Efficacy of Bupropion and the Selective Serotonin Reuptake Inhibitors in the Treatment of Major Depressive Disorder With High Levels of Anxiety (Anxious Depression): A Pooled Analysis of 10 Studies

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Objective: The goal of this work was to compare the efficacy of the norepinephrine and dopamine reuptake inhibitor bupropion with the selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depressive disorder with high levels of anxiety (anxious depression).

Method: Ten double-blind, randomized studies from 1991 through 2006 were combined (N = 2122). Anxious depression was defined as a 17-item Hamilton Rating Scale for Depression (HAM-D-17) anxiety-somatization factor score ≥ 7.

Results: Among patients with anxious depression (N = 1275), response rates were greater following SSRI than bupropion treatment according to the HAM-D-17 (65.4% vs. 59.4%, p = .03) and the Hamilton Rating Scale for Anxiety (61.5% vs. 54.5%, p = .03). There was also a greater reduction in HAM-D-17 mean ± SD scores (–14.1 ± 7.6 vs. –13.2 ± 7.9, p = .03) and a trend toward statistical significance for a greater reduction in HAM-A mean ± SD scores (–10.5 ± 7.4 vs. –9.6 ± 7.6, p = .05) in favor of SSRI treatment among patients with anxious depression. There was no statistically significant difference in efficacy between bupropion and the SSRIs among patients with moderate/low levels of anxiety.

Conclusions: There appears to be a modest advantage for the SSRIs compared to bupropion in the treatment of anxious depression (6% difference in response rates). Using the number-needed-to-treat (NNT) statistic as 1 indicator of clinical significance, nearly 17 patients would need to be treated with an SSRI than with bupropion in order to obtain 1 additional responder. This difference falls well above the limit of NNT = 10, which was suggested by the United Kingdom's National Institute of Clinical Excellence. Nevertheless, the present work is of theoretical interest because it provides preliminary evidence suggesting a central role for serotonin in the regulation of symptoms of negative affect such as anxiety.

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Anxious depression, defined as major depressive disorder (MDD) with high levels of anxiety symptoms, represents a relatively common depressive subtype.[1] For example, in the National Institute of Mental Health Epidemiologic Catchment Area Program, 43% of individuals with mood disorders were also diagnosed with a comorbid lifetime anxiety disorder.[2] Similarly, the Vantaa Depression Study found that 57% of patients with a new episode of MDD had 1 or more concurrent anxiety disorders.[3] In a parallel, older article by our group, the rates of current and lifetime comorbid anxiety disorders among patients with MDD were 44.7% and 50.6%, respectively.[4] In the largest study yet, Fava et al.[5] reported that as many as 45.1% of 2337 MDD subjects participating in the Sequenced Treatment Alternatives to Relieve Depression study met criteria for anxious depression.

Bupropion hydrochloride, available in the United States for the treatment of depression since 1989, is a norepinephrine and dopamine reuptake inhibitor (NDRI) with no clinically significant affinity for the serotonergic transporter or the serotonergic, cholinergic, adrenergic, or histaminergic receptors.[6,7] To date, several published articles demonstrate that bupropion is as effective as the selective serotonin reuptake inhibitors (SSRIs) in the overall treatment of MDD with regard to the resolution of depressive,[8,9] as well as anxious,[10] symptoms. However,

it has been argued that nonserotonergic agents, including bupropion, may prove less advantageous when treating a particular subset of patients with a high burden of "negative" affective symptoms, including anxiety and irritability (for further details, see Stahl et al.[7,11] and Nutt et al.[12]). In addition, unlike many of the SSRIs, bupropion does not currently have a U.S. Food and Drug Administration–approved indication for the treatment of anxiety disorders. Perhaps as a result, in a recent survey conducted in the United States, clinicians were less likely to choose bupropion over the SSRIs and other antidepressants for patients with anxious MDD.[13] However, there is a paucity of scientific evidence supporting this practice. In fact, in a pooled analysis of 2 double-blind, placebo-controlled trials comparing bupropion with the SSRI sertraline for MDD, Rush et al.[14,15] reported no difference in efficacy between the 2 treatment groups for patients with high levels of anxiety. Therefore, the purpose of the following work was to (1) confirm or refute earlier findings by Rush et al.[14,15] by using a much larger data set and (2) extend our knowledge regarding the relative efficacy of bupropion in anxious depression beyond sertraline to include other SSRIs (fluoxetine, paroxetine, escitalopram).

