

# Better Patient Persistence With Once-Daily Bupropion Compared With Twice-Daily Bupropion

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Evidence suggests that improving adherence and persistence to antidepressant therapy could enhance clinical and economic outcomes in depression. This study was conducted to assess the impact of dosing frequency (once daily with bupropion XL vs twice daily with bupropion SR) on adherence to bupropion therapy in a nationally representative prescription database in the United States. Demographics of patients with a prescription for bupropion XL or bupropion SR between October 1, 2005, and October 31, 2005, were similar between the XL group (n = 257,049; 69% female) and the SR group (n = 12,468; 67% female). Refill adherence over a 1-year period was greater with bupropion XL than bupropion SR. The percentage of patients with  $\geq 1$  refill over 1 year was 60.1% with bupropion XL compared with 51.3% with bupropion SR ( $P < 0.0001$ ). The percentage of patients with  $\geq 6$  refills over 1 year was 25.3% with bupropion XL compared with 9.5% with bupropion SR. Bupropion XL was associated with significantly greater likelihood of refilling a prescription than bupropion SR as shown by Kaplan-Meier curves ( $P < 0.0001$ , log-rank test). The medication possession ratio over a 9-month period was higher for bupropion XL (0.26) than it was for bupropion SR (0.16). Logistic regression analyses show that patients with a prescription for bupropion SR were significantly less likely to fill a future prescription than were patients with a prescription for bupropion XL. These data show that adherence to bupropion therapy in this sample was better with the once-daily XL formulation than with the twice-daily SR formulation across several measures.

*Keywords:* adherence, persistence, bupropion, antidepressant, depression

## INTRODUCTION

The humanistic and economic burdens of major depression remain high despite the availability of effective treatments. Major depression was the leading cause worldwide of nonfatal burden, measured in years lived with a disability, in the World Health Organization Global Burden of Disease 2000 Study.<sup>1</sup> Depression is associated with greater healthcare resource use and associated expenditures than other diagnoses without a concurrent diagnosis of

depression across every major cost determinant including primary care, specialty, and mental health consultations; emergency room visits; pharmacy costs; laboratory and other diagnostic examinations; and inpatient costs.<sup>2–5</sup> Depression is also among the most common and costly health problems affecting the workplace.<sup>6</sup> It is estimated that 2% to 4% of the U.S. labor force experiences major depression and that 37% to 48% of depressed workers experience short-term disability.<sup>7</sup>

Evidence suggests that poor adherence to antidepressant regimens constitutes a significant barrier to reducing the large humanistic and economic burdens of depression.<sup>8</sup> For most patients, depression is a chronic episodic disorder<sup>9</sup> that requires long-term daily therapy to prevent relapse.<sup>10</sup> Across studies and classes of antidepressants, 30% to 50% of patients discontinue treatment within 1 to 3 months of its initiation.<sup>11–14</sup> Compared with adherent patients, patients nonadherent with antidepressant regimens are more likely to relapse,<sup>15</sup> and they incur higher healthcare costs.<sup>16</sup>

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Improving adherence to antidepressant therapy should enhance clinical and economic outcomes in depression.

Medication adherence is determined by multiple patient-, context-, and therapy-dependent factors, only some of which are modifiable.<sup>8,11</sup> Dosing frequency is one potentially modifiable determinant of adherence. Across therapy areas, regimens requiring less frequent dosing are associated with better adherence than those requiring more frequent dosing.<sup>11,17-19</sup> This observation suggests that, other factors being equal, antidepressants requiring less frequent dosing should be chosen over those requiring more frequent dosing.

The antidepressant bupropion hydrochloride, previously available only in formulations dosed more than once daily, has also been developed as an extended-release formulation manufactured by Biovail Corporation, Mississauga, Ontario, Canada, for GlaxoSmithKline, Research Triangle Park, North Carolina, United States (bupropion XL or Wellbutrin XL) for once-daily dosing. Bupropion XL at a dosage of 300 mg once daily is bioequivalent to 150 mg bupropion SR twice daily and to 100 mg immediate-release bupropion 3 times daily.<sup>20</sup> The extended-release formulation was introduced to enhance dosing convenience while providing the benefits of the bupropion molecule, including a low risk of sexual side effects and other antidepressant-associated side effects such as weight gain. This study was conducted to assess the impact of dosing frequency (once daily with bupropion XL vs twice daily with bupropion SR) on adherence to bupropion therapy in a national prescription database in the United States.

