An 8-Week, Randomized Controlled Trial of Atomoxetine, Atomoxetine Plus Buspirone, or Placebo in Adults With ADHD

Suzanne M. Sutherland, MD; Lenard A. Adler, MD; Crystal Chen, MD; Michael D. Smith, PhD; and Douglas E. Feltner, MD

ABSTRACT

Objective: To examine the efficacy and safety of atomoxetine combined with buspirone versus atomoxetine monotherapy and placebo in adult attention-deficit/hyperactivity disorder (ADHD).

Method: In this randomized, 8-week, 3-arm, double-blind, placebo-controlled trial conducted from November 2004 through December 2005, 241 adults with ADHD were randomly assigned in a 2:2:1 ratio to receive up to twice-daily atomoxetine and thrice-daily buspirone (n = 97), twice-daily atomoxetine (n = 97), or placebo (n = 47). Participants met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria for ADHD. The primary efficacy measure was the adult ADHD Investigator Symptom Rating Scale (AISRS).

Results: Decrease in the AISRS total score was significantly greater for atomoxetine-buspirone than placebo at all time points from weeks 1 to 7, with an estimated mean difference of −4.80 ($P = .001$). Reduction in the mean AISRS total score was numerically greater for atomoxetine-buspirone than for atomoxetine at all time points, but statistically significant at week 4 only (estimated difference = −2.04, $P < .10$). The effect size for atomoxetine plus buspirone was 0.51, and for atomoxetine alone, it was 0.40. Insomnia, nausea, dry mouth, headache, and asthenia were frequently reported adverse events for both active treatment groups, and dizziness was also frequently reported for the atomoxetine-buspirone group. Discontinuations due to treatment-related adverse effects were 15.5% for atomoxetine-buspirone, 11.3% for atomoxetine, and 14.9% for placebo.

Conclusions: There was little indication of improvement for atomoxetine plus buspirone versus atomoxetine monotherapy, as most efficacy measures showed only slightly greater quantitative improvement for the combination, generally without statistical significance. It is of note, however, that the quantitative differences between these 2 groups were virtually all in the direction of greater efficacy for the atomoxetine plus buspirone group.

Trial Registration: clinicaltrials.gov Identifier: NCT00174226

J Clin Psychiatry 2012;73(4):445–450

Submitted: *December 14, 2010; accepted April 29, 2011.*
Online ahead of print: *January 10, 2012 (doi:10.4088/JCP.10m06788).*
Corresponding author: *Lenard A. Adler, MD, Professor of Psychiatry and Child and Adolescent Psychiatry, NYU School of Medicine, 650 First Ave, 7th Floor, New York, NY 10016 (lenard.adler@nyumc.org).*

Adult attention-deficit/hyperactivity disorder (ADHD) is a highly common (4.4% prevalence) and impairing disorder.[1–4] Comorbidities are common, with up to 50% of patients also having mood and/or anxiety disorders.[4] It is estimated that < 20% of adults with ADHD are diagnosed and treated.[5,6]

Pharmacotherapy with stimulants has long been the mainstay of treatment for ADHD, although the nonstimulant atomoxetine was the first approved medication for adults. Other US Food and Drug Administration–approved medications for adult ADHD include 4 sustained-release stimulants. Studies have documented the efficacy of long-acting stimulants in adults,[7–10] but many patients experience incomplete resolution of symptoms and some have dose-limiting side effects.[11] Consequently, medications are often combined for improved effectiveness and tolerability.[12]

Atomoxetine is a selective norepinephrine reuptake inhibitor that is thought to exert its efficacy in ADHD via its activity in the prefrontal cortex, where it increases both norepinephrine and dopamine by blocking the reuptake of these neurotransmitters at the norepinephrine receptor.[13] Atomoxetine has been shown to be effective in adults with ADHD.[14,15] In 2 placebo-controlled, 10-week studies, significant improvement in ADHD symptoms in the atomoxetine group was noted as early as 2 weeks and continued to increase throughout the trial.[14] Similarly, in a 14-week, placebo-controlled trial of adults with ADHD and comorbid social anxiety disorder, significant improvement was seen in ADHD symptoms after atomoxetine treatment.[15] In a 6-month trial in adults with ADHD, significant improvement was seen at the initial 10 weeks, and was maintained through 6 months, of atomoxetine therapy; the duration of effect extended into the evening despite once-daily dosing.[16] The anxiolytic buspirone, a partial 5-hydroxytryptamine 1A (5-HT_{1A}) receptor agonist, has also been shown to increase levels of both dopamine and norepinephrine in the frontal cortex of rats.[17] Although buspirone has been shown to be effective for ADHD in 2 open-label studies[18,19] and 1 small controlled study in children,[20] it has not been previously studied as monotherapy or adjunctive therapy for adult ADHD in a randomized placebo-controlled trial.

