Bupropion Extended Release Compared With Escitalopram: Effects on Sexual Functioning and Antidepressant Efficacy in 2 Randomized, Double-Blind, Placebo-Controlled Studies

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Objective: To compare the effects on sexual functioning and the antidepressant efficacy of once-daily bupropion extended release (XL) and escitalopram in adults with major depressive disorder (MDD).

Method: Adult outpatients with moderate to severe DSM-IV–defined MDD and normal sexual functioning were randomly assigned to receive bupropion XL (300–450 mg/day; N = 276), escitalopram (10–20 mg/day; N = 281), or placebo (N = 273) for up to 8 weeks in 2 identically designed, randomized, double-blind, parallel-group studies (study 1 conducted from February 6, 2003, to June 10, 2004; study 2 conducted from January 21, 2003, to June 15, 2004). Data were analyzed prospectively for each study individually, and pooled data were analyzed retrospectively.

Results: In both the individual studies and the pooled dataset, the incidence of orgasm dysfunction at week 8 (primary endpoint) and the incidence of worsened sexual functioning at the end of the treatment period were statistically significantly lower with bupropion XL than with escitalopram ($p < .05$), not statistically different between bupropion XL and placebo ($p \geq .067$), and statistically significantly higher with escitalopram than with placebo ($p \leq .001$). The percentages of patients with orgasm dysfunction at week 8 in study 1, study 2, and the pooled dataset, respectively, were 13%, 16%, and 15% with bupropion XL; 32%, 29%, and 30% with escitalopram; and 11%, 8%, and 9% with placebo. The respective percentages of patients with worsened sexual functioning at the end of the treatment period were 18%, 22%, and 20% with bupropion XL; 37%, 34%, and 36% with escitalopram; and 14%, 16%, and 15% with placebo. Mean changes in Changes in Sexual Functioning Questionnaire scores for all domains at week 8 were statistically significantly worse for escitalopram compared with bupropion XL ($p \leq .05$). Separation from placebo could not be established at a statistical .05 level for bupropion on 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score. However, escitalopram showed statistical superiority to placebo on HAM-D-17 total score in one of the 2 studies and in the pooled data. Bupropion XL did not statistically differ from escitalopram with respect to mean change in HAM-D-17 total score, HAM-D-17 response or remission rates, percentage of patients much or very much improved on Clinical Global Impressions-Improvement scale scores, or mean changes in the Hospital Anxiety and Depression (HAD) scale total score or Clinical Global Impressions-Severity of Illness scale score at week 8.

Conclusions: Bupropion XL had a sexual tolerability profile significantly better than that of escitalopram with similar HAM-D-17 remission rates and HAD total scores in patients with MDD.

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Sexual dysfunction can be a common side effect of antidepressant therapy and can also occur as a symptom of depression or other psychiatric and medical illnesses.[1] Effects on sexual functioning are an important consideration in selecting antidepressant therapy because sexual dysfunction can impact multiple aspects of patients' lives.[2,3] Among antidepressants, the selective serotonin reuptake inhibitors (SSRIs) and other medications that enhance serotonergic activity (e.g., tricyclic antidepressants, venlafaxine) are most likely to cause sexual dysfunction.[4–6] Across studies in which sexual dysfunction is a prospectively defined endpoint, sexual dysfunction is reported in 30% to 70% of patients using SSRIs,

approximately 65% of patients using venlafaxine, and 46% of patients using duloxetine.[3,4,7]

Bupropion, a norepinephrine and dopamine reuptake inhibitor chemically unrelated to other antidepressants, has demonstrated antidepressant efficacy similar to that of the SSRIs sertraline and fluoxetine with effects on sexual functioning comparable to those of placebo.[8–11] In controlled clinical trials prospectively designed to examine antidepressant effects on sexual functioning in patients with major depressive disorder (MDD), bupropion sustained-release (bupropion SR) had a sexual side effect profile similar to that of placebo with significantly less sexual dysfunction than sertraline or fluoxetine.[8–10]

Bupropion XL (bupropion hydrochloride extended release tablet), a once-daily formulation of bupropion, would be expected to have a sexual side effect profile similar to that of bupropion SR on the basis of its bioequivalence to bupropion SR[12]; however, sexual functioning effects of the XL formulation of bupropion have not previously been investigated. The 2 identically designed, randomized, double-blind, placebo-controlled studies reported here were undertaken to evaluate the effects on sexual functioning and the antidepressant efficacy of bupropion XL compared with the SSRI escitalopram in patients with MDD. Although escitalopram, like the racemic mixture citalopram, has been associated with an elevated incidence of orgasm dysfunction reported as an adverse event in double-blind clinical trials,[13] the effects of escitalopram on sexual functioning have not previously been prospectively evaluated and reported.

METHOD

Patients

Men and women aged ≥ 18 years were eligible for the studies if they had a primary diagnosis of MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[14] and assessed with a full psychiatric interview aided by the Mini-International Neuropsychiatric Interview[15]; had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[16] total score ≥ 19 at screening and on the day of randomization to treatment; were currently experiencing a major depressive episode (MDE) lasting ≥ 12 weeks and ≤ 2 years but were otherwise healthy; had normal orgasm function as assessed by the investigator interview and were willing to discuss their sexual functioning with the investigator; and engaged in sexual activity leading to orgasm at least once every 2 weeks. Exclusion criteria included any sexual dysfunction at screening or at randomization except sexual desire disorder related to depression as determined by the structured investigator interview; a history or current diagnosis of anorexia nervosa, bulimia, seizure disorder, or brain injury; a diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder within 12 months before study entry; a diagnosis of bipolar I or II disorder, schizophrenia, or other psychotic disorders; and a history of attempted suicide within 6 months before screening. Patients taking prescribed or over-the-counter medications that might affect sexual functioning were excluded. Patients with comorbid generalized anxiety disorder were eligible for study entry. Patients who had a sexual desire disorder were eligible for the study if the investigator considered it to be secondary to the MDE.

