

# Does Pretreatment Insomnia or Anxiety Predict Acute Response to Bupropion SR?

**A. JOHN RUSH, M.D.**

Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX, USA

**THOMAS J. CARMODY, Ph.D.**

Academic Computing Services, The University of Texas Southwestern Medical Center, Dallas, TX, USA

**BARBARA R. HAIGHT, PHARM.D and CAROL B. ROCKETT, Pharm.D.**

GlaxoSmithKline, Research Triangle Park, NC, USA

**SIDNEY ZISOOK, M.D.**

Department of Psychiatry, University of CA, San Diego Medical Center, La Jolla, CA, USA

**Background.** This retrospective analysis was conducted to determine whether pretreatment levels of insomnia or anxiety were associated with likelihood of or time to antidepressant response with bupropion sustained release (SR).

**Methods.** Data from an open-label, 8-week, acute phase multicenter study of 797 adult outpatients with recurrent, nonpsychotic major depressive disorder who received bupropion SR (300 mg/day) were used. Depressive symptom severity was measured by the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>), insomnia by totaling the three HAM-D<sub>17</sub> insomnia items (early, middle, late), and anxiety by the 14-item Hamilton Rating Scale for Anxiety.

**Results.** Overall, 67% (533/797) of patients responded (defined as  $\geq 50\%$  reduction in baseline HAM-D<sub>17</sub>). Neither baseline insomnia nor baseline anxiety was related to the likelihood of achieving response. Higher baseline insomnia and lower baseline anxiety were associated with an earlier onset of response (about one week sooner in each).

**Conclusions.** Predicting the likelihood of antidepressant response with bupropion SR cannot be based on either baseline insomnia or anxiety levels.

**Keywords** Anxiety, Insomnia, Depression, Bupropion SR, Response, Predictors.

## INTRODUCTION

Bupropion sustained release (SR) has equivalent antidepressant efficacy to sertraline (1-3), fluoxetine (4,5), and paroxetine (6) in randomized, double-blind, acute-phase studies in outpatients with nonpsychotic major depressive disorder (MDD). Not all patients, however, will respond to any single antidepressant (7,8).

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Address correspondence to A. John Rush, M.D., Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9086. E-mail: john.rush@utsouthwestern.edu

In selecting among antidepressant medications, some clinicians attempt to match medication side effects with presenting symptom features. For example, some select more sedating (less activating) agents for depressions in which insomnia is prominent (9), while more activating (less sedating) agents are selected for depressed patients with hypersomnia. In fact, the APA Guidelines (7) suggest that bupropion may be anxiogenic and should be avoided in anxious depressed patients (10). However, these common clinical beliefs are largely unsupported by the available studies (11-17).

Bupropion SR is among the least sedating antidepressants (18). Based on the above beliefs, one might suggest that bupropion would be less effective in depressed patients with substantial baseline insomnia or anxiety. Previous retrospective analyses

of acute phase trials have not found that the degree of baseline anxiety was a basis for selecting between bupropion SR and sertraline. Specifically, bupropion SR was associated with equivalent degrees of antidepressant response and antidepressant remission, as well as equivalent degrees of anxiolytic efficacy, as the selective serotonin reuptake inhibitor, sertraline. Both studies revealed that greater pretreatment anxiety was not associated with a lesser (or greater) antidepressant activity in either an 8-week (11) or a 16-week (12) acute phase trial. As expected, remission rates were higher in the longer 16-week trial than in the 8-week trial—a finding that is consistent with the notion that longer acute phase trials are uniformly associated with higher rates of remission independent of the type of drug used (19–21).

This report on a new dataset examines for the first time whether the degree of baseline insomnia is associated with response and further evaluates whether baseline anxiety is related to antidepressant response in an 8-week trial in outpatients with recurrent nonpsychotic MDD. The following specific questions concerning bupropion SR were addressed:

1. Were baseline insomnia levels associated with the likelihood of antidepressant response or with the time to antidepressant response?
2. Were the levels of baseline insomnia associated with the likelihood of clinically significant reduction in insomnia or time to improvement in insomnia?
3. Were higher levels of baseline insomnia associated with higher rates of increased insomnia?
4. Were baseline anxiety levels associated with the likelihood of antidepressant response or the time to antidepressant response?
5. Were the levels of baseline anxiety associated with the likelihood of clinically significant anxiolysis or time to improvement in anxiety?
6. Were higher levels of baseline anxiety associated with higher rates of increased anxiety?

