Bupropion XL in Adults with Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled Study

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Background: *Data remain limited on treatment strategies for adults with attention-deficit/hyperactivity disorder (ADHD). This study evaluated the efficacy and safety of an extended-release, once-daily formulation of bupropion (XL) in the treatment of adults with ADHD.*

Methods: *This multisite, placebo-controlled, 8-week prospective trial evaluated 162 adult patients diagnosed with ADHD (combined and inattentive types). Subjects were treated with up to 450 mg/day of bupropion XL. The primary efficacy endpoint was the proportion of ADHD responders (defined as at least a 30% reduction in the investigator-rated ADHD Rating Scale score) at week 8 (last observation carried forward [LOCF]).*

Results: *Bupropion XL responders (53%) exceeded placebo responders (31%) (*p *= .004 at week 8) with a significantly greater proportion of bupropion XL responders as early as week 2 (*p *= .01). Treatment effect size calculated for the ADHD Rating Scale total score was .6. Bupropion XL appeared to provide sustained benefit throughout the day compared with placebo (morning* p *= .033, afternoon* p *= .004, evening* p *= .024). Bupropion XL was safe and well tolerated, with no serious or unexpected adverse events and a low rate of drug-related study discontinuation (5%).*

Conclusions: *The results from this multisite study indicate that bupropion XL is an effective and well-tolerated nonstimulant treatment for adult ADHD.*

Key Words: ADHD, adults, bupropion, pharmacotherapy, antidepressant

Attention-deficit/hyperactivity disorder (ADHD) is a widespread neurobehavioral disorder of childhood onset with reported worldwide prevalence in children of 6% to 8% (Faraone et al 2003). Once considered a childhood disorder, it is now estimated that approximately 4% to 5% of the US adult population has ADHD and that 40% to 70% of children diagnosed with ADHD will continue to display behavior problems and symptoms into adolescence and adulthood (Barkley et al 1990; Biederman et al 1996; Fischer 1997; Kessler 2004; Mannuzza et al 1993; Murphy and Barkley 1996; Weiss et al 1985; Zametkin and Ernst 1999). Attention-deficit/hyperactivity disorder in adults is often associated with significant impairment (Biederman et al 1993; Mannuzza et al 1993; Millstein et al 1997; Weiss et al 1985) with far-reaching effects on quality of life and heath care utilization (Biederman et al 1996; Biederman 1998; Davis et al 2002; Kessler 2004; Mannuzza et al 1991; Silver 2000; Spencer et al 1996; Zametkin and Ernst 1999; Wender 1987). The high degree of comorbidity with major depressive disorder, bipolar disorder, anxiety disorders, and substance use disorders (Biederman et al 1994) further compounds the disability of adults with ADHD (Biederman 2004).

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Despite the increased recognition of adult ADHD and associated impairment, treatment data remain limited (McDermott and Wilens 2000; Ratey et al 1992; Wilens et al 1999a). Emerging literature suggests that pharmacotherapy is useful in the management of ADHD in adults (Spencer et al 1995; Wender et al 1981; Wilens 2003). Stimulants have demonstrated efficacy and are among first-line therapy for adults with ADHD (Conners et al 2001; Dulcan 1997). Multiple daily doses, however, may be required, and adverse effects and/or comorbid conditions may limit the usefulness of stimulants in some adults (Conners et al 2001). In addition, because control of ADHD symptoms is needed beyond the 8-hour workday, medications providing all-day symptom control appear to be advantageous (Barkley et al 2002). While various longer-acting stimulant preparations are commercially available, considerable interest persists in alternative, nonstimulant once-daily therapies for the management of adults with ADHD.

Nonstimulant options for adults with ADHD primarily include atomoxetine, bupropion, and desipramine. Atomoxetine, a norepinephrine reuptake inhibitor, is Food and Drug Administration (FDA)-approved for adults with ADHD and has demonstrated efficacy in one single-site and two large, multisite controlled clinical trials (Michelson et al 2003, Spencer et al 1998). While useful, a number of adults do not respond to or cannot tolerate atomoxetine, necessitating further exploration of nonstimulant agents (Michelson et al 2003). Though not an FDA-approved indication, the tricyclic antidepressant desipramine has also demonstrated efficacy in adults with ADHD. Its safety and tolerability profile, however, particularly with regard to overdose and cardiovascular effects, limits its usefulness (Wilens et al 1996).

