Duloxetine in the Treatment of Major Depressive Disorder: Comparisons of Safety and Efficacy in U.S. Hispanic and Majority Caucasian Patients

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Objective: To evaluate new pharmacotherapies for the treatment of major depressive disorder (MDD) in Hispanic Americans, the largest ethnic minority group in the United States.

Method: Efficacy and safety data were pooled from 7 double-blind, placebo-controlled clinical trials of duloxetine conducted from February 1999 through November 2002. English-speaking patients (aged ≥ 18 years) meeting DSM-IV criteria for MDD received duloxetine (40–120 mg/day; Hispanic, N = 58; Caucasian, N = 748) or placebo (Hispanic, N = 62; Caucasian, N = 594) for up to 9 weeks. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score, HAM-D-17 subscales, the Clinical Global Impressions-Severity of Illness scale, the Patient Global Impression of Improvement scale, and the Visual Analog Scales for pain. Safety was assessed using discontinuation rates, treatment-emergent adverse events, vital signs, and laboratory analyses. Three sets of data were analyzed using different pooling strategies, including exploratory analyses with 470 subjects (Hispanic, N = 51; Caucasian, N = 419) receiving the recommended dose of 60 mg.

Results: No evidence for a differential effect of duloxetine in Hispanic and Caucasian patients was found in efficacy outcomes. Discontinuation rates due to adverse events among duloxetine-treated patients were 14.0% for Hispanics and 17.0% for Caucasians, compared with 3.2% and 5.7%, respectively, for placebo-treated patients (p = .671). The type of adverse events and their individual rate of occurrence did not differ significantly between Hispanic and Caucasian patients. Mean changes from baseline for pulse, blood pressure, weight, and laboratory analytes were small and showed no significant differences between Hispanic and Caucasian patients.

Conclusion: In this analysis of pooled data, no evidence for a differential effect of duloxetine in Hispanic and majority Caucasian patients was found in efficacy or safety outcomes.

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Hispanic Americans are the largest and one of the fastest growing ethnic minority groups in the United States. According to census data for the year 2002, 37.4 million U.S. residents listed their ethnicity as Hispanic.[1] Two thirds are of Mexican descent.[1] By 2050, the number of Hispanic Americans is projected to increase to 97 million, or nearly one fourth of the U.S. population.

A number of epidemiologic studies have compared the rates of psychiatric disorders in Hispanic and non-Hispanic adults (in the following brief review of epidemiology and pharmacotherapy, we have attempted to retain the ethnic descriptions used by the original investigators). Data from the Epidemiologic Catchment Area Study indicate that the lifetime prevalence of major depressive disorder (MDD) in Hispanic Americans is similar to that in white Americans,[2] whereas the National Comorbidity Survey found a higher 12-month, but not lifetime, prevalence of affective disorders among English-speaking Hispanics when compared with non-Hispanic whites.[3]

Further investigations revealed other factors influencing the rate of psychiatric disorders among Hispanics, most notably the effect of nativity and acculturation.

Thus, although the rate of MDD among U.S.-born Mexican Americans tends to be similar to or lower than that of non-Hispanic whites, U.S.-born Mexican Americans have a significantly higher prevalence of major depression than immigrant (Mexican-born) Mexican Americans.[4–6] Markers of higher acculturation among immigrants, such as younger age of arrival in the United States, longer time spent in the country, and greater English fluency, are associated with higher rates of psychiatric disorder, including major depression.[7–10] Prevalence rates may also be affected by language of interview in partially or fully bilingual individuals, through variation in interviewer-assessed severity of psychopathology.[11] However, it is unclear whether use of the nondominant language results in higher or lower perceived rates of pathology.[11–12]

In contrast to our growing knowledge regarding the epidemiology of major depression in U.S. Hispanics, relatively little is known about the use and effectiveness of antidepressant therapy in this population. Previous research suggests that an area in which Hispanic Americans differ from non-Hispanics is in rates of antidepressant treatment. Although some studies indicate that Hispanics and non-Hispanic whites are equally likely to receive antidepressant medication from primary care providers,[13,14] other studies reveal that primary care physicians, as well as psychiatrists, are less likely to detect depression or to provide antidepressant treatment for depression in Hispanics when compared with Caucasians.[15–19] Taken as a whole, the weight of evidence indicates ethnic-specific undertreatment of depression in Hispanics in primary care and specialty mental health settings.