## METHODS

### Study Population

Data for these post hoc analyses were obtained during the open-label, 8-week treatment period with bupropion SR, which preceded the double-blind, placebo-controlled, parallel-group, multisite study that compared continuation phase bupropion SR with placebo (22) in outpatients with moderate to severe recurrent MDD based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria (23). The Institutional Review Board approved the protocol at each study site (n=21). Written informed consent was obtained from each patient after study procedures were fully explained and prior to the performance of any study procedure.

Subjects had to have a baseline score of at least 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D<sub>21</sub>)

(24,25) to enter the open-label, 8-week trial. Those with histories of any psychotic or bipolar disorder were excluded, as were those with current obsessive-compulsive, organic-mental, or eating disorders. Subjects could have generalized anxiety disorder, but could not meet criteria for current panic disorder or have a history of active substance abuse or dependence within the past year.

Following screening and baseline physical and psychiatric assessments, participants began bupropion SR (150 mg/day) for days 1–3. Bupropion SR (150 mg, b.i.d.) was then prescribed for the duration of the 8-week acute phase portion of the study. Only 20 patients (2.5%) received sedatives/hypnotics in the first 2 weeks of the study. During this open-label acute phase trial, assessments were made at baseline and at days 7, 14, 21, 28, 35, 42, 49, and 56. Efficacy was evaluated at each clinic visit by the HAM-D<sub>17</sub>, the 14-item Hamilton Rating Scale for Anxiety (HAM-A) (26), and the Clinical Global Impressions Severity of Illness (CGI-S) and Improvement of Illness (CGI-I) (27). The HAM-D<sub>17</sub> total score was the primary antidepressant efficacy scale used for these retrospective analyses.

### Analytic Procedures

Antidepressant response was defined *a priori* as an exit HAM-D<sub>17</sub> total score  $\leq 50\%$  of the baseline total HAM-D<sub>17</sub> score. Baseline insomnia was measured by the sum of the three HAM-D<sub>17</sub> insomnia items (total score ranges from 0–6). A clinically significant reduction in insomnia was declared when a  $\geq 50\%$  reduction in the baseline insomnia HAM-D<sub>17</sub> subscale was achieved. Clinically significant worsening of insomnia was defined by a  $\geq 25\%$  increase above baseline HAM-D<sub>17</sub> insomnia subscale score.

Baseline anxiety was defined by the baseline HAM-A total score. Significant anxiolysis was declared when the baseline HAM-A total score was reduced by  $\geq 50\%$ . Clinically significant induction of anxiety (anxiogenesis) was defined by a  $\geq 2$ -point increase from the baseline HAM-A total score.

The relationship between baseline insomnia (HAM-D<sub>17</sub> insomnia items total score) and antidepressant response at exit was evaluated for the intent-to-treat (ITT) sample using a logistic regression model to estimate the odds of response at exit. The model included terms for investigative site, baseline insomnia total score, and baseline HAM-D<sub>17</sub> total score (excluding the insomnia items). A similar analytic approach was used in which baseline insomnia total score was replaced with baseline HAM-A scores.

The relationship between baseline insomnia total score and time to antidepressant response was evaluated using Kaplan-Meier survival curves. The log-rank test was used to compare those with high (above median) versus low (below median) baseline insomnia total score. A similar model was used to evaluate the relationship between baseline anxiety (HAM-A) and time to antidepressant response.

The relationship between baseline insomnia (or anxiety) and clinically significant reduction in insomnia (or anxiety) was evaluated in the ITT sample using logistic regression to estimate how the odds of clinically significant reductions in insomnia (or anxiety) were influenced by baseline insomnia (or anxiety) after adjustment for investigative site and baseline HAM-D<sub>17</sub> total score (excluding the insomnia or anxiety items). This relationship was also investigated using the log-rank test to compare time to clinically significant reduction in insomnia (or anxiety) for those above versus below the median in baseline HAM-A or insomnia scores, respectively.

The relationship between high and low baseline insomnia (or anxiety) and incidence of increased insomnia (or anxiogenesis) was evaluated by a logistic regression model with terms for high versus low baseline insomnia (or anxiety), site, and baseline HAM-D<sub>17</sub> (excluding the insomnia or anxiety items).

Plots for the ITT sample were created to show the relationship between baseline insomnia and response and to show the relationship between the baseline HAM-A total score and percentage change (baseline to exit) in HAM-D<sub>17</sub> score. Kaplan-Meier survival curves were also plotted.

Finally, a receiver operating characteristic (ROC) analysis was conducted to determine if there was a clinically useful best threshold for baseline anxiety to predict antidepressant response at exit (28). The optimal threshold was chosen to maximize the quality index of efficiency (QI), which is a weighted average of the sensitivity and specificity. The performance of the threshold was determined by the percent correct, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

## RESULTS

### Study Samples

Altogether, 797 patients were available for efficacy evaluation and 519 patients (65.1% of the evaluable sample of 797 patients) completed the full 8-week trial. Table 1 shows the clinical and demographic features of the sample. Table 2 provides symptom information at baseline and endpoint.