Bupropion is a nonstimulant norepinephrine and dopamine reuptake inhibitor indicated for the treatment of major depressive disorder and as an aid to smoking cessation. Though structurally related to amphetamine, bupropion differs from d-amphetamine and methylphenidate in rate and extent of dopamine transporter blockade (Learned-Coughlin et al 2003) characteristics, which

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likely explain bupropion's low potential for abuse (Margolin et al 1995; Miller and Griffith 1983; Peck et al 1979; Rush et al 1998). Though not approved for the treatment of ADHD, bupropion has demonstrated efficacy in open (Hudziak et al 2000; Simeon et al 1986) and controlled (Barrickman et al 1995; Conners et al 1996) ADHD trials in children and adolescents, as well as open (Wender and Reimherr 1990) and controlled studies (Kuperman et al 2001; Reimherr et al 2000; Wilens et al 2001) in adults. In addition, intriguing findings have emerged from open trials of bupropion in adolescents and adults, suggesting efficacy in ADHD and comorbid mood (Daviss et al 2001; Wilens et al 2003) and substance use disorders (Levin et al 1998; Prince et al 2002; Riggs et al 1998; Solhkhah et al 2001). The majority of these studies, however, have involved small samples of subjects.

A new, once-daily reformulation of bupropion (bupropion XL) recently has been approved by the FDA for the treatment of major depressive disorder in adults. The reformulation of bupropion utilizes a diffusion-controlled vehicle that prolongs the time to peak concentration, while maintaining bioequivalence with the older formulations. The extended-release properties of bupropion XL allow administration of up to 450 mg of bupropion as a single daily dose.

Given compliance issues in treating adults with ADHD, we evaluated the usefulness of a once-daily nonstimulant in the treatment of adults with ADHD. We now report the findings of the first large, multicenter, randomized, double-blind, placebo-controlled, 8-week study evaluating the safety, tolerability, and efficacy of bupropion XL in this population. Although not indicated for the treatment of ADHD, based on the available literature, we hypothesized that bupropion XL would be significantly more effective in reducing symptoms of ADHD in adults compared with placebo.

Methods and Materials

Subjects

Men and women aged 18 to 60 years were eligible for the study if they met criteria for a current diagnosis of ADHD (all types) as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) (American Psychiatric Association 1994). Subjects were required to have met full DSM-IV criteria for a diagnosis of ADHD by age 7 (as determined by the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version 5), with a chronic course of ADHD from childhood to adulthood (Ambrosini 2000). In addition, subjects were required to have a moderate to severe level of impairment due to symptoms of ADHD at the randomization visit, with a minimum score of 4 (moderately ill) out of 7 on the Clinical Global Impression-Severity of Illness (CGI-S) scale as well as a 25 out of 54 on the investigator-rated ADHD Rating Scale (ADHD-RS) (Adler and Cohen 2004; Barkley 1990; DuPaul 1990). In addition, subjects were required to be in good general health based on physical and laboratory examinations and medical history. Premenopausal women, except those who had undergone surgical sterilization, were required to use a reliable form of contraception having a $<1\%$ failure rate throughout the study period.

Comorbid psychiatric conditions were assessed by the investigator using a modified Structured Clinical Interview for DSM-IV Axis I Disorders. Subjects with a current diagnosis of major depressive disorder; a current or lifetime diagnosis of bipolar or psychotic disorders; a current primary diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder; or who met criteria for alcohol or substance abuse within the last year were excluded. Subjects were also excluded if they were found during medical examination or interview to have an unstable medical disorder or a predisposition to seizures. In addition, subjects were queried during screening regarding previous pharmacotherapy for ADHD; those with a reported history of inadequate response to bupropion (for the treatment of ADHD) or inadequate responses to two or more adequate trials of psychostimulants were not eligible. A history of past successful treatment with bupropion or psychostimulants was not exclusionary. The use of psychoactive drugs, including benzodiazepines and psychostimulants, alpha-adrenergic antihypertensives, or beta-adrenergic antagonists, within 1 week of randomization was prohibited. The use of any potentially psychoactive herbal or nutritional supplements, 5-hydroxytryptophan or 5-hydroxy-1-tryptophan, anticonvulsants, antidepressants (excluding fluoxetine), or lithium within 2 weeks of randomization or fluoxetine within 4 weeks of randomization also was prohibited. Subjects with positive blood tests for alcohol or urine tests for substances of abuse at screening were not eligible for the study.

The study was approved by the following institutional review boards: Coast Independent Review Board, University of Massachusetts Medical School Office of Sponsored Research, The University of Vermont Committees on Human Research, the University of Nebraska Medical Center Institutional Review Board, and the Pharmacology Research Institute's Institutional Review Board. All subjects completed an informed consent after reviewing the protocol and associated risks and benefits. Subjects were not compensated for study participation other than nominal payments to cover mileage and parking fees.