This randomized, double-blind, placebo-controlled, 3-arm, parallel group study evaluated the efficacy and tolerability of augmenting atomoxetine with buspirone in a clinical population of adults with ADHD. We hypothesized that the addition of a 5-HT_{1A} partial agonist to a norepinephrine reuptake inhibitor would enhance overall efficacy, given the above-noted clinical studies in adult ADHD and the supportive preclinical data.

METHOD

Adults aged 18 to 60 years who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision

Clinical Points

- The short-term addition of buspirone to atomoxetine in adult ADHD was well tolerated.
- Adding buspirone to atomoxetine for 8 weeks in nonanxious adult ADHD patients had minor overall effects but may benefit some patients.

(*DSM-IV-TR*)[21] criteria for ADHD, via the Adult ADHD Clinician Diagnostic Scale version 1.2,[1] and scored ≥ 24 on the adult ADHD Investigator Symptom Rating Scale (AISRS)[22] were eligible to participate. Individuals were excluded if they had a lifetime or current history of psychosis, bipolar disorder, mental retardation or learning disability; had current anxiety or depressive disorders; had substance abuse or dependence within 3 months of screening or positive urine screen for drugs of abuse at screening; used atomoxetine, buspirone, or a monoamine oxidase inhibitor within 2 weeks prior to screening; had seizure disorder, urinary retention, narrow-angle glaucoma, or cardiac conduction defects; had any current general medical conditions considered clinically significant as judged by the investigator; or were poor metabolizers of cytochrome P450 2D6 (CYP2D6). Use of substances with psychoactive properties and potent CYP3A4 or CYP2D6 inducers or inhibitors was prohibited.

This study was conducted at 8 sites in the United States from November 2004 through December 2005. Institutional review board approval for each site was obtained by a central or local board prior to study initiation. Study conduct was in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice,[23] ethical principles originating in or derived from the Declaration of Helsinki,[24] and the standard operating procedures of Pfizer Inc. All participants provided written informed consent prior to initiating the study. The study is registered at clinicaltrials.gov (identifier: NCT00174226).

Participants were screened for a period of up to 28 days to establish eligibility. At baseline, eligible participants with scores of ≥ 24 on the AISRS, < 15 on the Hamilton Anxiety Rating Scale (HARS),[25] and < 20 on the Montgomery-Asberg Depression Rating Scale (MADRS)[26] were randomly assigned in a 2:2:1 ratio to atomoxetine and buspirone combination therapy, atomoxetine alone, or placebo for a 4-week dose titration and stabilization period, followed by a 3-week maintenance period and then a 1-week period during which the medication was tapered and discontinued. During the titration and stabilization period, atomoxetine was started at 40 mg/d for both active treatment groups and increased to 80 mg/d (40 mg every morning and 40 mg every evening) after 2 weeks. After 4 weeks, the dose of atomoxetine could be increased to 100 mg/d (60 mg every morning and 40 mg every evening) based on tolerability and efficacy. Buspirone was started at 15 mg/d (7.5 mg twice a day), increasing to 30 mg/d (15 mg twice a day) after 1 week and 45 mg/d (15 mg 3 times a day) after 3 weeks.

