Extended-Release Bupropion for Patients With Major Depressive Disorder Presenting With Symptoms of Reduced Energy, Pleasure, and Interest: Findings From a Randomized, Double-Blind, Placebo-Controlled Study

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Objective: This multicenter, double-blind, placebo-controlled study evaluated the efficacy and safety of extended-release bupropion (bupropion XL) in the treatment of major depressive disorder (MDD) with prominent symptoms of decreased energy, pleasure, and interest.

Method: Eligible adult outpatients meeting DSM-IV criteria for MDD were randomly assigned to bupropion XL 300 to 450 mg/day (N = 135) or placebo (N = 139) for 8 weeks. The primary efficacy measure, change from baseline on the 30-item Inventory of Depressive Symptomatology–Self Report (IDS-IVR-30) total score, was obtained using interactive voice response (IVR) technology. Secondary measures included change from baseline on the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C-30) total score and change in domain subset scores for energy, pleasure, and interest; for insomnia; and for anxiety. Response and remission rates were also calculated. Safety was assessed by withdrawal rates, adverse events (AEs), body weight, and vital signs. The study was conducted from June 24, 2003, to June 30, 2004.

Results: Bupropion XL was superior to placebo at endpoint in reducing the IDS-IVR-30 total score ($p = .018$) and the energy, pleasure, and interest domain ($p = .007$) and the insomnia domain ($p = .023$) scores. IDS-C-30 outcomes were also significant ($p < .001$; $p < .001$, and $p = .008$, respectively). Clinician-rated remission rates were significantly higher with bupropion XL than placebo (32% vs. 18%, IDS-C-30; 41% vs. 27%, IDS-IVR-30), as were response rates (50% vs. 35%, IDS-C-30; 53% vs. 38%, Clinical Global Impressions-Improvement of Illness). Most AEs were mild or moderate. The incidence of a ≥ 7% body weight loss was 3.7% with bupropion XL and 1.4% with placebo.

Conclusion: Bupropion XL was effective and well tolerated in MDD patients with decreased energy, pleasure, and interest.

(J Clin Psychiatry 2006;67:865–873)

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This research study was funded by GlaxoSmithKline, Research Triangle Park, N.C.

Financial disclosure appears at the end of the article.

The medical writing and editorial assistance of Marian S. Rhodes, Ph.D.; J. Neal Weakly, Ph.D.; and Charles G. Lineberry, Ph.D., of Lineberry Research Associates, L.L.C., are greatly appreciated.

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Major depressive disorder (MDD) affects approximately 14 million people in the United States in any given year and has a lifetime prevalence of 15.1% to 17.3%.[1] Depressed patients commonly exhibit symptoms of decreased energy, pleasure, and interest, which are among the required symptoms listed in DSM-IV for a diagnosis of MDD. The DEPRES II study, which evaluated 1884 depressed patients, found that 73% reported listlessness, feeling tired, or having no energy during their most recent depressive episode, symptoms secondary only to depressed mood (76%).[2] Moreover, in a recent study of 712 patients > 60 years of age with MDD, 99% reported decreased interest in work or activities and 97% reported decreased energy.[3]

The neurotransmitters dopamine, norepinephrine, and serotonin are believed to be associated with different aspects of mood, cognition, and behavior.[4,5] Currently available antidepressant medications impact 1 or more of these monoamines, although the exact mechanisms of antidepressant efficacy are unknown. Bupropion is a dual reuptake inhibitor that increases synaptic levels of norepinephrine and dopamine without a significant effect on serotonin reuptake.[6] Clinical studies with various formulations of bupropion have demonstrated efficacy and safety in the treatment of MDD with comparable antidepressant efficacy and some tolerability advantages

(less sexual dysfunction and sedation) in head-to-head comparisons with selective serotonin reuptake inhibitors (SSRIs) or venlafaxine.[7–9] Bupropion XL, a once-daily extended-release formulation of bupropion approved by the U.S. Food and Drug Administration in August 2003, was developed to improve convenience and thereby potentially assist in medication compliance.

The most common factors that affect the selection of antidepressant treatment reported by physicians include the desire to avoid specific side effects (e.g., sexual dysfunction or sedation), the presence of comorbid psychiatric disorders (e.g., anxiety), and the presence of specific clinical symptoms. For example, Zimmerman et al.[10] found that the "symptom profile" associated with the antidepressant was the most common reason cited by psychiatrists for drug selection. The specific symptoms most frequently cited were anxiety, insomnia, and fatigue. Yet the evidence to date has been contradictory. Two reports[11,12] found SSRIs more effective than a norepinephrine reuptake inhibitor (NRI) in anxious patients. The second of these found the NRI reboxetine more effective for retarded-anergic depressed patients. Other studies, however, found essentially the opposite association,[13,14] while 2 other studies found no difference in symptom response to an SSRI or an NRI[3] or no difference in the effects of an SSRI or bupropion sustained release (SR) on anxiety or insomnia.[15]

