A Prospective Safety Surveillance Study for Bupropion Sustained-Release in the Treatment of Depression

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Background: This prospective 105-site study was conducted to determine the rate of seizures and other serious adverse experiences associated with the therapeutic use of the sustained-release formulation of bupropion (bupropion SR).

Method: 3100 patients with a DSM-III-R diagnosis of depression without a current or past diagnosis of an eating disorder and with no personal or family history of seizure disorders were treated for up to 8 weeks with bupropion SR in an open-label study. Dosing was initiated at 50 mg b.i.d. and increased to a maximum of 150 mg b.i.d. unless not tolerated. Patients had the option to continue treatment with bupropion SR (50 mg b.i.d. to 150 mg b.i.d.) in a continuation phase lasting up to 1 year. During the acute and continuation phases, patients were evaluated for the occurrence of seizures and other serious adverse experiences. Clinical response to and tolerability of bupropion SR were also evaluated.

Results: Three patients each experienced a seizure associated with the therapeutic use of bupropion SR during the acute and continuation phases combined. The observed seizure rate during the 8-week acute phase was 2 seizures in 3094 evaluable patients, or 0.06%. The observed seizure rate for the acute and continuation phases combined was 3 seizures in 3094 patients, or 0.10%. Survival analysis yielded a cumulative seizure rate of 0.08% for the acute phase and 0.15% for both phases combined. Two patients who intentionally overdosed with bupropion SR also experienced seizures; however, these events were not included in calculations of the overall seizure rate. Therapeutic doses of bupropion SR were well tolerated and clinically efficacious.

Conclusion: The therapeutic use of bupropion SR at total daily doses up to 300 mg/day in depressed patients without predisposition to seizures is associated with a seizure rate that is well within the range observed with other marketed antidepressants.

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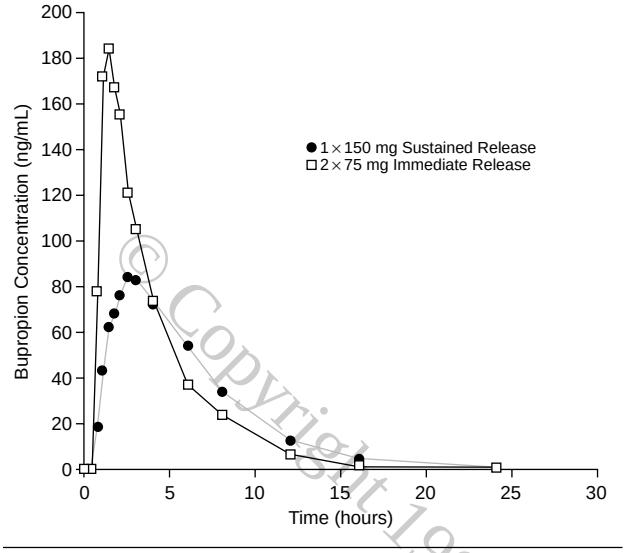
Bupropion hydrochloride, an aminoketone antidepressant chemically unrelated to other known antidepressant agents, has been shown to be efficacious and well tolerated in the treatment of depression.[1–6] Bupropion is available in both immediate-release (IR) and sustained-release (SR) formulations. The IR formulation of bupropion has been demonstrated in double-blind studies to be more effective than placebo[1] and as effective as other commonly used antidepressants.[2–6] Across studies,[1–6] bupropion has also been shown to be relatively free of anticholinergic, cardiovascular, sedative, and sexual side effects.

Bupropion IR has been associated with the occurrence of seizures in a small percentage of patients. Data from 2 independent samples[7,8] (N = 4262 and N = 3341) in which depressed patients received bupropion IR demonstrate a seizure rate of 0.4% at doses up to 450 mg/day. At doses of 450 mg/day and above, the rate of seizures with bupropion IR was strongly dose-related and an increase in seizure rate was noted in patients with bulimia.[9] The rate of seizures may also be related to peak bupropion levels: approximately 75% of patients experiencing a seizure with bupropion IR did so within 3 hours of their last dose.[7,8] Because the occurrence of seizures associated with the IR formulation was a cause of concern, the incidence of seizures in patients receiving the more recently developed SR formulation of bupropion was evaluated in the present study.

