.4 mg/kg per day

ANCOVA—analysis of covariance

LOCF—last-observation-carried-forward

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**O**PPPOSITIONAL DEFIANT DISORDER (ODD) is among the most common comorbid psychiatric disorders in patients with attention-deficit/hyperactivity disorder (ADHD), occurring in  $\leq 50\%$  of clinically referred populations.<sup>1</sup> The presence of ODD together with ADHD is a serious clinical problem. Children with ADHD combined with ODD tend to have more severe ADHD symptoms, peer problems, and family distress compared with children with ADHD alone.<sup>1</sup> However, few rigorous, adequately designed studies of pharmacologic treatments for ODD have been reported, although data from recent preliminary studies suggest that medications may be of benefit.<sup>2</sup>

There are genetic,<sup>3</sup> family environment,<sup>4</sup> and psychometric<sup>5</sup> studies that have suggested that ADHD and ODD have separate etiologies and pathophysiological mechanisms. In addition, the developmental trajectories of the 2 disorders

can be separated, with ADHD predicting academic and occupational dysfunction, whereas ODD and early conduct problems predict later delinquent behavior and substance misuse.<sup>6-8</sup> This said, there is a high degree of correlation between ADHD and ODD symptoms, and it should be noted that the 2 are frequently comorbid and may be developmentally related.<sup>9-14</sup>

Atomoxetine was approved by the US Food and Drug Administration in November 2002 as a treatment for ADHD. Previous research has demonstrated that patients with ADHD and comorbid ODD show statistically and clinically significant improvement in ADHD symptoms and global clinical functioning when treated with atomoxetine.<sup>15,16</sup> In addition, a recent analysis of data from 1 placebo-controlled study in children and adolescents showed that, compared with placebo, atomoxetine significantly reduced ODD symptoms and improved social and family functioning in children and adolescents with comorbid ADHD and ODD.<sup>17</sup> Our study was designed to assess the efficacy of atomoxetine in treating symptoms of ODD in children with ADHD and comorbid ODD.

## METHODS

### Participants

Patients were aged 6 to 12 years and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), diagnostic criteria for ADHD (any subtype) and comorbid ODD as determined by an investigator's clinical assessment; a structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version); Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) ADHD subscale score above age and gender norms; Clinical Global Impressions-Severity Scale score  $\geq 4$  at visits 1 and 2; and SNAP-IV ODD subscale score of  $\geq 15$  at both visits 1 and 2. If other comorbid conditions were present, either ADHD or ODD was the primary diagnosis.

Patients who had a history of bipolar I or II disorder, psychosis, or pervasive developmental disorder were excluded. Patients also were excluded if they had a current diagnosis of major depressive disorder, posttraumatic stress disorder, a Children's Depression Rating Scale-Revised total raw score  $>40$  at visit 1, or if they were determined to be at serious suicidal risk. Patients with a history of any seizure disorder (other than febrile seizures), a history of alcohol or drug abuse within the past 3 months, current cardiovascular disease or other conditions that could be aggravated by an increased heart rate or increased blood pressure, a medical condition that would markedly increase sympathetic nervous system activity, or severe gastrointestinal narrowing were excluded. Finally, patients who, in the investigator's judgment, were likely to need psychotropic medications apart from the drug under study or who at any time during the study were likely to begin structured psychotherapy were excluded.

This study was conducted at 17 sites in Europe and Australia. After verbal description of the study, written informed consent was obtained from a parent or guardian for each patient, and each youth provided written

assent. The study was reviewed and approved by each site's ethical review board and conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki as revised in 2000.<sup>18</sup>

### Measures

At the outset of the trial, investigators were trained on the administration of the study instruments. The primary efficacy measure was the investigator-rated ODD subscale of the SNAP-IV. The SNAP-IV is a 26-item scale that includes 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD and 1 item for each of the 8 symptoms contained in the DSM-IV diagnosis of ODD. Each item is scored on a 0 to 3 scale (0 = "not at all," 1 = "just a little," 2 = "pretty much," 3 = "very much"). The SNAP-IV has been validated and normed in a sample of school-aged children from the United States<sup>19,20</sup> and yields scores in 3 domains: inattention, hyperactivity/impulsivity, and oppositional.