Procedures

Institutional review boards approved the protocols for each of the study sites for these randomized, double-blind, double-dummy, placebo-controlled, multicenter studies (study 1, conducted from February 6, 2003, to June 10, 2004: GlaxoSmithKline protocol AK130927; study 2, conducted from January 21, 2003, to June 15, 2004: GlaxoSmithKline protocol AK130926). All patients provided written informed consent prior to any study activity.

The studies consisted of a 1-week screening phase and an 8-week treatment phase. Clinic visits occurred at screening, at randomization (defined as day 0), and at treatment weeks 1, 2, 3, 4, 6, and 8. Patients meeting eligibility criteria during the screening phase were randomly assigned on day 0 of the treatment phase to receive bupropion XL, escitalopram, or placebo (1:1:1). Patients in the bupropion XL group received 150 mg each morning during treatment week 1 and 300 mg each morning during treatment weeks 2 to 4. On the fifth treatment week, the daily dose could be increased to 450 mg (300 mg in the morning and 150 mg 8 hours later) if additional efficacy was desired and if the 300-mg daily dose was well tolerated. Patients in the escitalopram group received 10 mg each morning during treatment weeks 1 to 4. The escitalopram dose could then be increased to 20 mg each morning for the remainder of the treatment phase if additional efficacy was desired and the study medication was well tolerated. Patients unable to tolerate the 450-mg daily dose of bupropion XL or the 20-mg dose of escitalopram could have their dose reduced to the next lowest dose (300 mg/day for bupropion XL and 10 mg/day for escitalopram) for the remainder of the treatment period. Those unable to tolerate the latter doses were withdrawn from the studies. No prescription or nonprescription psychoactive medications were allowed, including treatment for sexual dysfunction. Zolpidem, zaleplon, and nonprescription sleep aids were permitted during the studies through treatment day 10.

Assessments

Sexual functioning was assessed by an investigator-guided interview of the patient (primary endpoint) and with the patient-completed Changes in Sexual Function-

ing Questionnaire (CSFQ) (secondary endpoint) at randomization and at the clinic visits at treatment weeks 1, 2, 4, 6, and 8. The investigator interview, although not validated for use in the public domain, has been shown to be sensitive and specific in earlier trials at detecting treatment-emergent changes in sexual functioning in clinical studies.[8–10] It is guided by a multiple-choice questionnaire read aloud to patients, with subsequent assessment by the clinician. The interview included ratings of the frequency of orgasm since the last clinic visit as well as assessments of orgasm delay and/or failure (all assessed as present or absent) and the patient's sexual functioning (better, worse, or unchanged from randomization). The CSFQ is a self-rated scale that has been validated and has demonstrated reliability in both clinical and research settings.[17] The version used in this study includes 14 items[18] that measure sexual functioning as a total score (14 items) and on the subscales of pleasure (1 item), desire/frequency (2 items), desire/interest (3 items), arousal (3 items), and orgasm (3 items). Two additional items are included in the total score, but do not map to a specific phase of the sexual response cycle. Lower scores are associated with worsened sexual functioning.

Antidepressant efficacy was assessed with the investigator-administered HAM-D-17 and the Clinical Global Impressions-Severity of Illness scale (CGI-S),[19] completed at randomization and at treatment weeks 2, 4, 6, and 8; the Hospital Anxiety and Depression (HAD) scale,[20] a self-reported scale validated to detect changes in depressive symptoms over time (7 questions assess depression and 7 questions assess anxiety on a 0–3 scale; higher scores indicate more severe symptoms) and completed by patients at randomization and weeks 2, 4, and 8; and the Clinical Global Impressions-Improvement scale (CGI-I),[19] completed at treatment weeks 2, 4, 6, and 8. Tolerability was assessed by recording adverse events (defined as any untoward medical occurrences regardless of suspected cause) observed in or reported by a patient in response to open-ended queries at each clinic visit. Sexual side effects were not recorded as adverse events because they were detected and recorded by other means described above.

Data Analyses

Endpoints. The primary sexual functioning endpoint was the percentage of patients with orgasm dysfunction (orgasm delay and/or orgasm failure as determined by investigator interview) at treatment week 8. Other sexual functioning endpoints were the percentage of patients having worsened sexual functioning at treatment week 8 relative to randomization and mean changes from randomization in CSFQ total scores and CSFQ subscale scores for pleasure, desire/frequency, desire/interest, arousal, and orgasm at weeks 1, 2, 4, 6, and 8.

The primary antidepressant efficacy endpoint was the mean change from randomization in HAM-D-17 total score at treatment week 8. Other efficacy endpoints included the percentages of patients with HAM-D-17 remission (HAM-D-17 total score ≤ 7), HAM-D-17 response ($\geq 50\%$ reduction from randomization in HAM-D-17 total score), CGI-I response (score of much improved or very much improved) at treatment week 8, and mean changes from randomization to treatment week 8 in CGI-S and HAD scale scores.

Tolerability was assessed as the percentage of patients with specific adverse events (regardless of suspected cause) during the treatment period and the percentage of patients prematurely withdrawn from the studies because of adverse events.

Statistics. For each sexual functioning and efficacy assessment, data were analyzed prospectively for each study individually and retrospectively with pooled data from the studies. The pooled analyses were possible because of the identical designs, methodologies, and patient characteristics of the studies.

The sample-size calculations were performed to achieve approximately 90% power to detect a difference between treatment groups at the nominal .05 two-sided significance level. Assuming that the incidence of patients with orgasm dysfunction was 15% with bupropion XL and 40% with escitalopram, a total of 65 patients per treatment group was required to detect this difference. Assuming a standard deviation estimate of 8 for mean change in HAM-D-17 total score, 140 patients per group were required to detect a 3-point difference between bupropion XL and placebo in mean-change-from-randomization HAM-D-17 total scores. Therefore, randomization of 140 patients per treatment group was planned for each study.

