Do Bupropion SR and Sertraline Differ in Their Effects on Anxiety in Depressed Patients?

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Objective: To examine the effects of bupropion sustained release (SR) and sertraline on anxiety in outpatients with recurrent DSM-IV–defined major depressive disorder.

Method: This retrospective analysis was conducted using pooled data from 2 identical, 8-week, acute-phase, double-blind, placebo-controlled, parallel-group studies of bupropion SR (N = 234), sertraline (N = 225), and placebo (N = 233). Symptoms of anxiety and depression were measured using the 14-item Hamilton Rating Scale for Anxiety (HAM-A) and the 21-item Hamilton Rating Scale for Depression (HAM-D-21), respectively. Percentage reduction in baseline HAM-A total score for each treatment week was calculated to determine whether the time to onset of anxiolytic activity differed among antidepressant responders to each agent. Central nervous system (CNS) adverse events were tabulated.

Results: Bupropion SR and sertraline were comparably effective, both were superior to placebo in reducing depressive symptoms, and they did not differ in their effect on anxiety symptoms. Antidepressant responders (≥ 50% reduction in baseline HAM-D-21 score) in both groups showed marked and comparable reductions in HAM-A scores (baseline to exit). There were no differences between bupropion SR and sertraline in the median time (4 weeks) to reach a clinically significant anxiolytic effect (≥ 50% reduction in baseline HAM-A score). CNS adverse events were comparable for bupropion SR and sertraline, except for somnolence, which was more common in sertraline-treated patients.

Conclusion: Bupropion SR and sertraline had comparable antidepressant and anxiolytic effects and an equally rapid onset of clinically significant anxiolytic activity. There was no difference in the activating effects between the 2 antidepressants. Selection between these 2 agents cannot be based on either anticipation of differential anxiolytic activity or differential CNS side effect profiles.

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Both bupropion sustained release (SR)[1–3] and sertraline[4–6] have established efficacy in acute-phase, double-blind, randomized, placebo-controlled studies in adult outpatients with major depressive disorder (MDD). Bupropion SR has also shown comparable efficacy to the selective serotonin reuptake inhibitors (SSRIs) paroxetine[7] and sertraline[1,2,8] in outpatients with recurrent MDD.

Approximately 50% to 70% of patients with major depression have significant anxiety symptoms.[9] Some antidepressant medications also have U.S. Food and Drug Administration–approved indications for anxiety disorders (e.g., paroxetine[10] and sertraline[11] for panic disorder and paroxetine,[10] sertraline,[11] and fluoxetine[12] for obsessive-compulsive disorder). Many clinicians believe that the reduction in anxiety (i.e., anxiolysis), when it occurs in the treatment of MDD, is more rapid or more complete when using antidepressants that have "dual" indications for both depression and anxiety.

The aim of acute-phase treatment of recurrent MDD is the symptomatic remission of both depression and associated anxiety symptoms. Thus, it is useful to know whether different antidepressants, while comparable in

antidepressant efficacy, differ in their capacity to induce anxiolysis or in the time to the onset of this effect.

We undertook a retrospective analysis using pooled data from 2 identical 8-week, acute-phase, double-blind studies in outpatients with recurrent MDD to evaluate the effects on anxiety in patients treated with bupropion SR or sertraline for recurrent MDD. In brief, patients in these 2 studies were randomly assigned to treatment with bupropion SR, sertraline, or placebo in equal proportions; additional details of these studies are provided elsewhere.[1,2] The present analyses were conducted to answer the following questions: (1) Do sertraline and bupropion SR differ in their overall effects on anxiety symptoms (baseline to study exit)? (2) For those patients whose depression responded to treatment (defined as at least a 50% reduction in total Hamilton Rating Scale for Depression [HAM-D] scores), does sertraline differ from bupropion SR in its effects on anxiety (baseline to exit)? (3) For those patients whose depression responded to either agent, does sertraline differ from bupropion SR in the time to the onset of clinically significant reduction in anxiety (defined as a ≥ 50% reduction in total HAM-A score from baseline)? and (4) Does the incidence of central nervous system (CNS) treatment-emergent adverse events differ between patients in the sertraline and bupropion SR treatment groups?

This is the second retrospective analysis performed on this data set. We previously found that the severity of baseline anxiety (Hamilton Rating Scale for Anxiety [HAM-A] total score) was unrelated to treatment response or remission with either bupropion SR or sertraline.[13] This article focuses on the nature and timing of anxiety symptoms following study entry.