The primary efficacy measure was the investigator-rated AISRS. The AISRS is an 18-item scale that assesses the 18 *DSM* symptoms of ADHD and has been found to be a valid measure of medication response in adults with ADHD.[22] Each item is scored on a 4-point scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe), with a maximum total score of 54.[27] The AISRS uses the same adult-specific language and adult-specific prompts as the Adult ADHD Clinician Diagnostic Scale version 1.2, creating a semistructured interview.[2] Rater training for the Adult ADHD Clinician Diagnostic Scale version 1.2 and AISRS was conducted according established guidelines.[27]

Secondary efficacy measures included the self-report Brown Attention-Deficit Disorder Scale[28] and the Clinical Global Impressions-severity of illness (CGI-S) scale.[29] The HARS[25] and the MADRS[26] were used to measure anxiety and depressive symptoms, respectively.

Safety was evaluated as the incidence of symptoms and adverse events at a given dose.

Statistical Analysis

The primary efficacy evaluation was the mean change in the AISRS total score from weeks 1 to 7 and in the individual weeks 1, 2, 3, 4, and 7. Additional planned pre hoc efficacy measures included the proportion of responders who achieved a ≥ 30% improvement in the AISRS total score by end of treatment and the proportion of responders who were rated as 1 (not at all ill) or 2 (borderline ill) on the CGI-S.

The efficacy analysis set (intent to treat) comprised all patients who were randomized to treatment and received at least 1 dose of study drug. All significance tests were assessed using a 1-sided significance level of .10 in order to evaluate the study hypotheses of superiority of both atomoxetine-buspirone combination therapy and atomoxetine versus placebo, and of the combined therapy versus atomoxetine alone. Accordingly, the 80% confidence interval is shown for all treatment comparisons.

The primary analysis was a comparison between treatment groups using a mixed model repeated-measures analysis for the change from baseline to weeks 1, 2, 3, 4, and 7, with model terms for baseline AISRS total score, study week, treatment group, and week-by-treatment interaction, as well as subject as a random effect. Estimates of the change from baseline to individual weeks 1, 2, 3, 4, and 7, and the overall change from weeks 1 to 7 were calculated for each treatment group and treatment comparisons. The inattentive and hyperactive/impulsive subscales of the AISRS and the Brown Attention-Deficit Disorder Scale total score were also examined using the same analytic method. The responder end points data were analyzed via generalized estimating equation models for repeated-measures data and binary response. The model terms include treatment, week, center, and treatment-by-week interaction.

Table 1. Repeated-Measures Analysis of Adult ADHD Investigator Symptom Rating Scale Total Score Change From Baseline

Variable	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1–7
Atomoxetine + buspirone vs atomoxetine						
LS mean (SE)[a]	−0.14 (1.11)	−0.23 (1.30)	−1.31 (1.44)	−2.04 (1.56)	−1.67 (1.72)	−1.08 (1.21)
80% CI	−1.57 to 1.28	−1.89 to 1.44	−3.16 to 0.54	−4.05 to −0.04	−3.89 to 0.55	−2.64 to 0.49
1-sided *P* value	.450	.431	.183	.096	.167	.188
Atomoxetine + buspirone vs placebo						
LS mean (SE)[a]	−4.23 (1.35)	−4.55 (1.58)	−4.93 (1.78)	−5.15 (1.95)	−5.13 (2.17)	−4.80 (1.50)
80% CI	−5.97 to −2.50	−6.58 to −2.52	−7.23 to −2.64	−7.65 to −2.64	−7.91 to −2.34	−6.72 to −2.87
1-sided *P* value	.001	.002	.003	.005	.010	.001
Atomoxetine vs placebo						
LS mean (SE)[a]	−4.09 (1.35)	−4.32 (1.57)	−3.63 (1.77)	−3.10 (1.93)	−3.46 (2.14)	−3.72 (1.49)
80% CI	−5.82 to −2.36	−6.34 to −2.31	−5.90 to −1.35	−5.58 to −0.62	−6.21 to −0.70	−5.63 to −1.81
1-sided *P* value	.001	.003	.021	.055	.054	.007

[a]From mixed model repeated-measures analysis.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, LS = least squares, SE = standard error.

RESULTS

Randomization and Outcome

A total of 241 adults were randomized to treatment, with 97 randomized to each of the 2 medication arms and 47 to the placebo arm. The study was completed by 67% of participants (n = 162): 65% for the atomoxetine and buspirone combination therapy group (n = 63), 72% for the atomoxetine alone group (n = 70), and 57% for the placebo group (n = 27). The intent-to-treat population was based on 241 participants, which included 97 in the atomoxetine and buspirone combination therapy and atomoxetine alone groups and 47 in the placebo group.