METHOD

The present work involved pooling individual patient data from 10 double-blind, randomized clinical trials[16–23] (1 unpublished: data on file, GlaxoSmithKline, Research Triangle Park, N.C.) sponsored by GlaxoSmithKline (Research Triangle Park, N.C.) comparing bupropion to an SSRI for the treatment of MDD. In the present work, we chose to conduct a meta-analysis of individual patient-level data (i.e., "pooled analysis") since such analyses are, generally, superior to meta-analyses of study-level data and since in the former case it is possible to control for across-subject as well as across-study variability. To our knowledge, only 2 other studies[24,25] comparing bupropion with an SSRI have been conducted. Both studies, however, were excluded from the present analysis because they were conducted in special populations (i.e., citalopram-resistant depression[24] and bipolar depression[25]). In fact, a MEDLINE/PubMed search using the search terms *bupropion* and *depression* or *depressive* failed to identify any additional studies.

All 10 studies included in the present analysis were conducted in accordance with guidelines set by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, including the administration of institutional review board–approved written informed consent.[26] Patients in all but 1 trial met criteria for MDD as defined in the *Diagnostic and Statistic Manual of Mental Disorders*, Fourth Edition (patients in Feighner et al.[16] met criteria for DSM-III-R MDD), and all studies included a 1-week washout period preceding the 6- to 16-week double-blind phase. All 10 trials employed the 17-item Hamilton Rating Scale for Depression[27] (HAM-D-17). Eight of 10 trials employed the Hamilton Rating Scale for Anxiety[28] (HAM-A). Characteristics of these trials are listed in Table 1.[16–23]

Table 1. Randomized Clinical Trials Comparing Bupropion With an SSRI That Were Included in the Pooled Analysis

Protocol	Study	Duration, wk	SSRI	HAM-A
88	Feighner et al[16] (1991)	6	Fluoxetine	Yes
209	Kavoussi et al[17] (1997)	16	Sertraline	Yes
4001	Croft et al[18] (1999)	8	Sertraline	Yes
4002	Coleman et al[19] (1999)	8	Sertraline	Yes
4003	Weihs et al[20] (2000)	8	Paroxetine	Yes
4006	Unpublished[a]	8	Fluoxetine	Yes
4007	Coleman et al[21] (2001)	8	Fluoxetine	Yes
130926	Clayton et al[22] (2006)	8	Escitalopram	No
130927	Clayton et al[22] (2006)	8	Escitalopram	No
140016	Kennedy et al[23] (2006)	8	Paroxetine	Yes

[a]Data on file: GlaxoSmithKline, Research Triangle Park, N.C.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, SSRI = selective serotonin reuptake inhibitor.

Definitions and Efficacy Assessments

In the literature, anxious depression has been defined as either MDD with high levels of anxiety (dimensional approach) or MDD with a comorbid disorder (syndromal approach).[1] In the present work, we have employed the dimensional approach to define anxious depression for the following reasons: (1) it is the most widely used definition of anxious depression in the literature, (2) it is the definition used in the 2 largest published reports of anxious depression,[1,5] and (3) it is less time consuming and more feasible for practitioners and, consequently, more easily applicable in specialty clinics as well as primary care clinics. Therefore, in the present work, we defined depression with high levels of anxiety (anxious depression) as MDD presenting with a HAM-D-17 anxiety-somatization factor (HAM-D-AS) score ≥ 7. The HAM-D-AS, derived from a factor analysis of the HAM-D conducted by Cleary and Guy,[29] includes 6 items from the original 17-item version: psychic anxiety, somatic anxiety, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight.