Sexual functioning and efficacy data were analyzed for the intent-to-treat population, defined as all randomized patients who took at least 1 dose of study medication, had no orgasm dysfunction reported from the sexual functioning assessment at randomization, had a HAM-D assessment completed at randomization, and provided at least 1 post-randomization HAM-D-17 and orgasm function assessment. Sexual functioning and efficacy data were analyzed using last-observation-carried-forward (LOCF) methods. For continuous measures, differences among treatments were tested using analysis of covariance (ANCOVA) with randomization value as a covariate and center, gender, and treatment as fixed effects. Unless otherwise stated, least square means and standard errors from ANCOVAs are reported. For categorical measures, differences among treatment groups were tested using the Cochran-Mantel-Haenszel test controlling for center and gender. For the purposes of analysis, worsened sexual functioning compared with randomization was dichotomized as 1 = worse and 0 = any other outcome. For the analyses based on the pooled data, an additional study-

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specific stratification variable was introduced into the statistical models. The individual studies specified a hierarchical method to control inflation in the type I error rate: the comparison between the bupropion XL group and the escitalopram group with respect to orgasm dysfunction served as a gatekeeper for the treatment comparisons with respect to change-from-randomization HAM-D-17 total score and all other secondary comparisons. The nominal .05 level of significance was used. The p values presented for all secondary endpoints were not adjusted for multiple comparisons.

Tolerability data were summarized with descriptive statistics for the pooled dataset for all randomized patients who took at least 1 dose of study medication, but no hypothesis testing was undertaken for these data.

RESULTS

Patients

The number of patients randomly assigned to treatment and receiving at least 1 dose of study medication was 830 (420 in study 1 and 410 in study 2) (Table 1). These patients comprised the safety population on which tolerability summaries were based. The number of patients in the intent-to-treat population was 785 (397 in study 1 and 388 in study 2) (Table 1). Numbers of patients were approximately equally divided among treatment groups in each study (Table 1). Studies 1 and 2 were pooled because, although both individual studies demonstrated separation between bupropion XL and escitalopram on the primary endpoint, treatment-emergent orgasm dysfunction, separation from placebo was not achieved on antidepressant efficacy in the individual studies because the power calculation did not take into account the high placebo response rate. Pooling identical protocols incurs higher power to detect changes/differences than the individual studies.

Demographics and mean duration of the current MDE were similar between studies and among groups (Table 1). Approximately three quarters of patients in each treatment group completed the study (Table 1). Being lost to follow-up was the most common reason for premature withdrawal across studies and treatment groups. Hypnotics were used by ≤ 1% of subjects in each treatment group across the 2 studies.

In study 1, the mean daily dose of bupropion XL was 323 mg (SD = 59.4), and that of escitalopram was 13 mg (SD = 2.6). The corresponding values in study 2 were 309 mg (SD = 58.3) for bupropion XL and 13 mg (SD = 3.2) for escitalopram.

Table 1. Demographics, Baseline Clinical Characteristics, and Patient Disposition

Characteristic	Bupropion XL	Escitalopram	Placebo
Safety population, N			
Study 1	141	138	141
Study 2	135	143	132
Pooled	276	281	273
Intent-to-treat population, N			
Study 1	134	133	130
Study 2	129	133	126
Pooled	263	266	256
Female, N (%)			
Study 1	85 (60)	83 (60)	88 (62)
Study 2	76 (56)	78 (55)	76 (58)
Pooled	161 (58)	161 (57)	164 (60)
White, N (%)			
Study 1	96 (68)	89 (64)	91 (65)
Study 2	97 (72)	103 (72)	99 (75)
Pooled	193 (70)	192 (68)	190 (70)
Black, N (%)			
Study 1	27 (19)	28 (20)	28 (20)
Study 2	27 (20)	25 (17)	19 (14)
Pooled	54 (20)	53 (19)	47 (17)
Age, mean (SD), y			
Study 1	37 (12)	35 (10)	35 (12)
Study 2	37 (13)	36 (12)	37 (11)
Pooled	37 (12)	36 (11)	36 (11)
Duration of current episode, mean (SD), wk			
Study 1	38 (23)	40 (25)	43 (27)
Study 2	38 (23)	41 (25)	45 (26)
Pooled	38 (23)	40 (25)	44 (27)
Completed study, N (%)			
Study 1	109 (77)	105 (76)	102 (72)
Study 2	99 (73)	105 (73)	105 (80)
Pooled	208 (75)	210 (75)	207 (76)
Withdrawn from study, N (%)			
Study 1	32 (23)	33 (24)	39 (28)
Study 2	36 (27)	38 (27)	27 (20)
Pooled	68 (25)	71 (25)	66 (24)
Reasons for premature withdrawal, N (%)			
Study 1			
Lost to follow-up	14 (10)	11 (8)	19 (13)
Consent withdrawn	7 (5)	7 (5)	6 (4)
Adverse event	4 (3)	7 (5)	7 (5)
Protocol violation	3 (2)	5 (4)	2 (1)
Other	4 (3)	3 (2)	5 (4)
Study 2			
Lost to follow-up	12 (9)	14 (10)	9 (7)
Consent withdrawn	5 (4)	9 (6)	7 (5)
Adverse event	13 (10)	5 (3)	6 (5)
Protocol violation	2 (1)	4 (3)	4 (3)
Other	4 (3)	6 (4)	1 (< 1)

Abbreviation: XL = extended release.