Study Design

This was a multicenter (16-site), randomized, double-blind, placebo-controlled, parallel-group, flexible-dose, 8-week treatment study consisting of seven clinic visits (one screening, one randomization, and five treatment visits). The screening visit included physical examinations, laboratory tests (blood and urine), electrocardiogram (ECG), medical and psychiatric histories, and determination of subject eligibility. Eligible subjects were randomized in a 1:1 manner to receive either bupropion XL or placebo at the randomization visit. Clinic visits occurred at weeks 1, 2, 4, 5, and 8, and subjects were contacted by telephone for follow-up 1 week following study conclusion or discontinuation.

Dosing

Bupropion XL was available in 150 mg and 300 mg tablets; placebo tablets were identical in appearance to the active medication. Bupropion XL or placebo was administered orally, once daily in the morning throughout the treatment phase, beginning with a dose of 150 mg during week 1. The daily dose was increased to 300 mg during weeks 2 through 4. Subjects whose score exceeded 2 on the Clinical Global Impressions-Improvement (CGI-I) scale, had an improvement in the ADHD-RS of less than 30%, and did not experience any bothersome adverse event were eligible to receive a daily dose of 450 mg of bupropion beginning at week 5 and continuing through the end of the study. If an increase in the dosage to 450 mg was not clinically indicated at week 5, subjects remained on a daily dose of 300 mg for the duration of the study. At any time, the investigator could decrease the study medication to a minimum

daily dose of 300 mg if clinically warranted. Compliance was assessed by pill counts at each scheduled visit.

Efficacy and Safety Assessments

The primary efficacy assessment was the investigator-rated ADHD-RS, a validated scale which assesses the 18 individual criteria symptoms from DSM-IV, using a severity grid ranging from 0 = "not present" to 3 = "severe" with a maximum score of 54 (Adler and Cohen 2004; Barkley 1990; DuPaul 1990). This scale has previously been shown to correlate with drug effects in adults with ADHD (Faries et al 2001; Michelson et al 2003; Spencer et al 1995, 2001; Wilens et al 2001). The primary efficacy endpoint was the percentage of subjects with at least a 30% reduction in the investigator-rated ADHD-RS (Barkley 1990; DuPaul 1990) score from randomization to week 8 or on premature discontinuation from the study. This endpoint has been shown to be psychometrically valid and has become a convention as an indicator of outcome in ADHD trials (Faries et al 2001; Spencer et al 1995; Wilens et al 1996, 2001; Wilens et al 1999b).

Various secondary outcome measures were utilized throughout the study to assess efficacy, safety, and tolerability. Global improvement (1 = "very much improved" to 7 = "very much worse") and disease severity (1 = "not ill" to 7 = "extremely ill") were assessed utilizing the ADHD Clinical Global Impression of Improvement and Severity scales (National Institute of Mental Health 1985). To assess the efficacy of once-daily bupropion XL throughout the day, study participants were asked to complete the Conners' Adult ADHD Rating Scale-Self Report (CAARS-S:S) at three specific time points within a 24-hour period (10:00 AM, 4:00 PM, and 10:00 PM) and to reflect their behavior over the preceding hour (Conners 1998). Though neither the CAARS-S:S nor any other instrument has been validated to measure ADHD symptom change throughout the day, this approach was employed in an attempt to detect efficacy beyond a single averaged time point. In addition to the self-rated Conners' scale, subjects were asked (but not required) to designate one person (e.g., spouse, co-worker) to complete the Conners' Adult ADHD Rating Scale-Observer (CAARS-O:S) at various times throughout the study (Conners 1998). Both the CAARS-S:S and CAARS-O:S ask the participant or observer to answer 26 questions pertaining to the frequency (0 = "not at all, never" to 3 = "very much, very frequently") of multiple, validated symptoms of ADHD. Investigators were neither encouraged nor forbidden to review the CAARS-S:S or CAARS-O:S ratings before completing the investigator-rated ADHD-RS.

Depression and anxiety were assessed utilizing the Hamilton Scale for Depression (HAM-D) (minimum = 0, maximum = 64) (Hamilton 1960) and the Hamilton Scale for Anxiety (HAM-A) (minimum = 0, maximum = 56) (Hamilton 1959). An additional secondary assessment was the Global Assessment of Functioning (GAF) scale (American Psychiatric Association 1994).

All efficacy assessments were collected at each clinic visit with the exception of the CAARS-S:S and CAARS-S:O, which were collected at baseline and weeks 4 and 8; the CAARS-S:S was collected three times daily at 10:00 AM, 4:00 PM, and 10:00 PM. The Hamilton scales and the GAF were collected at baseline and week 8.

Safety assessments included systolic and diastolic blood pressure, heart rate, weight, spontaneous report of adverse events (AEs), and the use of concomitant medications at each clinic visit.