### *Were Baseline Insomnia Levels Associated with the Likelihood of Antidepressant Response or with the Time to Antidepressant Response?*

Figure 1 shows the lack of a relationship between baseline insomnia scores and response at exit (ITT sample). Logistic regression showed no meaningful relationship between the severity of baseline insomnia and antidepressant response at exit (odds ratio [OR] = 1.005,  $\chi^2 = 0.01$ ,  $p = .92$ ) after adjustment for site and HAM-D<sub>17</sub> baseline score (excluding the sleep items).

Figure 2 shows the time to antidepressant response in relation to higher (scores of 4–6) versus lower (scores of 0–3)

**Table 1** Baseline Patient Clinical and Demographic Characteristics

Variable	Bupropion SR (n=797)
Female	67.8%
Ethnicity	
Caucasian	87.1%
African-American	6.2%
Hispanic	5.4%
Other	1.3%
Length of current episode	
2–6 months	53.2%
7–12 months	29.9%
12–24 months	16.9%
Patients not completing study for any reason	34.9%
Patients discontinued due to adverse events	10.0%
Age (years $\pm$ SD)	39.9 $\pm$ 11.6
Modal dose (mg/day)	294.9 $\pm$ 27.2

**Table 2** Baseline and End of Treatment (Last Observation Carried Forward) Visit Findings (n=797)

Variable	Baseline	Endpoint
HAM-D <sub>17</sub> score	22.3 $\pm$ 3.4	8.9 $\pm$ 7.9
CGI-S score	4.3 $\pm$ 0.6	2.3 $\pm$ 1.3
HAM-A score	16.3 $\pm$ 5.4	7.4 $\pm$ 7.0
HAM-D <sub>17</sub> insomnia subscale score <sup>a</sup>	3.7 $\pm$ 1.8	1.5 $\pm$ 1.8
Response by HAM-D <sub>17</sub> <sup>b</sup>	—	66.9%
Response by CGI-I <sup>c</sup>	—	68.5%
Remission by HAM-D <sub>17</sub> <sup>d</sup>	—	55.5%
HAM-D <sub>17</sub> score in HAM-D <sub>17</sub> responders (n=533)	22.0 $\pm$ 3.3	4.1 $\pm$ 3.2
HAM-D <sub>17</sub> score in HAM-D <sub>17</sub> nonresponders (n=264)	22.8 $\pm$ 3.6	18.6 $\pm$ 5.2
HAM-A score in HAM-D <sub>17</sub> responders (n=533)	15.9 $\pm$ 5.2	3.8 $\pm$ 3.5
HAM-A score in HAM-D <sub>17</sub> nonresponders (n=264)	17.2 $\pm$ 5.7	14.8 $\pm$ 6.4

<sup>a</sup>Range = 0–6.

<sup>b</sup>Defined as a reduction of at least 50% from baseline HAM-D<sub>17</sub> score.

<sup>c</sup>Defined as CGI-I score of 1 or 2.

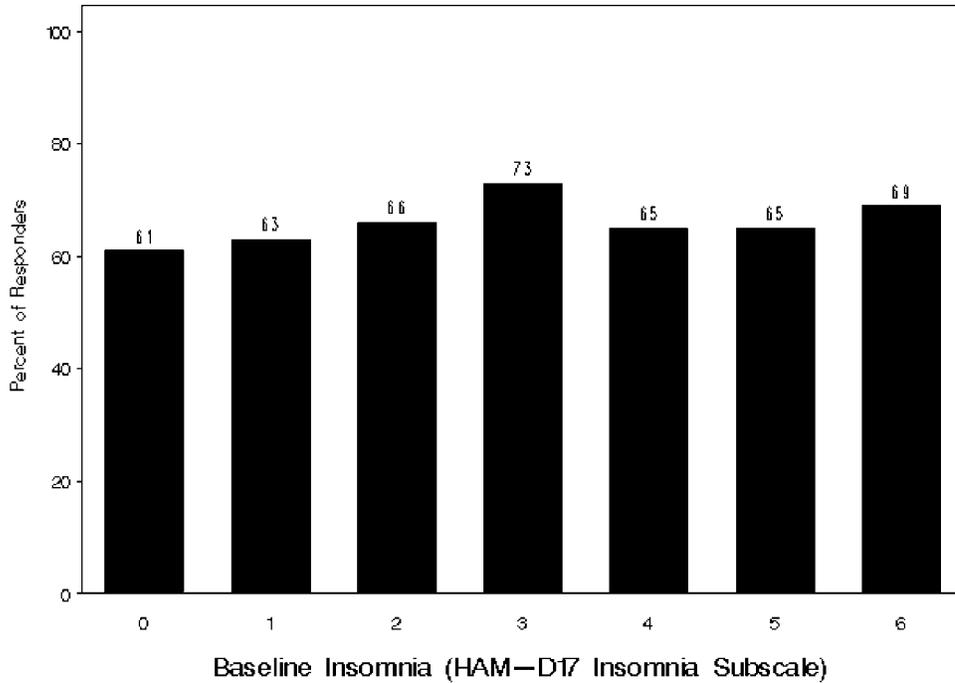
<sup>d</sup>Defined as final HAM-D<sub>17</sub> score  $\leq$  7.