All of these studies of symptoms predictive of response or those that change with treatment were retrospective analyses. To our knowledge, no study has prospectively selected patients having MDD with an anxious profile or with a retarded-anergic profile and examined response to a particular type of antidepressant. This study selected patients with a prospectively identified group of symptoms commonly occurring in MDD: decreased energy, pleasure, and interest. The objectives of this study were to evaluate the efficacy and safety of bupropion XL versus placebo in the acute treatment of adult outpatients with a diagnosis of nonpsychotic MDD and exhibiting common depressive symptoms of decreased energy, pleasure, and interest and to determine the effect of bupropion XL versus placebo on this symptom triad.

METHOD

Selection of Patients

After institutional review board approval and in accordance with the Declaration of Helsinki,[16] all patients provided written informed consent prior to any study procedures. Participants included male or female outpatients at least 18 years of age who met DSM-IV diagnostic criteria (assessed by a psychiatric interview and utilizing the Mini International Neuropsychiatric Interview) for nonpsychotic MDD. Eligible patients needed to have demonstrated symptoms of depression for at least 12 weeks but not more than 2 years before study entry and to have had a minimum score of 25 on the 30-item Inventory of Depressive Symptomatology (IDS-IVR-30)[17,18] when measured at the screening (day –7) and baseline (day –1) visits using interactive voice response (IVR) technology.[19,20] Eligible patients also had to have demonstrated a total score of ≥ 7 and a minimum score of 1 on at least 4 of the 5-item subset (Items 19, 20, 21, 22, 30) of the IDS-IVR-30 that assesses energy, pleasure, and interest at both screening and baseline visits. (See "Efficacy Measures" for further description of these items and their scoring.)

Exclusion criteria included current or past history of seizures or brain injury or any condition that predisposes to seizures; current or past history of anorexia nervosa or bulimia; unstable medical conditions; lifetime diagnosis of bipolar I or II disorder or schizophrenia or other psychotic disorder; primary diagnosis or treatment for panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder within the previous 12 months; history of alcohol or substance abuse or dependence within the past 12 months; treatment with psychotropic drugs, including psychoactive herbal preparations, within 2 weeks prior to the screening visit (4 weeks for fluoxetine); and total scores on the IDS-IVR-30 that increased or decreased by > 25% between the screening and baseline measurements.

Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled, flexible-dose study of extended-release bupropion hydrochloride (bupropion XL) conducted at 24 centers in the United States. Total study duration was 10 weeks, from June 24, 2003, to June 30, 2004, beginning with a 1-week screening period. Patients who satisfied inclusion/exclusion criteria, including those related to clinical laboratory, electrocardiogram, and/or physical examination assessments, were eligible for study participation. Following the screening period, 274 patients were randomly assigned 1:1 to receive bupropion XL (N = 135) or placebo (N = 139) and entered an 8-week treatment period. A total of 7 clinic visits were conducted, at day –7 (screening) and day –1 (baseline) and at the end of weeks 1, 2, 4, 6, and 8 of treatment. In addition, a follow-up telephone contact occurred 1 week posttreatment for collection of safety data. Study drug consisted of bupropion XL 150-mg and 300-mg tablets and matching placebo tablets.

Patients were scheduled to receive study drug in the morning, 150 mg/day for the first week of treatment, then 300 mg/day for the next 3 weeks. If clinically indicated at the end of the fourth week, an increase to 450 mg/day was permitted (given as single morning dose, or twice daily at the investigator's discretion). Patients unable to tolerate 450 mg/day were allowed to return to the 300-mg/day dose for the duration of the study. Patients unable to toler-

ate the increase to 300 mg/day could have their dose reduced to 150 mg/day once during the study, but they were required to return to 300 mg/day after 1 to 2 weeks on the lower dose. Patients unable to tolerate 300 mg/day were discontinued from the study. Use of zolpidem, up to 10 mg/day, or zaleplon, up to 20 mg/day, was allowed sparingly (up to 3–4 times per week) through day 10 of the treatment phase. Study drug was discontinued without tapering at week 8.

Efficacy Measures

The severity of depression was assessed using the Inventory of Depressive Symptomatology (IDS), a 30-item scale administered in 2 versions with identical items: a self-rated version (IDS-IVR-30) and a clinician-reported version (IDS-C-30).[17,18,21,22] Each item was rated on a 4-point categorical scale (0–3), with zero indicating "no symptoms" and higher numbers reflecting progressive increase in symptom severity.