Statistical Analyses

All analyses were conducted on the population of subjects who received at least one dose of study medication. Treatment comparisons of baseline characteristics were made using a chi-square test for categorical data and a *t* test for continuous data. Missing values for efficacy measures were imputed using the last observation carried forward (LOCF) approach. Treatment group comparisons for categorical efficacy measures (postbaseline) such as the primary endpoint were made using the Cochran-Mantel-Haenszel (CMH) method controlling for clinical center. The interaction between clinical center and treatment for the primary endpoint was tested via the Breslow-Day test (Breslow and Day 1980). Continuous measures, except CGI-I, were analyzed using an analysis of covariance (ANCOVA) with treatment and clinical center as fixed effects and baseline value of the continuous measure as a covariate. The Clinical Global Impressions-Improvement scale was analyzed using an analysis of variance (ANOVA). Treatment effect size was calculated by dividing the treatment difference (active and placebo) of the ADHD-RS total score by the pooled standard deviation. Exploratory analyses included repeated measure analysis on the primary endpoint, several secondary efficacy endpoints, vital signs, and weight, utilizing observed values. The primary efficacy measure acted as gatekeeper for the statistical testing of secondary efficacy measures. For the CAARS-S:S and the CAARS-O:S, statistical analysis occurred in a sequential manner to adjust for multiple comparisons (e.g., analysis of week 8 preceded week 4 for both the CAARS-S:S and CAARS-O:S; analysis of the 10:00 AM time point occurred first, followed sequentially by the 4:00 PM and 10:00 PM time points for the CAARS-S:S). No other adjustments for multiplicity were made.

Results

Demographics and Subject Distribution

A total of 162 subjects met study entry criteria and were randomly assigned to receive either bupropion XL or placebo (81 subjects in each group). At baseline, there were no statistically significant differences between treatment groups with respect to demographic variables (Table 1). The majority of subjects were men (60% of the bupropion XL group and 59% of the placebo group) and most were diagnosed with the combined type of ADHD (68% of the bupropion XL group and 58% of the placebo group); there were no subjects with the predominantly hyperactive-impulsivity type. The percentage of subjects who had received pharmacotherapy for ADHD prior to study enrollment for the bupropion XL or placebo group was 47% and 39%, respectively. Of the 37 subjects in the bupropion XL group who had been previously treated with medication for ADHD, 35 had taken at least one psychostimulant. Among the 30 subjects in the placebo group who had been previously treated with medication for ADHD, 23 had taken at least one psychostimulant.

During the course of the study, 16 (20%) of the bupropion XL group and 13 (16%) of the placebo group withdrew prematurely for the following reasons: 8 withdrew consent (5 bupropion XL, 3 placebo); 4 for AEs (all bupropion XL group); 8 were lost to follow-up (3 bupropion XL, 5 placebo); 2 for protocol violations (1 from each group); and 7 for other reasons (3 for lack of efficacy [1 bupropion XL, 2 placebo], 2 for noncompliance [1 bupropion XL, 1 placebo], 1 for taking an excluded medication [placebo], and 1 for appropriate rater not available [bupropion XL]). The remaining 133 (82%) subjects (65 bupropion XL, 68 placebo) completed the 8 weeks of treatment.

Table 1. Demographics and Clinical Information

Subject Population	Bupropion XL ($n = 81$)	Placebo ($n = 81$)
Gender		
Female	32 (40%)	33 (41%)
Male	49 (60%)	48 (59%)
Ethnic Origin		
American Hispanic	3 (4%)	3 (4%)
Asian	1 (1%)	1 (1%)
Black	6 (7%)	4 (5%)
White	71 (88%)	72 (89%)
Other	0	1 (1%)
Mean Age (Years) (SD)	39.1 (10.3)	41.4 (10.0)
ADHD Type		
Combined	55 (68%)	47 (58%)
Inattentive	26 (32%)	34 (42%)
Hyperactive	0	0
Current Smoker	11 (14%)	12 (15%)
Received Previous Treatment for ADHD	37/79 (47%)	30/77 (39%)
Past Psychostimulant Exposure	35/81 (43%)	23/81 (28%)
Social Class	$n = 74$	$n = 69$
Upper	7 (9%)	3 (4%)
Upper-middle	30 (41%)	26 (38%)
Middle	25 (34%)	28 (41%)
Lower-middle	10 (14%)	11 (16%)
Lower	2 (3%)	1 (1%)

SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder.

Efficacy

There were no statistically significant differences between treatment groups with respect to mean ADHD-RS, CAARS-S:S, CAARS-O:S, CGI-S, GAF, HAM-A, and HAM-D scores at baseline (Table 2).