Recent research on ethnic differences in depression treatment has also focused on potential differences in antidepressant pharmacokinetics and pharmacodynamics.[20,21] Results obtained from clinical trials featuring largely majority Caucasian patient cohorts are generally assumed to be applicable to Hispanic patients. However, Hispanics have been reported to differ from non-Hispanic patients with respect to optimal antidepressant dosages,[22] degree of placebo response,[23,24] and sensitivity to side effects.[22,23] In an open-label study of nefazodone in Hispanic outpatients, 42% of the sample dropped out of treatment before the study endpoint, although the primary reasons were family or work difficulties or loss to follow-up, and only 14% discontinued due to adverse events.[25] Given the extremely limited database currently available, additional studies of antidepressant medications in Hispanic patients are required to further elucidate the nature and magnitude of any differences in psychopharmacologic response across ethnic groups.

The antidepressant duloxetine is a potent reuptake inhibitor of both serotonin (5-HT) and norepinephrine (NE). The efficacy of duloxetine in the treatment of MDD has been established in randomized, double-blind, placebo-controlled studies of up to 9 weeks' duration.[26] In an analysis of data from a 52-week, open-label study,[27] the efficacy and safety profiles of duloxetine (80–120 mg/day) in Hispanic patients residing in Mexico were found to be similar to those observed in Hispanics living outside Mexico and to non-Hispanic patients, but the lack of a placebo arm in that study hampered its ability to compare effect sizes or rates of placebo response across groups. To address those limitations, the present study utilizes pooled data from 7 double-blind, placebo-controlled trials of duloxetine (40–120 mg/day) to compare the efficacy and safety in U.S. Hispanic patients with that observed in Caucasian patients. Given the general lack of published data in this area and our desire to fully utilize the available dataset and test the robustness of our results across analytic approaches, 3 different pooling strategies were employed in the analyses of efficacy: (1) data from all 7 studies; (2) data from the 4 positive studies; and (3) data from the 2 studies utilizing the target therapeutic duloxetine dose recommended in some countries.

METHOD

Study Design

All 7 studies included in these analyses were randomized, multicenter, double-blind, placebo- or active comparator–controlled (or both) clinical trials conducted from February 1999 through November 2002. These studies represented all available data from U.S.-based, placebo-controlled clinical trials of duloxetine in patients with MDD. (Data from 2 additional placebo-controlled studies carried out in Eastern Europe were not included because no Hispanic patients were enrolled.) Key design elements of all the studies were similar, as pooling of data from these trials was anticipated during study design. All studies incorporated double-blind, variable-duration placebo lead-in periods to blind patients and investigators to the start of active therapy. All studies were of similar duration (7–9 weeks). Each study included initial weekly assessments followed by biweekly assessments. Study protocols were reviewed and approved by the ethical review board at each participating center, in accordance with the principles of the Declaration of Helsinki, and all patients signed informed consent documents prior to the administration of any study procedures or study drug. Safety and efficacy results from studies 1,[28] 4,[29] 5,[30] 6,[31] and 7[32] have been published previously, and summaries of results from studies 2[33] and 3[34] are available online.

Patients

Patients were 18 years of age or older, met criteria for MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[35] and had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[36] total score ≥ 15 and a Clinical

Global Impressions-Severity of Illness (CGI-S)[37] score ≥ 4 at the screening and randomization study visits. In study 7, patients were also required to have a Brief Pain Inventory (BPI) average pain score ≥ 2 at the second study visit. Patients had to be sufficiently fluent in English to be able to understand and communicate intelligibly with the investigator and study coordinator. Patients were excluded for the following reasons: a current and primary Axis I disorder other than MDD; an Axis II disorder that could interfere with protocol compliance; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy; serious medical illness; a serious risk of suicide; a history of substance abuse or dependence within the last year; or a positive urine drug screen.

Concomitant medications with primarily central nervous system activity were not permitted, with the exception of episodic use of chloral hydrate or zolpidem for insomnia. Chronic use of prescription analgesic medications was not allowed; episodic use was permitted at the discretion of the physician in charge of the study. Use of antihypertensive medications was not permitted unless the patient had been receiving a stable dose for at least 3 months prior to study entry.