The IDS was chosen as the primary depression rating scale because of potential advantages over the Hamilton Rating Scale for Depression (HAM-D)[23] and the Montgomery-Asberg Depression Rating Scale (MADRS).[24] Unlike the HAM-D or MADRS, the IDS rates all 9 of the DSM-IV–defined MDD criterion symptom domains. In addition, the IDS, with ratings of "1" indicating a modest level of symptomatology, may be more sensitive to residual symptoms than the HAM-D or MADRS.[18,25]

The IDS was developed as a paper-and-pencil version that allowed patients to self-report symptoms. The paper-and-pencil version has been previously validated against the clinician-rated version and was converted to administration by IVR to facilitate the collection of data for this study (data on file, Healthcare Technology Systems, Inc., Madison, Wis.). The items in the IDS-IVR-30 version and the scoring are identical to those used in the paper-and-pencil self-report version and the clinician-administered version. The primary efficacy outcome measure was the mean change on the total score of the IDS-IVR-30 from baseline to week 8/study exit.

Secondary measures included the IDS-C-30 total score, calculated at each visit, and the Clinical Global Impressions-Improvement of Illness (CGI-I)[26] obtained at every study visit after the first treatment week. Both the IDS-C-30 and the CGI-I were administered by site personnel who were trained on the use of these instruments. Secondary measures of efficacy also included item subsets of the IDS-IVR-30 and IDS-C-30 that assess the following: energy, pleasure, and interest; insomnia; and anxiety. The energy, pleasure, and interest subset included 5 items (Items 19, general interest/involvement; 20, energy/fatigability; 21, pleasure/enjoyment; 22, sexual interest; and 30, leaden paralysis/physical energy). The insomnia subset included 3 items (Items 1, sleep onset insomnia; 2, mid-nocturnal insomnia; and 3, early morning insomnia). The anxiety subset included 4 items (Items 6, mood-irritable; 7, mood-anxious; 24, psychomotor agitation; and 27, panic/phobic symptoms). Response and remission at the end of the study (endpoint analyses) were also included as secondary measures of efficacy. Response for the IDS-IVR-30 and IDS-C-30 was defined as reduction of ≥ 50% from baseline and for the CGI-I as a score of "much" or "very much" improved. Remission definitions were based on the original paper-and-pencil self-report and clinician-rated versions of the IDS.[17] Remitters were defined as patients with an IDS-IVR-30 total score of ≤ 15 or an IDS-C-30 total score of ≤ 13.

Safety Assessments

Safety assessments included body weight, blood pressure, and heart rate, recorded at each study visit, and adverse events monitored throughout the study, including a telephone call 1 week after administration of the last dose of study drug (week 9) or a telephone call 1 week after premature withdrawal. Systolic blood pressure ≥ 150 mm Hg and diastolic blood pressure ≥ 95 mm Hg were defined as exclusionary at screening and baseline. Clinically significant changes from baseline in blood pressure were defined as a systolic blood pressure increase of ≥ 20 mm Hg; a systolic blood pressure of ≤ 90 mm Hg and a decrease of ≥ 20 mm Hg; diastolic blood pressure increase of ≥ 15 mm Hg; or diastolic blood pressure of ≤ 50 mm Hg and a decrease of ≥ 15 mm Hg. Clinically significant changes from baseline in heart rate were defined as a rate ≥ 120 bpm and an increase of ≥ 15 bpm; or ≤ 50 bpm and a decrease of ≥ 15 bpm. A clinically significant change in weight was defined as ≥ 7% change from baseline.

Sustained changes in vital signs were defined as changes that occurred over 3 consecutive visits. Sustained changes included increases from baseline in systolic blood pressure of ≥ 15 mm Hg for 3 consecutive visits or increases in diastolic blood pressure of ≥ 10 mm Hg for 3 consecutive visits; or an increase in heart rate of ≥ 10 bpm for 3 consecutive visits.

Statistical Methods

Safety analyses were conducted on the population of patients who took at least 1 dose of the study drug. Efficacy analyses were conducted on the intent-to-treat population, which consisted of all patients who took at least 1 dose of the study drug and provided a baseline and at least 1 postbaseline IDS-IVR-30 assessment. The study was designed to have 90% power to detect a difference of 3.8 points on the IDS-IVR-30 between the bupropion XL and placebo groups with respect to mean change from baseline on the IDS-IVR-30 total score, assuming a standard deviation of 10.6 and a 1-sided significance level of 0.05. This set the sample size at 268 (134 per treatment group).

The protocol-specified statistical analysis for the primary efficacy variable (mean change from baseline to study exit in IDS-IVR-30 total score) was performed using an analysis of covariance (ANCOVA), with scores at baseline as a covariate, and center and treatment group as independent factors. The secondary continuous efficacy variables (mean change from baseline to study exit/week 8 in IDS-C-30 total score and in IDS-IVR-30 and IDS-C-30 5-item subset score for energy, pleasure, and interest; 3-item insomnia subset score; and 4-item anxiety subset score) were analyzed similarly. Categorical measures (number and percentage of responders and remitters) were analyzed using a Cochran-Mantel-Haenszel test controlling for center. The least squares means, along with the corresponding 1-sided p values from the ANCOVA for testing between-treatment-group differences, are reported for the change and total scores. One-sided testing was prespecified in the study protocol based on known effectiveness of bupropion compared with placebo for treatment of MDD. Efficacy data were analyzed using last-observation-carried-forward (LOCF) methods.