For the primary outcome measure, defined as those subjects with at least a 30% reduction in the ADHD-RS total score from randomization at week 8 (LOCF), the percentage of bupropion XL responders (53%) was greater than placebo (31%) ($CMH = 8.13$, $df = 1$, $p = .004$) (Figure 1). The treatment separation in favor of bupropion XL was seen as early as week 2 (bupropion XL responders [44%] vs. placebo [25%] [$CMH = 6.62$, $df = 1$, $p = .01$]) and remained significant throughout the treatment phase. Clinical center by treatment interaction was not statistically significant at week 8 (Breslow-Day ChiSq = 11.97, $df = 14$, $p = .61$).

Table 2. Efficacy Variables at Baseline

Efficacy Measure	Baseline Score: Bupropion XL $n = 81$, Mean (SD)	Baseline Score: Placebo $n = 81$, Mean (SD)
ADHD Rating Scale	35.8 (6.8)	36.2 (7.5)
Clinical Global Impression-Severity of Illness	4.6 (.7)	4.5 (.6)
Conners' Adult ADHD Rating Scale–Self-Report[a]		
10 AM	48.7 (10.9)	49.5 (11.5)
4 PM	48.3 (12.5)	48.1 (11.6)
10 PM	45.5 (12.5)	46.7 (12.1)
Conners' Adult ADHD Rating Scale-Observer[a]	46.0 (12.2)	43.6 (13.4)
Hamilton Scale for Anxiety	4.8 (3.6)	5.5 (4.1)
Hamilton Scale for Depression	4.3 (3.1)	4.8 (3.3)
Global Assessment of Functioning	57.1 (10.0)	58.1 (10.9)

ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation.
[a]n varied from 72 to 81.

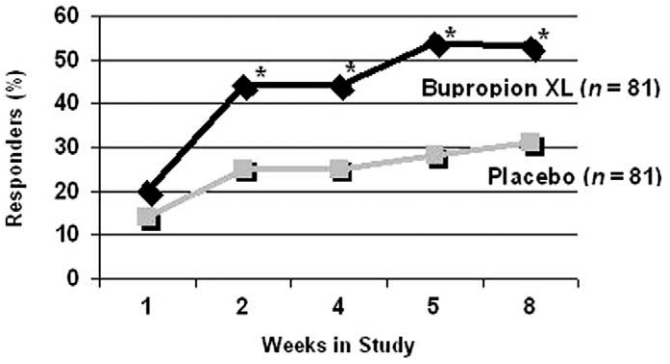

Figure 1. ADHD-RS responders (LOCF). Depicts the percentage of subjects with a reduction of ≥30% from baseline in the ADHD-RS (Investigator-rated) at every time point. Bupropion XL responders significantly outnumbered placebo responders as early as week 2 and continuing through Week 8 (53% vs. 31%, $p = .004$). Analyses were performed using Cochran-Mantel-Haenszel test controlling for clinical center. *$p < .05$ for week 2 through week 8. ADHD-RS, ADHD Rating Scale; LOCF, last observation carried forward.

Bupropion XL was also superior to placebo on secondary ADHD outcome measures. Statistically significant differences between mean change from randomization to week 8 with bupropion XL compared with placebo were observed for ADHD-RS total score ($F = 12.85$, $df = 1145$, $p < .001$), the ADHD-RS Inattentive symptom domain ($F = 9.31$, $df = 1145$, $p = .003$), and the ADHD-RS Hyperactive symptom domain ($F = 13.0$, $df = 1145$, $p < .001$) (Figure 2). The treatment effect size for the ADHD-RS total score was .6.

Bupropion XL appeared to provide sustained benefit throughout the day compared with placebo as shown in significant improvements at week 8 from randomization in total CAARS-S:S scores at 10:00 AM ($F = 4.67$ $df = 1123$, $p = .033$), 4:00 PM ($F = 8.81$, $df = 1139$, $p = .004$), and 10:00 PM ($F = 5.17$, $df = 1141$, $p = .024$) (Table 3). Furthermore, bupropion XL was significantly more effective than placebo at improving symptoms of ADHD as assessed by independent observers with respect to mean change

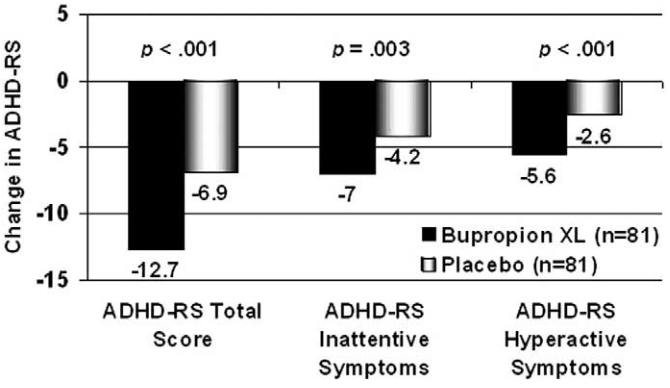

Figure 2. Mean change in ADHD-RS from randomization to week 8 (LOCF). Depicts the mean change in ADHD-RS from randomization to week 8. Bupropion XL was statistically superior to placebo in reducing the ADHD-RS total score ($p < .001$), ADHD-RS inattentive symptom domain ($p < .003$), and the ADHD-RS hyperactive symptom domain ($p < .001$). The p-values for between treatment group comparisons were computed using ANCOVA. ADHD-RS, ADHD Rating Scale; LOCF, last observation carried forward; ANCOVA, analysis of covariance.

