Double-Blind Comparison of Bupropion Sustained Release and Sertraline in Depressed Outpatients

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Background: A sustained-release formulation of bupropion (bupropion SR), developed with an improved pharmacokinetic profile to permit less frequent dosing than the immediate-release form, has not been evaluated in active comparator trials. This randomized, double-blind, parallel-group trial was conducted to compare the efficacy and safety of bupropion SR and sertraline.

Method: Outpatients with moderate to severe major depressive disorder (DSM-IV) received bupropion SR (100–300 mg/day) or sertraline (50–200 mg/day) for 16 weeks. Psychiatric evaluations, including the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A), the Clinical Global Impressions scale for Severity of Illness (CGI-S), and for Improvement (CGI-I) were completed, and adverse events were assessed in the clinic periodically throughout treatment. Patients' orgasm function was also assessed.

Results: Mean HAM-D, HAM-A, CGI-I, and CGI-S scores improved over the course of treatment in both the bupropion SR group and the sertraline group; no between-group differences were observed on any of the scales. Orgasm dysfunction was significantly ($p < .001$) more common in sertraline-treated patients compared with bupropion SR–treated patients. The adverse events of nausea, diarrhea, somnolence, and sweating were also experienced more frequently ($p < .05$) in sertraline-treated patients. No differences were noted between the two treatments for vital signs and weight.

Conclusion: This double-blind comparison of bupropion SR and sertraline demonstrates that bupropion and sertraline are similarly effective for the treatment of depression. Both compounds were relatively well tolerated, and orgasm dysfunction, nausea, diarrhea, somnolence, and sweating were reported more frequently in sertraline-treated patients.

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Advances in neuroscience research have yielded new treatment options for depression, including the serotonin selective reuptake inhibitors (SSRIs), the mixed serotonin-norepinephrine reuptake inhibitors, and the atypical antidepressants.[1,2] These classes of antidepressants generally cannot be distinguished from one another or from the older tricyclic antidepressants or monoamine oxidase inhibitors on the basis of efficacy, but, consistent with their distinct mechanisms of action, their side effect profiles differ.[1–3] Side effects of the older antidepressants are often attributed to their anticholinergic, antihistaminergic, and α-adrenergic blocking activity.[1–4] Although side effect profiles of the new-generation antidepressants are improved relative to older agents' profiles,[1,2] many of the new-generation antidepressants are associated with side effects predominantly related to serotonergic activity.[5,6]

The antidepressant bupropion hydrochloride, chemically unrelated to other antidepressant medications, is thought to act by enhancing noradrenergic (as reflected by reductions in norepinephrine turnover and in firing rates of locus ceruleus neurons) and/or dopaminergic (via dopamine reuptake blockade) function.[7] Bupropion does not affect serotonergic function and has no known affinity for postsynaptic receptors.[7,8] Bupropion has consistently been demonstrated to be relatively free of sexual, cardiovascular, and sedative side effects.[9–13] In double-blind studies of depression, bupropion was more effective than placebo[14,15] and as effective as other antidepressants, including amitriptyline,[12,13] doxepin,[10] trazodone,[11] and fluoxetine.[9]

A sustained-release formulation of bupropion (bupropion SR) was developed that has an improved pharmacokinetic profile compared with the immediate-release formulation (bupropion IR). The altered distribution half-life of bupropion SR permits less frequent dosing, and the reduced peak concentrations may result in improved safety. This double-blind trial compares the efficacy and safety of bupropion SR and the SSRI sertraline.

METHOD

Patients

Men and women at least 18 years of age who were diagnosed with major depressive disorder (DSM-IV) and currently experiencing a major depressive episode with duration ≥ 4 weeks but ≤ 24 months were eligible for the study if they provided written, informed consent. Patients were required to be in a stable relationship with normal sexual functioning. Excluded were pregnant or lactating women, patients with a history or current diagnosis of bulimia and/or anorexia nervosa, patients with a known predisposition to seizures, and patients who were actively suicidal. Patients could not have been previously treated with either bupropion or sertraline and could not have received any psychoactive drug within 1 week of study drug treatment (2 weeks for monoamine oxidase inhibitors or protriptyline, and 4 weeks for fluoxetine). Patients were stratified by gender at randomization to ensure equivalence between treatment groups in their proportion of men and women.