For safety analyses, the frequencies of adverse events (AEs) and serious adverse events (SAEs) were computed, descriptive statistics for changes in weight were calculated for each clinic visit, and patients with clinically significant changes were identified and listed. Analyses of the percentage of patients with clinically significant changes from baseline in vital signs and weight were conducted using the Fisher exact test.

Table 1. Baseline Demographic/Psychiatric Characteristics and Patient Disposition

Characteristics	Placebo (N = 139)	Bupropion XL (N = 135)
Demographic/psychiatric		
Age, mean (range), y	39.8 (19–69)	40.0 (20–68)
Female, N (%)	96 (69)	89 (66)
Weight, mean (SD), kg	82.9 (23.2)	82.4 (19.2)
Duration of current depressive episode, mean (SD), wk	43.2 (23.2)	40.4 (23.3)
Race/ethnicity, N (%)[a]		
White	108 (78)	104 (77)
Black	12 (9)	13 (10)
Hispanic	15 (11)	13 (10)
Other	4 (3)	5 (4)
Patient disposition		
Randomly assigned, N (%)	139 (100)	135 (100)
Safety population[b]	139 (100)	135 (100)
Intent-to-treat population[c]	137 (99)	133 (99)
Completed study, N (%)	110 (79)	103 (76)
Prematurely withdrawn, N (%)	29 (21)	32 (24)
Adverse event	3 (2)	12 (9)[d]
Consent withdrawn	3 (2)	4 (3)
Lost to follow-up	12 (9)	11 (8)
Protocol violation	3 (2)	2 (1)
Lack of efficacy	6 (4)	1 (1)
Other	2 (1)	2 (1)

[a]Totals are greater than 100% due to rounding.
[b]Safety population: any randomly assigned patient who had at least 1 dose of study medication.
[c]Intent-to-treat population: all randomly assigned patients who took at least 1 dose of study drug and provided a baseline IDS-IVR-30 assessment and at least 1 IDS-IVR-30 assessment postrandomization.
[d]One patient in the bupropion XL group withdrew during posttreatment; 11 patients (8%) withdrew due to adverse events during the 8-week treatment period.
Abbreviation: IDS-IVR-30 = 30-item Inventory of Depressive Symptoms-Self-Report, interactive voice response version.

RESULTS

Patient Characteristics

Table 1 summarizes the baseline demographic and clinical characteristics and the disposition of randomly assigned patients, all of whom met DSM-IV criteria for MDD. A total of 274 patients were randomly assigned, 135 to bupropion XL and 139 to placebo. Baseline demographics and clinical features at the time of randomization were similar for the 2 treatment groups.

All 274 randomly assigned patients received the study drug and therefore constituted the safety population. Of these, 270 (bupropion XL, N = 133; placebo, N = 137) constituted the intent-to-treat population. The percentage of randomly assigned patients who successfully completed the study was comparable for the bupropion XL (76%) and placebo (79%) groups. Reasons for premature withdrawal were similar between treatment groups except that more bupropion XL-treated patients withdrew because of AEs (bupropion XL, 9%; placebo, 2%) and more placebo-treated patients withdrew due to a lack of efficacy (placebo, 4%; bupropion XL, 1%).

All 133 patients in the intent-to-treat population received an initial dose of 150 mg/day bupropion XL. Two patients were unable to increase this dose and exited the study. In the remaining 131 patients whose dose was increased from 150 to 300 mg/day, 2 did not tolerate 300 mg/day and were inadvertently continued in the study at the 150-mg/day dose level; 45 remained at 300 mg/day; and 84 subsequently had a dose increase to 450 mg/day. Of these 84 patients, 6 had the dose reduced to 300 mg/day, while 78 remained at 450 mg/day. The final number of patients at each dose level of bupropion XL at study exit was 150 mg/day, N = 4 (3%); 300 mg/day, N = 51 (38%); and 450 mg/day, N = 78 (59%). The mean duration of patient exposure to bupropion XL was 49.1 days (SD = 15.83 days). Two percent of subjects in each treatment group reported taking hypnotics during the study.