Patients were assigned to majority Caucasian and Hispanic groups based on their responses to a question on the Clinical Report Form (CRF) that addressed ethnic origin. Patients within the Hispanic group declared their ethnic origin as being consistent with the following description: Hispanic (Mexican-American, Mexican, Central and South American). Other choices of ethnic origin on the CRF were Caucasian (European, Mediterranean, Middle Eastern), African descent, East/Southeast Asian, Western Asian, and Other (mixed-racial parentage, American Indian, Eskimo). Data on Hispanic subgroup origin, nativity, socioeconomic status, level of acculturation, and degree of fluency in Spanish and English were not obtained.

Data-Pooling Strategies

Safety analyses included data from Hispanic and Caucasian patients in all 7 studies—placebo: Hispanic (N = 62), Caucasian (N = 594); duloxetine (40–120 mg/day): Hispanic (N = 58), Caucasian (N = 748). Efficacy analyses were performed on 3 sets of data, obtained using the following pooling strategies:

1. Data from all 7 studies (hereafter referred to as "all studies")—placebo: Hispanic (N = 62), Caucasian (N = 594); duloxetine (40–120 mg/day): Hispanic (N = 58), Caucasian (N = 748);
2. Data from the 4 studies that demonstrated a significant advantage for duloxetine over placebo on the primary efficacy measure (1, 4, 5, and 6, "positive studies")—placebo: Hispanic (N = 39), Caucasian (N = 343); duloxetine (40–120 mg/day): Hispanic (N = 40), Caucasian (N = 418);
3. Data from the 2 MDD studies in which patients received the target duloxetine dose of 60 mg once daily (q.d.) recommended in some countries (5 and 6, "focus studies")—placebo: Hispanic (N = 31), Caucasian (N = 212); duloxetine (60 mg q.d.): Hispanic (N = 20), Caucasian (N = 207).

Analysis of data from all studies provided an assessment of comparative efficacy in Hispanic and Caucasian patients across the largest possible dataset. The analysis of data from the 4 positive studies allowed differential efficacy to be studied without the potential confounding influence of nonpositive data. Analyses of data from the 2 focus studies are of particular clinical relevance since they examine treatment effects in Hispanic and Caucasian patients receiving the recommended therapeutic duloxetine dose. Furthermore, these 2 studies were identical in design, and thus pooling these studies fostered useful assessments of the time course in responses. Because the 60 mg, once-daily dose is the most widely utilized dose in clinical practice, results from these 2 studies are presented in greater detail than those obtained from pooling strategies (1) and (2), which cover a dose range of 40 to 120 mg/day. However, because of the small sample size of Hispanics in the focus studies, these analyses should be considered exploratory.

Efficacy Measures

Efficacy was assessed using the HAM-D-17 total score, the CGI-S scale, the Patient Global Impression of Improvement (PGI-I) scale,[37] Visual Analog Scales (VAS)[38] for pain, and the Quality of Life Depression Scale (QLDS).[39]

Some researchers have suggested that the Hamilton Rating Scale for Depression (HAM-D) is an imperfect measure of depression severity due to its multidimensional nature,[40] and efforts have been made to construct unidimensional subscales of the HAM-D.[41] In the current study, the following HAM-D-17 subscales were utilized as secondary efficacy measures: anxiety (items 10, 11, 12, 13, 15, and 17),[42] core factor (items 1, 2, 3, 7, and 8), Maier (items 1, 2, 7, 8, 9, and 10),[43] retardation (items 1, 7, 8, and 14),[42] and sleep (items 4, 5, and 6).[42] The core and Maier subscales focus on core emotional symptoms of depression, including depressed mood, feelings of guilt, psychomotor retardation, anxiety, and loss of interest in work and activities.

Criteria for identifying responders and remitters were prospectively defined in the study protocols: patients were defined as responders if they had a decrease from baseline of at least 50% on the HAM-D-17 total score at endpoint; patients were defined as remitters if they had a HAM-D-17 total score ≤ 7 at endpoint.