Study Design and Procedures

This randomized, double-blind, parallel-group, multicenter study was conducted to compare the efficacy and safety of bupropion SR (100–300 mg/day) administered twice daily and sertraline (50–200 mg/day) administered once daily in the outpatient treatment of moderate to severe depression. The study comprised a 1-week screening phase, which served as a washout period for other psychotropic medications, and a 16-week treatment phase, during which patients received bupropion SR or sertraline using a double-dummy technique. No other psychoactive drugs, with the exception of chloral hydrate for nighttime sedation (Days 1–14), were permitted during the treatment phase.

Patients receiving bupropion SR initiated dosing on treatment Day 1 at 100 mg/day for 3 days. If clinically appropriate, the dose could be increased on treatment Day 4 to 200 mg/day and again on treatment Day 7 to 300 mg/day. Patients receiving sertraline initiated dosing on treatment Day 1 at 50 mg/day for 7 days. If clinically appropriate, the dose could be increased on treatment Day 8 to 100 mg/day and again on treatment Days 15 and 22 to 150 mg/day and 200 mg/day, respectively. Compliance with the prescribed dosing regimen was determined by returned tablet counts.

Clinic visits were conducted on the first days of the screening and treatment phases and at the end of treatment Weeks 1, 2, 3, 4, 6, 8, 12, and 16. Psychiatric evaluations, including the Hamilton Rating Scale for Depression (HAM-D),[16,17] the Hamilton Rating Scale for Anxiety (HAM-A),[18] and the Clinical Global Impressions scale for Severity of Illness (CGI-S),[19] were completed at each visit. The Clinical Global Impressions scale for Improvement (CGI-I)[19] was completed at each visit beginning with the end of treatment Week 1 visit (i.e., not at the screen visit). Adverse events (defined as any untoward medical occurrence, potentially drug-related or not) were also assessed at each clinic visit. Reports of adverse events were elicited by the investigators by asking patients, "Have you had any difficulties or has anything unusual occurred since I last saw you?" In addition, patients' orgasm functioning was assessed in investigator-conducted structured interviews/questionnaires modified from those employed in the Kinsey Institute Interviewer Ratings of Sexual Function.[20,21]

Data Analysis

Mean daily dose and medication compliance. All patients who received at least one dose of study medication and completed at least one postbaseline efficacy assessment were included in the daily dose and compliance analyses. Mean daily dose was calculated for each patient over the duration of treatment. Medication compliance during the 112-day treatment phase (expressed as a percentage) was calculated by dividing total dose taken across patients by total dose prescribed across patients.

Efficacy scales. All patients who received at least one dose of study medication and completed at least one postrandomization efficacy assessment were included in the efficacy analyses, which were conducted on both observed and last-observation-carried-forward (LOCF) scores. In the LOCF method, the last known observation was carried forward to subsequent weeks that had missing observations. Differences between the bupropion SR group and the sertraline group at each treatment week were tested using analysis of variance (ANOVA) for the HAM-D and HAM-A scores and using the Cochran-Mantel-Haenszel test for the CGI-S and CGI-I scores.

Adverse events. The frequency of patients' reporting a treatment-emergent adverse event (one emerging or worsening after the beginning of study medication treatment) with an incidence of at least 5% in either group was compared between groups using Fisher's exact test.

Sexual function. Because sexual function was assessed in investigator-conducted structured interviews, it was not analyzed as an adverse event. The percentage of patients experiencing orgasm delay or failure was compared between groups at each treatment week using the Cochran-Mantel-Haenszel test.