Efficacy

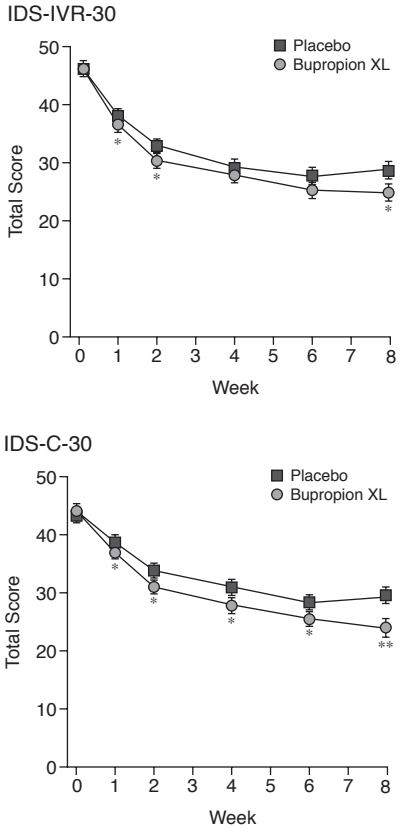
Results from analysis of the mean change from baseline in IDS-IVR-30 (primary efficacy measure) and IDS-C-30 total scores at study exit, and for each week, are summarized in Table 2. The mean total IDS-IVR-30 and IDS-C-30 scores for each week are depicted in Figure 1. The bupropion XL group showed greater mean improvement compared with the placebo group on the

Table 2. Change From Baseline in IDS-IVR-30 and IDS-C-30 Total Scores by Treatment Week (LOCF)

Total Score	Placebo (N = 137), Least Squares Mean (SEM)	Bupropion XL (N = 133), Least Squares Mean (SEM)[a]	p Value[b]
IDS-IVR-30			
Baseline	46.0 (0.8)	45.9 (0.8)	NA
Week 1	–8.0 (0.9)	–9.9 (0.9)	.046
Week 2	–13.2 (1.1)	–15.6 (1.1)	.043
Week 4	–16.9 (1.2)	–18.3 (1.2)	.186
Week 6	–18.4 (1.3)	–20.8 (1.3)	.080
Week 8/ study exit	–17.6 (1.4)	–21.3 (1.4)	.018
IDS-C-30			
Baseline	43.9 (0.7)	44.5 (0.7)	NA
Week 1	–5.9 (0.7)	–7.5 (0.7)	.041
Week 2	–10.7 (0.9)	–12.9 (0.9)	.035
Week 4	–13.7 (1.1)	–16.5 (1.1)	.022
Week 6	–16.1 (1.2)	–19.0 (1.2)	.028
Week 8/ study exit	–14.9 (1.3)	–20.6 (1.3)	< .001

[a]Means (SEM) for every time point excluding baseline are based on ANCOVA. Baseline means (SEM) are unadjusted.
[b]One-sided p value for difference between bupropion XL and placebo values, by ANCOVA.
Abbreviations: ANCOVA = analysis of covariance, IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated; IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology–Self-Report, interactive voice response version; LOCF = last observation carried forward.

Figure 1. Mean IDS-IVR-30 and IDS-C-30 Total LOCF Scores (± SE) for Placebo and Bupropion XL



Mean and SE values were calculated using ANCOVA of total scores at baseline and each evaluation visit; p values were derived from ANCOVA of change from baseline.
*p < .05 (change from baseline).
**p ≤ .01 (change from baseline).
Abbreviations: ANCOVA = analysis of covariance, IDS-C-30 = 30-item Inventory of Depressive Symptomatology-Clinician Rated, IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology-Self-Report, interactive voice response version; LOCF = last observation carried forward.

IDS-IVR-30 total score at weeks 1, 2, and 8 ($p < .05$, mean change from baseline). Patients treated with bupropion XL also showed greater mean improvement in IDS-C-30 total scores versus placebo after 8 weeks of treatment ($p < .001$, mean change from baseline), as well as at the 1-, 2-, 4-, and 6-week assessments ($p < .05$ at each time point).

Table 3 summarizes improvement in subsets of depressive symptoms in patients at study exit with bupropion XL. Significantly greater mean reductions from baseline in bupropion XL-treated patients versus placebo-treated patients at study exit were noted in the IDS-IVR-30 and IDS-C-30 subset scores measuring energy, pleasure, and interest ($p = .007$ and $p < .001$, respectively), and insomnia ($p = .023$ and $p = .008$, respectively). As early as week 1 and at every subsequent study visit, significantly greater mean reductions in the energy, pleasure, and interest subset of the IDS-IVR-30 and IDS-C-30 scores were observed in the bupropion XL group compared with the placebo group. The difference between the bupropion XL and the placebo groups on the anxiety subset was not statistically significant at week 8/study exit for either the IDS-IVR-30 or IDS-C-30.

Response rates derived from the IDS-C-30 and CGI-I scales were statistically significantly greater for the bupropion XL group than the placebo group at week 8/study exit, 50% versus 35% ($p = .009$) and 53% versus 38% ($p = .006$), respectively (Figure 2). The response rate on the IDS-IVR-30 for the bupropion XL group (53%) was higher than for the placebo group (45%), but the difference was not statistically significant at week 8 ($p = .084$).

