Comparing the Rapidity of Response During Treatment of Major Depressive Disorder With Bupropion and the SSRIs: A Pooled Survival Analysis of 7 Double-Blind, Randomized Clinical Trials

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This work was supported by National Institute of Mental Health grant K23 MH069629 to Dr. Papakostas/Massachusetts General Hospital.

Financial disclosure appears at the end of the article.

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Objective: Several controlled studies, as well as a meta-analysis, suggest that the efficacy of bupropion, a norepinephrine-dopamine reuptake inhibitor, is comparable to that of the selective serotonin reuptake inhibitors (SSRIs). The current analysis was undertaken to determine if these antidepressants differ in rapidity of clinical effect.

Method: Individual patient data were obtained from 7 double-blind, randomized studies of 8 weeks' duration that compared bupropion (N = 836) and SSRIs (sertraline, paroxetine, fluoxetine, and escitalopram; N = 836). Time to first response and first remission were compared between treatment groups with the use of Cox proportional hazards regression models, stratified by trial number, with depression severity at baseline as a covariate. A secondary analysis compared outcomes in the 2 bupropion versus escitalopram studies. Random-effects meta-analyses were then conducted to confirm the survival-analysis findings.

Results: There was no statistically significant difference between bupropion and the SSRIs in time to first response (hazard ratio [HR] = 0.955; p = .43) and first remission (HR = 1.00; p = .97). Similarly, there was no statistically significant difference between bupropion and escitalopram in time to first response (HR = 0.897; p = .29), and first remission (HR = 0.999; p = .99). These results were confirmed with the use of random-effects meta-analyses (p > .05, all 4 analyses).

Conclusion: There does not appear to be any statistically detectable difference in the rapidity of antidepressant effect between bupropion and the SSRIs overall or escitalopram specifically.

(J Clin Psychiatry 2007;68:1907–1912)

Despite the progressive increase in the number of available antidepressant treatments,[1] many patients suffering from depression continue to be symptomatic. For example, in the first level of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[2] only about 30% of patients remitted following up to 12 weeks of therapy with citalopram. Moreover, it has been recently reported that as many as one half of all patients enrolled in 2 academically-based depression specialty clinics did not achieve remission despite receiving a series of adequate trials of antidepressant therapies.[3] Incomplete remission of major depression is not only a common clinical problem, it is associated with poorer psychosocial functioning,[4] as well as increased relapse rates[5] and a reduced likelihood of long-term recovery.[6]

Although full remission of symptoms is the ultimate goal of treatment, early improvement of symptoms is also an important goal for several reasons. First, there is often a significant delay in the onset of antidepressant activity for all pharmacotherapeutic strategies identified to date. Given that many patients with major depressive disorder (MDD) experience little if any reduction in symptoms following a single treatment,[3] a substantial proportion of MDD patients will require several treatments before achieving remission of their depression. As a result, overall treatment time may accumulate, leaving many patients symptomatic for an extended period of time. Second, a

delayed onset of antidepressant activity has been linked to poorer psychosocial adjustment.[4] Furthermore, in addition to prolonging physical and psychosocial impairment, a delayed clinical response places patients at increased risk for treatment noncompliance and suicide. Finally, a number of patients drop out of treatment during each failed treatment trial, further reducing their chances for eventual recovery. Therefore, given the potential benefits of rapidly acting antidepressants, it would be helpful for patients and clinicians alike to know whether certain antidepressants work faster than others.

Despite the obvious public health importance of this topic, few clinical trials have been specifically designed to evaluate and compare the time to onset of clinical improvement between 2 antidepressants. In fact, of 95 published trials comparing various pairs of newer antidepressants (reference list available upon request), fewer than 10% were found to report on survival-analysis–based comparisons of time to response or remission.[7–14]