Several scales were used as secondary outcome measures. The Clinical Global Impressions-Severity Scale (CGI-S),<sup>21,22</sup> as used in this study, measured the severity of the patient's ADHD and comorbid ODD symptoms. The Clinical Global Impressions-Improvement Scale (CGI-I),<sup>21,22</sup> as used in this study, measured the improvement (or worsening) of ADHD and ODD symptoms. The Conners' Global Index-Parent Version (CGI-P) is a 10-item rating scale completed by the parent(s) to assess problem behaviors.<sup>23</sup> The Social Readjustment Rating Scale was completed by the parent(s) and provided an indication of the level of stress in the family unit.<sup>24</sup> The ADHD Impact Module (AIM) is a specific ADHD health-outcomes instrument that has been developed recently but has not been extensively validated (J. Landgraf, MS, Lilly Research Laboratories, unpublished internal report, 1999). It was designed to measure the impact of ADHD on the emotional and social well-being of the child and family.

### Study Design

The primary objective of this study was to test the hypothesis that atomoxetine, given at a dose of 1.2 mg/kg per day (atomoxetine 1.2; once daily) for ~8 weeks, is superior to placebo in the treatment of ODD symptoms in children and adolescents with comorbid ADHD. Symptom change was measured by mean reduction in the ODD subscale of the SNAP-IV.

After a 3- to 28-day screening and washout period (study period 1), eligible patients were randomly assigned to receive double-blind treatment with atomoxetine or placebo in a 2:1 ratio for ~8 weeks (study period 2). At visit 3, after 2 weeks on atomoxetine 1.2 given once daily, each patient's blood was drawn for the determination of atomoxetine plasma concentration. Atomoxetine plasma concentration results partially determined study period 3 treatment options. Patients with a peak plasma atomoxetine concentration  $<800$  ng/mL and who failed to achieve adequate ODD symptom remission (defined as a score of  $<9$  on the SNAP-IV ODD subscale and a score of 1 or 2 on the CGI-I) were reran-

domized in a double-blind, 1:1 ratio to either remain on atomoxetine 1.2 or to be titrated up to atomoxetine at 2.4 mg/kg per day (atomoxetine 2.4). Patients with peak plasma atomoxetine concentration levels of  $\geq 800$  ng/mL or who achieved remission of ODD symptoms remained on atomoxetine 1.2. Patients who received placebo during study period 2 were titrated up to atomoxetine 1.2 during study period 3. An open-label treatment extension phase (study period 4) offered  $\sim 1$  year of additional treatment with atomoxetine.

All of the participants had an extensive medical evaluation at baseline, including a physical examination and the following laboratory measures: clinical chemistry, hematology, urinalysis, urine drug screen, cytochrome P450 2D6 genotype, thyroid stimulating hormone, and electrocardiogram. Clinical chemistry, hematology, and urinalysis were repeated during each study period. Safety was assessed at each visit by open-ended questioning for adverse events and vital sign measurements.

Study medication was given once daily in the morning during study period 2. Dosing with atomoxetine was initiated at  $\sim 0.8$  mg/kg per day for 3 days and then increased to the target dose of atomoxetine 1.2. Patients who were unable to tolerate the atomoxetine 1.2 were discontinued from the study. Twice-daily dosing was optional during the remaining study periods.

### Statistical Methods

The primary efficacy variable was the SNAP-IV ODD total score. The primary efficacy analysis was a repeated-measures analysis based on the restricted maximum likelihood method, assuming an unstructured covariance matrix during study period 2. Additionally there was a comparison of least-square means across treatment at the final week of study period 2 (visit 5) using a Satterthwaite approximation for the denominator degrees of freedom in the *t* test. The independent effects in the model included the investigator, treatment, visit, and treatment-by-visit interaction. Baseline was defined as scores obtained for visit 1 or visit 2. In the repeated-measures analysis, postbaseline SNAP-IV ODD data obtained at visits other than the scheduled visits for this questionnaire were carried forward to the next scheduled visit for the questionnaire. The sample size used had  $\sim 90\%$  power to detect a difference from placebo of 2.0 points, assuming a common SD of 4.1 points. This effect size is consistent with the effect sizes observed when using similar scales in previous placebo-controlled atomoxetine studies.

Secondary analysis of the SNAP-IV subscales was conducted using analysis of covariance (ANCOVA) on the last-observation-carried-forward (LOCF) change from baseline to end point. The independent effects in the ANCOVA model were investigator, treatment, and baseline score. Secondary variables, including the CGI-S total score, CGI-P total score, and the Social Readjustment Rating Scale total score, also were analyzed by ANCOVA using the LOCF change from baseline to end point. Because no baseline values are available for study period 2 CGI-I scores, that variable was analyzed using an analysis of variance model with terms for investigator and

treatment. End points for other secondary objectives used data from study period 3. Given that there is no true baseline for this period, these analyses are considered to be descriptive and exploratory rather than definitive in nature.