## MATERIALS AND METHODS

### Data source

Patients of any age in the United States with a prescription for bupropion XL or bupropion SR during time periods specific to the measures of interest (described subsequently) were identified from the prescription database maintained by Catalina Health Resource, a subsidiary of Catalina Marketing Corporation (Saint Petersburg, FL). The prescription database contains deidentified records covering more than 12,600 pharmacy retail chain outlets and more than 90 million unique patients who can be tracked longitudinally. The database covers approximately one third of all U.S. retail prescriptions and is compliant with the 1996 Health Insurance Portability and Accountability Act. A documented diagnosis of depression during the study period was not a requirement for inclusion in the sample because this study was based on prescription data and did not include linked medical data.

## MEASURES

Measures included demographics and several assessments of adherence and persistence. Age and gender were summarized for patients with a prescription for bupropion XL or bupropion SR between October 1, 2005, and October 31, 2005.

Patients were included in the persistence study if they had no prescriptions for bupropion XL or bupropion SR in the 90 days before October 2004 and their first prescription for a bupropion product occurred during October 2004. These criteria identified new users of bupropion or patients prescribed bupropion for a new episode.

Adherence and persistence were compared between bupropion XL and bupropion SR using multiple approaches:

- Refill adherence over time was calculated as the percentage of patients with  $\geq 1$ , 2, 3, 4, 5, and 6+ refills from October 2004 to October 2005. Persistence was considered to be maintained if the days of medication supply from the previous prescription plus a 30-day grace period exceeded the number of days between the previous prescription date and the current prescription fill date. Authorized refills were included in this summary. This summary included new patients, defined as those who had their first prescription for bupropion XL or bupropion SR (regardless of dose) filled during October 2004 and who had no antidepressant prescriptions filled during the 9 months before October 2004.
- Kaplan-Meier estimates of the likelihood of remaining persistent over time were determined by following the cohort of new patients and tracked prescription transactions for 1 year. New patients were defined as those who had their first prescription for bupropion XL or bupropion SR (regardless of dose) filled during November 2004 and who had no antidepressant prescriptions filled during the 9 months before November 2004. Patient follow up was censored either 30 days after the last refill or at the end of the follow-up period if for patients still active. Patients were considered to be persistent during the times that they refilled a bupropion prescription within twice the number of days of supply of the previous prescription. The log rank test was used to test the difference in persistence between bupropion XL and bupropion SR.
- The medication possession ratio was determined for patients who filled at least 2 prescriptions for bupropion XL or bupropion SR during the period

from October 2004 to July 2005. The medication possession ratio was calculated as the sum of the number of days of supply of bupropion XL or bupropion SR prescriptions from October 2004 to July 2005 divided by the total days during that time period.

The likelihood of adherence was further assessed using multivariate logistic regression models to control for other factors that could affect adherence and refills of bupropion XL and bupropion SR. Patients who filled a prescription for bupropion XL or bupropion SR in April 2005 were included and were considered to have refilled a prescription if the date of filling a prescription was less than the current fill date + (days of supply remaining in the current prescription × 2). Factors assessed in the logistic regression analyses included patient age (>65, ≤65), patient gender, medication (bupropion XL, bupropion SR), number of days of supply of the current prescription, number of days of supply in the past year, number of days late with the current prescription, whether or not the patient had insurance, whether or not any refill remained, and whether the prescription was new or a refill.

## RESULTS

### Demographics

Demographics of patients with a prescription for bupropion XL or bupropion SR in October 2005 were similar between the XL group (n = 257,049) and the SR group (n = 12,468). For bupropion XL, 69% of patients were female, and mean age was 42.6 years for females and 42.3 years for males. For bupropion SR, 67% of patients were female, and mean age was 47.3 years for females and 45.0 years for males.