Other antidepressants have also been associated with the occurrence of seizures.[10–15] The risk of seizure associated with administration of antidepressants may vary with factors such as daily dose, rate of dosage increase, and patient predisposition.[14] It is possible that therapeutic

Figure 1. Plasma Levels Following Single Doses of Bupropion IR and Bupropion SR



doses of bupropion SR, which have lower peak plasma bupropion levels than the IR formulation, may be associated with a lower rate of seizures. Results from bioequivalence testing comparing single equal doses of bupropion SR and bupropion IR indicate that a single dose of the SR formulation reaches half the peak plasma concentration (C_{max}) of bupropion IR but maintains equivalent area under the plasma concentration curve (AUC) values for bupropion and its metabolites. Plasma levels following single doses of bupropion IR and bupropion SR are illustrated in Figure 1. Chronic dose testing has also demonstrated the lower peak plasma concentrations for the SR formulation and equivalent AUC values of the 2 formulations (data on file, Glaxo Wellcome Inc.). This 105-site study was conducted to evaluate the tolerability and seizure incidence rate associated with bupropion SR under conditions of general clinical practice.

METHOD

Patients

Male or female patients at least 18 years of age diagnosed with depression (including major depression, dysthymia, bipolar I or II depression, depression not otherwise specified [NOS], or bipolar depression NOS) using DSM-III-R criteria were eligible for the study if they provided written, informed consent. Diagnoses were made during the clinical interview by the treating physician at each study site. Patients were excluded from the study if they had been previously treated with either bupropion IR or bupropion SR. Patients with a history or current diagnosis of bulimia and/or anorexia nervosa or with a known predisposition to seizures (including febrile seizure during childhood, epilepsy, brain tumor, significant head trauma, family history of idiopathic seizure disorder, current treatment with seizure threshold–lowering medications) were excluded. Patients who were pregnant or lactating or who were actively suicidal were also excluded. Patients could not have received any neuroleptic or antidepressant during or within 1 week of study drug treatment (2 weeks for monoamine oxidase inhibitors, clomipramine, maprotiline, or protriptyline; and 4 weeks for fluoxetine). Except for long-acting benzodiazepines, the use of medications that raise the seizure threshold was not permitted during the study. The use of mood stabilizers with anticonvulsant properties was likewise not permitted during the study.

Study Design and Procedures

During screening for this open-label, 105-site study, investigators used the Clinical Global Impressions scale for Improvement (CGI-I) to assess patients' responses to their last antidepressant taken (if any) for the current episode of depression. In addition, investigators evaluated the tolerability of the last antidepressant (if any) according to the following 5 ratings: no side effects, side effects present but did not significantly interfere with patients' functioning, side effects significantly interfered with patients' functioning, side effects outweighed therapeutic effect, or tolerability unknown.

During the 8-week acute treatment phase, patients received bupropion hydrochloride sustained release (bupropion SR). Dosing was initiated at 100 mg/day (50 mg b.i.d.) for 4 days. The dose was increased on treatment day 5 to 200 mg/day (100 mg b.i.d.) and again on treatment day 8 to 300 mg/day (150 mg b.i.d.). Patients were to be maintained at a dose of 300 mg/day for the remainder of the treatment phase unless this dose was not tolerated. If intolerance developed, dosage reduction was allowed to a minimum of 100 mg/day (50 mg b.i.d.). Patients received verbal dosing instructions as well as written instructions on take-home diaries at each clinic visit. Compliance with the prescribed dosing regimen was determined by returned-tablet counts.

Investigator contact with patients occurred at least every 2 weeks. A clinic visit was required on treatment days 14, 28, and 56 and at patient discontinuation. Investigators contacted patients by telephone on treatment day 42. At each contact (telephone or clinic visit), reports of serious adverse experiences, including seizures and seizure-like events, were elicited by the investigators asking patients, "Have you had any difficulties or has anything unusual occurred since I last saw you?" Serious adverse experiences were defined as events that represented a significant hazard, including any experience that was fatal, life-threatening, or permanently disabling; required inpatient hospitalization or prolonged hospitalization; or were congenital abnormalities (offspring of patient), cancer, or

overdose. (In order to ensure that seizures were defined consistently from investigator to investigator, guidelines for the differential diagnosis of seizures were reviewed with all investigators prior to study initiation and were outlined in the clinical procedures manual provided to all investigators. Investigators were also instructed to report seizure-like events to ensure that such events were fully evaluated and diagnosed.) Unlike other untoward medical occurrences, increased depressive symptomatology requiring psychiatric hospitalization was not recorded as an adverse event unless it comprised a suicide attempt or the investigators felt that the symptomatology was outside the natural progression of the patient's disease.