Table 1. Patient Demographics and Dosing

Characteristic	Bupropion SR	Sertraline
Number of patients	122	126
Mean age, y (range)	39 (19–76)	40 (18–74)
Gender, N (%)		
Female	59 (48)	60 (48)
Male	63 (52)	66 (52)
Ethnic origin, N (%)		
White	113 (93)	119 (94)
Black	7 (6)	4 (3)
Other	2 (2)	3 (2)
Prior antidepressant use for current episode, N (%)	27 (22)	26 (21)
Duration of present episode, N (%)		
4 w–2 mo	11 (9)	9 (7)
3–6 mo	26 (21)	35 (28)
7–12 mo	44 (36)	48 (38)
13–24 mo	41 (34)	34 (27)
Reason for premature discontinuation, N (%)		
Adverse experience	4 (3)	17 (13)
Condition deteriorated	0 (0)	2 (2)
Inadequate response	8 (7)	6 (5)
Lost to follow-up	7 (6)	1 (1)
Consent withdrawn	12 (10)	14 (11)
Protocol violation	3 (2)	3 (2)
Other	1 (1)	0 (0)
Total discontinued	35 (29)	43 (34)
Mean dose over treatment phase, mg/d	238	114
Compliance, mean % of prescribed dose	98	99

Figure 1. Mean 21-Item Hamilton Rating Scale for Depression Scores (LOCF) in Depressed Outpatients Receiving Bupropion SR or Sertraline for 16 Weeks

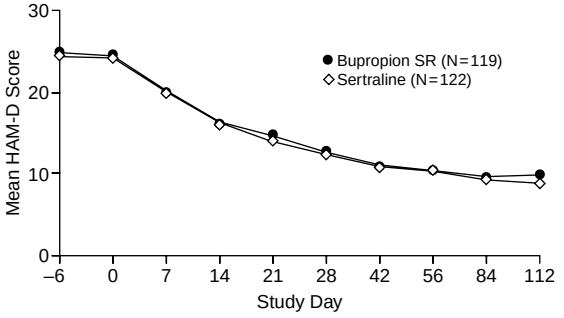
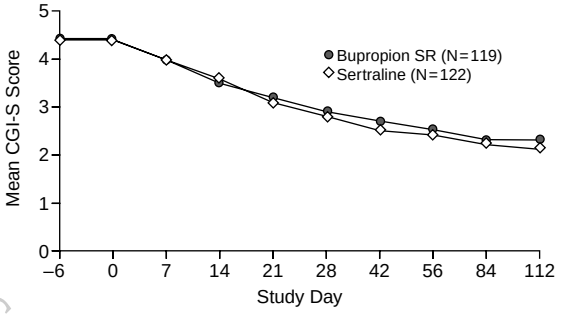


Figure 2. Mean Clinical Global Impressions for Severity of Illness Scores (LOCF) in Depressed Outpatients Receiving Bupropion SR or Sertraline for 16 Weeks



RESULTS

Sample Composition

Two hundred forty-eight patients (122 bupropion SR and 126 sertraline) were randomly assigned to treatment. All 248 patients were included in the safety analyses; the 241 patients (119 bupropion SR and 122 sertraline) who received at least one dose of study medication and completed at least one postrandomization efficacy assessment were included in the efficacy, orgasm function, and compliance analyses. Approximately two thirds of the patients in each group (87 of 122 in the bupropion SR group and 83 of 126 in the sertraline group) completed the study. Reasons for patient discontinuation are listed in Table 1.

Patient Demography and Compliance

Forty-eight percent of patients in each treatment group were women (Table 1). Patients' mean ages in the bupropion SR and sertraline groups were 39 (range, 19–76) and 40 (range, 18–74) years, respectively. Less than one quarter of the population had received antidepressant treatment for their current episode of depression. In the bupropion SR and sertraline groups, the mean daily doses were 238 and 114 mg/day, respectively, and the mean compliance rates (total dose taken/total dose prescribed) were 98% and 99%, respectively.

Efficacy Results

Observed and LOCF data were similar for both the bupropion SR and the sertraline groups for all four efficacy scales. LOCF data are reported.

HAM-D scores. Mean baseline HAM-D scores were similar between the bupropion SR group and the sertraline group (Figure 1). Both groups demonstrated a greater than 50% improvement in HAM-D scores by Day 42. This degree of improvement was maintained through the remainder of the 16-week treatment phase. There were no statistically significant differences between the bupropion SR group and the sertraline group at any treatment week.