baseline insomnia severity. We used a median split to divide the group into those with lower and higher levels of baseline insomnia. Baseline insomnia was not related to the time to achieve antidepressant response (log-rank test,  $p = .84$ ).

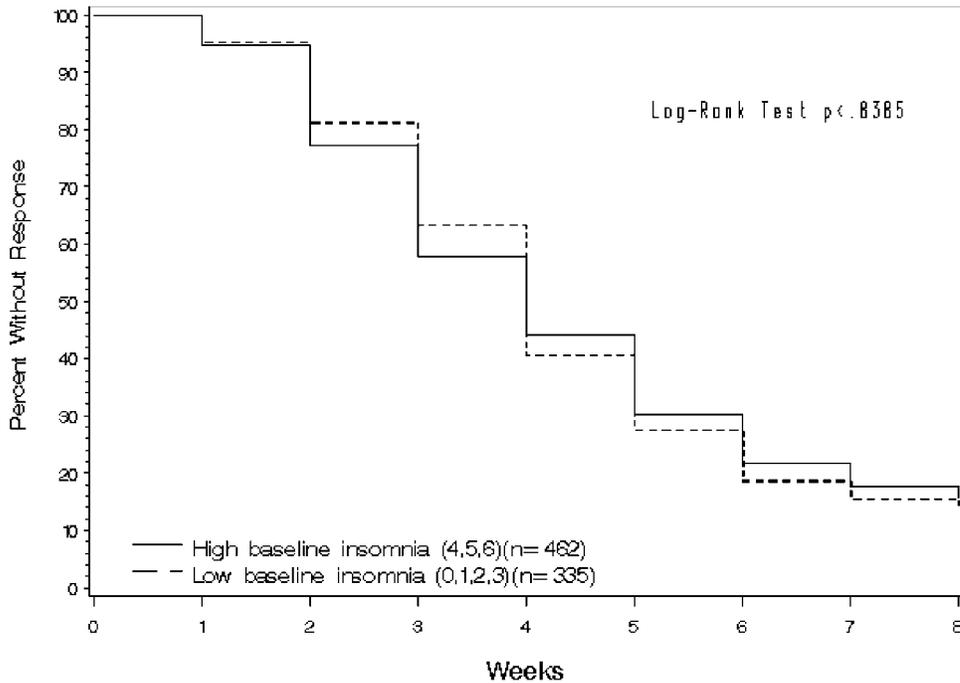
### *Were the Levels of Baseline Insomnia Associated with the Likelihood of Clinically Significant Reduction in Insomnia or Time to Improvement in Insomnia?*

Logistic regression showed no relationship between baseline insomnia and the likelihood of clinically significant reduction in insomnia at exit (OR = 1.02,  $\chi^2 = 0.13$ ,  $p = .72$ ) after adjustment for site and baseline HAM-D<sub>17</sub> score (excluding the sleep items).

Figure 3 shows the survival analysis for those with higher (versus lower) levels of baseline insomnia in relation to time to



**Figure 1** Antidepressant response rates at exit (LOCF) in relation to baseline HAM-D<sub>17</sub> insomnia subscale score (n=797).