Health outcomes/quality-of-life analyses were performed by using ANCOVA on the LOCF change from baseline to end point during study period 2. Safety analyses for study period 2 included all of the randomly assigned patients who took  $\geq 1$  dose of study medication. For study period 3, safety analyses included all of the patients (randomly assigned and not randomly assigned) who took  $\geq 1$  dose of study medication. Results are reported on the basis of treatment, either placebo or atomoxetine, in study period 2, and by the atomoxetine dose received in study period 3. The atomoxetine group was then further analyzed according to the dose that they received in the study period. All of the statistical analyses were performed by using SAS 8 (SAS Institute, Inc, Cary, NC).

## RESULTS

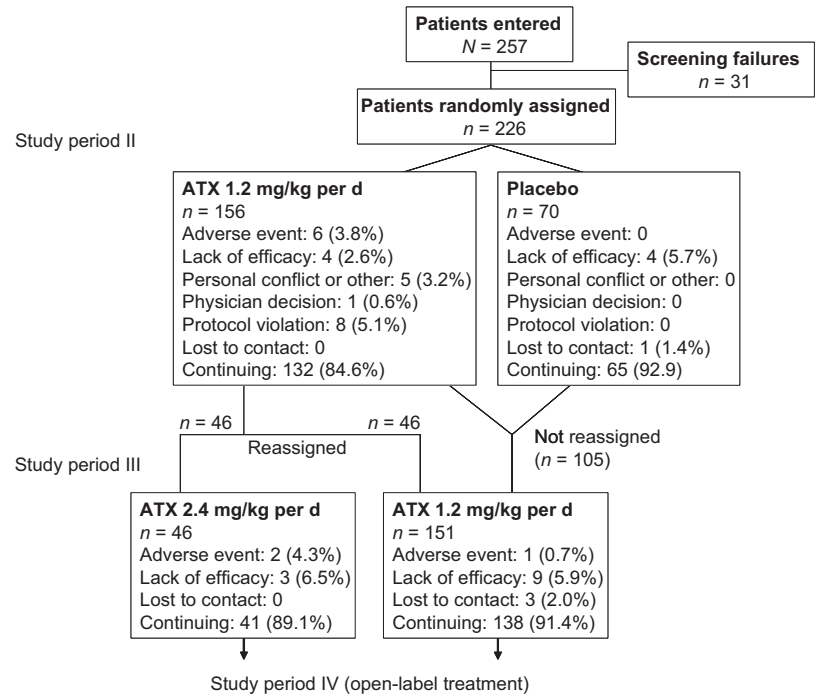
### Study Period 2

Of 257 patients initially assessed, 226 met entry criteria and were randomly assigned to treatment (Fig 1). Patient demographics and characteristics (Table 1), as well as baseline symptom measures (Table 2), were similar for both treatment groups. Results of the repeated-measures analysis on the SNAP-IV ODD total score demonstrated that overall treatment effect of atomoxetine was statistically significantly greater than that of placebo ( $P = .01$ ). Additional analyses, however, showed significant pairwise treatment differences at weeks 2 and 5 but not at week 8 postbaseline (Fig 2). In addition, an LOCF analysis indicated that SNAP-IV ODD total scores for atomoxetine and placebo groups were not significantly different (mean change  $\pm$  SD: atomoxetine,  $-3.7 \pm 5.3$ ; placebo:  $-2.9 \pm 4.3$ ;  $P = .252$ ; Table 2 and Fig 3). Importantly, on ADHD subscales of the SNAP-IV, atomoxetine was superior to placebo (Table 2 and Fig 3). A posthoc repeated-measures analysis of the overall treatment effect on SNAP-IV ODD total score was not statistically significant ( $P = .223$ ) when improvement in SNAP-IV-combined ADHD subscore was taken into account.

Interestingly, a posthoc analysis revealed that patients with dysthymia, general anxiety, or separation anxiety ( $n = 14$ ) had smaller reductions (LOCF, mean change from baseline) in ODD scores than those without these conditions, and this difference was statistically significant (with dysthymia, general anxiety, or separation anxiety:  $-1.5$ ; without any of these conditions:  $-3.5$ ;  $P = .0185$ ). However, excluding these patients from the overall (LOCF) analysis had no effect, because there were so few of them ( $P = .2369$ ).