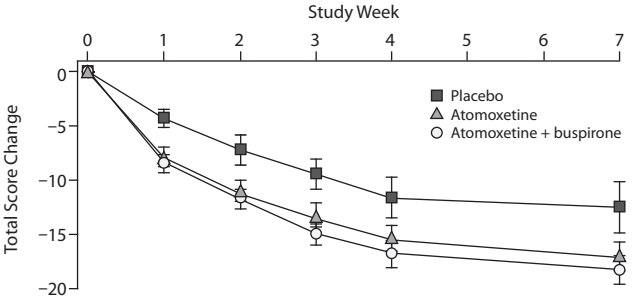
There were no significant differences in height, weight, or demographic characteristics between the 3 groups, and the study sample was comparable to samples in prior studies of atomoxetine in adult ADHD. The mean age of participants was 37 years; 59% of the sample was male. Approximately 80% of the sample identified themselves as white, 10% as Hispanic, 7% African American, and 3% as other/mixed ethnicity. The mean ± SD dose of atomoxetine achieved was the same in the atomoxetine-alone and atomoxetine and buspirone combination therapy groups and was 39.1 ± 6.1 mg and 39.6 ± 6.0 mg during weeks 1 and 2, 74.6 ± 9.6 and 74.4 ± 12.9 during weeks 3 and 4, and 89.7 ± 21.6 and 90.7 ± 20.9 during weeks 5–7 for the atomoxetine-alone and atomoxetine and buspirone combination therapy groups, respectively.

Efficacy Analysis

Total scores on the AISRS did not differ between groups at baseline, with mean (SD) scores of 36.6 (7.3), 36.3 (7.8), and 37.4 (8.3) for atomoxetine and buspirone combination therapy, atomoxetine alone, and placebo, respectively. The AISRS total score decreased at each time point from baseline to week 7 for all treatment groups, and, at week 7, the mean (SD) scores were 18.2 (11.2), 19.0 (11.4), and 22.9 (14.2) for atomoxetine and buspirone combination therapy, atomoxetine alone, and placebo, respectively.

The summary change scores for all treatment groups and all weeks are presented in Table 1. There was significantly greater reduction in the AISRS total score for atomoxetine and buspirone combination therapy versus placebo at all time points from weeks 1 to 7 (Figure 1), with an estimated mean change from baseline to week 7 of −4.80 (SE = 1.50; *P* = .001). The reduction in AISRS total score was numerically greater for atomoxetine and buspirone combination therapy than for atomoxetine alone at all weeks, but the difference was statistically significant only at week 4. The effect size for atomoxetine and buspirone combination therapy was 0.51, and, for atomoxetine alone, it was 0.40.

Figure 1. Change in Adult ADHD Investigator Symptom Rating Scale Total Score by Treatment and Week



Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

The summary repeated-measures analysis results for the inattentive and impulse/hyperactivity subscales are presented in Table 2. The mean AISRS inattentive subscale score decreased from baseline to week 7 for all treatment groups. The mean (SE) change from baseline to week 7 was significantly greater for atomoxetine and buspirone combination therapy than for placebo (−1.60 [1.0], *P* = .049) and numerically greater but not statistically significant for atomoxetine and buspirone combination therapy versus atomoxetine alone. However, a statistically significant difference in the inattentive subscale score for atomoxetine and buspirone combination therapy versus atomoxetine alone was observed at week 4 (−1.91, *P* = .046) and remained so at week 7 (−2.41, *P* = .017). The mean AISRS hyperactivity/impulsivity subscale score decreased from baseline to week 7 for all treatment groups, with the mean change from

Table 2. Repeated-Measures Analysis of Score Change From Baseline on Adult ADHD Investigator Symptom Rating Scale Subscales