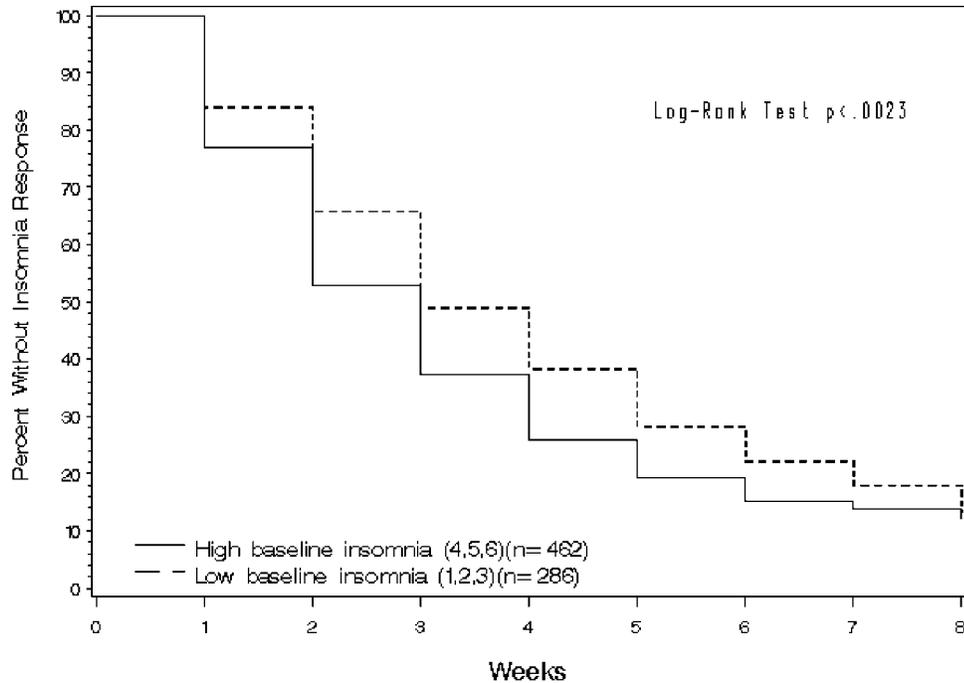


**Figure 2** Time to antidepressant response ( $\geq 50\%$  improvement) in relation to baseline insomnia.

clinically significant improvement in insomnia. Note that higher baseline insomnia levels were associated with shorter times to clinically significant improvement in insomnia as compared to those with lower levels of baseline insomnia (log-rank test,  $p = .0023$ ) (i.e., higher levels of baseline insomnia improve more rapidly than lower levels of baseline insomnia).

*Were Higher Levels of Baseline Insomnia Associated with Higher Rates of Increased Insomnia?*

Logistic regression showed those (n=286) with lower baseline levels of insomnia (baseline insomnia ratings of 1–3: percent change could not be computed for those with a baseline



**Figure 3** Time to insomnia reduction ( $\geq 50\%$  improvement) in relation to baseline insomnia.

insomnia rating of zero) were more likely to encounter increased insomnia (25% increase from baseline) at exit than those with greater levels of baseline insomnia ( $n=462$ ) ( $OR=5.1$ ,  $\chi^2=15.2$ ,  $p=.0001$ ) after adjustment for site and baseline HAM-D<sub>17</sub> score (excluding the sleep items). Altogether, 11.5% of patients with low baseline insomnia encountered increased insomnia versus 2.2% of those with high baseline insomnia.

*Were Baseline Anxiety Levels Associated with the Likelihood of Antidepressant Response or with the Time to Antidepressant Response?*

Baseline anxiety was unrelated to the likelihood of antidepressant response. Figure 4 shows that there is no relationship between baseline HAM-A scores and change in HAM-D<sub>17</sub> scores (ITT sample) (Pearson correlation=0.17). Logistic regression showed only a trend relationship between baseline HAM-A score and probability of response to bupropion SR at exit ( $OR=0.96$ ,  $\chi^2=3.5$ ,  $p=.06$ ) after including terms for site and baseline HAM-D<sub>17</sub> score (excluding the anxiety items).