Statistical Tests

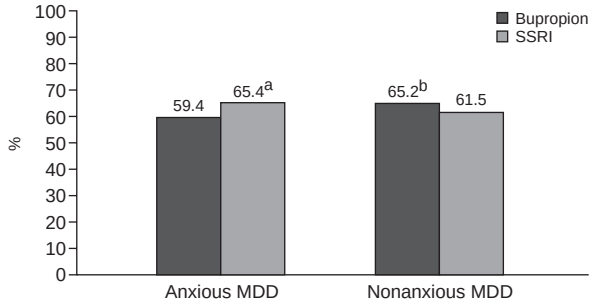
All statistical testing was conducted at the nominal 2-sided .05 level of significance. An intent-to-treat analysis was used to define the study data set. The last-observation-carried-forward method was used to define symptom severity at endpoint for patients who prematurely discontinued treatment. Treatment groups were compared on the basis of the following efficacy measures: (1) the mean change in HAM-D-17 and HAM-A total

Table 2. Baseline Demographic and Clinical Characteristics

Variable	Bupropion	SSRI
Anxious depression		
N, total	653	622
Women, N (%)	364 (55.7)	357 (57.4)
Age, mean ± SD, y	39.3 ± 12.9	38.9 ± 13.5
HAM-D-17 score, mean ± SD	24.0 ± 3.5	24.0 ± 3.7
HAM-D-AS score, mean ± SD	8.2 ± 1.3	8.3 ± 1.3
HAM-A score, mean ± SD	18.7 ± 6.2	18.8 ± 6.2
Nonanxious depression		
N, total	408	439
Women, N (%)	226 (55.4)	232 (52.8)
Age, mean ± SD, y	38.6 ± 12.5	39.6 ± 12.2
HAM-D-17 score, mean ± SD	20.7 ± 2.6	20.7 ± 2.5
HAM-D-AS score, mean ± SD	5.3 ± 0.9	5.5 ± 0.9
HAM-A score, mean ± SD	14.8 ± 4.6	14.8 ± 4.6

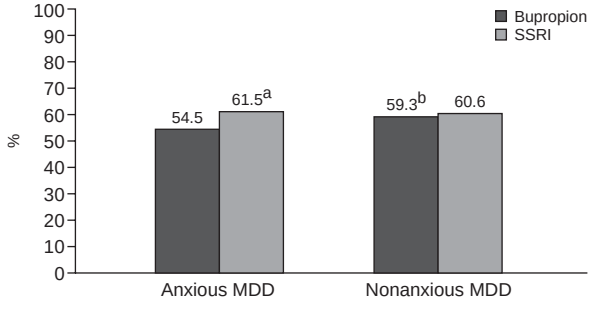
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-AS = Hamilton Rating Scale for Depression anxiety-somatization factor, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Response Rates (HAM-D-17)



[a]p = .03.
[b]p = .2.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Response Rates (HAM-A)



[a]p = .03.
[b]p = .7.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

scores during treatment, (2) HAM-D-17– and HAM-A–based response status (50% decrease in scores, baseline to endpoint), and (3) HAM-D-17– and HAM-A–based remission status (HAM-D-17 or HAM-A score at endpoint < 8). Differences in mean change in symptom severity between the 2 treatment groups were compared using an analysis of covariance, controlling for study (measure of across-study variability), treatment assignment, and corresponding baseline symptom scores (measure of across-patient variability). Differences in response and remission rates between treatment groups were compared using generalized linear models for the logit of response and remission probabilities,[30] controlling for study and treatment assignment.

RESULTS

Baseline demographic and clinical characteristics of MDD patients enrolled in the 10 trials are reported in Table 2. There was no statistically significant difference in any of these variables at baseline among patients with or without anxious depression who received treatment with either bupropion or an SSRI (p > .05, all pairwise comparisons). Patients with anxious MDD had greater HAM-D-17, HAM-A, and HAM-D-AS scores at baseline than patients without anxious MDD (p < .001, all 3 comparisons).