	Inattentive		Hyperactivity/Impulsivity	
Variable	Week 7	Weeks 1–7	Week 7	Weeks 1–7
Atomoxetine + buspirone vs atomoxetine				
LS mean (SE)[a]	−2.41 (1.1)	−0.50 (0.8)	1.06 (1.21)	−0.30 (0.99)
80% CI	−3.85 to −0.96	−1.49 to 0.51	−0.50 to 2.61	−1.57 to 0.98
1-sided *P* value	.017	.263	.808	.383
Atomoxetine + buspirone vs placebo				
LS mean (SE)[a]	−2.96 (1.4)	−1.60 (1.0)	−1.97 (1.53)	−3.24 (1.22)
80% CI	−4.80 to −1.11	−2.84 to −0.36	−3.94 to −0.00	−4.81 to −1.67
1-sided *P* value	.020	.049	.100	.004
Atomoxetine vs placebo				
LS mean (SE)[a]	−0.55 (1.4)	−1.10 (1.0)	−3.03 (1.51)	−2.95 (1.21)
80% CI	−2.37 to 1.27	−2.33 to 0.12	−4.97 to −1.08	−4.51 to −1.39
1-sided *P* value	.348	.124	.023	.008

[a]From mixed model repeated-measures analysis.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, LS = least squares, SE = standard error.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥ 10% Subjects in Any Group

Adverse Event	Placebo (n = 47), n (%)	Atomoxetine (n = 97), n (%)	Atomoxetine + Buspirone (n = 97), n (%)
Asthenia	8 (17.0)	25 (25.8)	22 (22.7)
Headache	6 (12.8)	28 (28.9)	26 (26.8)
Vasodilatation	0 (0.0)	5 (5.2)	10 (10.3)
Anorexia	3 (6.4)	19 (19.6)	16 (16.5)
Constipation	3 (6.4)	8 (8.2)	14 (14.4)
Dry mouth	6 (12.8)	29 (29.9)	36 (37.1)
Nausea	4 (8.5)	25 (25.8)	30 (30.9)
Dizziness	5 (10.6)	13 (13.4)	31 (32.0)
Insomnia	10 (21.3)	42 (43.3)	41 (42.3)
Libido decreased	2 (4.3)	12 (12.4)	4 (4.1)
Nervousness	4 (8.5)	17 (17.5)	14 (14.4)
Paresthesia	1 (2.1)	4 (4.1)	10 (10.3)
Somnolence	8 (17.0)	16 (16.5)	22 (22.7)
Sweating	1 (2.1)	10 (10.3)	7 (7.2)

baseline similar for atomoxetine and buspirone combination therapy and for atomoxetine alone, both of which were significantly greater than placebo. The changes from baseline for atomoxetine and buspirone combination therapy and atomoxetine alone were greater than those for placebo for each time point from weeks 1 to 7.

The percentage of responders on the AISRS increased from week 1 to week 7 for all treatment groups. At week 7, the responder rate was 78% for the atomoxetine and buspirone combination therapy group, 69% for the atomoxetine-alone group, and 47% for the placebo group. The response on the AISRS was significantly better for atomoxetine and buspirone combination therapy compared to placebo at all time points ($P < .014$) and numerically greater than atomoxetine alone, but it was significant only at week 3 (70% versus 58%, $P = .084$). The percentage of responders on the CGI-S was greater for the 2 active treatment groups than for placebo for all weeks. At week 7, the percentage of CGI-S responders was 25% for both atomoxetine and buspirone combination therapy and atomoxetine-alone groups and 17% for the placebo group.

The Brown Attention-Deficit Disorder Scale total score decreased over the course of treatment for each arm, with mean (SD) changes from baseline to end of treatment of −35.4 (27.7) for the atomoxetine and buspirone combination therapy group, −32.3 (25.6) for atomoxetine alone, and −22.2 (26.3) for placebo. The mean decrease from baseline to week 7 in the Brown Attention-Deficit Disorder Scale total score was significantly greater for atomoxetine and buspirone combination therapy than for placebo (−11.23, $P = .004$), and it was numerically in favor of atomoxetine and buspirone combination therapy versus atomoxetine alone, but not significant ($P > .12$).