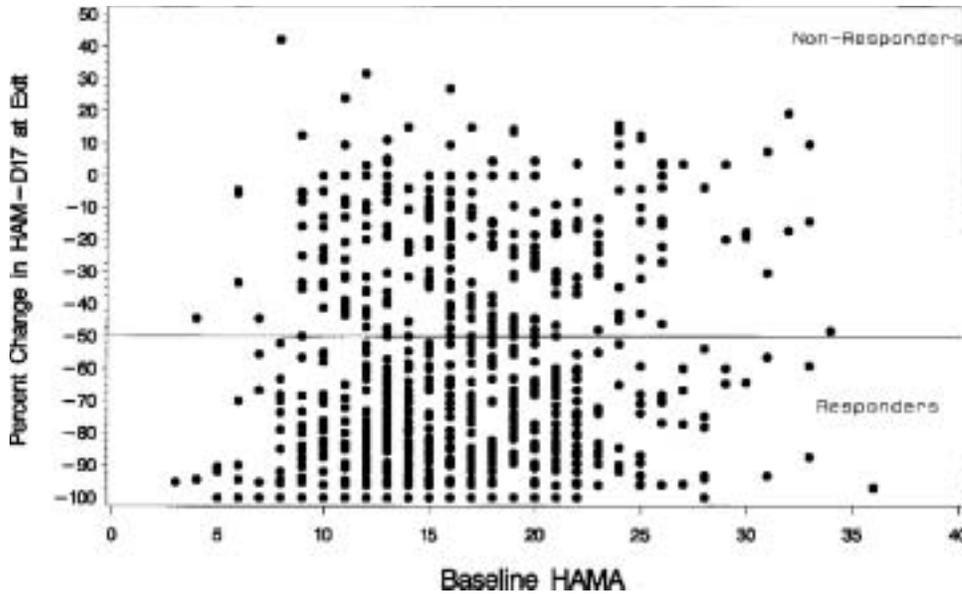
To further examine this trend finding, we conducted ROC analyses to search for the most predictive baseline HAM-A threshold by which to determine whether a patient will or will not respond to bupropion SR. The optimum ROC threshold (defined by the Optimal Quality Index) for the full sample was a baseline HAM-A score of 22. Even at this optimal threshold, however, performance was so poor as to be of no clinical utility (sensitivity = 91%, specificity = 18%, PPV = 69%, NPV = 50%). This threshold correctly classified 67% of

the sample. Altogether, 91% of those who responded had a HAM-A baseline  $<22$ , and only 18% of nonresponders had a HAM-A score  $>22$ . However, 69% of those below the threshold responded, while 50% of those above this threshold also responded.

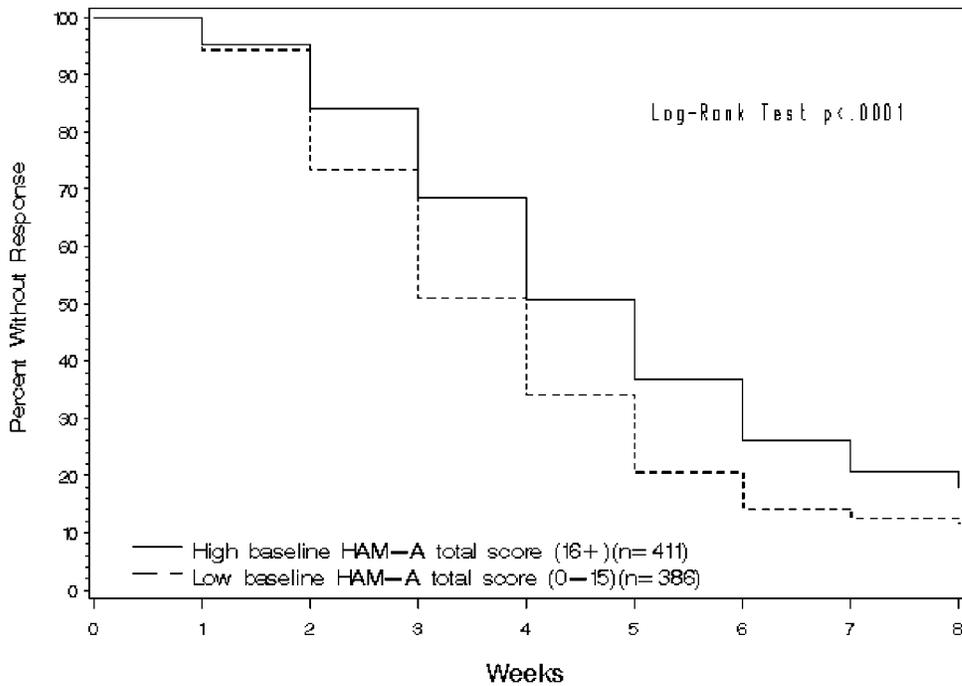
Figure 5 shows the survival curve for time to response for those with higher (HAM-A score  $\geq 16$ ) and lower (HAM-A score  $<16$ ) levels of baseline anxiety (based on median split of baseline HAM-A total score). Those with higher levels of baseline anxiety ( $n=411$ ) (and, consequently, higher levels of baseline depression) were slower to achieve antidepressant response (log rank test,  $p=.0001$ ). Figure 5 shows that 50% achieved a response by week 3 (low baseline anxiety) or week 4 (higher baseline anxiety). Both groups achieved equivalent response rates based on a logistic regression analysis. After adjustment for site and for baseline HAM-D<sub>17</sub> score (excluding the anxiety items), no relationship between higher or lower HAM-A baseline score and response at week 8 ( $OR=0.6$ ,  $\chi^2=1.7$ ,  $p=.19$ ) was found. Thus, baseline anxiety levels did not predict the likelihood of achieving an antidepressant response, but higher baseline anxiety levels were associated with about a 1-week delay in achieving antidepressant response compared with lower levels.