The remission rate at study exit, based on a final IDS-IVR-30 total score ≤ 15, was significantly higher in the bupropion XL group (41%) than in the placebo group (27%; $p = .01$). Using an IDS-C-30 total score of ≤ 13, remission rates were also greater for bupropion XL patients (32%) than for placebo patients (18%; $p = .005$) (Figure 3). The number needed to treat (NNT) for remission of symptoms, a useful measure of clinical significance, was 8 (95% CI: 5 to 27 and 5 to 42) for both IDS-C-30 and IDS-IVR-30.

Safety

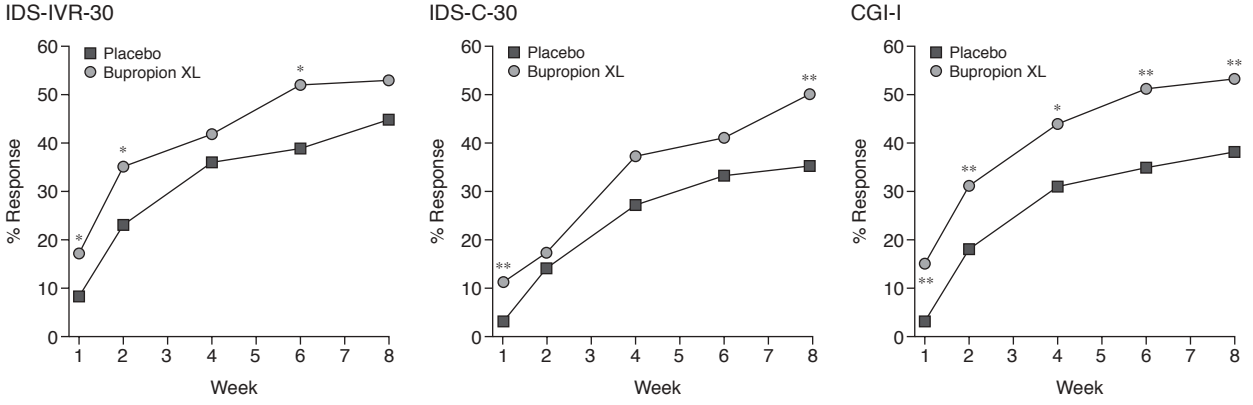
During the treatment phase, more patients reported at least 1 AE in the bupropion XL group (79%) than in the

Table 3. Change From Baseline in Energy, Pleasure, and Interest Subset and Insomnia and Anxiety Subset Scores at Week 8/Study Exit (LOCF)

Subset Total Score	Placebo (N = 137), Least Squares Mean (SEM)	Bupropion XL (N = 133), Least Squares Mean (SEM)	p Value[a]
Energy, pleasure, and interest (IDS-IVR-30)	–5.3 (0.4)	–6.7 (0.4)	.007
Energy, pleasure, and interest (IDS-C-30)	–3.7 (0.4)	–5.5 (0.4)	< .001
Insomnia (IDS-IVR-30)	–1.5 (0.2)	–2.1 (0.2)	.023
Insomnia (IDS-C-30)	–1.7 (0.2)	–2.5 (0.2)	.008
Anxiety (IDS-IVR-30)	–2.1 (0.3)	–2.4 (0.3)	.158
Anxiety (IDS-C-30)	–1.6 (0.2)	–2.0 (0.2)	.094

[a]One-sided p value for difference between bupropion XL and placebo values, by ANCOVA.
Abbreviations: ANCOVA = analysis of covariance, IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated; IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology–Self-Report, interactive voice response version; LOCF = last observation carried forward.

Figure 2. Response Rates for Placebo and Bupropion XL Derived From IDS-IVR-30, IDS-C-30, and CGI-I Scores (LOCF)



*p < .05.
**p < .01.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician Rated, IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology–Self-Report, interactive voice response version, LOCF = last observation carried forward.

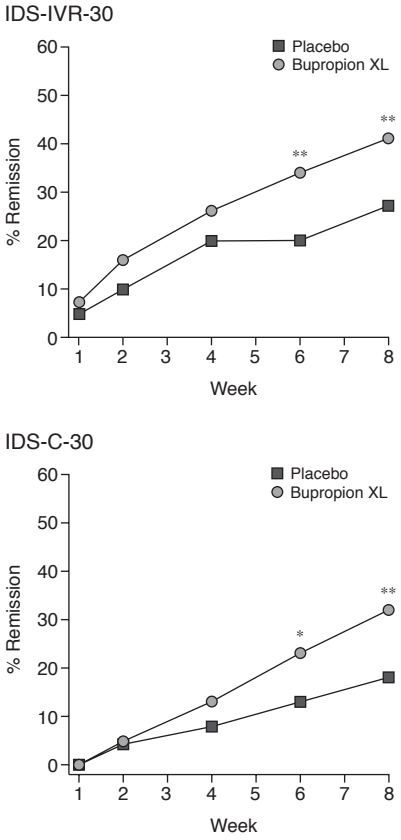
placebo group (61%). Most AEs were mild or moderate (bupropion XL, 89% of AEs; placebo, 89% of AEs). No SAEs or deaths were reported in either treatment group. No patients in either group reported suicidal ideation, self-mutilation, or intentional self-injury.