Atomoxetine was superior to placebo on the CGI-I and CGI-S, as well as the child and child self-control subscales but not on the family subscales of the AIM (Table 2). For the CGI-P, atomoxetine was significantly better than placebo on the total and restless/impulsive

FIGURE 1  
Patient flow diagram. ATX indicates atomoxetine.



subscales but not on the emotional lability subscale (Table 2).

### Safety

For the atomoxetine group, the mean  $\pm$  SD final dose was  $1.2 \pm 0.28$  mg/kg per day, and the mean  $\pm$  SD maximum dose was  $1.52 \pm 0.54$  mg/kg per day. Rates of adverse events were generally low and similar between the atomoxetine and placebo groups. However, rates of decreased

appetite, nausea, and fatigue were significantly higher for atomoxetine than for placebo (decreased appetite: atomoxetine, 24.4%; placebo, 1.4%;  $P < .001$ ; nausea: atomoxetine, 20.5%; placebo, 8.6%;  $P = .033$ ; fatigue: atomoxetine, 17.3%; placebo, 5.7%;  $P = .021$ ).

Changes in vital signs and weight were generally low and consistent with known effects of norepinephrine reuptake inhibitors. However, rates of diastolic blood pressure increase were significantly higher in the atomoxetine group compared with the placebo group (categorical change, increase of  $\geq 5$  mm to above the 95th percentile: atomoxetine 1.2: 14 of 144 [9.7%]; placebo: 1 of 63 [1.6%];  $P = .042$ ). Rates of weight decrease also were significantly higher in the atomoxetine group (categorical change, decrease of 3.5% from baseline weight: atomoxetine 1.2: 60 of 154 [39.0%]; placebo: 2/69 [2.9%];  $P < .001$ ). Categorical changes in systolic blood pressure, pulse (increase of  $\geq 25$  to a value of  $\geq 110$ ), high temperature (increase of  $\geq 1.0$  to a value of  $\geq 37.7$ ), and low temperature (decrease of  $\geq 1.3$  to a value of  $\leq 35.6$ ) were not significantly different between treatment groups. Overall, rates of discontinuation for the 2 groups in study period 2 were low and not significantly different (atomoxetine: 15.4%; placebo: 7.1%;  $P = .130$ ; Fig 1).

### Study Period 3

Of 131 patients continuing from study period 2 who were originally randomized to the atomoxetine group, 92 were nonresponders who also did not have atomoxetine plasma levels  $>800$  ng/mL. These patients were rerandomized either to continue receiving atomoxetine 1.2 or a higher dose of atomoxetine 2.4. There were no statistically significant differences between the 2 treat-

TABLE 1 Patient Demographics

Variable	Atomoxetine (N = 156)	Placebo (N = 70)
Age, mean (SD)	9.5 (1.9)	9.7 (1.9)
Origin, %		
White	94.9	95.7
Gender, %		
Male	91.7	97.1
Female	8.3	2.9
ADHD subtype, %		
Combined	84.6	84.3
Inattentive	9.0	11.4
Hyperactive/impulsive	6.4	4.3
Previous stimulant exposure, %		
Yes	66.7	74.3
No	33.3	25.7
Height, mean (SD), cm	136.6 (11.7)	139.3 (12.2)
Weight, mean (SD), kg	33.2 (8.8)	36.3 (10.7) <sup>a</sup>
CDRS-R total score, mean (SD)	26.5 (4.6)	26.7 (5.4)
Final dose atomoxetine, mean (SD), mg/kg per d	1.20 (0.28)	—
Max dose atomoxetine, mean (SD), mg/kg per d	1.52 (0.54)	—

CDRS-R indicates Children's Depression Rating Scale-Revised.

<sup>a</sup>  $P = .024$ .