CGI-S scores. Mean baseline CGI-S score was 4.4 in both the bupropion SR group and the sertraline group (Figure 2). CGI-S scores improved steadily throughout the treatment phase. There were no statistically significant differences between the bupropion SR group and the sertraline group at any treatment week.

CGI-I scores. Mean baseline CGI-I scores were similar between the bupropion SR group and the sertraline group (Figure 3). CGI-I scores steadily improved throughout the treatment phase. There were no statistically significant differences between the bupropion SR group and the sertraline group at any treatment week.

Figure 3. Mean Clinical Global Impressions for Improvement Scores (LOCF) in Depressed Outpatients Receiving Bupropion SR or Sertraline for 16 Weeks

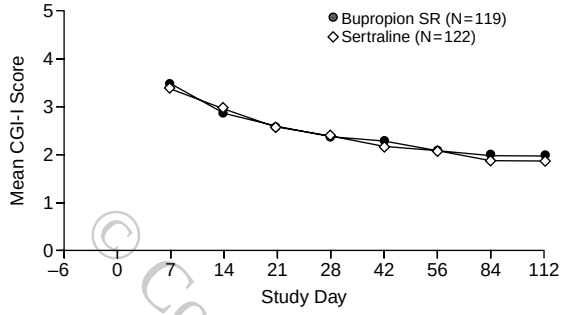
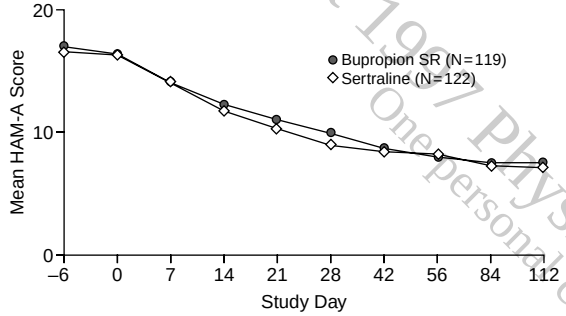


Figure 4. Mean Hamilton Rating Scale for Anxiety Scores (LOCF) in Depressed Outpatients Receiving Bupropion SR or Sertraline for 16 Weeks



HAM-A scores. Mean baseline HAM-A scores were similar between the bupropion SR group and the sertraline group (Figure 4). By Day 56, both groups demonstrated a 50% improvement, which was maintained through the remainder of the treatment phase. There were no statistically significant differences between the bupropion SR group and the sertraline group at any treatment week.

Adverse Events and Other Safety Data

Adverse events that emerged during the treatment phase and were experienced by > 5% of patients in either the bupropion SR or the sertraline group are listed in Table 2. The most common adverse event was headache, experienced by 34% of bupropion SR–treated patients and 32% of sertraline-treated patients. Significantly more patients in the sertraline group ($p < .05$) experienced the gastrointestinal adverse events of nausea (30% of sertraline patients; 10% of bupropion SR patients) and diarrhea (22% of sertraline patients; 3% of bupropion SR patients). Similarly, significantly more patients in the sertraline group ($p < .05$) had somnolence (13% of sertraline patients; 2% of bupropion SR patients) and sweating (10% of sertraline patients; 2% of bupropion SR patients).

Seventeen patients in the sertraline group and 4 patients in the bupropion SR group were discontinued from the study due to sexual dysfunction or other adverse effects ($p = .004$; Table 3). Sexual dysfunction, nausea/vomiting, and nervousness accounted for the majority of withdrawals in the sertraline group.