At screening and the end of the 8-week acute phase, investigators completed the Clinical Global Impressions scale for Severity (CGI-S) and the CGI-I (end of treatment only) to evaluate response to bupropion SR. Investigators rated the tolerability of bupropion SR according to the 5-point scale described above.

After completing the 8-week acute phase, at the investigators' discretion, patients had the option to continue treatment with bupropion SR in a continuation phase lasting up to 1 year, during which patients could continue to receive bupropion SR (50 mg b.i.d. to 150 mg b.i.d.). At monthly visits, investigators continued to elicit reports of serious adverse events, including seizures and seizure-like events.

Data Analysis

Medication compliance. Medication compliance (expressed as a percent) was calculated for each patient based on total dose taken divided by total dose prescribed through 56 days of treatment or until premature discontinuation from the study. The overall mean medication compliance for the study was computed from individual patient compliance values.

Seizure rate. Two methods of calculating seizure rate were employed. First, observed rates with upper 95% confidence limits (CL) were calculated for the 8-week acute phase as well as for the acute and continuation phases combined. The denominator used in these calculations included all patients known to have received at least 1 dose of study medication and who had no prior exposure to bupropion. Second, a survival analysis was conducted using the actuarial or life-table method[16,17] on a cohort of patients who during the acute phase received a minimum of 90% of the total cumulative dose required for a 100 mg/day regimen (the lowest dose used in this study). For the purposes of this analysis, these patients were divided into 3 groups: 90% compliant with regimens of 300 mg, 200 mg, and 100 mg/day, respectively. Survival analysis was conducted for the acute phase as well as for the acute and continuation phases combined. Of the patients enrolled in the study, the occurrence of seizure was determined in all but those lost to follow-up.

Serious adverse experiences. The number and percentage of patients reporting serious adverse experiences were tabulated.

Response and tolerability. Antidepressant response and tolerability analyses were conducted for patients receiving at least 1 dose of bupropion SR as well as for patients completing the 8-week acute phase. Two-sided, paired t tests were used to compare mean CGI-S scores at screening with those at study discontinuation. Results of the CGI-I and the side effect rating scales were summarized.

RESULTS

Sample Composition

Three thousand one hundred sixty-seven patients were enrolled across 105 sites (range, 1–167 patients/site; mean number of patients enrolled per site = 30). Data from 67 patients who possibly or definitely did not take study medication were excluded from all analyses. The remaining 3100 patients, included in the demographic, psychiatric history, and adverse experience analyses, constituted the primary study population (Figure 2). Of the 3100 patients who entered the study, 2057 patients (66%) completed the 8-week acute phase of the study. Of these 2057 patients, 1577 (77%) entered the continuation phase of the study.

Of the 3100 patients available for analysis, 6 patients were excluded from the calculation of observed seizure rate because they had received prior treatment with bupropion IR (Figure 2). None of these 6 patients experienced a seizure. Of the remaining 3094 patients, 2958 met compliance criteria for inclusion in the survival analysis for the calculation of the cumulative seizure rate (Figure 2). Antidepressant response and tolerability analyses were conducted for the 3094 patients receiving study medication as well as for the subset of 2057 patients who completed the 8-week acute phase. Thirty-six patients known to have ingested study medication, but with no usable study drug record data, were excluded from the medication compliance summaries and analyses (N = 3064; Figure 2).

Demographic and Patient Characteristics

The majority of patients were female, and most were white (Table 1). Seventy-four percent of patients were diagnosed with major depression; less than one half of the population had received antidepressant treatment for their current episode of depression (Table 1).