Table 1. Patient Baseline Demographics and Psychiatric History (all studies)

Characteristic	Caucasian (N = 1342)	Hispanic (N = 120)	p Value
Gender, female, N (%)	863 (64.3)	92 (76.7)	.007
Age, y			
Mean (SD)	42.3 (13.1)	36.3 (11.7)	< .001
Range	18–82	18–75	
Weight, mean (SD), kg	83.4 (21.2)	78.3 (20.4)	.020
HAM-D-17 total score, mean (SD)	21.1 (4.1)	22.3 (3.7)	.004
CGI-S score, mean (SD)	4.30 (0.55)	4.39 (0.61)	.180
VAS overall pain score, mean (SD)	31.2 (25.1)	32.7 (24.9)	.493
Age at onset, mean (SD), y	29.7 (14.5)	27.3 (12.3)	.335
Previous episode of MDD, N (%)	856 (63.8)	77 (64.2)	.453
Duration of current episode, mean (median), wk	83.1 (32)	59.6 (24)	.543
Duration of last episode, mean (median), wk	60.9 (24.5)	49.6 (27)	.823
Number of previous episodes, mean (median)	7.7 (3)	6.2 (3)	.804
Time between episodes, mean (median), wk	120.4 (40)	127.9 (52)	.450
Atypical features, N (%)	49 (3.7)	5 (4.2)	.805
Melancholic features, N (%)	776 (57.8)	79 (65.8)	.259

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, VAS = Visual Analog Scales.

Safety Measures

Safety was evaluated on the basis of discontinuation rates, treatment-emergent adverse events, vital signs, electrocardiograms, and laboratory analyses.

Vital signs (supine and standing blood pressure and pulse) were recorded at each visit. Treatment-emergent elevated blood pressure was defined as either of the following's occurring during the treatment phase: supine systolic blood pressure ≥ 140 mm Hg and an increase from baseline ≥ 10 mm Hg or supine diastolic blood pressure ≥ 90 mm Hg and an increase from baseline ≥ 10 mm Hg.

Sustained hypertension was defined as meeting the preceding hypertensive criteria at 3 consecutive visits.

Statistical Analyses

All patients who received at least 1 dose of study medication were included in the analyses of safety and efficacy. Mean changes from baseline to last observation in laboratory analytes and vital signs were assessed using an analysis of variance (ANOVA) with models that included treatment, ethnicity (Caucasian or Hispanic), investigative site, and the treatment-by-ethnicity interaction as independent variables. The treatment-by-ethnicity interaction was the main basis upon which differential treatment effects between Caucasians and Hispanics were assessed. Within-ethnic-group contrasts between duloxetine and placebo were used to assess the clinical relevance of treatment effects. The rates of discontinuations due to adverse events, treatment-emergent adverse events, and treatment-emergent abnormal values in laboratory analytes and vital signs (categorical changes) were assessed in a similar manner, with the Breslow-Day test as the primary basis for detecting differential treatment effects between ethnic groups and with the Fisher exact test used to test within-ethnic-group differences between duloxetine and placebo.

Efficacy variables were also compared using the mean change to last observation carried forward analysis (LOCF) as previously described. The time course of mean changes and categorical changes (estimated probabilities) was assessed using a likelihood-based, mixed-effects model repeated-measures approach (MMRM). The general rationale and merits for this analytic approach have been discussed in detail elsewhere.[44,45] In the present analyses, the MMRM approach was used for analyses of the focus data only because the assessment schedules were identical for these studies, and thus they were the best data source for assessing the time course of changes. For the positive studies and for all studies, the assessment schedules were not identical, and the MMRM approach would have to have been modified in order to account for the differing assessment schedules. Focus studies were also analyzed via LOCF in order to be consistent with the other data pools. In other settings, analyses similar to MMRM have been referred to as random regression or hierarchical models.[46] The mean change analyses included treatment, visit, investigative site, baseline value, ethnicity, and the 2- and 3-way interactions between treatment, visits, and ethnicity. The percentages of responders and remitters at last observation were also tabulated.

With 114 Hispanic patients in the all-study cohort providing postbaseline data on efficacy outcomes, the difference between duloxetine and placebo would have to equal an effect size of 0.53 in order for this study to have 80% power to detect a difference between duloxetine and placebo in Hispanic patients. Given that the effect size seen in all patients is approximately 0.35, this study was probably underpowered to detect difference within the Hispanic cohort. In addition, although precise power calculations for treatment-by-subgroup interactions are problematic to implement, power for these assessments of differential efficacy were lower than the power in either individual cohort because the variability within and between each cohort contributes to the overall variability.[47]

RESULTS

Patient Characteristics

Baseline patient demographics are summarized in Table 1. The Hispanic group contained a significantly larger proportion of female patients when compared with the majority Caucasian group (p = .007). Hispanic patients were significantly younger (p < .001) and had