Among patients with high levels of anxiety (anxious depression) (N = 1275), response rates were greater following treatment with an SSRI than with bupropion according to the HAM-D-17 (65.4% vs. 59.4%, p = .03) and the HAM-A (61.5% vs. 54.5%, p = .03) (Figures 1 and 2). SSRI treatment also favored bupropion in producing a greater reduction in HAM-D-17 mean ± SD scores (–14.1 ± 7.6 vs. –13.2 ± 7.9, p = .03) and a trend toward statistical significance for a greater reduction in HAM-A mean ± SD scores (–10.5 ± 7.4 vs. –9.6 ± 7.6, p = .05). There was no statistically significant difference in remission rates between SSRI- and bupropion-treated patients with high levels of anxiety as defined using the HAM-D-17 (50.0% vs. 46.8%, p = .2) or HAM-A (50.4% vs. 46.9%, p = .2).

There was no statistically significant difference in any of these 6 outcome measures between bupropion and the SSRIs among patients with moderate/low levels of anxiety (see Figures 1 and 2). The mean ± SD change in HAM-D-17 scores among patients with moderate/low levels of anxiety was –11.7 ± 7.2 versus –11.2 ± 7.1 for bupropion and the SSRIs, respectively (p = .2). The mean ± SD change in HAM-A scores among patients with moderate/low levels of anxiety was –7.5 ± 6.4 versus –7.4 ± 6.1 for bupropion and the SSRIs, respectively (p = .7). HAM-D-17–based remission rates among patients with moderate/low levels of anxiety treated with either bupropion or an SSRI were 55.7% and 53.2%, respectively (p = .4). HAM-A–based remission rates among

patients with moderate/low levels of anxiety treated with either bupropion or an SSRI were 54.6% and 52.1%, respectively (p = .5). HAM-D-17–based response rates among patients with moderate/low levels of anxiety treated with either bupropion or an SSRI were 65.2% and 61.5%, respectively (p = .2). Finally, HAM-A–based response rates among patients with moderate/low levels of anxiety treated with either bupropion or an SSRI were 59.3% and 60.6%, respectively (p = .7).

DISCUSSION

Previous pooled analysis of randomized, double-blind clinical trials comparing bupropion with an SSRI for the treatment of patients with MDD did not report a difference in terms of antidepressant[8,9] or anxiolytic[10] efficacy between the 2 treatments. However, it appears that anxious MDD status (i.e., the presence versus absence of the anxious MDD subtype) may serve as a treatment moderator with respect to the relative anxiolytic efficacy of bupropion and the SSRIs in MDD. Specifically, the results of the present analysis suggest a small advantage for the SSRIs when compared to bupropion for the treatment of MDD accompanied by high levels of anxiety (anxious depression). Pooling data from 10 double-blind, randomized clinical trials revealed a greater resolution of depressive as well as anxiety symptoms following the treatment of anxious MDD with the SSRIs than with bupropion. The difference in response rates between the 2 groups was approximately 6% in favor of SSRI treatment. Although the difference favoring the SSRIs was statistically significant, it was also quite small (6%), of uncertain clinical significance, and might not be readily apparent to an astute clinician with extensive experience prescribing antidepressants. Using the number-needed-to-treat (NNT) statistic as 1 indicator of clinical significance, nearly 17 patients would need to be treated with an SSRI in order to obtain 1 additional responder. This difference falls well above the limit of NNT = 10, which was suggested by the United Kingdom's National Institute of Clinical Excellence. Finally, there was no difference in outcome for patients without anxious MDD who were treated with either bupropion or an SSRI.

The present work is in contrast to a large body of literature that suggests no difference in efficacy among the major antidepressant classes when treating anxious depression. Specifically, earlier studies reported no difference in efficacy when comparing the tricyclic antidepressants (TCAs) with the monoamine oxidase inhibitors (MAOIs),[31–34] SSRIs,[35–40] or nefazodone[41,42] or when comparing the NDRI bupropion with the SSRIs,[14,15] regardless of whether anxious depression was defined using the syndromal[31–33,40,42] or dimensional approach.[14,34–41] In light of the magnitude of the difference in response rates estimated by our work, a mere 6%, the discrepancy between our findings and previous studies may be due to the limited statistical power of previous studies to detect such a treatment difference (the largest of which was the report by Tollefson et al.[36] involving a total 1036 patients with anxious depression in the pairwise comparison of TCA and SSRI).