Medication Compliance and Exposure

Mean compliance with study medication was greater than 90% in 83% of patients (Table 1). Of the 2958 patients who fulfilled requirements for inclusion in the survival analysis, 2080 (70%) were exposed to a 300-mg/day regimen, 777 (26%) were exposed to 200-mg/day regi-

Figure 2. Summary of Sample Sizes Used in Data Analyses

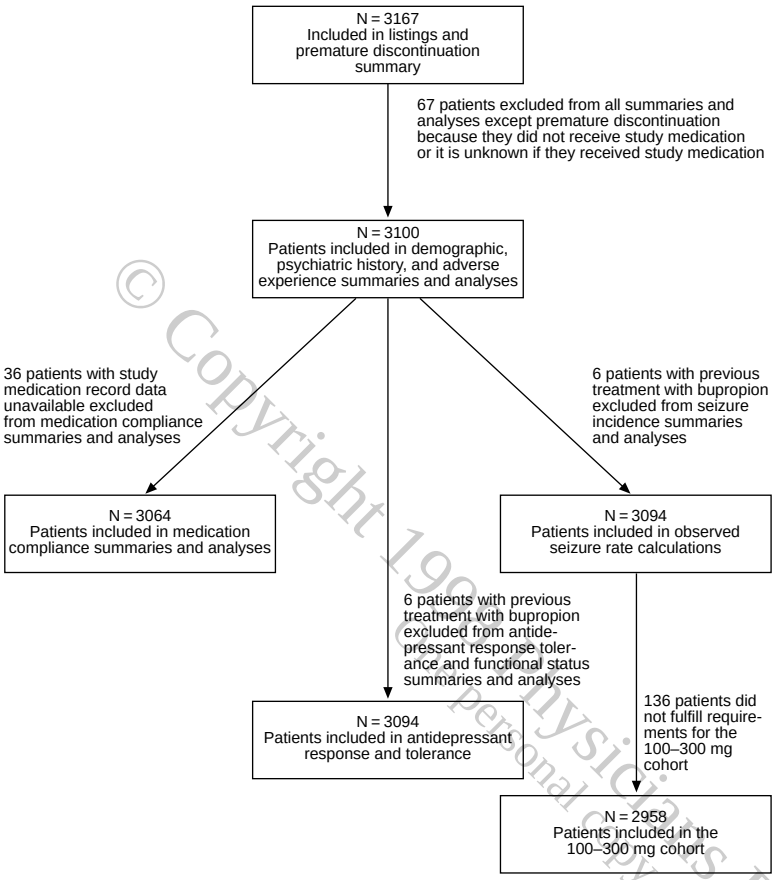


Table 1. Demographic and Patient Characteristics[a]

Variable	Value
Age, y	
Mean ± SD	42 ± 12
Range	18–86
Gender, N (%)	
Male	1167 (37.6%)
Female	1933 (62.4%)
Race, N (%)	
White	2776 (89.5%)
Black	217 (7.0%)
Other	107 (3.5%)
Diagnosis, N (%)	
Major depression	2304 (74.3%)
Bipolar disorder, depressed	78 (2.5%)
Dysthymic disorder	342 (11.0%)
Depressive disorder, NOS	301 (9.7%)
Bipolar disorder, NOS	27 (0.9%)
Other	48 (1.5%)
Prior antidepressant for present episode, N (%)	
Yes	1188 (38.3%)
No	1912 (61.7%)
Category of last antidepressant, N (%)	
Serotonin reuptake inhibitor	733/1188 (61.7%)
Tricyclic/tetracyclic	318/1188 (26.8%)
Monoamine oxidase inhibitor	12/1188 (1.0%)
Other	77/1188 (6.5%)
Unknown	48/1188 (4.0%)
Dosing compliance, N (%)	
Less than 60%	43/3064 (1.4%)
60%–69%	47/3064 (1.5%)
70%–79%	85/3064 (2.8%)
80%–89%	353/3064 (11.5%)
90%–100%	2536/3064 (82.8%)

[a]N = 3100 unless otherwise noted.

men, and 101 (3%) were exposed to a 100-mg/day regimen. At the end of the 8-week acute phase, 2037 (69%) patients still remained in the cohort, with 1546 (76%) of these patients exposed to a 300-mg/day dosing regimen.

Seizure Rate

The observed seizure rate associated with the therapeutic use of bupropion SR during the 8-week acute phase was 2 seizures in 3094 patients, or 0.06%, with an upper 1-sided 95% CL of 0.14%. The observed seizure rate for the acute and continuation phases combined in patients who received therapeutic doses of bupropion SR was 0.10% with an upper 1-sided 95% CL of 0.19%. In patients who consumed therapeutic doses of bupropion SR, the survival analysis yielded a cumulative seizure rate of 0.08% with an upper 1-sided 95% CL of 0.18% for the acute phase and a rate of 0.15% with an upper 1-sided 95% CL of 0.30% for both phases combined.