### Refill adherence

Refill adherence over a 1-year period was greater with bupropion XL than bupropion SR (Fig. 1). The percentage of patients with ≥1 refill over 1 year was 60.1% with bupropion XL compared with 51.3% with bupropion SR ( $P < 0.0001$ ). The percentage of patients with ≥6 refills over 1 year was 25.3% with bupropion XL compared with 9.5% with bupropion SR.

### Persistence

Bupropion XL was associated with significantly greater likelihood of refilling a prescription than bupropion SR as shown by the Kaplan-Meier curves ( $P < 0.0001$ , log rank test) (Fig. 2). The most significant drop in persistence was after the initial prescription for both formulations; however, the separation between

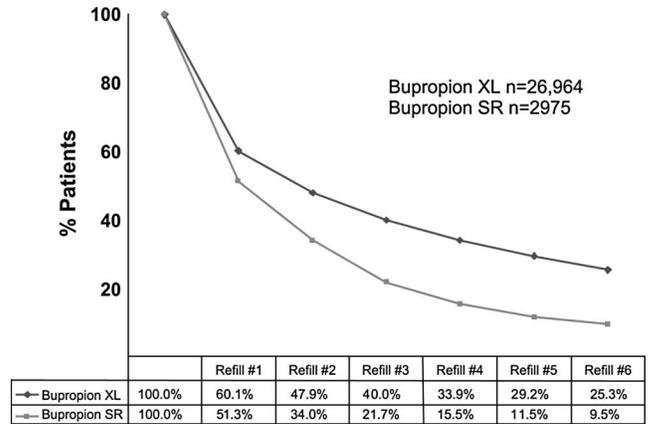


FIGURE 1. Refill adherence with bupropion XL versus bupropion SR.

bupropion XL and bupropion SR was consistent from that point forward.

The medication possession ratio over a 9-month period was 1.5-fold higher for bupropion XL (0.26) than it was for bupropion SR (0.16), a finding that suggests that those on the XL formulation were likely to remain on bupropion for 50% longer than those on the SR formulation.

Logistic regression analyses show that patients with a prescription for bupropion SR were significantly less likely to fill a future prescription than were patients with a prescription for bupropion XL even after controlling for multiple competing factors (Table 1). Being late in filling the current prescription compared with filling it on time was also associated with a lower likelihood of filling a future prescription. Factors increasing the likelihood of filling a future prescription included being female, having insurance, having authorized refills remaining in the current prescription, having a repeat refill for the current prescription, and having a greater number of total days of supply in the past year (Table 1).

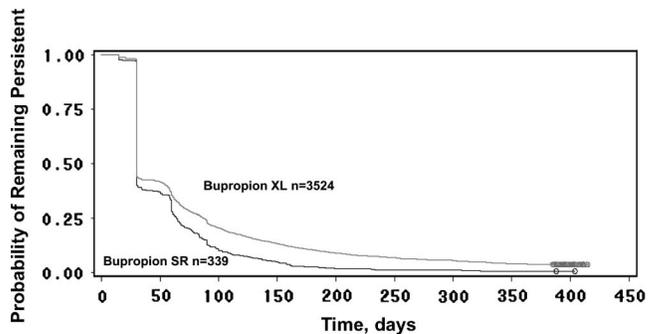


FIGURE 2. Kaplan-Meier estimates of persistence with bupropion XL versus bupropion SR.

**Table 1.** Results of logistic regression: likelihood of refilling a prescription.

Effect	Point estimate	95% Wald confidence limits
Product (bupropion SR vs bupropion XL)	0.442	0.367–0.533
Gender (female vs male)	1.087	1.001–1.181
Payment method (insurance vs cash)	3.017	2.477–3.674
Any refills remaining (yes, no)	1.489	1.371–1.618
Prescription type (refill vs new prescription)	1.421	1.304–1.548
Total days of supply in the past year	1.007	1.006–1.007
Total days that the current script is late in being picked up	0.996	0.995–0.997

## DISCUSSION

In this investigation involving a national database of prescriptions, patients receiving bupropion XL, the once-daily formulation of bupropion, were significantly more adherent and persistent with their prescribed regimen than patients receiving bupropion SR, the twice-daily formulation, across several measures including refill adherence, persistence probability, and medication possession ratio. The reason for the higher adherence with the XL formulation compared with the SR formulation cannot be definitively determined on the basis of the study design. However, because bupropion XL and bupropion SR contain the same active drug (bupropion) and have similar clinical profiles and differ only with respect to dosing frequency, the difference is most likely attributable to dosing frequency. These data are critical when considered in the context of previous research documenting poorer clinical and economic outcomes with low adherence to medication regimens.<sup>15,16</sup> Compared with the non-adherent patient, the patient adherent with maintenance therapy for depression arguably is less likely to relapse and may therefore incur lower depression-associated workplace and healthcare costs. These possibilities should be assessed in future studies.