Table 3. Mean Change from Randomization in Total CAARS-S:S and CAARS-O:S Scores (LOCF) Add CGI-S

Efficacy Measure	Change from Randomization (SD) Treatment Arm: Bupropion XL Mean (SD)	Change from Randomization (SD) Treatment Arm: Placebo Mean (SD)	*p* Value
Conners' Adult ADHD Rating Scale–Self-Report[a]			
Week 8			
10 AM	−8.4 (12.7)	−4.8 (11.2)	.033
4 PM	−9.3 (14.1)	−3.4 (12.3)	.004
10 PM	−6.9 (14.3)	−2.8 (12.5)	.024
Conners' Adult ADHD Rating Scale-Observer[a]			
Week 4	−7.4 (11.5)	−2.4 (8.8)	.019
Week 8	−7.8 (13.0)	−2.6 (11.6)	.044

p values for between-treatment group comparisons were computed using ANCOVA.

CAARS-S:S, Conners' Adult ADHD Rating Scale–Self-Report; CAARS-O:S, Conners' Adult ADHD Rating Scale-Oberver; LOCF, last observation carried forward; CGI-S, Clinical Global Impression-Severity of Illness; SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder; ANCOVA, analysis of covariance.

[a] *n* varied from 72 to 79.

from randomization in CAARS-O:S total scores both at week 4 ($F = 5.67$, $df = 1136$, $p = .019$) and week 8 ($F = 4.13$, $df = 1136$, $p = .044$).

We further evaluated the response rate to treatment by evaluating the Clinical Global Impression-Improvement (CGI-I). The percent of subjects with a clinical response on the CGI-I, defined as a rating of 1 or 2 ("much improved" to "very much improved"), was significantly higher in the bupropion XL group (37%) compared with the placebo group (18%) beginning at week 5 ($CMH = 7.47$, $p = .006$) and continuing throughout the study (38% vs. 18%, respectively) ($CMH = 8.69$, $p = .003$ at week 8). The mean CGI-I scores reflected significantly greater improvement in the bupropion XL group compared with placebo beginning at week 2 ($F = 4.84$, $df = 1145$, $p = .029$) and continuing throughout the study ($F = 6.83$, $df = 1145$, $p = .010$ at week 8). The mean change in CGI-S scores also reflected statistically significant improvement in the bupropion XL group compared with the placebo group at week 4 ($F = 6.53$, $df = 1145$, $p = .012$) and continuing through the end of the study ($F = 6.96$, $df = 1145$, $p = .009$ at week 8). Mean changes from randomization to week 8 in GAF scores reflected significantly greater improvements in the bupropion XL group as compared with the placebo group ($F = 4.55$ $df = 1145$, $p = .035$) (Table 4).

Baseline ratings of depression (HAM-D) and anxiety (HAM-A) were comparable between the two groups (Table 2). There were no statistically significant differences between treatment groups with respect to mean change in HAM-D score ($F = .24$, $df = 1145$, $p = .623$) or HAM-A score ($F = .05$, $df = 1145$, $p = .816$) from randomization to week 8 (Table 4).

Exploratory (repeated measures) analyses of the ADHD-RS responders suggested a treatment effect for male subjects ($n = 97$) regardless of ADHD type and for female subjects of the combined type ($n = 36$); no treatment effect was apparent for female subjects of the inattentive type ($n = 29$). A differential treatment effect by sex was not apparent in similar analyses of the CGI-I and CGI-S.

Safety and Tolerability

In the active treatment group, the mean final daily dose of bupropion XL was 393 mg (63% at 450 mg/day, 35.8% at 300 mg/day, 1.2% at 150 mg/day). Compliance rates were comparable between the two groups (98.9% bupropion XL, 99.8% placebo). The maximum daily dose of 450 mg was well tolerated by most subjects, with six subjects requiring the daily dose to be reduced to 300 mg and only one subject discontinuing due to an AE.