Sexual Functioning

Investigator interview. The percentages of patients with orgasm dysfunction at week 8 in study 1, study 2, and the pooled dataset, respectively, were 13%, 16%, and 15% with bupropion XL; 32%, 29%, and 30% with escitalopram; and 11%, 8%, and 9% with placebo. In both the individual studies and the pooled dataset, the incidence of orgasm dysfunction at the end of the treatment period was statistically significantly lower with bupropion XL than with escitalopram ($p < .001$ for study 1 and the pooled dataset; $p < .05$ for study 2), not statistically different between bupropion XL and placebo ($p = .348$ study 1; $p = .094$ study 2; $p = .067$ pooled dataset), and higher

Table 2. Sexual Functioning and Efficacy Data (LOCF)

Variable	Bupropion XL	Escitalopram	Placebo	p Value: Bupropion XL vs Placebo	p Value: Escitalopram vs Placebo	p Value: Bupropion XL vs Escitalopram
N						
Study 1	134	133	130			
Study 2	129	133	126			
Pooled data	263	266	256			
Orgasm dysfunction, N (%)						
Study 1	18 (13)	43 (32)	14 (11)	.348	< .001	< .001
Study 2	21 (16)	38 (29)	10 (8)	.094	< .001	.014
Pooled data	39 (15)	81 (30)	24 (9)	.067	< .001	< .001
Worsened sexual functioning, N (%)						
Study 1	24 (18)	49 (37)	18 (14)	.279	< .001	< .001
Study 2	28 (22)	45 (34)	20 (16)	.389	.001	.027
Pooled data	52 (20)	94 (36)	38 (15)	.169	< .001	< .001
HAM-D-17 total score, mean change (SE)						
Study 1	–13.2 (0.6)	–14.2 (0.7)	–12.1 (0.7)	.184	.015	.260
Study 2	–13.1 (0.7)	–12.9 (0.7)	–11.9 (0.7)	.179	.252	.833
Pooled data	–13.2 (0.5)	–13.6 (0.5)	–12.0 (0.5)	.053	.011	.533
HAM-D-17 remission, N (%)						
Study 1	54 (40)	65 (49)	40 (31)	.042	.002	.278
Study 2	59 (46)	56 (42)	48 (38)	.185	.458	.531
Pooled data	113 (43)	121 (45)	88 (34)	.018	.005	.755
HAM-D-17 response, N (%)						
Study 1	82 (61)	90 (68)	69 (53)	.087	.007	.438
Study 2	81 (63)	82 (62)	64 (51)	.081	.053	.954
Pooled data	163 (62)	172 (65)	133 (52)	.015	.001	.610
HAD scale, mean change (SE)						
Study 1	–11.0 (0.7)	–11.5 (0.7)	–8.6 (0.7)	.015	.003	.570
Study 2	–9.9 (0.8)	–10.8 (0.8)	–7.5 (0.8)	.026	.002	.394
Pooled data	–10.5 (0.5)	–11.1 (0.5)	–8.1 (0.5)	.001	< .001	.343
CGI-S, mean change (SE)						
Study 1	–1.9 (0.1)	–1.9 (0.1)	–1.6 (0.1)	.079	.055	.862
Study 2	–2.0 (0.1)	–1.8 (0.1)	–1.6 (0.1)	.037	.277	.306
Pooled data	–1.9 (0.1)	–1.9 (0.1)	–1.6 (0.1)	.007	.031	.576
CGI-I response, N (%)						
Study 1	87 (65)	92 (69)	77 (59)	.267	.101	.675
Study 2	89 (69)	86 (66)	69 (55)	.021	.122	.622
Pooled data	176 (67)	178 (67)	146 (57)	.016	.024	.965

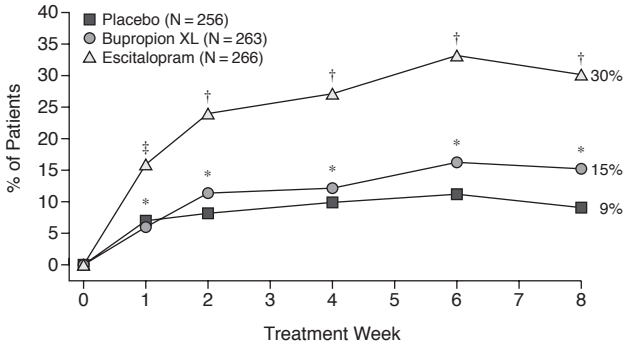
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAD = Hospital Anxiety and Depression, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, XL = extended release.

with escitalopram than with placebo ($p < .001$ for individual studies and pooled data) (Table 2 and Figure 1). This pattern of results was observed as early as week 1 and at all other treatment weeks (Figure 1 for pooled data) and is supported by the results from the CSFQ. The relative risks for treatment-emergent orgasm dysfunction (vs. placebo) were 1.2 and 2.0 for bupropion XL and 2.9 and 3.6 for escitalopram in studies 1 and 2, respectively.

In both the individual studies and the pooled dataset, the incidence of worsened sexual functioning at the end of the treatment period compared with randomization was statistically significantly lower with bupropion XL than with escitalopram ($p < .001$ for study 1 and the pooled dataset; $p < .05$ for study 2), not statistically different between bupropion XL and placebo ($p = .279$ study 1; $p = .389$ study 2; $p = .169$ pooled dataset), and higher with escitalopram than with placebo ($p \leq .001$ for individual studies and pooled data) (Table 2 and Figure 2). The percentages of patients with worsened sexual functioning at the end of the treatment period in study 1, study 2, and the pooled dataset, respectively, were 18%, 22%, and 20% with bupropion XL; 37%, 34%, and 36% with escitalopram; and 14%, 16%, and 15% with placebo.