METHOD

Patients and Procedures

Two randomized, double-blind, placebo-controlled, parallel-group, multicenter studies (Glaxo Wellcome AK1A4001 and AK1A4002) with identical protocols[1,2] were conducted in outpatients diagnosed with moderate-to-severe recurrent MDD based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria.[14] The study protocol was approved by the Institutional Review Board for each study site. Written informed consent was obtained from each patient after the procedures and possible side effects had been fully explained. Patients with a history of, or current diagnosis of, any psychotic, bipolar, or eating disorder were excluded, as were those with a current obsessive-compulsive or organic mental disorder. Patients could have generalized anxiety disorder, but could not have met criteria for current panic disorder or have a history of substance abuse or dependence within the past year. In addition, patients could not have used any psychoactive drug within 1 week of study drug treatment (2 weeks for monoamine oxidase inhibitors or protriptyline, 4 weeks for fluoxetine or any investigational drug).

Following screening and baseline physical and psychiatric assessments, patients were randomly assigned to receive bupropion SR (150–400 mg/day), sertraline (50–200 mg/day), or placebo for up to 8 weeks. Patients enrolled in these studies were required to have recurrent MDD with a baseline score of at least 18 on the 21-item HAM-D (HAM-D-21)[15,16] and be suitable for treatment with bupropion SR or sertraline. Assessments of depression and anxiety were made at days 7, 14, 21, 28, 42, and 56. As part of each individual protocol, efficacy was evaluated at each clinic visit using the HAM-D-21 (the HAM-D-21 total score was the primary efficacy scale used for this retrospective analysis), the HAM-A,[17] the Clinical Global Impressions-Severity of Illness scale (CGI-S),[18] and the Clinical Global Impressions-Improvement scale (CGI-I).[18]

Bupropion SR dosing was initiated at 150 mg/day on day 1 of the study and, if clinically indicated, could be increased to a maximum of 400 mg/day no earlier than day 15. Sertraline dosing was initiated at 50 mg/day and, if clinically indicated, could be increased to a maximum of 200 mg/day no earlier than day 22. The dose of bupropion SR could be decreased to a minimum of 150 mg/day, and the dose of sertraline could be decreased to a minimum of 50 mg/day if clinically necessary due to intolerable side effects. To maintain blinding, all dose changes were similarly adjusted among treatment groups so that increases or decreases were made for both medications.

Statistical Methods

Change in HAM-D-21 total score was analyzed using both observed (nonimputed) values and last-observation-carried-forward (LOCF) imputed values via analysis of covariance (ANCOVA) at each timepoint. The ANCOVA models included terms for baseline HAM-D-21 score, investigator, and treatment. Single degree-of-freedom contrasts were used to compare the 2 active treatment groups.

Discontinuation rates due to adverse events were tabulated for each treatment group and compared via a 2-sided Fisher exact test. Treatment-emergent CNS adverse events reported at least once by at least 5% of patients in any treatment group were also tabulated. The mean modal dose for each treatment group was computed by averaging the most frequent dose (mode) for each patient.

ANCOVA methodology was also used to examine changes in HAM-A total score and to compute confidence intervals for the difference in the 2 active treatments, using models similar to those for the HAM-D-21. These models were repeated for subgroups of patients with minimal (HAM-A score ≤ 14), moderate (HAM-A score 15–19), and severe (HAM-A score ≥ 20) baseline HAM-A scores. The models were also repeated based on division of the patients into groups of antidepressant responders

Table 1. Patient Clinical and Demographic Characteristics at Baseline[a]

Characteristic	Placebo (N = 233)	Bupropion SR (N = 234)	Sertraline (N = 225)
Age, mean ± SD, y	38 (11)	37 (11)	37 (11)
Female, N (%)[b]	128 (55)	123 (53)	115 (51)
Racial origin			
White, N (%)	205 (88)	203 (87)	204 (91)
African American, N (%)	20 (9)	22 (9)	16 (7)
Other, N (%)	8 (3)	9 (4)	5 (2)
Length of current depressive episode			
2–6 months, N (%)	102 (44)	94 (40)	89 (40)
7–12 months, N (%)	56 (24)	75 (32)	67 (30)
12–24 months, N (%)	75 (32)	65 (28)	69 (31)

[a]Abbreviation: SR = sustained release.
[b]Enrollment was stratified to ensure that an equal proportion of men and women entered the study.