There were no serious AEs reported during the trial. A total of 52 (64%) and 60 (74%) subjects reported AEs in the placebo and bupropion XL groups, respectively ($p = .23$) (Table 5). Of the four subjects in the bupropion XL group who prematurely withdrew from the study due to AEs, one reported hives, rash, and swelling; another reported somnolence and nausea; a third subject reported irritability; and a fourth subject reported rash. All AEs resolved without sequelae. No subjects in the placebo group withdrew due to AEs. Of the subjects who discontinued the study prematurely due to AEs, three received daily doses of 300 mg and one received a daily dose of 450 mg.

There was no statistically significant treatment effect across time with respect to change from randomization in diastolic

Table 4. Mean Change from Randomization for Secondary Endpoints (Week 8 LOCF)

Endpoint	Change from Randomization (SD) Treatment Arm: Bupropion XL (*n* = 81) Mean (SD)	Change from Randomization (SD) Treatment Arm: Placebo (*n* = 81) Mean (SD)	*p* Value
Clinical Global Impression-Severity of Illness	−.96 (1.19)	−.51 (.9)	.009
Hamilton Scale for Anxiety	.11 (4.0)	−.46 (3.8)	.816
Hamilton Scale for Depression	.31 (3.1)	−.12 (3.6)	.623
Global Assessment of Functioning	7.3 (10.4)	4.0 (8.0)	.035

p values for between-treatment group comparisons were computed using ANCOVA.

LOCF, last observance carried forward; SD, standard deviation; ANCOVA, analysis of covariance.

Table 5. Adverse Events Reported for at Least 5% of Subjects

Adverse Event	Adverse Events by Treatment Arm, *n* (%)	
	Bupropion XL (*n* = 81)	Placebo (*n* = 81)
Headache	14 (17%)	11 (14%)
Dry Mouth	10 (12%)	4 (5%)
Insomnia[a]	10 (12%)	6 (7%)
Nausea	7 (9%)	3 (4%)
Nasopharyngitis	7 (9%)	2 (2%)
Dizziness	5 (6%)	1 (1%)
Constipation	5 (6%)	2 (2%)
Irritability	5 (6%)	2 (2%)
Fatigue	5 (6%)	4 (5%)
Tinnitus	5 (6%)	0
Somnolence	2 (2%)	5 (6%)
Upper Respiratory Tract Infection	2 (2%)	5 (6%)

[a] Includes all Medical Dictionary for Regulatory Activities codes related to insomnia.

blood pressure. For systolic blood pressure, there was a statistically significant treatment by visit interaction ($F = 3.33$, $df = 4144$, $p = .012$) with respect to change from randomization: statistically significant treatment effects were seen at week 2 (bupropion XL − placebo = 3.4, $t = 2.17$, $df = 144$, $p = .032$) and week 5 (bupropion XL − placebo = 3.8, $t = 2.51$, $df = 144$, $p = .013$). Further, relative to placebo, bupropion XL showed a small but statistically significant increase in pulse over time (bupropion XL – placebo = 2.6, $t = 3.18$, $df = 144$, $p = .002$). These vital sign results were not judged to be clinically significant and there were no premature discontinuations due to hypertension or tachycardia. For weight, there was a statistically significant decrease for bupropion XL relative to placebo starting at week 2 (−.5 kg bupropion XL vs. .2 kg placebo, $t = -3.20$, $df = 144$, $p = .002$) and continuing through week 8 (−1.1 kg bupropion XL vs. .1 kg placebo, $t = -3.30$, $df = 144$, $p < .002$).

Discussion

Bupropion XL was significantly more effective than placebo in the treatment of ADHD in adults in this multicenter, randomized, double-blind, placebo-controlled trial. Attention-deficit/hyperactivity disorder efficacy was demonstrated on the primary endpoint (proportion of ADHD responders based on a 30% or greater reduction in the investigator-rated ADHD rating scale) and multiple secondary endpoints (including reduction in overall ADHD symptomatology as rated by the investigator, subject, and observer). The reduction in ADHD symptomatology by bupropion XL was rapid, with bupropion XL responders significantly outnumbering placebo responders by week 2 and continuing throughout the study. The response to bupropion also appeared to be sustained into the evening. Moreover, the study drug was generally well tolerated with no serious AEs occurring and the number of subjects reporting one or more AEs not differing significantly between drug and placebo. These data suggest that bupropion XL is an effective and well-tolerated agent for the treatment of ADHD in adults, although it should be noted that no formulation of bupropion is FDA approved for the treatment of ADHD in adults or children.