Table 4 lists adverse events that occurred in ≥ 5% of bupropion XL-treated patients and that were reported at an incidence ≥ 1.5-fold higher than in placebo-treated patients. Twelve bupropion XL-treated patients (9%) and 3 placebo-treated patients (2%) withdrew prematurely because of adverse events. The most common reasons were headache (2 patients in the bupropion XL group, 1 patient in the placebo group) and rash (2 patients in the bupropion XL group). All other adverse events leading to withdrawal in the bupropion XL or placebo group were each reported in only 1 patient.

Patients in the bupropion XL group had a mean weight decrease of 1.1 kg during the 8-week treatment period, while the placebo group showed a mean increase of 0.2 kg (p < .05). In the bupropion XL group, 5 of 135 patients (3.7%) showed a weight change of ≥ 7% of baseline weight, all 5 exhibiting weight loss. In the placebo group, 3 of 139 patients (2.2%) showed a weight change of ≥ 7% of baseline weight, with 2 exhibiting weight loss (1.4%).

Clinically significant changes in vital signs, as previously defined, were (bupropion XL-treated patients, placebo-treated patients): systolic blood pressure increases (10%, 9%); diastolic blood pressure increases (11%, 8%); and heart rate decreases (< 1% in both groups). Most of these changes were transient. Sustained changes in vital signs, as previously defined, were (bupropion XL-treated patients, placebo-treated patients): sys-

Figure 3. Remission Rates for Placebo and Bupropion XL Derived From IDS-IVR-30 and IDS-C-30 Scores (LOCF)



*p < .05.
**p ≤ .01.
Abbreviations: IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated; IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology–Self-Report, interactive voice response version; LOCF = last observation carried forward.

tolic blood pressure increases (2%, 1%); diastolic blood pressure increases (3%, 4%); and heart rate increases (8%, 3%). None of the sustained changes in vital signs differed significantly between treatment groups, and only 1 of the changes was considered clinically significant. One subject treated with bupropion XL had clinically significant sustained elevations in systolic and diastolic blood pressure. No instances of sustained increases in heart rate above the normal range (100 bpm) were reported.

DISCUSSION

This randomized, double-blind, placebo-controlled study demonstrated that bupropion XL, administered in doses of 300 to 450 mg/day, was effective in the treatment of MDD, as demonstrated by the statistically significant differences in mean decrease from baseline in the IDS-IVR-30 and IDS-C-30 total scores compared with placebo, observed as early as week 1 of treatment. Aside from depressed mood, the most common symptoms associated with MDD are fatigue, low energy, and anhedonia, occurring in at least 70% of patients with MDD.[2,27] In a reliability assessment of the internal consistency of the self-reported IDS, it was found that 3 of the symptoms that measure decreased energy, pleasure, and interest (lack of involvement, decreased energy, and decreased capacity for pleasure) are among the items that most highly correlate with the IDS total score.[17] The current study required the presence of these common symptoms, and, in fact, of the 690 patients screened for the study, 76% met the criteria for decreased energy, pleasure, and interest, although the study design had a minimal threshold for these symptoms. Statistically significant improvement in this triad of symptoms was observed in the bupropion XL treatment group versus placebo when measured by mean change from baseline in the 5-item subset score of the IDS-IVR-30 and IDS-C-30. The positive response to treatment with bupropion XL in these patients is consistent with the possibility that these symptoms of depression may be especially responsive to catecholamine reuptake inhibitors such as bupropion XL. However, whether improvement in lack of interest, pleasure, and energy is related to the unique pharmacologic profile of bupropion (norepinephrine/dopamine) can only be determined by direct comparison with antidepressants of differing profiles (e.g., SSRIs or serotonin-norepinephrine reuptake inhibitors).

In this study, the IDS-IVR-30 and IDS-C-30 baseline total scores were higher than those in other reports using the IDS scales to evaluate patients with MDD.[17,28,29] Using the item response theory analysis comparison (HAM-D-17 total score × 2.0 = IDS-IVR-30 Total Score),[30] the patient population was represented by moderately to severely depressed patients and appears to be similar in severity to the populations evaluated in other depression studies using bupropion XL.[31,32] In addition, the IDS-IVR-30 total scores were higher than the IDS-C-30 total scores, a finding also observed in the paper-and-pencil

Table 4. Adverse Events Reported by at Least 5% of Patients Taking Bupropion XL and at a Rate ≥ 1.5 Times That Observed on Placebo