Each of the 3 patients who experienced a seizure had a single generalized seizure characterized by sudden loss of consciousness and tonic-clonic contractions (1 patient experienced only tonic contractions) followed by a period of postictal confusion (Table 2). Predisposing factors were present in 2 of the 3 seizures (Table 2). Patient 1 admitted to a history of an alcohol withdrawal seizure 11 years prior to the study; according to reports by the emergency room physician, there had been recent alcohol use. Patient 2 had a history of loss of consciousness following a motor vehicle accident. In addition, there was daily use of alcohol (2 beers and 4–6 drinks/day) with questionable alcohol abuse. Although patient 3 had a history of alcohol abuse, he denied recent use of alcohol and indicated he last consumed alcohol 3 months prior to the seizure.

Two of the seizures (patients 1 and 2) were associated with a bupropion SR dose of 300 mg/day (150 mg b.i.d.; Table 2). The patients had been on the current dose for 46 and 66 days, respectively. Patient 3 experienced the seizure on the third day of dosing at 100 mg/day (50 mg b.i.d.). Doses by body weight were 4.2 mg/kg, 3.5 mg/kg, and 1.1 mg/kg for patients 1, 2, and 3, respectively.

Five seizures that were not associated with therapeutic use of bupropion SR were not included in the overall seizure incidence calculation (Table 3). Patient 4 experienced a seizure prior to ingesting any study medication. A computerized tomographic head scan conducted following the seizure revealed evidence of a cerebellar hemor-

Table 2. Summary of Seizures Associated With Therapeutic Use of Bupropion SR

Pt. #	Age (y)	Gender	Daily Dose (mg) at Time of Event	Dose by Body Weight	Total Days on Dose	Time After Last Dose	Total Days on Bupropion SR	Attribution[a] to Bupropion SR	Concomitant Medications	Possible Predisposing Factors	Patient Considered Predisposed to Seizures
1	49	M	300	4.2 mg/kg	46	3 h	54	Reasonably attributable	None	History of alcohol withdrawal seizure 11 y prior to study; possible recent alcohol use.	Yes
2	43	M	300	3.5 mg/kg	66	4 h[b]	73	Possibly attributable	None	Loss of consciousness following a motor vehicle accident 25 y prior to study; daily alcohol use; questionable history of alcohol abuse.	Yes
3	44	M	100	1.1 mg/kg	3	8 h	3	Reasonably attributable	Diazepam (20–30 mg qhs plus 5 mg b.i.d. prn)	History of alcohol abuse; denial of recent use indicating that alcohol was last consumed 3 months prior to event.	No

[a]Rated by the investigator.
[b]Patient took morning dose prior to work and experienced seizure at approximately 12:00 p.m.; a 4-hour time interval was estimated.

Table 3. Summary of Seizures Associated With the Nontherapeutic Use of Bupropion SR Including Overdoses

Pt. #	Age (y)	Gender	Daily Dose (mg) at Time of Event	Total Days on Bupropion SR	Attribution[a] to Bupropion SR	Concomitant Medications	Possible Predisposing Factors	Patient Considered Predisposed to Seizures	Reasons Not Included in Seizure Risk Calculation
4	73	F	0	0	Not reasonably attributable	Unknown	CT scan following seizure revealed a cerebellar hematoma	Yes	Patient never ingested study medication.
5	28	F	0	1	Not reasonably attributable	Nortriptyline (50 mg), fluoxetine (20 mg), alprazolam (0.25 mg)	Family history of seizure disorder	Yes	Patient had not ingested study medication for 39 days prior to seizure and was taking other psychotropic agents associated with seizure at the time of the event.
6	44	F	0	35	Not reasonably attributable	Phencyclidine (×2), chlordiazepoxide 10-mg tablets (50–100)	Overdose with phencyclidine and chlordiazepoxide; recent use of cocaine on 3 occasions on days immediately prior to overdose	Yes	Patient had not ingested study medication for 3 days prior to seizure and overdosed on substances known to be associated with seizures.
7	34	F	300[b]	228	Reasonably attributable	Novolin 70/30 (43 units)	Overdose with bupropion SR	Yes	Patient overdosed with bupropion SR by ingesting a "handful" of 150-mg tablets.
8	35	M	300[b]	111	Reasonably attributable	Percocet (4–6 tabs qd), sumatriptan (6 mg)	Loss of consciousness following vehicle accidents in 1974 and 1983	Yes	Patient overdosed with bupropion SR by intentionally ingesting 450 mg (150 mg in am and 300 mg in pm) on the day before the seizure and 300 mg on the day of the seizure.