*Were the Levels of Baseline Anxiety Associated with the Likelihood of Clinically Significant Anxiolysis or Time to Improvement in Anxiety?*

There was no relationship between baseline HAM-A score and likelihood of clinically significant anxiolysis at exit ( $OR=1.003$ ,



**Figure 4** Baseline anxiety (HAM-A score) in relation to percent change in HAM-D<sub>17</sub> (baseline to exit) (n=797).

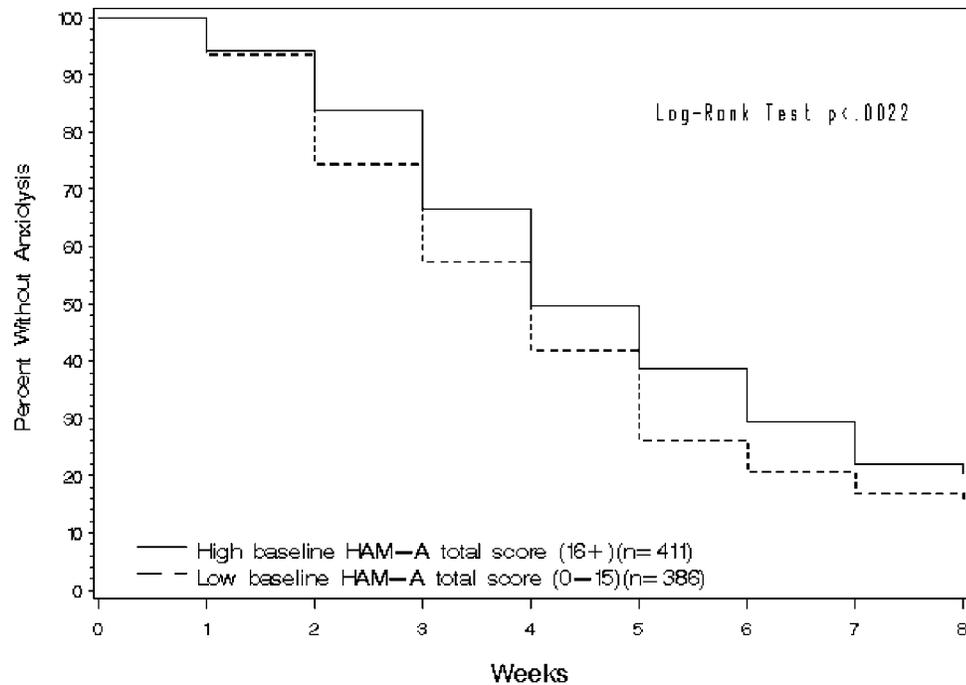


**Figure 5** Time to antidepressant response ( $\geq 50\%$  improvement) in relation to baseline anxiety (HAM-A).

$\chi^2=0.03$ ,  $p = .85$ ) after adjustment for site and baseline HAM-D<sub>17</sub> score (excluding the anxiety items) based on a logistic regression analysis.

Figure 6 shows the survival curve for those with higher versus lower levels of baseline anxiety (defined by the median split) using clinically significant anxiolysis (a  $\geq 50\%$  reduction

in baseline HAM-A total score) as the outcome. Those with higher levels of baseline anxiety were slightly slower to achieve clinically significant anxiolysis than those with lower baseline levels of anxiety (log-rank test,  $p = .0022$ ), although by 8 weeks, the probability of anxiolysis was virtually identical for both groups. Logistic regression showed no relationship



**Figure 6** Time to significant anxiolysis ( $\geq 50\%$  improvement) in relation to baseline anxiety (HAM-A).

between probability of anxiolysis at week 8 and higher or lower baseline HAM-A score (OR=0.998,  $\chi^2 = .00001$ ,  $p=.99$ ) after adjustment for site and baseline HAM-D<sub>17</sub> score (excluding the anxiety items).

#### *Were Higher Levels of Baseline Anxiety Associated with Higher Rates of Increased Anxiety?*

We used the median split of baseline HAM-A scores ( $\geq 16$  versus  $< 16$ ) to define higher versus lower anxiety groups. We then counted the incidence of anxiogenesis (defined as a  $\geq 2$ -point increase in the baseline HAM-A total score) for each group. Those with lower baseline HAM-A scores ( $< 16$ ) ( $n=386$ ) tended to have a greater likelihood of significant anxiogenesis than those ( $n=411$ ) with higher HAM-A scores (OR=1.94,  $\chi^2 = 3.8$ ,  $p = .053$ ) (logistic regression after adjusting for site and baseline HAM-D<sub>17</sub> score, excluding the anxiety items). The unadjusted figures showed 8.3% of low baseline anxiety patients encountered anxiogenesis at exit versus 6.6% of high baseline anxiety patients.