**TABLE 2 Study Period 2 Secondary Analyses**

Variable	Atomoxetine			Placebo			P
	N	Baseline, Mean (SD)	Mean Change, Mean (SD)	N	Baseline, Mean (SD)	Mean Change, Mean (SD)	
SNAP-IV							
ODD	153	18.9 (2.3)	-3.7 (5.3)	68	18.9 (2.4)	-2.9 (4.3)	.252
Combined	153	44.7 (6.4)	-9.6 (11.4)	68	45.3 (5.7)	-4.4 (8.4)	<.001
Inattentive	153	22.7 (3.2)	-5.0 (6.0)	68	22.2 (3.7)	-2.2 (4.8)	<.001
Hyperactivity/impulsivity	153	22.1 (4.4)	-4.6 (6.2)	68	23.1 (3.3)	-2.2 (4.5)	.003
CGI-I	154	3.5 (1.4)		69	3.5 (1.4)	3.9 (1.0)	.037
CGI-S	152	5.3 (0.8)	-0.7 (1.4)	68	5.4 (0.8)	-0.3 (1.1)	.013
ADHD impact module							
Child	152	29.5 (14.6)	10.2 (20.3)	67	27.9 (16.2)	2.5 (18.4)	.002
Child self-control	151	2.9 (0.9)	0.13 (1.00)	66	2.9 (0.9)	0.17 (1.00)	.715
Family	151	31.1 (22.0)	9.4 (20.9)	67	29.0 (21.0)	3.5 (16.1)	.018
CGI-P							
Total	150	24.2 (3.9)	-4.7 (6.9)	67	23.9 (3.5)	-1.6 (5.2)	.002
Restless/impulsive	150	18.0 (2.8)	-3.7 (5.2)	67	18.1 (2.5)	-1.2 (3.9)	<.001
Emotional lability	150	6.2 (1.9)	-1.0 (2.5)	67	5.7 (2.0)	-0.4 (2.1)	.383

ment groups on any measure, including the SNAP-IV ODD, CGI-I, CGI-S, AIM, and CGI-P.

The average  $\pm$  SD maximum prescribed dose for the atomoxetine 1.2 group was  $1.23 \pm 0.14$  mg/kg per day and for the atomoxetine 2.4 group was  $2.29 \pm 0.25$  mg/kg per day. Despite the dose difference, there were no significant differences between treatment groups in the rates of any adverse event appearing in  $\geq 5\%$  of patients. (Note that the safety analyses for the atomoxetine 1.2 group in study period 3 included rerandomized patients [ $n = 46$ ], as well as those patients continuing to study period 3 who were not rerandomized [ $n = 105$ ]). Changes in vital signs and weight were generally low, and none were significantly different between treatment groups. Overall, the rates of discontinuation for the 2 groups in study period 3 were low and not significantly different (atomoxetine 1.2: 8.6%; atomoxetine 2.4: 10.9%;  $P = .770$ ; Fig 1).

**DISCUSSION**

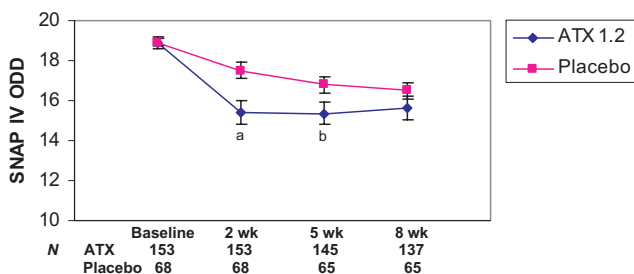
Repeated-measures analysis of the overall treatment effect demonstrated statistically significant superiority of atomoxetine over placebo in reducing ODD symptoms in this sample of patients with comorbid ADHD. However, the pattern of differences between the atomoxetine and

placebo groups was improvement favoring atomoxetine at weeks 2 and 5 but convergence by week 8 (the study end point). Thus, analyses that focused on end point data demonstrated no statistically significant advantage for atomoxetine. Repeated-measures analyses are more sensitive to group differences than to end point analyses. Landmark analyses based on end point data are generally preferred by regulatory authorities, because they demonstrate the durability of treatment effect<sup>25</sup> but are vulnerable to outlying scores in either the treatment or control group and to the influence that time on treatment may have on outcome. Inadequate time on treatment can lead to type 1 errors if the advantages of active treatment compared with placebo are lost over time or type 2 errors if insufficient time has been allowed for the treatment to reach its maximal effect.