Alternatively, the difference in findings between the present study and previous works may be attributed to the different types of antidepressants involved. Specifically, in the present work, we compared the efficacy of a serotonergic drug with a nonserotonergic antidepressant, while nearly all of the aforementioned studies involved a comparison between antidepressants that, to one extent or another, all influenced serotonergic function (i.e., MAOIs, TCAs, SSRIs, nefazodone). Thus, the present findings, along with a previous article suggesting a greater resolution of somnolence and fatigue among bupropion- than SSRI-treated patients,[43] provide preliminary evidence suggesting a differential monoaminergic regulation of depressive symptoms. According to this theory, it had been proposed that "positive" affective symptoms, including fatigue and somnolence, are predominantly influenced by dopaminergic-catecholaminergic function, while "negative" affective symptoms, including anxiety and irritability, are predominantly influenced by serotonergic function (for review, see Stahl et al.[7,11] and Nutt et al.[12]). Prospectively testing the validity of this theory may lead to the further refinement of existing pharmacotherapeutic strategies and practice algorithms for MDD or the further refinement of future antidepressant drugs. Specifically, it is quite possible that better treatment outcomes (i.e., greater response/remission rates or a lower burden of residual symptomatology resulting from the simultaneous "targeting" of both "negative" and "positive" affective symptoms) can be achieved by combining either the SSRIs or the serotonin-norepinephrine reuptake inhibitors (SNRIs) with the NDRI bupropion from the onset of treatment. In a similar fashion, it is also quite possible that developing agents that simultaneously enhance serotonergic, noradrenergic, and dopaminergic neurotransmission, the so-called "triple reuptake inhibitors," may lead to more effective treatments. Unfortunately, however, to the best of our knowledge, randomized clinical trials comparing an NDRI-SSRI combination, an NDRI-SNRI combination, or a "triple reuptake inhibitor" with SSRI, SNRI, or NDRI monotherapy have not yet been conducted. Establishing whether these strategies or treatments can result in superior outcome could, clearly, help further advance the standard of care for people with MDD.

There are several limitations to this study that should be considered when interpreting the results and recommendations. First, the analysis involved pooling studies comparing bupropion with escitalopram, fluoxetine, sertraline, and paroxetine. Since studies involving fluvoxamine and citalopram were not included, conclusions

drawn from this study cannot be generalized to these latter 2 SSRIs. Second, our definition of anxious depression is based on the severity of anxiety symptoms, as measured by the HAM-D-AS. Although the HAM-D does include anxiety items, only a limited number of anxiety symptoms are captured by the HAM-D, and, therefore, the possibility of a misclassification (i.e., patients with anxious depression classified as not having anxious depression) cannot be ruled out. However, a recent work reporting a significant correlation between a dimensional definition of anxious depression and the degree of anxiety disorder comorbidity suggests that such risk may be relatively low.[1]

Other limitations specifically pertain to the identification of studies to be included in pooled analyses or meta-analyses and include the phenomenon of publication bias as well as the file drawer phenomenon. Thus, although we included all eligible studies sponsored by GlaxoSmithKline, regardless of whether they have been published or not, it is quite possible that studies sponsored by other sources have been conducted but not yet published or presented at major scientific meetings. In addition, pooled analyses and meta-analyses involve combining studies of heterogeneous design. In general, a single, well-designed clinical trial of equivalent sample size can yield more accurate estimates of a treatment effect. However, trials pooled in the present analysis had many similarities, including a 1-week washout period prior to randomization, a forced-titration dosing schedule, a comparable baseline depression severity threshold for inclusion, and similar treatment duration. Finally, all but 1 study[17] included in the analysis were of 6 to 8 weeks in duration. Whether the present findings would extend beyond the acute phase of treatment remains to be determined.

In conclusion, there appears to be a small advantage for the SSRIs compared to bupropion in the treatment of anxious depression (6% difference in response rates). Using the NNT statistic as one indicator of clinical significance, we found that nearly 17 patients would need to be treated with an SSRI in order to obtain 1 additional responder. This difference falls well above the limit of NNT = 10, which was suggested by the United Kingdom's National Institute of Clinical Excellence. Nevertheless, the present work is of theoretical interest because it provides preliminary evidence suggesting a central role for serotonin in the regulation of symptoms of negative affect such as anxiety.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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