Bupropion hydrochloride, available in the U.S. for the treatment of depression since 1989, is a norepinephrine and dopamine reuptake inhibitor with no clinically significant affinity for the serotonergic transporter or the serotonergic, cholinergic, adrenergic, or histaminergic receptors.[15] For nearly 2 decades, bupropion has been one of the principal alternatives to the selective serotonin reuptake inhibitors (SSRIs), the most widely prescribed class of antidepressants in the United States and many other industrialized countries. A number of controlled studies comparing bupropion and the SSRIs have been conducted in patients with MDD, and a meta-analysis of the first 7 of these studies indicated that bupropion is, on average, as effective as the SSRIs fluoxetine, sertraline, and paroxetine.[16] However, neither the individual studies nor the meta-analysis address rapidity of antidepressant effect. Moreover, 3 additional controlled studies comparing bupropion with either paroxetine or escitalopram have since been completed. We therefore performed a second analysis, emphasizing the rapidity of antidepressant effect, which we defined as the time to first response or first remission, comparing bupropion with the SSRIs. In contrast to the original meta-analysis, which focused on remission rates at study endpoints, survival analysis was chosen as the method for comparison of time-to-event outcomes, because it is considered a rigorous and sensitive measure of early clinical improvement.[17,18] We also conducted a secondary analysis comparing bupropion and escitalopram because of reports that this SSRI may have a particularly rapid onset of antidepressant effect.[14,19] We then confirmed these analyses with the use of a random-effects meta-analysis. Given that a previous pooled analysis had failed to show a difference in response or remission rates between the SSRIs and bupropion,[16] our research hypothesis was that there would be no difference in the rapidity of antidepressant effect between these 2 treatment groups. Therefore, the null hypothesis—namely, that there would be no difference in outcome (time to first response or remission) between the treatment groups (bupropion vs. the SSRIs, then bupropion vs. escitalopram)—was selected as the a priori hypothesis for all statistical analyses.

METHOD

The present work used individual patient data from all 8-week, double-blind, randomized clinical trials sponsored by GlaxoSmithKline (GSK) comparing bupropion to an SSRI for the treatment of MDD. Studies of 8 weeks' duration were chosen because that is the most common trial duration in the bupropion-SSRI data set. Ten GSK-funded studies have been conducted: 3 used sertraline, 3 used fluoxetine, 2 used paroxetine, and 2 used escitalopram as the SSRI comparator. Among these, 3 studies of duration other than 8 weeks were excluded in order to avoid biasing the survival analysis. (Kavoussi et al.[20] was 16 weeks in duration; Feighner et al.[21] and Weihs et al.[22] were 6 weeks in duration.) To our knowledge, only 2 other studies comparing bupropion with an SSRI were not included, and these studies were of special populations (i.e., subjects with citalopram-resistant depression[11] and bipolar depression[23]).

All 7 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 (ICH),[24] including the administration of institutional review board–approved written informed consent. All patients met criteria for MDD as defined in *The Diagnostic and Statistic Manual of Mental Disorders*, Fourth Edition, and all studies included a 1-week screening phase preceding the double-blind phase.

In each of the studies selected, efficacy assessments were performed during at least 5 study visits, each separated by 2 weeks (baseline and weeks 2, 4, 6, and 8). Additional assessments at weeks 1 and 3 were available for 4 of the studies, and at weeks 5 and 7 for 2 of the studies. All assessments were identical. Characteristics of these trials are listed in Table 1.

Statistical Tests

Clinical response was defined as a 50% or greater reduction in 17-item Hamilton Rating Scale for Depression (HAM-D-17)[30] scores. Remission of depression was defined as a HAM-D-17 score of less than 8. Mean changes in HAM-D-17 scores, baseline to endpoint, were compared between bupropion and the SSRIs using analysis of covariance, which accounted for the effects of study and treatment groups and corresponding baseline scores as covariates. The time to discontinuation between bupropion and the SSRIs overall or escitalopram specifically was compared using Cox proportional hazards regression