[a]Rated by the investigator.
[b]Patient was prescribed 300 mg/day but intentionally misdosed.

rhage. The patient confirmed that no study drug had been taken, and all medication was returned intact in the original blister card packaging. Patient 5 learned of a family history of seizure after taking a single dose (50 mg) of study medication. She was discontinued from the study and alternative antidepressant therapy was initiated. The patient experienced a seizure 39 days later while receiving nortriptyline, fluoxetine, and alprazolam. Patient 6 experienced a seizure in the emergency room following an overdose of chlordiazepoxide and phencyclidine. She had also used cocaine on several occasions on the days leading up to the overdose. The patient had stopped taking bupropion SR 3 days prior to the overdose.

Two seizures involved intentional overdosing with bupropion SR. Patient 7 ingested a "handful" of 150-mg bupropion SR tablets. Upon admission to the emergency

room, she appeared lethargic and confused. During treatment of the overdose, she experienced a witnessed generalized tonic-clonic seizure. After gastric lavage and treatment with charcoal and magnesium citrate, the patient was released from the emergency room without other sequelae. Patient 8 experienced a seizure after intentional misdosing of bupropion SR that exceeded both the maximum single and total daily doses. This patient reportedly missed several doses earlier in the week preceding his seizure and doubled 2 consecutive doses in order to "catch up." On the day prior to the seizure, the patient took 150 mg of bupropion SR in the morning and 300 mg in the evening. The next morning, he took a single dose of 300 mg and experienced the seizure approximately 6 hours later.

One event for which a diagnosis of seizure cannot be confirmed or entirely ruled out occurred in a patient 3 days after she discontinued the study due to worsening depression. The patient experienced dizziness and lost her balance while leaning to extinguish a cigarette. Her next memory was being in a wheelchair in the emergency room. Although the emergency room report indicates that the patient had experienced a tonic-clonic seizure, no hospital records describing the symptomatology have been located. Due to the vague history of the event, it was not possible for a consulting neurologist to determine whether or not an actual seizure occurred, although he considered it unlikely. He indicated that the event probably represented either a syncopal episode or an isolated epileptic event. Because the patient had been off study medication for 3 days and the diagnosis of seizure was unclear, this event was not included in the seizure rate analysis.

Other Serious Adverse Events

Fifty patients experienced 54 serious adverse events other than seizure during the acute and continuation phases combined. None of these events were considered by the investigator to be reasonably attributable to the administration of bupropion SR. The most common serious adverse events were suicide attempt or overdose (9 patients), accidental injury (4 patients), and myocardial infarction (3 patients, each of whom had preexisting cardiovascular pathology).

Six deaths (3 suicides, 2 cardiac complications, 1 homicide) occurred during the study. None of the events precipitating the deaths of these 6 patients were considered by the investigator to be attributable to bupropion SR.

Response and Tolerability

Of the 2057 patients completing the 8-week acute phase, 73% were rated as "much improved" or "very much improved" with bupropion SR treatment on the CGI-I scale. The mean CGI-S score at screening was 4.2 ± 0.7; the mean CGI-S score at discontinuation was 2.5 ± 1.1 ($p < .0001$). The mean CGI-I score at study discontinuation was 2.0 ± 0.9. Of the 3094 patients receiving at least 1 dose of study medication, 52% were rated as "much improved" or "very much improved" with bupropion SR treatment on the CGI-I scale.

Of the 771 patients who completed the 8-week acute phase and had received antidepressant treatment for the present depressive episode prior to enrolling in the study, 507 (66%) were rated as "much improved" or "very much improved" with bupropion SR. Of the 287 patients who completed 8 weeks of treatment and who failed to respond to their previous antidepressant treatment (CGI-I ratings of no change, minimally worse, much worse, or very much worse), 253 patients (88%) were rated as either "minimally improved," "much improved," or "very much improved" with bupropion SR based on CGI-I scores, whereas 33 patients (12%) were rated as "minimally worse" or as having "no change."