In our trial, the failure of atomoxetine to separate from placebo at end point on the primary outcome measure was not the result of an unexpectedly large response to placebo. For example, the mean reduction in SNAP-IV ODD scores from baseline to end point for the placebo group (15%) was substantially less than the 28% mean reduction in Conners' conduct problems scores obtained for the placebo group in a trial of clonidine added to psychostimulant medication for children and young adolescents with ADHD and ODD.<sup>26</sup> Also, the failure to detect separation between the atomoxetine and placebo groups on the SNAP-IV ODD scale was not the result of inclusion of patients with dysthymia or anxiety disorders. These patients did not, in fact, improve as much as other patients, but their small numbers were not enough to influence the overall outcome. The separation of atomoxetine from placebo at end point did occur on secondary measures, including SNAP-IV ADHD ratings, CGI-I, CGI-S, AIM, and CGI-P.

**LIMITATIONS**

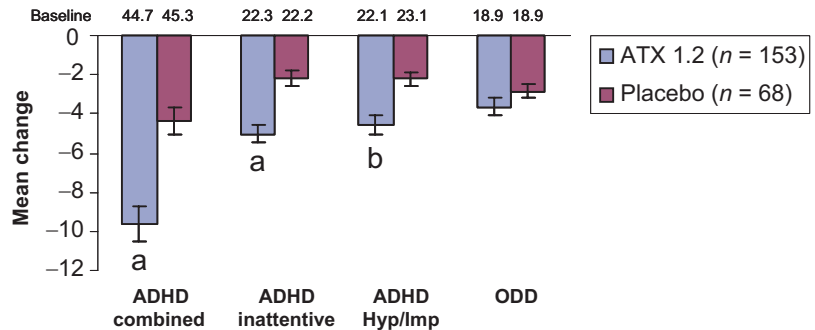
The findings from the present study do not provide conclusive evidence as to whether the effect on ODD symptoms would be apparent in the absence of comor-



**FIGURE 2** Repeated-measures analysis of the SNAP-IV ODD subscale. <sup>a</sup>  $P < .01$  for atomoxetine 1.2 versus placebo; <sup>b</sup>  $P < .05$  for atomoxetine 1.2 versus placebo. The overall treatment effect was significant:  $P = .01$ . ATX indicates atomoxetine.

FIGURE 3

Secondary SNAP-IV analyses (last observation carried forward).  
<sup>a</sup>  $P < .001$  for atomoxetine versus placebo; <sup>b</sup>  $P < .01$  for atomoxetine versus placebo. ATX indicates atomoxetine.



bid ADHD. In addition, it is not possible, from the existing data, to predict whether convergence on the ODD measure would be sustained over subsequent weeks. Eight weeks was chosen as the end point for the study, because previous research has shown that most responders to atomoxetine, on the basis of measures of ADHD symptoms, have demonstrated significant improvement by this time. However, ODD symptoms may require more time to show improvement. In addition, the cutoff score for ODD in the SNAP-IV scale of  $\geq 15$  points may have been a rather high threshold for patients to enter the study. As a result, the patients in the study had considerable ODD symptom severity, potentially making it difficult to show significant medication effect on these symptoms.

The benefits seen at weeks 2 and 5 in our study may have been a nonspecific effect of sedation. Countering this argument, separation was not seen between clonidine and placebo on conduct symptoms in the early weeks of an augmentation trial involving similar patients to those in this study, yet clonidine is generally more sedating than atomoxetine.<sup>26</sup>

The Clinical Global Impressions improvement and severity instruments were not designed to tease out differential responses in ADHD or ODD symptoms. It is not possible, therefore, to determine whether changes in ODD symptoms contributed to the separation between atomoxetine and placebo on global improvement. When improvement in SNAP-IV ADHD ratings was taken into account, the repeated-measures analysis of SNAP-IV ODD scores was not significant. However, this posthoc analysis must be interpreted with caution. The correlation between ADHD and ODD measures does not imply causality.

In study period 3, titration to 2.4 mg/kg per day of atomoxetine was not achieved for most patients. However, previous research has shown that patients with comorbid ADHD and ODD show a significant reduction in ADHD symptomatology once a dose of 1.8 mg/kg per day has been achieved.<sup>16</sup>

## CONCLUSIONS

Our study confirms previous findings<sup>15,16</sup> that patients with ADHD and comorbid ODD show statistically and clinically significant improvement in ADHD symptoms and global clinical functioning when treated with atomoxetine. It remains uncertain whether atomoxetine ex-

erts a specific and enduring effect on ODD symptoms. Patients with ADHD and ODD will not be disadvantaged by treatment with atomoxetine, but additional pharmacologic or psychological strategies may need to be used to address the oppositional symptoms. Early reduction in ODD symptoms after the introduction of atomoxetine should not be mistaken for a sustained medication effect on these symptoms.

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