Table 1. Bupropion Versus SSRI Comparator Studies

GSK Protocol	Study	Placebo	SSRI	SSRI Dose, Range (Mean ± SD), mg	Bupropion Dose, Range (Mean ± SD), mg
4001	Croft et al,[25] 1999	Yes	Sertraline	50–200 (120.6 ± 39.6)	150–400 (292.6 ± 70.2)
4002	Coleman et al,[26] 1999	Yes	Sertraline	50–200 (106.2 ± 45.4)	150–400 (289.6 ± 64.5)
4006	Unpublished	Yes	Fluoxetine	20–60 (28.1 ± 7.3)	150–400 (282.8 ± 61.0)
4007	Coleman et al,[27] 2001	Yes	Fluoxetine	20–60 (29.5 ± 7.2)	150–400 (288.9 ± 62.7)
130926	Clayton et al,[28] 2006	Yes	Escitalopram	10–20 (12.9 ± 3.2)	300–450 (308.8 ± 58.3)
130927	Clayton et al,[28] 2006	Yes	Escitalopram	10–20 (12.9 ± 2.5)	300–450 (322.6 ± 59.3)
140016	Kennedy et al,[29] 2006	No	Paroxetine	20–40 (23.3)[a]	150–300 (178.5)[a]

[a]Value is range (mean), mg.
Abbreviations: GSK = GlaxoSmithKline, SSRI = selective serotonin reuptake inhibitor.

models stratified by trial number, with HAM-D-17 score at baseline as a covariate. The reasons for premature discontinuations were tabulated and compared between treatment groups using the Cochran-Mantel-Haenszel test of general association.

Time to first response and remission were compared between bupropion and SSRIs using Cox proportional hazards regression models stratified by trial number, with HAM-D-17 score at baseline as a covariate.[31] This analysis was repeated comparing bupropion with escitalopram alone. In order to confirm our findings, we then compared the mean time to response and remission between bupropion and the SSRIs overall or escitalopram specifically with the use of a random-effects meta-analysis.

All between–treatment-group testing was 2-sided at the nominal .05 level of significance. A 2-tailed test was chosen in order to test whether the time to response or remission was different for bupropion than it was for the SSRIs or escitalopram as opposed to simply examining whether the antidepressant effects of bupropion were either more rapid or not than the SSRIs (or vice versa). A total of 1672 patients were randomly assigned to either bupropion or an SSRI, yielding a power greater than 90% to detect a difference in time to onset of response or remission of at least 1 week between the 2 treatment groups.

RESULTS

There were no statistically significant differences in baseline demographic and clinical characteristics of MDD patients enrolled in the 7 bupropion-SSRI comparator trials (54.6% [471/863] vs. 54.2% [468/863] women; mean [SD] age 37.1 [11.2] vs. 65.9 [11.1] years; baseline HAM-D-17 scores 22.7 [3.6] vs. 22.5 [3.6] for bupropion vs. the SSRIs, respectively; $p > .05$, all analyses). There was also no statistically significant difference in overall antidepressant efficacy between bupropion and the SSRIs as measured by changes in HAM-D-17 total score (mean [SD] change 12.1 [7.6] vs. 12.3 [7.3] for bupropion and the SSRIs, respectively; $p = .50$). The association between treatment group (bupropion or SSRI) and reason for discontinuation was not statistically significant ($p = .104$; Table 2). Survival analysis did not suggest a significant difference in time to discontinuation between bupropion and the SSRIs (hazard ratio [HR] = 1.402, 95% CI = 0.935 to 1.16, $p = .455$) or escitalopram (HR = 1.016, 95% CI = 0.0844 to 1.22, $p = .866$).

Table 2. Summary of Discontinuations

Variable	Bupropion* (N = 836)	SSRIs* (N = 836)
Reason for Discontinuation*		
Lack of efficacy	7.1%	7.4%
Adverse event	6.7%	5.1%
Other	12.4%	16.2%
Total discontinued	26.2%	28.7%

*p Value for general association between treatment group and reasons for discontinuation = .104.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Similarly, there were no statistically significant differences in baseline demographic and clinical characteristics of MDD patients enrolled in the 2 bupropion-escitalopram comparator trials (58.9% [155/263] vs. 56.8% [151/266] women; mean [SD] age 37 [12.3] vs. 35.7 [11.3] years; mean [SD] baseline HAM-D-17 scores 23.5 [3.2] vs. 23.3 [3.2] for bupropion and escitalopram, respectively; $p > .05$, all analyses). A comparison of the overall antidepressant efficacy between bupropion and escitalopram, as measured by changes in HAM-D-17 total score, is reported in Clayton et al.[28] ($p > .05$).