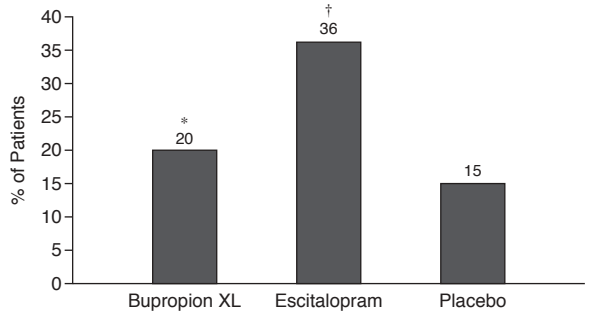
CSFQ. Mean total scores and subscale scores on the CSFQ were similar among treatment groups at randomization in each study (Table 3). Of the subjects entering the studies with no orgasm disorder based on the cutoff criteria of the CSFQ, 35% of the escitalopram-treated patients and 13% of the bupropion- and placebo-treated patients reported scores below the threshold, indicating clinically significant sexual orgasm dysfunction at the end of treatment. Crossing the threshold cutoff score into dysfunction is clinically significant as these scores were determined by non-overlap of the 95% confidence intervals around the mean for subjects with MDD versus normal control subjects.[21] At treatment week 8, escitalopram was associated with statistically significantly worse

Figure 1. Percentage of Patients With Orgasm Dysfunction While Receiving Bupropion XL, Escitalopram, or Placebo (pooled LOCF data)



*p ≤ .001 bupropion XL vs. escitalopram.
†p < .001 escitalopram vs. placebo.
‡p = .006 escitalopram vs. placebo.
Abbreviations: LOCF = last observation carried forward, XL = extended release.

Figure 2. Percentage of Patients at Treatment Week 8 With Worsened Sexual Functioning Relative to Randomization (pooled LOCF data)



*p < .001 bupropion XL vs. escitalopram.
†p < .001 escitalopram vs. placebo.
Abbreviations: LOCF = last observation carried forward, XL = extended release.

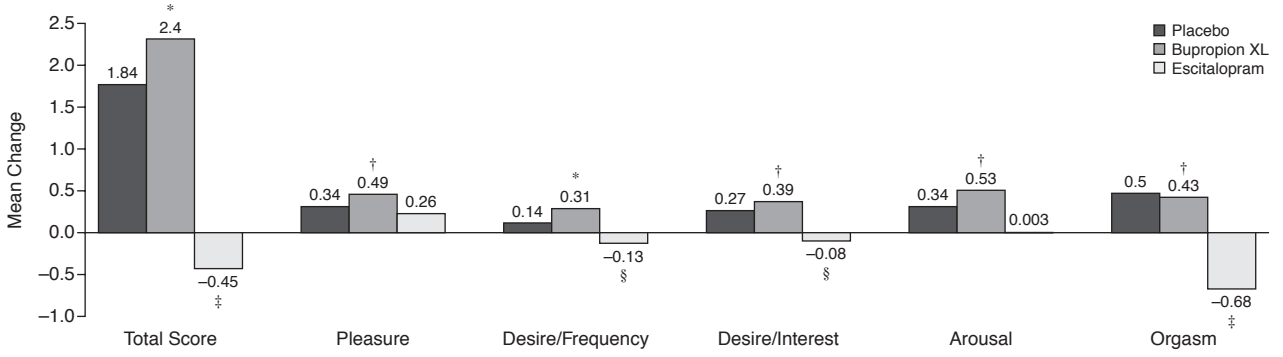
Table 3. CSFQ Scores at Randomization and Changes at Treatment Week 8 (LOCF) in Patients Receiving Bupropion XL, Escitalopram, or Placebo

	Bupropion XL			Escitalopram			Placebo		
		CSFQ			CSFQ			CSFQ	
CSFQ Score	N	Score at Randomization, Mean (SE)	Change at Week 8, Least Square Mean (SE)	N	Score at Randomization, Mean (SE)	Change at Week 8, Least Square Mean (SE)	N	Score at Randomization, Mean (SE)	Change at Week 8, Least Square Mean (SE)
Total score									
Study 1	133	50.5 (0.7)	2.7* (0.7)	130	52.1 (0.7)	0.2† (0.7)	127	51.8 (0.7)	2.4 (0.7)
Study 2	129	53.8 (0.6)	2.1‡ (0.7)	133	53.4 (0.7)	–1.1† (0.7)	125	52.9 (0.6)	1.3 (0.7)
Pleasure									
Study 1	133	3.0 (0.1)	0.5* (0.1)	131	3.2 (0.1)	0.3 (0.1)	126	3.2 (0.1)	0.4 (0.1)
Study 2	129	3.2 (0.1)	0.5 (0.1)	130	3.3 (0.1)	0.2 (0.1)	125	3.3 (0.1)	0.3 (0.1)
Desire/frequency									
Study 1	132	6.9 (0.1)	0.4 (0.1)	131	7.2 (0.1)	0.1 (0.1)	126	7.2 (0.1)	0.2 (0.1)
Study 2	129	7.3 (0.1)	0.2‡ (0.1)	131	7.4 (0.1)	–0.3† (0.1)	125	7.2 (0.1)	0.1 (0.1)
Desire/interest									
Study 1	133	9.5 (0.2)	0.4 (0.2)	127	9.7 (0.2)	0.1 (0.2)	128	9.6 (0.2)	0.3 (0.2)
Study 2	129	10.4 (0.2)	0.4* (0.2)	131	9.8 (0.2)	–0.3 (0.2)	124	9.9 (0.2)	0.2 (0.2)
Arousal									
Study 1	133	10.8 (0.2)	0.6 (0.2)	129	11.4 (0.2)	0.1 (0.2)	127	11.2 (0.2)	0.5 (0.2)
Study 2	127	11.7 (0.2)	0.4* (0.2)	130	11.6 (0.2)	–0.1 (0.2)	124	11.4 (0.2)	0.2 (0.2)
Orgasm									
Study 1	133	11.5 (0.2)	0.5‡ (0.2)	130	11.7 (0.2)	–0.6§ (0.2)	127	11.7 (0.2)	0.6 (0.2)
Study 2	129	12.1 (0.2)	0.4‡ (0.2)	131	12.1 (0.2)	–0.8§ (0.2)	125	11.9 (0.2)	0.4 (0.2)

*p < .05 bupropion XL versus escitalopram.
†p < .05 escitalopram versus placebo.
‡p < .001 bupropion XL versus escitalopram.
§p < .001 escitalopram versus placebo.
Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, LOCF = last observation carried forward, XL = extended release.