## **DISCUSSION**

Baseline insomnia was of no clinical utility in predicting either the likelihood of antidepressant response to bupropion SR in this 8-week open trial, nor the time to achieve an antidepressant response. In terms of time to improvement in insomnia, *higher baseline insomnia was associated with a more rapid improvement in insomnia*. Those with lower baseline levels of

insomnia were more likely to encounter an increase in insomnia (11.5%) than were those with higher levels of baseline insomnia (2.2%).

Baseline anxiety was not predictive of the likelihood of antidepressant response to bupropion SR. We could not identify a clinically useful baseline HAM-A threshold by which to distinguish those who were and those who were not antidepressant responders using ROC analysis.

For those with higher baseline anxiety, the time to antidepressant response was about one week longer. This finding contradicts a prior report that failed to find a relationship between baseline anxiety and time to onset of antidepressant response (11). It is notable that only 300 mg/day was used in this trial, while 400 mg/day was allowed in the Rush et al. (11) report. On the other hand, the current study, with a much larger sample, increases the likelihood of detecting findings.

Both higher and lower baseline anxiety groups achieved an equivalent degree of anxiolysis by study exit. This lack of relationship between baseline anxiety and the likelihood of achieving clinically significant anxiolysis is consistent with Rush et al. (12). However, the time to significant anxiolysis was also slightly longer (4–7 days) for those with higher baseline anxiety.

Furthermore, there was a nonsignificant trend ( $p=.053$ ) for anxiogenesis to occur in those with lower as opposed to higher levels of baseline anxiety (8.3% vs. 6.6%, respectively). This difference was not clinically significant. These results agree with Rush et al. (12).

These findings are in substantial agreement with other reports that baseline anxiety levels and antidepressant response to bupropion SR were not related (11,12,16). Other studies with

fluoxetine (13,15,29,30), paroxetine (30), sertraline (30), monoamine oxidase inhibitors (MAOIs), or tricyclic antidepressants (17) mirror these findings. Only one study (31) found that SSRI responders (n=28) had greater baseline anxiety/agitation levels than did responders to norepinephrine reuptake inhibitors.

These findings, along with the prior reports noted above, stand in stark contrast to the common practice (7,10) and recommendation (7) that individual symptoms at baseline provide a reliable basis for selecting among antidepressants. Anxiety or insomnia was not related to retention or efficacy in this large sample. True, occasional depressed patients on any antidepressant (including SSRIs, some of which have FDA approval for use in anxiety disorders) do become more anxious with treatment. These case reports, however, should be judged in the context of replicated scientific evidence. It is notable that across studies comparing bupropion SR (n=688) with SSRIs (sertraline, fluoxetine, or paroxetine, n=698) rates of insomnia (17% vs. 16%), anxiety (6% vs. 5%), or agitation (10% vs. 7%, bupropion SR vs. SSRIs, respectively) were similar (p>0.05 for each comparison). Moreover, discontinuation rates due to each of these adverse events were nearly identical (0.4% vs. 0.6% due to insomnia for bupropion SR or SSRIs, respectively, 0.4% for both bupropion SR and SSRIs for anxiety, and 0.3% for both bupropion SR and SSRIs for discontinuation due to agitation) (32) (Data on File, GlaxoSmithKline, 2004). In addition, in clinical trials versus placebo, discontinuation rates for bupropion due to insomnia or anxiety were <1% or similar to placebo (Package Insert).

Several limitations pertain to this report: 1) the analyses were retrospective; 2) only outpatients were included; 3) patients with current formal panic or obsessive-compulsive disorders were excluded, yet patients with generalized anxiety disorder were not; 4) the trial was only 8 weeks in duration; 5) the trial was open-label; and 6) only up to 300 mg/d of bupropion SR was allowed. On the other hand, the sample size was large, and patients were likely representative of moderately-to-severely depressed outpatients. This large sample size provided a substantial amount of power for detecting clinically meaningful differences. Thus, the failure to find a relationship between baseline anxiety or baseline insomnia and antidepressant effects is not due to a lack of sufficient power.

In sum, most patients (67%) responded and the majority (55%) remitted. Depressive, anxiety, and insomnia symptoms all improved. Furthermore, neither baseline insomnia nor baseline anxiety provided a basis for predicting antidepressant response to bupropion SR. Additional longer-term trials are needed to search for clinically useful predictors of sustained remission to bupropion SR.

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