(at least a 50% reduction in HAM-D-21 score at study exit) and nonresponders.

Median time to the first significant reduction in HAM-A score (at least a 50% reduction) was computed for each treatment group, and survival analysis techniques and log-rank tests were used to compare the time to significant reduction. Furthermore, comparisons between the treatment groups in the number of patients who experienced significant increases (≥ 3 HAM-A points), decreases (≤ 3 HAM-A points), or no changes (up to ± 2 HAM-A points) in HAM-A total score were generated and evaluated for the 2 active groups using 2-sided Fisher exact tests. Lastly, ANCOVA models as above were used to compare the treatment groups with respect to the psychic and somatic subscales of the HAM-A.

RESULTS

Data from 692 patients were available for efficacy evaluations across the 2 studies. Table 1 summarizes the clinical and demographic features of the pooled sample. Characteristics were similar among the 3 treatment groups. The mean modal doses were 331 ± 98 mg/day and 137 ± 63 mg/day for bupropion SR and sertraline, respectively. Table 2 provides depression symptom information at baseline and endpoint (LOCF).

Overall, both agents displayed comparable antidepressant activity. Both bupropion SR and sertraline were more effective than placebo using both LOCF and observed-cases ANCOVA. LOCF HAM-D-21 change scores at the end of the study indicated a mean decrease of 14.1 for the bupropion SR and sertraline groups and 11.8 for the placebo group (Figure 1). Antidepressant response was seen in 65% and 64% of bupropion SR–treated and sertraline-treated patients, respectively, when defined as a ≥ 50% reduction in baseline HAM-D-21 total score. Defining response as a CGI-I score of 1 or 2 yielded a 56% response rate for both bupropion SR and sertraline. Most of the patients whose depression responded to treatment were also remitters (defined as final HAM-D-21 score ≤ 8), with 44% of bupropion SR–treated and 48% of sertraline-treated patients meeting this threshold (Table 2).

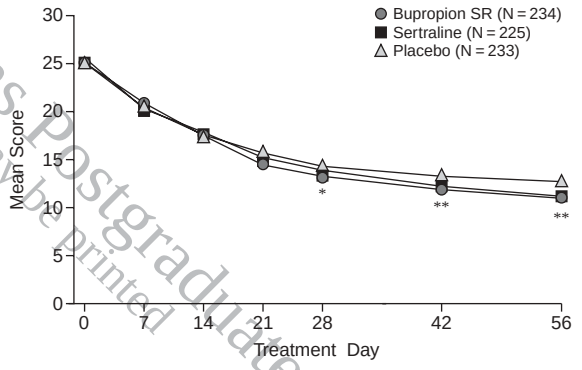
Discontinuation rates were comparable among the 3 treatment groups (sertraline, 31%; bupropion SR, 24%; placebo, 30%; p = .075 for sertraline vs. bupropion SR). Adverse event discontinuations were comparable between the 2 active treatment groups (p = .841) and greater for both active treatments than for the placebo group (sertraline, 5%; bupropion SR, 6%; placebo, < 1%; p = .001 for sertraline vs. placebo and bupropion SR vs. placebo). Of those patients discontinued due to an adverse event,

Table 2. Baseline and End-of-Treatment (LOCF) Findings in Depressed Patients[a]

Group	Placebo (N = 233)	Bupropion SR (N = 234)	Sertraline (N = 225)
All patients			
Baseline HAM-D-21 score, mean (SD)	24.9 (5.2)	25.2 (5.2)	25.2 (5.2)
Last visit HAM-D-21 score, mean (SD)	13.1 (8.9)	11.1 (8.4)	11.0 (8.3)
Baseline CGI-S score, mean (SD)	4.1 (0.5)	4.2 (0.5)	4.1 (0.5)
Last visit CGI-S score, mean (SD)	2.8 (1.2)	2.5 (1.3)	2.5 (1.2)
Last visit status			
Patients with response[b] (HAM-D-21), N (%)	116 (50)	152 (65)	145 (64)
Patients with response[c] (CGI-I), N (%)	97 (42)	130 (56)	127 (56)
Patients with remission[d] (HAM-D-21), N (%)	78 (33)	104 (44)	109 (48)

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, SR = sustained release.
[b]Defined as a reduction of at least 50% from baseline HAM-D-21 score.
[c]Defined as CGI-I score of 1 or 2.
[d]Defined as final HAM-D-21 score of 8 or less.