The current results with bupropion XL extend the findings of previous open-label (Daviss et al 2001; Hudziak et al 2000; Prince et al 2002; Riggs et al 1998; Simeon et al 1986; Solhkhah et al 2001; Wender and Reimherr 1990) and controlled (Barrickman et al 1995; Conners et al 1996; Kuperman et al 2001; Reimherr et al 2000; Wilens et al 2001) studies in adults and adolescents, which found multiple daily doses of twice or thrice daily bupropion formulations to be effective in reducing the symptoms of ADHD. The exclusion of adults with clinically significant anxiety or depression in the current study also suggests that the efficacy of bupropion in ADHD is independent of potential antidepressant or anxiolytic effects. It is also noteworthy that the treatment effect size of bupropion XL in this study (.6) is in the range of those recently reported for FDA-approved medications for the treatment of ADHD, such as atomoxetine in adults (.35 and .40) (Michelson et al 2003) and methylphenidate in children and adolescents (.78 and .54, as reported by teachers and parents, respectively) (Schachter et al 2001).

Previous ADHD studies that have explored the influence of gender on responsiveness to pharmacotherapy (including studies of bupropion) have not detected an effect (Wilens and Spencer 2000; Wilens et al 2001; Michelson et al 2003). Though we did not expect to see a gender by treatment interaction in this study, post hoc exploratory analyses of the primary endpoint revealed a differential response for male subjects versus female subjects of the inattentive type of ADHD: male subjects responded to bupropion XL regardless of ADHD type, while female subjects of the combined, but not inattentive type, responded. Similar analyses of the CGI-I and the CGI-S failed to corroborate this interaction, suggesting that the treatment interaction finding with the primary endpoint might be spurious. Prospective investigation of gender effect by ADHD subtype in a study designed to explore such differences would be necessary to further assess the significance of this finding.

Studies of adults with ADHD highlight that the symptoms and impairment of ADHD in adults are not limited to the workday but also extend into the late afternoon and evening hours (Barkley et al 2002), necessitating corresponding treatment coverage. The current trial is the first with bupropion to query specifically for ADHD symptoms throughout the day and into the evening. This was accomplished by having subjects complete the Conners' Rating Scale in the morning, afternoon, and evening. Though not a validated use of this scale, results provide an encouraging signal that bupropion XL administered in the morning provides sustained benefit throughout the day and into the evening compared with placebo. Given that ADHD is associated with impairments in diverse realms such as interpersonal conduct and driving, the implications of demonstrable coverage of symptoms into the evening is of considerable importance in the management of ADHD adults (Barkley et al 1993, 2002; Murphy and Barkley 1996; Richards et al 2002).

Preclinical and clinical data indicate that the mechanism of action of bupropion likely involves reuptake inhibition of dopamine and norepinephrine (Ascher et al 1995; Cooper et al 1980; Ferris et al 1983; Li et al 2002; Nomikos et al 1989, 1992; Golden et al 1988; Learned-Coughlin et al 2003; Stahl et al 2004; Szabo et al, unpublished data). The results of the current study support the notion that pharmacological agents effective in reducing ADHD symptoms have similar catecholaminergic properties (Spencer et al 1996; Zametkin and Liotta 1998). Agents such as the psychostimulants, nonstimulants, and antidepressants appear to facilitate norepinephrine and dopamine neurotransmission, whereas the mainly nicotinic cognitive enhancers may indirectly affect such systems (Rezvani and Levin 2001; Wilens et al 1999b).

The results of this study should be viewed in light of methodological limitations. Exclusion of subjects who had failed

two or more adequate trials with psychostimulants may limit generalizability of the current finding to treatment-resistant subjects, while exclusion of depressed subjects or subjects with a primary anxiety disorder, a current diagnosis of substance use disorder, or lifetime history of bipolar disorder or psychosis may limit generalizability to subjects with comorbid psychiatric conditions. Other limitations include the general shortage of validated measures for ADHD in adults, the use of a relatively short exposure to the highest dose of bupropion XL, the lack of longer term safety and tolerability data in this population of adults, relying on spontaneous report of adverse events rather than a structured assessment, and an 18% dropout rate. Finally, while we comment on effect sizes in this report, it should be recognized that observed differences among studies in effect size may not be entirely driven by the pharmacologic activity of the compounds studied but also by other factors such as study design and chance.

Despite these limitations, the results of this multisite controlled clinical trial show that bupropion XL significantly improved ADHD symptoms in adults, as measured by multiple endpoints. The onset of efficacy of bupropion XL was observed as early as week 2 and was maintained throughout the 8-week study. Moreover, once daily morning dosing of the medication appeared to sustain efficacy until 10:00 PM. Bupropion XL was well tolerated in this study. Finally, given its efficacy in depression (Coleman et al 1999; Croft et al 1999) and for smoking cessation (Hurt et al 1997; Jorenby et al 1999), two comorbidities commonly reported in adults with ADHD (Biederman et al 1993; Pomerleau et al 1995; Shekim et al 1990), the use of bupropion for adults with ADHD and other comorbidities remains an intriguing area requiring further evaluation.

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