Baseline orgasm function scores were not significantly different between groups. Orgasm function was impaired in more sertraline-treated patients than in bupropion SR–treated patients throughout the 16-week treatment phase. Beginning on treatment Day 7, a significantly ($p < .001$) greater proportion of sertraline-treated patients compared with bupropion SR–treated patients experienced orgasm delay and/or failure (Figure 5). Also, gender-specific analyses demonstrated that between-group differences in rates of patients who experienced orgasm dysfunction at any time during the study were observed for both men (10% for bupropion SR, 61% for sertraline; $p < .001$) and

Table 2. Number and Percentage of Patients Experiencing an Adverse Event During the Treatment Phase*

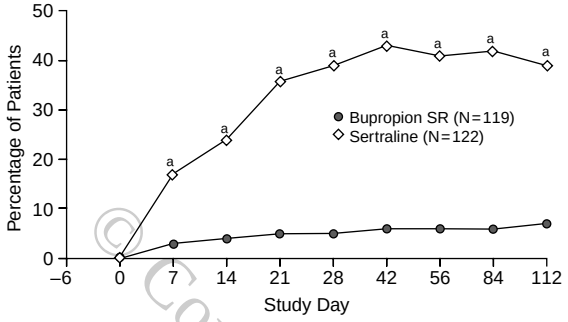
	Bupropion SR (N = 122)		Sertraline (N = 126)	
Event	N	%	N	%
Headache	42	34	40	32
Nausea[a]	12	10	38	30
Insomnia	22	18	24	19
Dry mouth	19	16	19	15
Infection	22	18	12	10
Diarrhea[a]	4	3	28	22
Flu syndrome	15	12	7	6
Anxiety	9	7	12	10
Dyspepsia	10	8	9	7
Somnolence[a]	3	2	16	13
Asthenia	6	5	11	9
Nervousness	5	4	11	9
Dizziness	10	8	6	5
Rhinitis	10	8	6	5
Sweating[a]	2	2	12	10
Tremor	3	2	7	6

*Adverse events occurring in > 5% of patients in either group are reported.
[a]$p < .05$ sertraline vs bupropion SR.

Table 3. Number of Patients Prematurely Discontinued From the Study Due to Sexual Dysfunction and Other Adverse Events

Event	Bupropion SR (N = 122)	Sertraline (N = 126)
Sexual dysfunction	0	4
Nausea/vomiting	0	4
Nervousness	0	2
Headache	0	1
Generalized anxiety	0	1
Activation	0	1
Loose bowels	0	1
Rash	0	1
Insomnia	0	1
Poor concentration	0	1
Flu syndrome	1	0
Nose bleed	1	0
Fatigue	1	0
Hostility	1	0

Figure 5. Percentage of Patients Experiencing Orgasm Failure and/or Delay During Treatment With Bupropion SR or Sertraline for 16 Weeks



[a]p < .001.

women (7% for bupropion SR, 41% for sertraline; p < .001).

Abnormalities in systolic blood pressure, diastolic blood pressure, or pulse were infrequent and occurred with similar frequency in the bupropion SR and sertraline groups. After 16 weeks, patients in both treatment groups experienced a small and similar mean decrease in body weight (sertraline = –0.7 lb; bupropion SR = –1.2 lb).

DISCUSSION

The results of this study demonstrate that bupropion SR and sertraline are similarly efficacious in the treatment of depression. Comparable improvements were observed with the HAM-D, the CGI-S, the CGI-I, and the HAM-A. There were no statistically significant differences between bupropion SR and sertraline in scores for any of these four scales at any assessment point.

The similar improvement in HAM-D and HAM-A scores over time for both bupropion SR and sertraline is noteworthy. These results demonstrate that as depression improves, anxiety improves equally for both bupropion SR and sertraline. This finding confirms the results of an earlier study in which corresponding improvements in depression and the symptoms of anxiety associated with depression were observed in patients treated with bupropion and fluoxetine.[9] Results from that study and the one presented here indicate that bupropion is beneficial not only for symptoms of depression but also for relief of the symptoms of anxiety associated with depression.

The magnitude of improvement in efficacy scale scores in this study is similar to that observed in controlled clinical trials in which bupropion or sertraline had been demonstrated to be statistically and clinically superior to placebo.[14,15,22,23] This across-study consistency in response rates lends support to the contention that the improvements observed in our study are attributable to study drug medication. However, the absence of a placebo group in our study precludes an estimate of the degree to which clinical improvements are attributable to study drug treatment.