Figure 1. Mean 21-Item HAM-D Scores (LOCF)[a]



[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, SR = sustained release.
*p < .05, bupropion SR vs. placebo.
**p < .05, bupropion SR and sertraline vs. placebo.

Table 3. Central Nervous System Adverse Events Reported by at Least 5% of Patients[a]

	Bupropion SR (N = 237)	Sertraline (N = 233)	Placebo (N = 240)
Adverse Event	N (%)	N (%)	N (%)
Insomnia	39 (16)	41 (18)	13 (5)
Somnolence	7 (3)	30 (13)	12 (5)
Dizziness	17 (7)	19 (8)	11 (5)
Agitation	17 (7)	9 (4)	12 (5)
Tremor	14 (6)	14 (6)	1 (< 1)

[a]Abbreviation: SR = sustained release.

Table 4. Baseline and End-of-Treatment (LOCF) Findings for Anxious Patients[a]

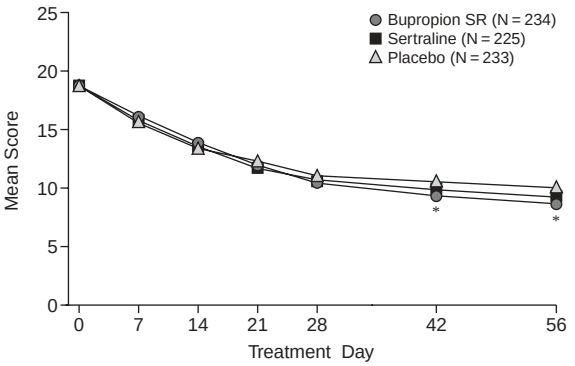
	Placebo (N = 233)		Bupropion SR (N = 234)		Sertraline (N = 225)	
Group	Mean	SD	Mean	SD	Mean	SD
All patients						
Baseline HAM-A score	18.6	7.1	18.8	7.3	18.6	7.4
Last-visit HAM-A score	10.2	8.9	8.9	6.8	9.2	7.1
Baseline psychic HAM-A subscale score	12.9	3.6	13.1	3.7	13.0	3.7
Last-visit psychic HAM-A subscale score	7.2	4.9	6.2	4.5	6.0	4.5
Baseline somatic HAM-A subscale score	5.7	4.2	5.7	4.3	5.6	4.2
Last-visit somatic HAM-A subscale score	2.9	3.4	2.7	2.8	3.2	3.4
Responders						
Baseline HAM-A score	18.9	7.6	18.7	7.8	18.5	7.3
Last-visit HAM-A score	5.6	4.5	5.3	4.1	5.9	4.5
Nonresponders						
Baseline HAM-A score	18.3	6.5	19.1	6.5	18.9	7.6
Last-visit HAM-A score	14.7	7.1	15.5	5.6	15.2	7.1

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SR = sustained release.

27% and 23% of bupropion SR–treated and sertraline-treated patients, respectively, were discontinued for CNS adverse events that were considered to have a reasonable possibility of being caused by a study drug. Table 3 presents treatment-emergent CNS adverse events reported at least once by at least 5% of patients in any treatment group. The reported incidence of CNS-related adverse events was comparable between the 2 active treatment groups, except for somnolence, which was reported by 13% of sertraline-treated patients compared with 3% of bupropion SR–treated patients (p = .001, Fisher exact test).

Table 4 provides anxiety symptom information at baseline and endpoint. Both active treatment groups differentiated from placebo in terms of change from baseline in HAM-A total scores toward the end of the 8-week treatment period. LOCF change scores at the end of the study indicated a mean decrease of 9.9, 9.4, and 8.4 points for the bupropion SR, sertraline, and placebo groups, respectively. Bupropion SR was superior to placebo (p = .01 and p = .04) at days 42 and 56 using HAM-A LOCF scores and was superior to placebo at day 56 using observed scores (p = .04). Sertraline was superior to placebo at day 56 using observed (p = .03), but not LOCF, scores (Figure 2 shows LOCF findings).