Ninety-seven percent (N = 1991) of the 2057 patients completing the 8-week acute phase experienced either no side effects or side effects that did not significantly interfere with functioning. Of the 3094 patients receiving at least 1 dose of study medication who were included in the treatment response and tolerability analyses, 84% were rated as experiencing either no side effects or side effects that did not significantly interfere with functioning.

Of the 771 patients who completed the 8-week acute phase and had received antidepressant treatment for the present depressive episode prior to enrolling in the study, 96% (N = 763) were rated as having no side effects or side effects that did not significantly interfere with functioning during bupropion SR treatment. Of the 222 completing patients who failed to tolerate their previous antidepressant (i.e., "side effects significantly interfered with patients' functioning" or "side effects outweighed therapeutic effect"), 211 (95%) were rated as having no side effects or side effects that did not significantly interfere with functioning during bupropion SR treatment.

DISCUSSION

This is the first study to prospectively examine the seizure rate associated with the sustained-release (SR) formulation of bupropion hydrochloride. The results of this 3100-patient study demonstrate that in patients receiving therapeutic daily doses of up to 150 mg b.i.d. of bupropion SR, the rate of seizure is approximately 0.10% (1/1000). The 2 seizures occurring during the 8-week acute phase yielded an observed seizure rate of 0.10% and a cumulative rate of 0.08%. The third seizure occurring during the continuation phase yielded an observed rate of 0.06% and a cumulative rate of 0.15%. Two of the 3 patients who experienced seizures while taking therapeutic doses of bupropion SR were considered to have predisposing conditions (alcohol in both cases and history of head trauma in 1 case). This finding corroborates previous findings with bupropion IR[7,8] and with other classes of an-

tidepressants[10–15] of a relationship between predisposition to seizure and seizure rate during the study, underscoring the importance of appropriate patient selection.

To compare the relative seizure risk among antidepressants, risk should be estimated at therapeutic and effective doses.[14] Two patients who intentionally overdosed with bupropion SR, 1 in a suicide attempt and 1 in an attempt to catch up for missed doses, also experienced seizures. Because seizures following overdoses with psychotropic agents are not uncommon, these results were not unexpected and these events were not included in the overall seizure rate calculations.

Extreme care was taken in this study to ensure the reliability and validity of the seizure risk estimates that were obtained. This study employed methodological criteria (such as large sample size, known duration of treatment, use of systematic monitoring to determine number of seizures) recently advanced as essential for providing valid, reliable estimates of seizure risk associated with antidepressant use.[13,16] During this prospective study, 3100 patients received bupropion SR; 2057 were exposed to therapeutic doses for at least 8 weeks. Compliance with the prescribed dosing was excellent. More than two thirds of the patients (2080 of 3100) were maintained at 300 mg/day, the usual target dose. In addition, systematic methods for determining the number of patients who experienced a seizure were utilized. Contact with the investigators was required at least every 2 weeks during the 8-week acute phase; monthly contact was required throughout the continuation phase. In order to minimize the number of patients lost to follow-up, investigators were instructed to make every effort to contact patients who missed clinic appointments. It is highly probable that all seizures were detected as the status of 3164 of the 3167 patients enrolled in the study was ascertained for the duration of their study participation. One limitation of the study outcome is that the relative seizure risk for individual dose regimens of bupropion SR cannot be determined on the basis of data from this study, which required dose escalation to the maximum dose of 300 mg/day (if tolerated). With two thirds of the sample population maintained at 300 mg/day, there were not enough patients on the 100-mg or 200-mg/day regimens to provide a reliable estimate of seizure risk based on dose. In addition, the seizure rate associated with the maximum bupropion SR dose (400 mg/day) recommended in the package labeling was not assessed in this study. The package labeling for bupropion SR recommends that dosing start at 150 mg/day. Dosage may be increased as early as day 4 to the usual target dose of 300 mg, given as 150 mg b.i.d. At this target dose, results from this study demonstrate that the rate of seizures is low and similar to the rate observed with other marketed antidepressants.[10–15]