Consistent with the exclusion of subjects with current anxiety and mood disorders, the baseline scores for the HARS and MADRS were low for all 3 groups. The mean (SD) HARS total score at baseline was 7.1 (3.7) for the atomoxetine and buspirone combination therapy group, 7.0 (4.1) for the atomoxetine-alone group, and 6.4 (4.2) the for placebo group. The mean (SD) MADRS total score at baseline was 8.6 (4.8) for the atomoxetine and buspirone combination therapy group, 7.9 (4.6) for the atomoxetine-alone group, and 7.5 (4.9) for the placebo group. Changes over the course of treatment were small and not significant for any of the groups.

Safety Analysis

There were no deaths in the study. No serious adverse events related to treatment were reported. The total number of withdrawals attributed to treatment-related adverse events was 15 (15.5%) for the atomoxetine and buspirone combination therapy group, 11 (11.3%) for the atomoxetine-alone group, and 7 (14.9%) for the placebo group. A review of all adverse events showed that the most affected body system was the nervous system, followed by the digestive system.

Insomnia was the most frequently reported adverse event in both the atomoxetine and buspirone combination therapy and the atomoxetine-alone groups (42.3% and 43.3%, respectively), compared to 21.3% in the placebo group (Table 3). Other adverse events reported by ≥ 20% of the atomoxetine and buspirone combination therapy group included somnolence, dizziness, nausea, dry mouth, headache, and asthenia. Other adverse events reported by ≥ 20% of the atomoxetine-alone group included asthenia, headache, dry mouth, and nausea.

DISCUSSION

Results for all of the primary and secondary objectives that measured ADHD symptoms, including the CGI-S scores, showed that the atomoxetine-buspirone combination therapy was significantly superior to placebo at weeks 4 and 7 and cumulatively from baseline to end of treatment.

The change of 3.46 (SE = 2.14) in the AISRS total score seen at week 7 in the atomoxetine-alone group is similar to those reported for in 2 pivotal studies of atomoxetine in adult ADHD (3.50 for one and 3.8 for the other),[14] and also similar to the 3.70 difference seen at 10 weeks in a more recent adult ADHD trial.[16] The addition of buspirone to atomoxetine did not appear to make a difference in overall tolerability to treatment, although somnolence and dizziness were more frequently reported in the atomoxetine and buspirone combination therapy group, and decreased libido was more common in the atomoxetine-alone group.

There was little indication of improvement for atomoxetine-buspirone over atomoxetine alone; most efficacy measures showed only slightly greater improvement for the combination, generally without statistical significance. However, the numerical changes were almost always greater for the combined atomoxetine and buspirone combination therapy group versus the atomoxetine-alone group. When there was a statistically significant difference between the 2 groups, it was generally in favor of the atomoxetine and buspirone combination therapy group. The exception to this was in the hyperactivity/impulsivity subscale of the AISRS on which the score for the atomoxetine and buspirone combination therapy group decreased slightly more than the atomoxetine-alone group over the first 3 weeks of treatment, but the atomoxetine-alone group showed slightly greater improvement from weeks 4 to 7. In spite of this, the overall improvement in total AISRS score remained greater for the atomoxetine and buspirone combination therapy group, reflecting the more substantial improvement seen for that group in the AISRS inattentive subscale. For the primary end point, the AISRS total score, statistical significance was reached at week 4 but was not maintained at week 7 for the atomoxetine and buspirone combination therapy group as compared with the atomoxetine-alone group, a finding that suggests that adding buspirone to atomoxetine might result in earlier improvement as compared with atomoxetine alone. A longer treatment trial may have yielded greater improvement and perhaps allowed for greater differentiation between the treatment groups.

The secondary ADHD efficacy measures also reflect the general trend of numerical benefit for the atomoxetine and buspirone combination therapy group as compared with the atomoxetine-alone group, although the benefit was generally not statistically significant. The responder analysis based on the AISRS total score shows statistically significant superiority at week 3 for atomoxetine and buspirone combination therapy versus atomoxetine alone, but this superiority is no longer significant at week 7, although the actual percentage of responders is greater at all time points (78% for atomoxetine and buspirone combination therapy and 69% for atomoxetine alone). On the CGI-S, the percentage of responders is again numerically greater for atomoxetine and buspirone combination therapy versus atomoxetine alone at all time points, but without statistical significance for the final responder analyses. The Brown Attention-Deficit Disorder Scale shows results that are similar to the AISRS scale.