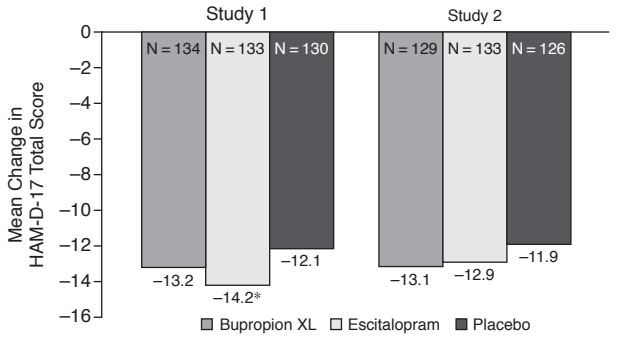
sexual functioning than bupropion XL with respect to mean changes in total score and the subscale scores for pleasure and orgasm in study 1; in the total score and the subscale scores for desire/frequency, desire/interest, arousal, and orgasm in study 2; and in the total score and the subscale scores for pleasure, desire/frequency, desire/interest, arousal, and orgasm in the pooled dataset (Table 3 and Figure 3). Bupropion XL did not differ from placebo with respect to mean change from randomization in the total score or subscale scores, but escitalopram was associated with significantly poorer sexual functioning than placebo with respect to mean change from randomization in the total score and the subscale score for orgasm in study 1; in the total score and the subscale scores for desire/frequency and orgasm in study 2; and in the total score and the subscale scores for desire/frequency, desire/interest, and orgasm in the pooled dataset at week 8 (Table 3 and Figure 3).

Figure 3. Mean Changes From Randomization to Treatment Week 8 in CSFQ Scores (pooled LOCF data)



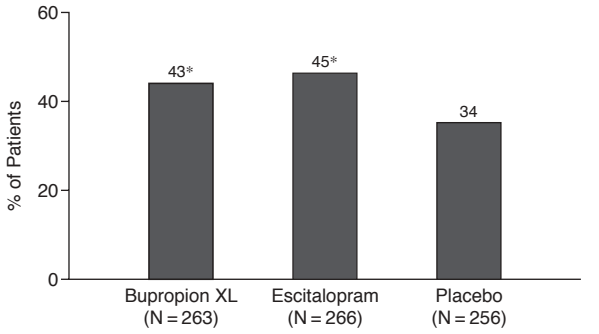
*p < .001 bupropion XL vs. escitalopram.
†p < .05 bupropion XL vs. escitalopram.
‡p < .001 escitalopram vs. placebo.
§p < .05 escitalopram vs. placebo.
Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, LOCF = last observation carried forward, XL = extended release.

Figure 4. Mean Change From Randomization to Treatment Week 8 in HAM-D-17 Total Score in Studies 1 and 2 (LOCF data)



*p < .05 vs. placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, XL = extended release.

Figure 5. Percentage of Patients Who Met the Criterion for Remission (HAM-D-17 total score ≤ 7) at Treatment Week 8 (pooled LOCF data)



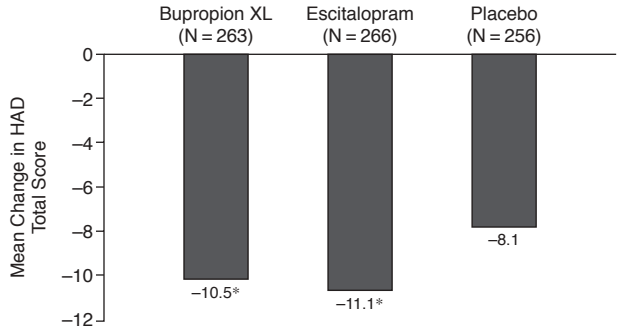
*p < .05 vs. placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, XL = extended release.

Efficacy

HAM-D-17 total scores (mean ± SE) at randomization were similar among treatment groups (23.9 ± 0.3 for bupropion XL, 23.3 ± 0.3 for escitalopram, 23.3 ± 0.2 for placebo in study 1 and 23.2 ± 0.3 for bupropion XL, 23.3 ± 0.3 for escitalopram, 23.3 ± 0.3 for placebo in study 2). In both the individual studies and the pooled dataset, mean ± SE change from randomization to treatment week 8 in HAM-D-17 total scores reflected improvement compared with randomization in all treatment groups and was not statistically different between bupropion XL and escitalopram (p = .260 study 1; p = .833 study 2; p = .533 pooled dataset) (Table 2). Bupropion XL did not differ statistically from placebo on HAM-D-17 in either trial. Escitalopram was statistically different from placebo on this measure in study 1, but not study 2 (Table 2 and Figure 4).

The percentages of patients meeting criteria for HAM-D-17 remission or response at the end of the treatment period did not differ statistically between the bupropion XL group and the escitalopram group in the individual studies or in the pooled dataset (Table 2 and Figure 5). Significantly more patients receiving bupropion XL or escitalopram compared with placebo met the criterion for HAM-D-17 remission in study 1 (bupropion XL 40%, escitalopram 49%, placebo 31%) and in the pooled dataset (bupropion XL 43%, escitalopram 45%, placebo 34%) (p < .05), but neither active treatment differed from placebo on this measure in study 2 (bupropion XL 46%, escitalopram 42%, placebo 38%; Table 2 and Figure 5). Simi-

Figure 6. Mean Change From Randomization to Treatment Week 8 in the HAD Total Score (pooled LOCF data)



*p ≤ .001 vs. placebo.
Abbreviations: HAD = Hospital Anxiety and Depression, LOCF = last observation carried forward, XL = extended release.