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Table 2. Summary of Efficacy Measures

Measure	Mean Change (SD) Duloxetine	Mean Change (SD) Placebo	p Value[b]	Effect Size	p Value[c]
HAM-D-17 total score[a]					
All studies					
Caucasian (N = 1300)	–7.72 (7.07)	–5.99 (7.44)	< .001	0.24	.785
Hispanic (N = 114)	–8.67 (9.06)	–7.53 (7.31)	.107	0.14	
Positive studies					
Caucasian (N = 737)	–8.04 (7.04)	–5.58 (7.19)	< .001	0.35	.402
Hispanic (N = 73)	–10.62 (9.09)	–6.36 (6.93)	.154	0.53	
Focus studies					
Caucasian (N = 407)	–8.75 (6.71)	–6.31 (7.58)	< .001	0.34	.084
Hispanic (N = 47)	–12.58 (8.45)	–5.89 (7.08)	.008	0.86	
CGI-S					
All studies					
Caucasian (N = 1301)	–1.31 (1.24)	–1.03 (1.25)	< .001	0.22	.876
Hispanic (N = 115)	–1.45 (1.44)	–1.24 (1.19)	.249	0.16	
Positive studies					
Caucasian (N = 738)	–1.31 (1.23)	–0.96 (1.23)	< .001	0.28	.685
Hispanic (N = 74)	–1.68 (1.49)	–1.11 (1.14)	.418	0.43	
Focus studies					
Caucasian (N = 408)	–1.42 (1.19)	–1.04 (1.27)	.001	0.31	.323
Hispanic (N = 47)	–1.95 (1.39)	–1.04 (1.04)	.062	0.75	
PGI-I					
All studies	Mean (SD)				
Caucasian (N = 1301)	2.77 (1.30)	3.15 (1.29)	< .001	0.29	.918
Hispanic (N = 114)	2.75 (1.36)	3.10 (1.41)	.041	0.25	
Positive studies					
Caucasian (N = 738)	2.79 (1.32)	3.29 (1.33)	< .001	0.38	.685
Hispanic (N = 73)	2.70 (1.41)	3.31 (1.51)	.158	0.42	
Focus studies					
Caucasian (N = 408)	2.81 (1.28)	3.29 (1.33)	< .001	0.37	.109
Hispanic (N = 47)	2.37 (1.16)	3.46 (1.50)	.010	0.82	

[a]Results are from the last observation carried forward.
[b]p Value for duloxetine vs. placebo.
[c]p Value for treatment-by-ethnicity interaction.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, PGI-I = Patient Global Impression of Improvement scale.

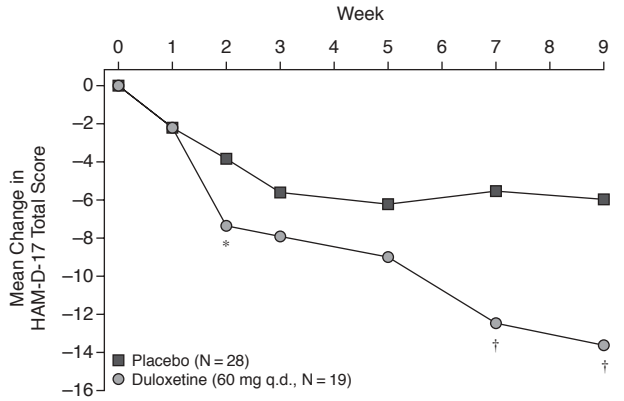
significantly lower mean body weight (p = .020) when compared with Caucasian patients. Hispanic patients had a significantly higher mean baseline HAM-D-17 total score when compared with Caucasians (22.3 vs. 21.1, respectively; p = .004). Hispanic and Caucasian patients exhibited no significant differences in any aspect of psychiatric history (Table 1).