Although comorbid anxiety symptoms are common in adult ADHD, the sample in this clinical trial had little comorbid anxiety, as reflected in the low baseline HARS scores.[30] If an advantage had been seen in this study for the combination therapy, it might have been presumed related to the anxiolytic effect of buspirone on anxiety symptoms; however, no significant effects were seen on total HARS scores for either the atomoxetine and buspirone combination therapy or the atomoxetine-alone groups.

While these results clarify the clinical effects of buspirone in adult ADHD, their relevance to the hypothesis that 5-HT_{1A} partial agonism will enhance norepinephrine reuptake inhibitor efficacy is more nuanced. Buspirone is a 5-HT_{1A} partial agonist, with a reported Ki at the 5-HT_{1A} receptor of 8.9 nM.[31] Buspirone is also a moderately high affinity dopamine D_2 and D_3 antagonist (Ki = 34.0 and 12.0 nM, respectively). Risperidone, a 5-HT_2/D_2 antagonist has been reported to reduce ADHD symptoms in children.[32,33] Further, buspirone has highly variable pharmacokinetics in humans, and is metabolized to 1-pyrimidinylpiperazine,[33] a low-affinity antagonist for the human α_{2A} receptor (Ki = 301 nM).[31] Exposure to 1-pyrimidinylpiperazine is about 16-fold higher than buspirone, suggesting that the α_{2A} antagonist activity of 1-pyrimidinylpiperazine may also be relevant.

There are several limitations to the generalizability of these findings. Patients with comorbid mood and anxiety disorders were excluded, which limited the levels of symptoms of anxiety and depression that were allowed. Since comorbid anxiety and mood disorders are common in the adult ADHD population, it is possible that buspirone would be of benefit for treating anxiety and perhaps mood symptoms in a more typical clinical population. The possible potentiative effects of the addition of buspirone in patients with adult ADHD and comorbid anxiety disorders may be particularly important given atomoxetine's efficacy in patients with adult ADHD and social anxiety disorder.[15]

While this study does not demonstrate significant overall superior efficacy for the combination of buspirone and atomoxetine versus atomoxetine monotherapy, the numerical benefit found on virtually all efficacy measures at the majority of time points, along with the several instances of statistically significant superiority, suggests that this combination may be of some benefit to adults with ADHD. This advantage may be clinically significant only during the first 3 to 4 weeks of treatment, and less so over continued treatment. The fact that the potential additive effects of 1 agent to augment the effects of a clinically therapeutic agent did not have significant overall effects is not surprising, given the documented efficacy of atomoxetine.

Drug names: atomoxetine (Strattera and others), risperidone (Risperdal and others).

Author affiliations: Medical Sciences, Astellas, Deerfield, Illinois (Dr Sutherland); Department of Psychiatry, NYU School of Medicine and Psychiatry Service, Department of Veterans Affairs New York Harbor Healthcare System, New York (Dr Adler); Pfizer Global Research and Development, New London, Connecticut (Drs Chen and Smith); and Department of Psychiatry, University of Michigan, Ann Arbor (Dr Feltner).

© Copyright 2012 Physicians Postgraduate Press, Inc.

Potential conflicts of interest: **Dr Adler** has received grant/research support from Shire, Eli Lilly, National Institute of Drug Abuse, and Chelsea Therapeutics; has served on advisory boards of and been a consultant to Major League Baseball, Shire, i3 Research, and AstraZeneca; and has been a consultant to Otsuka, United Biosource, Epi-Q INC Research, and Major League Baseball Players Association; and has received royalty payments (as inventor) from NYU for license of adult ADHD scales and training materials since 2004. **Dr Chen** is an employee of Pfizer. **Dr Smith** is an employee of and stock shareholder in Pfizer. **Dr Feltner** is a former employee and a stock shareholder in Pfizer. **Dr Sutherland** has no financial or other potential conflicts of interest to report.
Funding/support: The study was funded by Pfizer Global Research and Development, New London, Connecticut.
Role of sponsor: The sponsor developed the protocol and conducted the clinical research and statistical analysis for this study.
Previous presentation: Findings of the study were presented in part at ADHD: Current Concepts and Future Developments Program 2010; November 5–6, 2010; Washington, DC.
Acknowledgment: The authors would like to thank Kimberly Kovacs, MA (Department of Psychiatry, NYU School of Medicine), for providing editorial assistance in the preparation of this article. Ms Kovacs has no conflicts of interest to report.