Table 4. Number (percentage) of Patients With Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients in Any Group and Reported ≥ 1.5 Times More Frequently With Either Active Treatment Than Placebo or With One Active Treatment Than Another (pooled dataset)

Adverse Event	Bupropion XL (N = 276)	Escitalopram (N = 281)	Placebo (N = 273)
Dry mouth	62 (22)	37 (13)	30 (11)
Fatigue	12 (4)	39 (14)	16 (6)
Insomnia	39 (14)	28 (10)	21 (8)
Constipation	26 (9)	9 (3)	16 (6)
Somnolence	8 (3)	22 (8)	14 (5)
Decreased appetite	13 (5)	16 (6)	10 (4)
Nasopharyngitis	14 (5)	14 (5)	8 (3)
Irritability	14 (5)	3 (1)	10 (4)
Yawning	2 (< 1)	15 (5)	3 (1)

Abbreviation: XL = extended release.

larly, a greater percentage of patients from the active treatment groups compared with the placebo group met the criterion for being HAM-D-17 responders in the pooled dataset, although in the individual studies the differences between active treatment and placebo were statistically significant only for escitalopram in study 1 (p = .007; Table 2).

Mean ± SE HAD total scores were similar among groups at randomization (25.4 ± 0.5 for bupropion XL, 23.9 ± 0.5 for escitalopram, 24.4 ± 0.5 for placebo in study 1; 23.8 ± 0.6 for bupropion XL, 24.8 ± 0.5 for escitalopram, 24.7 ± 0.5 for placebo in study 2). No statistically significant differences between the bupropion XL group and the escitalopram group were observed for mean change from randomization to the end of the treatment period in HAD total scores in the individual studies or the pooled dataset (Table 2 and Figure 6). Both bupropion XL and escitalopram were more effective than placebo with respect to mean change from randomization in HAD total score at week 8 in the individual studies (study 1: bupropion XL p = .015 and escitalopram p = .003; study 2: bupropion XL p = .026 and escitalopram p = .002) and in the pooled dataset (Table 2).

No statistically significant differences between the bupropion XL group and the escitalopram group were observed for the percentage of patients with CGI-I response (defined as having a score of much improved or very much improved) or mean change from randomization to treatment week 8 in CGI-S scores in either study or in the pooled dataset (Table 2). Bupropion XL statistically differed from placebo on both of these measures in study 2 and the pooled dataset, but not in study 1. Escitalopram statistically differed from placebo on both of these measures in the pooled dataset only.

Tolerability

Adverse events reported in ≥ 5% of patients in any treatment group and reported ≥ 1.5 times more frequently in an active treatment than in the placebo group or in one active treatment group than another are listed in Table 4 for the pooled dataset. Adverse events meeting these criteria for bupropion XL versus placebo were dry mouth, insomnia, constipation, and nasopharyngitis. Adverse events meeting these criteria for escitalopram versus placebo were fatigue, somnolence, decreased appetite, nasopharyngitis, and yawning.

Among patients receiving bupropion XL, there were no reports of adverse events of suicide, suicidal ideation, self-harm, or intentional self-injury in study 1 or study 2. Among patients receiving escitalopram, suicidal ideation was reported in 3 patients in study 1. Among patients receiving placebo, suicidal ideation was reported in 1 patient in study 1, and self-mutilation and intentional self-injury were each reported in 1 patient (different patients) in study 2.

The incidence of premature withdrawal because of adverse events was similar among groups (6% bupropion XL, 4% escitalopram, 5% placebo in the pooled dataset). In study 1, the only single adverse events leading to the premature withdrawal of more than 1 patient were rash (2 patients on bupropion XL), vomiting (1 escitalopram, 1 placebo), and suicidal ideation (1 escitalopram, 1 placebo). In study 2, the only single adverse events leading to the premature withdrawal of more than 1 patient were insomnia (2 bupropion XL, 1 placebo), sedation (2 escitalopram), and urticaria (1 bupropion XL, 1 placebo).

One death occurred during the studies. A patient being treated with placebo in study 1 died of sudden cardiac death. The medical examiner determined that the manner was natural and attributed the death to preexisting disease.

DISCUSSION

Antidepressant-associated sexual dysfunction can impact multiple aspects of patients' lives.[1–3] The results

of the 2 identically designed, double-blind, placebo-controlled studies reported here show that bupropion XL had a sexual tolerability profile similar to that of placebo and that escitalopram-treated patients reported significantly worse sexual functioning across several measures during an 8-week course of therapy. In the pooled dataset, the incidence of orgasm dysfunction measured by the investigator's structured interview at the end of the treatment period was 2 times higher with escitalopram (30%) than with bupropion XL (15%). Escitalopram was also associated with significantly worse sexual functioning than bupropion XL with respect to the incidence of patient-reported worsened sexual functioning at the end of the treatment period and the CSFQ total score and subscale scores. Overall, at study endpoint, there were no significant differences in sexual functioning between bupropion XL and placebo, results suggesting that sexual dysfunction is not a side effect of bupropion XL. Results were consistent between studies and across multiple investigator- and patient-rated outcome measures.

This research corroborates previous data showing that the SSRIs are frequently associated with orgasm dysfunction as well as impairment of other aspects of the sexual response cycle.[5] This effect appears to be related to inhibition of orgasm by stimulation of serotonin-2 (5-HT_2) receptors.[22] It may also be related to reduced vasocongestion secondary to inhibition of nitric oxide synthase,[23] and effects on genital sensation by SSRIs. Approximately 1 in 3 patients treated with escitalopram in these studies developed orgasm dysfunction while on therapy. Possibly because of the use of direct questioning to assess sexual functioning, the incidence of orgasm dysfunction in this study is higher than the incidence of sexual side effects reported as adverse events in clinical studies of escitalopram. In placebo-controlled trials, the incidence of spontaneously reported ejaculation disorder was 9% among 225 escitalopram-treated males compared with 0% among 188 placebo-treated males.[13] The current studies add to a substantial body of evidence showing that antidepressants acting on the serotonin system have significantly greater negative effects on sexual functioning than antidepressants that do not inhibit serotonin reuptake.