Survival analyses yielded the following results: there was no statistically significant difference between bupropion and the SSRIs in the time to first response (HR = 0.955; 95% CI = 0.85 to 1.07; $p = .43$; see Figure 1) and first remission (HR = 1.00; 95% CI = 0.876 to 1.14; $p = .97$; see Figure 1). Baseline HAM-D-17 score entered as a covariate in the survival analysis was significant for time to first remission ($p < .001$) but not time to first response ($p = .24$). The mean (SD) times to first response for bupropion and the SSRIs were 4.68 (2.09) weeks and 4.83 (2.06) weeks, respectively. The mean (SD) times to first remission for bupropion and the SSRIs were 6.0 (1.7) weeks and 6.02 (1.7) weeks, respectively. For both the SSRIs and bupropion, the mean survival time and its standard deviation were underestimated, because the largest

Figure 1. Bupropion Versus SSRI

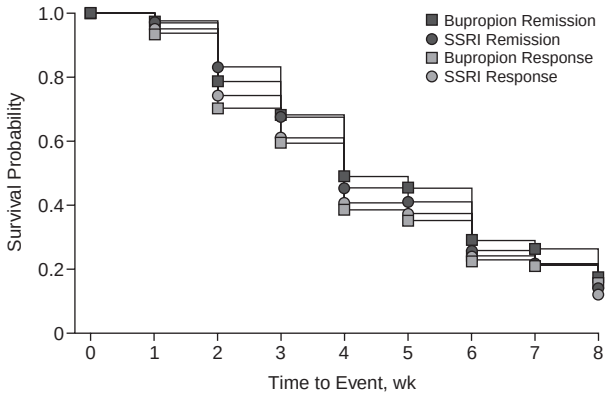
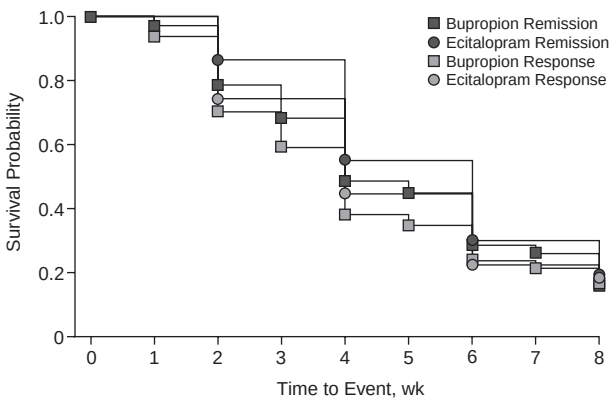


Figure 2. Bupropion Versus Escitalopram



observation was censored, and the estimation was restricted to the largest event time.

Similarly, there was no statistically significant difference between bupropion and escitalopram in the time to first response (HR = 0.897; 95% CI = 0.731 to 1.10; p = .29; see Figure 2), and first remission (HR = 0.999; 95% CI = 0.786 to 1.26; p = .99; see Figure 2). Baseline HAM-D-17 score, entered as a covariate in the survival analysis, was significant for time to first remission (p = .008) but not time to first response (p = .44). The mean (SD) times to first response for bupropion and escitalopram were 4.68 (2.09) weeks and 5.13 (1.91) weeks, respectively. The mean (SD) times to first remission for bupropion and escitalopram were 6.38 (1.73) weeks and 6.38 (1.46) weeks, respectively. Again, for both escitalopram and bupropion, the mean survival time and its SD were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Finally, random-effects meta-analyses also did not demonstrate a statistically significant difference in time to onset of response or remission between bupropion and the SSRIs overall or escitalopram specifically (p > .05, all 4 analyses), confirming the results of the survival analysis.