REFERENCES

1. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am*. 2004;27(2):187–201.
2. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237–248.
3. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67(4):524–540.
4. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716–723.
5. Kessler RC, Adler LA, Barkley R, et al. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. *Biol Psychiatry*. 2005;57(11):1442–1451.
6. Castle L, Aubert RE, Verbrugge RR, et al. Trends in medication treatment for ADHD. *J Atten Disord*. 2007;10(4):335–342.
7. Adler LA, Zimmerman B, Starr HL, et al. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *J Clin Psychopharmacol*. 2009;29(3):239–247.
8. Spencer TJ, Adler LA, McGough JJ, et al; Adult ADHD Research Group. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;61(12):1380–1387.
9. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr*. 2006;11(8):625–639.
10. Adler LA, Goodman DW, Kollins SH, et al; 303 Study Group. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69(9):1364–1373.
11. Adler LA. Pharmacotherapy for adult ADHD. *J Clin Psychiatry*. 2009;70(5):e12.
12. Adler LA, Reingold LS, Morrill MS, et al. Combination pharmacotherapy for adult ADHD. *Curr Psychiatry Rep*. 2006;8(5):409–415.
13. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology*. 2002;27(5):699–711.
14. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry*. 2003;53(2):112–120.
15. Adler LA, Liebowitz M, Kronenberger W, et al. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. *Depress Anxiety*. 2009;26(3):212–221.
16. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month, double-blind trial. *J Clin Psychopharmacol*. 2009;29(1):44–50.
17. Riblet LA, Eison AS, Eison MS, et al. Neuropharmacology of buspirone. *Psychopathology*. 1984;17(suppl 3):69–78.
18. Malhotra S, Santosh PJ. An open clinical trial of buspirone in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1998;37(4):364–371.
19. Niederhofer H. An open trial of buspirone in the treatment of attention-deficit disorder. *Hum Psychopharmacol*. 2003;18(6):489–492.
20. Davari-Ashtiani R, Shahrbabaki ME, Razjouyan K, et al. Buspirone versus methylphenidate in the treatment of attention deficit hyperactivity disorder: a double-blind and randomized trial. *Child Psychiatry Hum Dev*. 2010;41(6):641–648.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
22. Spencer TJ, Adler LA, Meihua Qiao, et al. Validation of the adult ADHD Investigator Symptom Rating Scale (AISRS). *J Atten Disord*. 2010;14(1):57–68.
23. The International Conference on Harmonisation. The International Conference on Harmonisation Web site. http://www.ich.org/home.html. Accessed October 20, 2011.
24. The Declaration of Helsinki. World Medical Association Web site. http://www.wma.net/en/20activities/10ethics/10helsinki/. Accessed October 20, 2011.
25. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
26. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
27. Adler LA, Spencer T, Faraone SV, et al. Training raters to assess adult ADHD: reliability of ratings. *J Atten Disord*. 2005;8(3):121–126.
28. Brown TE. *Brown Attention-Deficit Hyperactivity Disorder Scales for Adolescents and Adults*. Toronto, ON: Psychological Corporation, Harcourt Assessment Canada; 1996.
29. Guy W. Clinical global impressions. In: Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology (Revised)*. US Department of Health Education and Welfare publication (ADM)76-338. Rockville, MD: National Institute of Mental Health; 1976:217–221.
30. Matza LS, Morlock R, Sexton C, et al. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223–232.
31. Gobert A, Rivet JM, Cistarelli L, et al. Buspirone modulates basal and fluoxetine-stimulated dialysate levels of dopamine, noradrenaline and serotonin in the frontal cortex of freely moving rats: activation of serotonin1_A receptors and blockade of α_2-adrenergic receptors underlie its actions. *Neuroscience*. 1999;93(4):1251–1262.
32. Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. *J Child Adolesc Psychopharmacol*. 2004;14(2):243–254.
33. Mahmood I, Sahajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet*. 1999;36(4):277–287.