Figure 2. Mean HAM-A Scores (LOCF)[a]



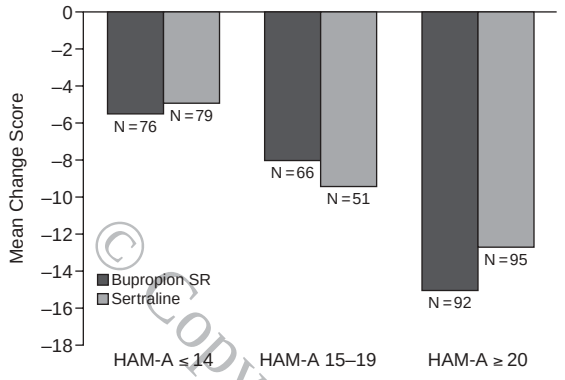
[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SR = sustained release. *p < .05, bupropion SR vs. placebo.

To examine whether sertraline and bupropion SR differed in their overall effect on anxiety, we used ANCOVA to compare the 3 treatment groups using HAM-A total score at each visit with both LOCF and observed data. No significant differences between the 2 active treatments at any timepoint using either LOCF or observed scores (all p > 0.41) were found. Confidence intervals for the differences between the active treatment groups (sertraline minus bupropion SR) in the change in total HAM-A score at day 56 from baseline were –0.72 to 1.62 and –1.33 to 1.04 for the LOCF and observed scores, respectively.

Further examination was conducted on the effects of bupropion SR and sertraline on patients with differing levels of baseline anxiety. Figure 3 shows the effects of bupropion SR and sertraline on anxiety scores (LOCF) at day 56 for those with minimal (≤ 14), moderate (15–19), and more severe (≥ 20) baseline anxiety levels (HAM-A total scores). Within each of the 3 baseline anxiety level groups, there were no statistically significant differences between bupropion SR and sertraline (all p > .104).

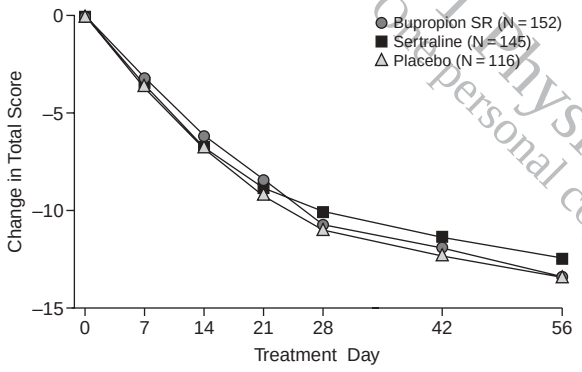
Do sertraline and bupropion SR differ in anxiety reduction for patients whose depression responded to each agent? Figure 4 shows the change from baseline in HAM-A total score for those whose depression responded (defined as ≥ 50% reduction in baseline HAM-D-21 score) to placebo, to sertraline, or to bupropion SR at each visit (LOCF). No differences were found between antidepressant responders in each of the 2 active treatment groups at any timepoint using either LOCF or observed scores (all p > .28) (ANCOVA). Confidence intervals for the differences (sertraline minus bupropion SR) between bupropion SR and sertraline in the change in total HAM-A score at day 56 from baseline were –0.64 to 0.97 and –0.38 to 1.29 for the LOCF and observed scores, respectively.

Figure 3. HAM-A Mean Change Scores (LOCF) at Day 56 for Patients With Different Baseline Scores[a]



[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SR = sustained release.

Figure 4. HAM-A Total Score (LOCF) Change From Baseline in Antidepressant Responders[a]

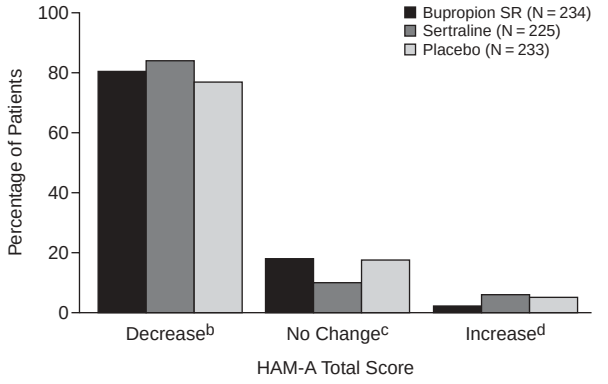


[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SR = sustained release.

Did sertraline differ from bupropion SR in the rapidity of reduction in anxiety for those patients whose depression responded to each agent? The 2 treatment groups did not show a difference in time to reduction in anxiety ($p = .496$). The median time to a 50% reduction in anxiety for both active treatment groups was 4 weeks.