DISCUSSION

These results confirm those of the earlier meta-analysis (i.e., that bupropion and SSRIs have similar efficacy) and extend that work with the new finding that bupropion and the SSRIs have comparable rapidity of antidepressant effect. Our results also broaden the comparison versus the SSRI class by including 2 studies using escitalopram as the SSRI comparator. Confirmation that bupropion and the SSRIs are comparably effective, in terms of both the likelihood of remission at the end of acute phase therapy and the speed of response, does not mean that the drugs are equally useful for particular depressed patients. Indeed, given the heterogeneity of major depressive disorder and the relative advantage of bupropion or the SSRIs over placebo in these randomized controlled trials, it is possible that subgroups of patients are more responsive to one or the other type of antidepressant.

There are several limitations to this study that need to be taken into consideration. First, the analysis involved pooling individual data from studies comparing bupropion with escitalopram, fluoxetine, sertraline, and paroxetine. Since trials involving citalopram and fluvoxamine were not included, it is not certain that conclusions drawn from this analysis can be extended to both of these 2 SSRIs. A second potential limitation specifically pertains to the identification of studies included in meta-analyses. Thus, although we were able to review and evaluate all studies sponsored by GlaxoSmithKline regardless of whether they have been published or not, it is possible that studies sponsored by other sources have been conducted but have not yet been published or presented at major scientific meetings. Another potential limitation of meta-analysis is related to the inherent limitations of the individual studies that are included. Specifically, the samples in randomized controlled trials are typically more homogeneous than depressed patients seeking treatment in nonresearch settings and, as such, generalizability of findings to routine clinical practice can be questioned. All studies included in this meta-analysis, for example, required that patients be sexually active on a regular basis. In this respect, a single clinical trial of equivalent sample size can yield more accurate estimates of a treatment effect. However, all of the trials included in the present analysis used random assignment, 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, it should be pointed out that the studies pooled were not specifically designed to compare the rapidity of

bupropion and the SSRIs but, rather, their overall efficacy. For example, even though assessments were identical, there were differences in the timing of some of the assessment visits among the studies pooled (3 studies did not involve a week 1 and week 3 assessment, for example). However, all between–treatment-group comparisons reported in our work were performed using a Cox proportional hazard regression model, a semiparametric technique that implements a stratified analysis. In effect, the bupropion-SSRI comparisons are performed within each study, and the results are then pooled across studies. Thus, although some of the assessment schedules differed, the stratification performed controlled for any study-to-study differences. In addition to a uniform assessment schedule, other elements of study design that would serve to enhance the ability to detect a difference in time to clinical improvement between 2 antidepressants include more frequent assessments (e.g., twice per week) and a variable double-blind, placebo lead-in as proposed by Leon et al.[32] Unfortunately, none of the studies pooled in the present analysis included either of these 2 design elements. Therefore, given the post hoc nature of our work, conclusions drawn can be considered as suggestive but not definitive.

In conclusion, there does not appear to be any statistically detectible difference in the rapidity of antidepressant effect either between bupropion and the SSRIs overall or between bupropion and escitalopram specifically. However, it should also be pointed out that depression is a heterogeneous condition, and differences may exist between treatments in particular subgroups of patients.

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

Financial disclosure: **Dr. Papakostas** has served as a consultant for Aphios, Bristol-Myers Squibb, GlaxoSmithKline, Evotec, Inflabloc, Jazz, PAMLAB, and Pfizer; has received honoraria from Evotec, GlaxoSmithKline, Inflabloc, Jazz, PAMLAB, Pfizer, and Titan; and has received research support from Bristol-Myers Squibb, PAMLAB, and Pfizer. **Dr. Montgomery** has acted as a consultant to or served on speakers/advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Neuslim, Pfizer, Pierre Fabre, Roche, sanofi, Sepracor, Servier, Shire, and Wyeth. **Dr. Thase** has provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Sepracor, Shire US, and Wyeth; has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, sanofi-aventis, and Wyeth; has equity holding in Med Avante; and receives royalty/patent income from American Psychiatric Publishing, Guilford, and Herald House. Dr. Thase's spouse is Senior Medical Director of Advogent. **Mr. Krishen** and **Dr. Tucker** are employees of GlaxoSmithKline. **Ms. Katz** reports no financial affiliations or other relationships relevant to the subject of this article.

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