Diminished libido can be a symptom of depression or a side effect of antidepressant therapy. In these studies, patients could be enrolled if they experienced diminished libido as a depressive symptom. This symptom might be expected to resolve as the depression improved with treatment. Such an outcome was seen with bupropion XL. However, despite comparable therapeutic response rates between the 2 active treatment groups, diminished libido was present in patients treated with escitalopram at significantly higher rates than with either bupropion XL or placebo after 8 weeks of treatment. These data suggest that low libido is an escitalopram-related adverse side effect possibly secondary to actions of serotonergic medications to reduce testosterone levels[24] and to diminish dopamine[25] and norepinephrine[26] neurotransmission.

Sexual dysfunction with SSRIs is particularly evident in effects on orgasm function as this complaint is not commonly associated with the depression itself. All patients were free of orgasm disorder at study entry. However, escitalopram-treated patients experienced significant orgasm dysfunction as early as the end of the first week on treatment with the medication. Escitalopram-associated orgasm dysfunction persisted throughout the study and occurred at a significantly higher incidence than with bupropion XL or placebo. Orgasmic delay or failure in escitalopram-treated patients at week 8 was present at nearly twice the rate seen with bupropion XL. This result is consistent with the change-from-baseline score of the orgasm subscale of the CSFQ, which reflected comparable orgasmic function between bupropion XL and placebo and worsened orgasmic function with escitalopram. The cutoff score for the CSFQ orgasm subscale is ≤ 13 for men and ≤ 11 for women. A clinically significant change (or difference between groups) for each item is usually 0.5. Overall, for the orgasm subscale, a difference of 1.0 to 1.5 is clinically meaningful. Using the CSFQ, the difference between bupropion and escitalopram at endpoint is 1.1. Additional analysis of the CSFQ data reflects a very similar outcome to the investigator interview, with over one third of the escitalopram-treated subjects experiencing clinically significant orgasm dysfunction (by definition clinically significant) at the end of treatment versus 13% of those receiving placebo or bupropion (no statistical or clinical difference).

The lower incidence of orgasm dysfunction in clinical trials with escitalopram (9% ejaculation disorder in males by spontaneous report) compared with the current studies (30% with orgasm disorder in the pooled dataset) likely arises from the well-documented failure of patients' spontaneous reports for assessing the presence of sexual dysfunction in clinical trials.[27] Patients may be reluctant to discuss their sexual functioning with clinicians, and direct questioning is more apt to elicit reports of sexual dysfunction than reliance on open-ended questions about tolerability or spontaneous reporting. Additionally, many patients may not recognize that sexual dysfunction may be a side effect of treatment and may instead misattribute it to other factors. General tolerability questions are less likely than explicit questions about sexuality to elicit reports of sexual dysfunction and can result in significant underestimation of the incidence of sexual dysfunction, observations that have been confirmed in research in patients with depression.[27,28] For example, in a study assessing sexual dysfunction both with spontaneous reports and with a questionnaire in patients with major depression treated with SSRIs, only 14% (28 of 200) of patients spontaneously reported sexual dysfunction compared with 58% (200 of 344) of those who were specifically asked about

sexual functioning.[29] These data highlight the need for the clinician prescribing antidepressant therapy to query patients about sexual functioning and potential adverse effects of antidepressant treatment.

While bupropion XL had a better sexual tolerability profile than escitalopram in the current studies, both active treatments were better than placebo at improving depressive symptoms as reflected in the incidence of remission (i.e., HAM-D-17 score ≤ 7) and in change in HAD total scores. Bupropion XL did not differ statistically from escitalopram on mean change in HAM-D-17 total scores, HAM-D-17 response rate, HAM-D-17 remission rate, or mean change in the total HAD score in either study. In addition, bupropion XL did not differ from escitalopram with respect to percentage of patients with CGI-I response or mean change in CGI-S score. Although bupropion XL did not differ from escitalopram in efficacy, separation from placebo could not be established at a statistical .05 level for bupropion XL on the HAM-D-17. Separation from placebo was established for escitalopram on the HAM-D-17 total score in one study and in the pooled data. Antidepressant efficacy versus placebo has previously been established for both active treatments in studies designed with a primary objective of demonstrating efficacy.

Study limitations include the failure to show consistent efficacy of active treatment groups versus placebo across all psychiatric scales, including the failure of bupropion XL to separate from placebo on the primary efficacy endpoint in both studies and escitalopram in one study even though both active treatments are approved antidepressants. In this study as in others, a large placebo response may have decreased the ability to differentiate the active treatment groups from the placebo group on some measures.[29,30] A nonvalidated instrument was used as the primary outcome measure to assess treatment-emergent sexual dysfunction; however, the results from the validated secondary endpoint, the CSFQ, supported the findings of the primary outcome measure. These findings are not generalizable to patients with preexisting sexual dysfunction.

In conclusion, the prospectively assessed sexual tolerability profile of bupropion XL in these randomized, double-blind studies was significantly better than that of escitalopram and not statistically different from that of placebo. While bupropion XL had a better sexual tolerability profile than did escitalopram, similar HAM-D-17 remission rates and HAD total scores were reported in the bupropion XL and escitalopram groups. These studies demonstrate that bupropion XL has advantages over escitalopram in preserving sexual functioning in patients receiving treatment for MDD.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), sertraline (Zoloft), venlafaxine (Effexor), zaleplon (Sonata), zolpidem (Ambien).

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