To provide an overview of whether the treatments might have differed in the rates of anxiogenesis in a small subgroup of patients (Figure 5), we defined a priori significant increase (≥ 3), decrease (≤ 3), or no change (up to ± 2) in levels of anxiety in HAM-A total score (baseline to exit). The 2 active agents had comparable proportions of patients with increases, decreases, or no change in anxiety levels. While sertraline produced decreases in HAM-A scores in 84% of patients, bupropion SR produced decreases in 81% of patients, and placebo produced decreases in 77% of patients ($p = .326$, sertraline vs. bupropion SR). Increases in HAM-A scores were seen in significantly ($p = .03$) more sertraline-treated patients (6%) compared with bupropion SR–treated patients (2%). Five percent of placebo patients had increases in HAM-A scores.

Figure 5. End-Of-Study Change in HAM-A Total Score (LOCF)[a]



[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SR = sustained release.
[b]Defined as a score a minimum of 3 points lower than baseline.
[c]Defined as a change of up to 2 points from baseline.
[d]Defined as a score a minimum of 3 points higher than baseline.

Analyses of the somatic and psychic subscales of the HAM-A showed results similar to those of the complete HAM-A (Table 4). Both active agents showed differences from placebo ($p < .003$), but not from each other ($p = .819$) for the psychic component. The somatic component, however, did not differentiate between any of the 3 treatment groups (all $p > .205$).

DISCUSSION

As previously reported,[1,2] these retrospective analyses revealed that bupropion SR and sertraline were indistinguishable with regard to their antidepressant effects; both were more effective than placebo. Bupropion SR and sertraline had comparable overall effects on anxiety; however, only bupropion SR showed statistically significant differences from placebo.

We have explored multiple ways in which the purported anxiogenic effects of bupropion SR could have been manifested. In the overall study population, using LOCF data, the bupropion SR group, but not the sertraline group, had a statistically greater mean decrease in HAM-A total score from baseline at the end of the study than the placebo group. Use of LOCF data meant that any patients who dropped out prematurely from the study with high anxiety scores were still included in the analysis. Additionally, when patients whose depression responded to treatment were isolated from the overall study population, no differences between bupropion SR and sertraline were found at any timepoint.

To address concerns about possible differences in the onset time of anxiolysis, examination of median time to a 50% reduction in anxiety was performed, and bupropion SR and sertraline were found to be equivalent. Yet another analysis used baseline anxiety level categories and also failed to differentiate bupropion SR from sertraline in terms of mean change from baseline in total HAM-A score. We also examined changes at the end of the study to determine if the active agents had different proportions of patients with predefined increases, decreases, or no change in HAM-A total score. Again, the 2 active treatment groups were comparable. Finally, to confirm that anxiogenesis was not demonstrated via reported adverse events, CNS events were examined, and no differences in possibly anxiogenic-type effects (e.g., agitation, insomnia, and tremor) were seen, although somnolence was more prevalent in sertraline-treated patients. In summary, there was no evidence that bupropion SR had more anxiogenic activity than sertraline. Moreover, the time to onset of the anxiolytic effect was not different for bupropion SR and sertraline.

These data should be interpreted in light of the study population (outpatients only, and patients were excluded if they had current formal panic or obsessive-compulsive disorders). The limitations of this study are similar to those of other double-blind, randomized, controlled trials of subjects (symptomatic volunteers) with MDD. And yet, the relatively large sample sizes in this analysis provide a substantial amount of power for detecting clinically meaningful differences. Whether other antidepressant medications with allegedly more profound anxiolytic activity (e.g., nefazodone, venlafaxine, mirtazapine) than the SSRIs would also be indistinguishable from bupropion SR in anxiolytic activity deserves study. In addition, studies evaluating the effects of antidepressant medications on anxiety-related symptoms among patients with MDD in a naturalistic setting are also needed. In conclusion, these results, taken together with previous findings,[13,19] indicate that the selection of either bupropion SR or sertraline as an antidepressant cannot be based either on the patient's level of baseline anxiety, nor on the incorrect assumption that anxiolysis is either more likely to occur or more likely to occur sooner with sertraline as compared with bupropion SR.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), protriptyline (Vivactil), sertraline (Zoloft), venlafaxine (Effexor).

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