The results of this investigation corroborate other recent findings based on a retrospective analysis of pharmacy and medical claims for patients with depression.<sup>21</sup> Among 3132 patients having a diagnosis of depression based on International Classification of Diseases, 9th Revision (ICD-9) codes and initiating therapy with bupropion XL or bupropion SR, the once-daily XL formulation compared with the twice-daily

SR formulation was associated with a higher medication possession ratio (0.52 vs 0.25) and a higher frequency of medication possession ratio  $\geq 7.0$  (35% vs 12%). That study differed from the current investigation in including only patients with an ICD-9 diagnosis of depression who were prescribed bupropion XL or bupropion SR. The current study, on the other hand, included all prescriptions for bupropion XL or bupropion SR regardless of the diagnosis associated with the prescription. Because the vast majority of prescriptions for bupropion XL are written for depression, disease characteristics of the sample in the current study are likely to be largely similar to those in the study that included only patients with an ICD-9 code for depression. Results of the multivariate analysis are consistent with expected behavior. Tardiness in filling the current prescription compared with filling it on time was associated with a lower likelihood of filling a future prescription. Greater likelihood of prescription refill was associated with being prescribed bupropion XL, being female, having insurance, having outstanding refills remaining in the current prescription, having a repeat refill for the current prescription, and having a greater number of total days of supply in the past year.

The data from this investigation should be interpreted in the context of its strengths and limitations. Strengths of this investigation include the national representativeness of the sample and its conduct in the context of actual clinical practice. The real-world setting of the study facilitates more accurate assessments of compliance as it occurs in clinical practice than can be obtained in clinical trials in which compliance rates are generally artificially high. A limitation of this investigation is the retrospective, observational design, which allows for the possibilities of confounding and introduction of various biases that may not be detectable as a result of lack of linked clinical data and unrecognized confounders. Other shortcomings include lack of information about reasons for nonadherence and the assumption of the investigation that all patients who initiated bupropion should remain on it for the duration of the relevant follow-up period (9 or 12 months, depending on the analysis). Other limitations include the inability to determine the indication for which bupropion was prescribed because of the prescription-level nature of the analysis and the absence of assessment of the impact of chronic conditions or severity of depression on the study outcomes.

The results of this study should not necessarily be extrapolated to antidepressants other than bupropion because patients prescribed bupropion XL or bupropion SR could differ systematically from patients prescribed other classes of antidepressants such as selective

serotonin reuptake inhibitors. This possibility notwithstanding, the recent demonstration of greater compliance among patients with anxiety or depression initiating immediate-release selective serotonin reuptake inhibitors, some of which are dosed more than once daily, compared with controlled-release paroxetine, which is dosed once daily, corroborates the findings of the current study.<sup>22</sup> However, the latter study, unlike the current one, did not compare different formulations of the same molecule. It is possible that compliance was influenced in the latter study by factors in addition to or instead of dosing frequency (eg, different tolerability profiles between immediate-release formulations and controlled-release paroxetine).

In conclusion, patients with prescriptions for bupropion XL, the once-daily formulation, were significantly more adherent to therapy than were patients with prescriptions for bupropion SR, the twice-daily formulation, across several measures. Over a 1-year period, approximately 3 times more patients obtained  $\geq 6$  refills with bupropion XL than bupropion SR, and the likelihood of refilling a prescription for bupropion XL was more than double that for bupropion SR. These data are consistent with the possibility that the less frequent dosing regimen with bupropion XL improves adherence relative to that with bupropion SR. Because better adherence may be associated with better clinical and economic outcomes, healthcare providers should consider the potential benefits of initiating candidates for bupropion on bupropion XL and of switching patients on bupropion SR to bupropion XL.

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