In addition to complementing the results of placebo-controlled studies, this study extends the data describing comparative effectiveness of antidepressants by demonstrating that bupropion SR and sertraline are similarly efficacious. Both bupropion and sertraline have been shown previously to be at least as effective as amitriptyline in the treatment of depression.[12,13,22,23] Bupropion has also been shown to be as effective as fluoxetine,[9] trazodone,[11] and doxepin.[10]

Although bupropion SR and sertraline were similarly effective in alleviating depression in this study, their side effect profiles differed. More withdrawals due to adverse events, most commonly sexual dysfunction and nausea/vomiting, were observed in patients receiving sertraline compared with bupropion SR. Of the treatment-emergent adverse events reported by > 5% of patients in either treatment group, headache, insomnia, and dry mouth occurred with approximately equal frequency in bupropion SR– and sertraline-treated patients; however, sertraline was significantly more likely than bupropion SR to be associated with gastrointestinal adverse events such as nausea and diarrhea. In addition, a significantly greater proportion of sertraline-treated patients compared with bupropion-treated patients reported somnolence and sweating. These data corroborate results of previous studies.[9,11,23]

Bupropion SR and sertraline also differed in their effects on orgasm function. Sertraline was consistently associated with impairment in orgasm function compared with bupropion SR. Onset of impairment occurred as early as treatment Day 7 at daily doses as low as 50 mg and persisted for the duration of the treatment phase. The data from this double-blind study suggest that the incidence of sexual dysfunction with sertraline (41%–61% for orgasm delay and/or failure) may be higher than the 15.5% incidence rate for sexual dysfunction quoted in package labeling.[24] Because incidence rates quoted in package labeling and cited in most studies rely on spontaneous reports of sexual dysfunction, they may underestimate actual incidence rates; whereas the current study employed explicit questioning about sexual function. In contrast to previous reports,[23,25] the data from the current study also suggest that sexual function impairments observed with sertraline are not transient but last throughout a 16-week course of treatment.

Sertraline is not unique among SSRIs in its side effect profile or its association with the development of sexual dysfunction. While the relative incidence of side effects for both treatment groups was lower in a previous study comparing bupropion SR with fluoxetine,[9] an SSRI different from that used in the current study, the difference is most likely related to methodological differences (e.g., study duration) rather than to differences in SSRI side ef-

fect profiles. The few studies that have directly compared SSRIs have found no statistical differences in efficacy or side effects and similar rates of withdrawal due to adverse events.[26] Meta-analytic reviews have also failed to demonstrate any significant differences in adverse events between SSRIs.[27] Sexual dysfunction, in particular, has been reported as an important side effect for other SSRIs, including fluoxetine,[28,29] paroxetine,[30] and fluvoxamine,[31] presumably reflecting the serotonergic activity of that class of drugs.[6]

The current study had the advantage over other studies of obtaining sexual dysfunction information through explicit questioning, leading to more realistic and complete data than in previous reports.[9,32] There are also several limitations of the current study design. First, patients with chronic (> 24 months' duration) depression were excluded. Also, the equivalent gender distribution created by stratification and the entry criterion of normal sexual functioning at baseline, both required for the purposes of obtaining definitive data on the effects of these antidepressants on sexual function in both sexes, influenced the population of depressed patients studied and may influence the comparison of these results with those of other studies. Lastly, a placebo arm was not included.

The results of this double-blind trial comparing bupropion SR and sertraline with respect to efficacy, safety, and effects on orgasm function demonstrate that bupropion is as effective as sertraline. Both medications were well tolerated, although their side effect profiles differed. Sertraline was much more likely than bupropion SR to be associated with gastrointestinal adverse events. A higher percentage of sertraline-treated patients compared with bupropion-treated patients experienced impaired orgasm function. Therefore, bupropion SR may be an antidepressant of choice if avoidance of sexual dysfunction is of importance to the patient.

Drug names: amitriptyline (Elavil and others), bupropion SR (Wellbutrin), chloral hydrate (Noctec), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), protriptyline (Vivactil), sertraline (Zoloft), trazodone (Desyrel and others).

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