Because one of the goals of the development of bupropion SR was to decrease its peak plasma levels and, therefore, the seizure rate associated with bupropion, the results of this study may be interpreted relative to the seizure risk associated with bupropion IR. The incidence of seizures with bupropion IR was determined in a prospective surveillance study[8] that was similar in design to the present study. The 2 studies were similar in terms of sample size, patient demographics, psychiatric diagnoses, and duration of exposure to the study drug. The majority of patients in both studies were maintained at the maximum recommended dose for the respective formulation (450 mg/day for bupropion IR and 300 mg/day for bupropion SR). Although comparisons across studies have limitations, the similarities between the 2 studies allow the results to be compared within the context of these limitations. The incidence of seizure was 0.40% with bupropion IR compared with 0.10% with bupropion SR. The cumulative risk of seizure was for an 8-week exposure was 0.38% with bupropion IR and 0.08% with bupropion SR. Although cumulative risk including the continuation phase data was not calculated in the bupropion IR study, life-table survival estimates were calculated for an independent sample of 4262 patients treated with bupropion.[7] The cumulative risk of seizures in patients receiving up to 450 mg/day of bupropion IR was 0.48% up to day 720, whereas the cumulative risk of seizure in patients treated with up to 300 mg/day of bupropion SR was 0.15% up to 1 year. Although it cannot be determined whether total daily doses or lower peak bupropion levels, alone or in combination, account for the lower seizure rate associated with bupropion SR relative to bupropion IR, the risk of seizure associated with the therapeutic use of bupropion SR is considerably lower than that associated with bupropion IR.

Comparison of the seizure risk with other antidepressant drugs is more difficult. Depending on the doses evaluated, published reports indicate that the incidence of seizure associated with tricyclic and tetracyclic antidepressants ranges from 0.4% to 1.0%.[10–14] Because these estimates are based primarily on findings from reviews of case histories and retrospective studies, the reliability of these estimates is unclear and the risk derived from these methods may be underestimated. Some of the studies involved small sample sizes, the dose and duration of treatment were not always known, and the seizure data were not systematically collected. Seizure incidence estimates for the more recently marketed antidepressants such as fluoxetine (0.2%),[18] paroxetine (0.1%),[19] sertraline (< 0.1%),[20] and venlafaxine (0.26%)[21] may be more accurate and useful for comparison even though the estimates of risk for these antidepressants were based on data pooled from across clinical studies rather than from prospective surveillance studies. These rates are more reliable because the number of patients at risk and the duration of treatment were known and the studies were systematically monitored, increasing the probability that all seizures were detected. Taking into consideration the

methodological limitations of these studies when making comparisons, the risk of seizure associated with bupropion SR is clearly within the range of other currently marketed antidepressants.

The serious adverse experience data obtained with the SR formulation of bupropion in this study are consistent with those obtained with bupropion IR in demonstrating that the drug is well tolerated.[1–6,8] Only 54 serious adverse experiences other than seizure, none of which were considered by the investigator to be reasonably attributable to the administration of bupropion SR, were reported during the acute and continuation phases of the study. In addition, 97% of the 2057 patients completing the 8-week acute phase experienced "no side effects" or "side effects that did not significantly interfere with patient functioning." This favorable side effect profile was particularly beneficial for many of the patients who poorly tolerated their previous antidepressant. While bupropion SR was well tolerated, it was also clinically efficacious, with 73% of 2057 patients rated as "much improved" or "very much improved" on the CGI-I scale. Even those patients who did not previously respond to other antidepressants for the current depressive episode benefited from bupropion SR therapy: 59% were rated as "much improved" or "very much improved."

In summary, the results of this study demonstrate that bupropion SR, an effective antidepressant, is safe and well tolerated when used in the recommended therapeutic doses. The risk of seizure associated with the usual adult target dose of 300 mg/day of bupropion SR in patients without predisposition to seizures is well within the range of risk estimated for other currently marketed antidepressants.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), chlordiazepoxide (Librium and others), clomipramine (Anafranil), diazepam (Valium and others), fluoxetine (Prozac), maprotiline (Ludiomil), nortriptyline (Pamelor and others), paroxetine (Paxil), phencyclidine (Sernylan), protriptyline (Vivactil), sertraline (Zoloft), sumatriptan (Imitrex), venlafaxine (Effexor).

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