Adverse Event	Placebo (N = 139), N (%)	Bupropion XL (N = 135), N (%)
Dry mouth	8 (6)	17 (13)
Dizziness*	3 (2)	14 (10)
Nausea	7 (5)	14 (10)
Insomnia*	2 (1)	10 (7)
Anxiety*	1 (< 1)	8 (6)
Dyspepsia*	0	8 (6)
Sinusitis	3 (2)	7 (5)
Tremor*	0	7 (5)

*p < .05 (uncorrected for multiplicity), bupropion XL vs. placebo.

self-report version,[28,29] reconfirming that depressed patients may report their symptom severity as being higher than clinicians do. The IDS-C-30, however, showed more sensitivity to change than the IDS-IVR-30 for both total change and for early change. Similar findings of greater sensitivity to change with the IDS-C-30 were observed in an evaluation of depressed inpatients assessed with both the clinician- and patient-rated IDS.[25] While comparable outcomes for measuring depressive symptoms appear to result with either the clinician-rated or patient self-reported IDS formats, our results suggest that the clinician-rated methodology in this trial was more sensitive in detecting a treatment effect.

It is widely recognized that MDD is a chronic illness. The achievement of remission from an acute major depressive episode is important, as it is associated with a lower risk of relapse and better functional improvement compared with clinical response.[33–38] The effectiveness of bupropion XL in treating MDD was demonstrated by the significantly higher percentage of patients in the bupropion XL group, relative to those in the placebo group, who met remission criteria at the end of the 8-week study period. Additionally, as shown in Figure 3, remission rates had not reached a plateau by week 8 in the bupropion group, suggesting that increased remission rates may be expected with bupropion treatment beyond 8 weeks. This is consistent with other research that suggests that recovery from a major depressive episode is a progressive process that extends for 12 to 16 weeks[39,40] or longer.[41] The short duration of this study precludes a full assessment of the longer term treatment effects with bupropion XL.

Tolerability of antidepressant agents is important for both acute and maintenance treatment. Overall, treatment with bupropion XL in this population of depressed patients was well tolerated, and side effects were consistent with the established pharmacology profile of bupropion.[6] The low withdrawal rates due to adverse events in both treatment groups were similar to rates observed in other bupropion trials.[42]

The bupropion XL group had a statistically significant reduction in insomnia measured by the changes in IDS-IVR-30 and IDS-C-30 insomnia subset scores compared with the placebo group, which supports other reports of improvement in depression-related insomnia in bupropion-responsive patients.[43] Bupropion showed improvement in depression-related anxiety in a pooled data set of bupropion SR studies.[15] A trend toward greater improvement was observed in the anxiety subset scores of the IDS-IVR-30 and IDS-C-30 in the bupropion XL group relative to the placebo group; however, the difference between treatment groups was not statistically significant for either comparison.

Clinically meaningful weight loss in the present study (defined as ≥ 7% from baseline) was found in 3.7% of bupropion XL and 1.4% of placebo-treated patients, which corroborates a previous report. In a pooled analysis of data from three 8-week clinical trials of bupropion sustained-release tablets, 11% of patients treated with bupropion versus 6% of patients treated with placebo exhibited a weight loss of > 2.3 kg.[42]

This study demonstrates the effectiveness of bupropion XL (the extended-release formulation of bupropion) in the treatment of MDD, similar to the antidepressant efficacy established with other formulations of bupropion. The results showed bupropion XL at doses of 300–450 mg/day to be safe and well tolerated compared with placebo. Patients with MDD who presented with the common symptoms of decreased energy, pleasure, and interest showed significant improvement in their overall depression symptoms with bupropion XL and in this symptom triad when measured by both versions of the IDS. Further investigation using the symptom triad of decreased energy, pleasure, and interest as a state marker for MDD and the response of MDD to treatment is indicated.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), venlafaxine (Effexor), zaleplon (Sonata), zolpidem (Ambien).

Financial disclosure: Dr. Jefferson has received grant/research support from Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Organon, Pfizer, Roche, Solvay, UCB, and Wyeth; is a consultant for GlaxoSmithKline, Schwarz, Shire, and Organon; has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Eli Lilly, Pfizer, Schwarz, and Shire; is a stock shareholder of Bristol-Myers Squibb, GlaxoSmithKline, and SciClone; and is a principal of Healthcare Technology Systems Inc. Dr. Rush is a consultant for GlaxoSmithKline. Dr. Nelson has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Organon, Pfizer, and Wyeth; is a consultant or serves on the advisory boards for Abbott, Biovail, Bristol-Myers Squibb, Corcept, Eli Lilly, GlaxoSmithKline, Orexigen, Organon, Pfizer, Sepracor, and Shire; and has received research support from Eli Lilly, Forest, and Pfizer. Drs. VanMeter and Modell, Messrs. Krishen and Hampton, and Ms. Wightman are employees of GlaxoSmithKline.

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