Efficacy: All Studies

Analyses of efficacy data from all 7 studies are presented in Table 2. Advantages for duloxetine over placebo in HAM-D-17, CGI-S, and PGI-I measures were highly significant (p < .001) among majority Caucasian patients. In Hispanic patients, mean PGI-I score showed a significant advantage for duloxetine over placebo (p = .041). Effect sizes for these treatment outcomes ranged from 0.22 to 0.29 in Caucasian patients and from 0.14 to 0.25 in Hispanics. Treatment-by-ethnicity interactions were not statistically significant (all p > .75), indicating that the magnitude of duloxetine's treatment effects did not differ significantly between Hispanic and Caucasian patients. Although there were significant baseline differences in demographics between Caucasians and Hispanics, results were not substantially influenced by these differences. For example, the treatment-by-ethnicity interaction for HAM-D-17 total score prior to adjusting for age and gender (p = .785) was similar to that after inclusion of age and gender as covariates (p = .858).

Baseline-to-endpoint improvements in VAS overall pain severity were observed in duloxetine-treated Hispanic and Caucasian patients, with duloxetine's advantage over placebo achieving statistical significance in the Caucasian group (mean change –10.47 vs. –6.31 for duloxetine and placebo, respectively; p = .005). In the smaller group of Hispanic patients, the mean change for duloxetine was numerically greater than that for placebo, but the difference was not statistically significant (mean change –10.94 vs. –5.58 for duloxetine and placebo, respectively). Effect sizes were very similar in both ethnic groups (Hispanics 0.19, Caucasians 0.17). The treatment-by-ethnicity interaction was not statistically significant (p = .981), indicating that the magnitude of duloxetine's

Figure 1. Mean Change in HAM-D-17 Total Score for Hispanic Patients Receiving Duloxetine (60 mg q.d.) or Placebo



*p < .05 vs. placebo.
†p < .005 vs. placebo.

treatment effects did not differ significantly between Hispanic and Caucasian patients.

Efficacy: Positive Studies

Analyses of pooled efficacy data from the 4 positive studies yielded results similar to those from the pooling of all studies (Table 2). The disparity in sample sizes (Caucasian, N = 738; Hispanic, N = 74) resulted in Caucasian patients' demonstrating highly significant outcomes (p < .001), whereas duloxetine's advantage over placebo in Hispanic patients did not achieve significance. Effect sizes for change in HAM-D-17 total score, CGI-S score, and PGI-I score ranged from .42 to .53 in Hispanic patients and from .28 to .38 for Caucasians. Treatment-by-ethnicity interactions for these outcomes were not statistically significant (all p values > .40), indicating that the magnitude of duloxetine's treatment effects did not differ significantly in Hispanic and Caucasian patients.

Efficacy: Focus Studies

In the 2 studies in which patients received the recommended therapeutic duloxetine dose (60 mg q.d., studies 5 and 6), duloxetine-treated Hispanic patients demonstrated significantly greater improvement in mean HAM-D-17 total score compared with Hispanic patients receiving placebo (Table 2 LOCF analyses and Figure 1). Significant advantages for duloxetine over placebo were also observed in 4 of the 5 assessed HAM-D-17 subscales (core, Maier, retardation, and sleep; Table 3). On both clinician-rated (CGI-S) and patient-rated (PGI-I) assessments of global improvement, Hispanic patients receiving duloxetine demonstrated significantly greater reductions in mean score compared with placebo-treated Hispanic patients (Table 3) as analyzed using the repeated-measures method. Caucasian patients receiving duloxetine 60 mg q.d. in Studies 5 and 6 demonstrated significantly greater improvement in mean HAM-D-17 total score (p < .001), all 5 assessed HAM-D-17 subscales, and both CGI-S and PGI-I scales when compared with placebo-treated Caucasian patients (Tables 2 and 3). Effect sizes on the HAM-D-17 total score, CGI-S score, and PGI-I score ranged from .75 to .86 for Hispanic patients and from .31 to .37 for Caucasian patients. The treatment-by-ethnicity interaction approached significance for the HAM-D-17 total score, providing marginal evidence for a greater difference in Hispanic patients for this outcome.

Response rates (≥ 50% improvement in HAM-D-17 total score) among Hispanic patients in these 2 studies were 68% versus 32% for patients receiving duloxetine and placebo, respectively (p = .019), and remission rates were 42% versus 14% for duloxetine and placebo, respectively (p = .045). In the group of Caucasian patients, response rates were 47% versus 29% for duloxetine and placebo, respectively (p < .001), and remission rates were 30% versus 20% for duloxetine and placebo, respectively (p = .039).

In Caucasian patients, mean change in QLDS score in the duloxetine treatment group was significantly greater than that observed in the placebo group (p < .001, effect size = 0.32). In the smaller group of Hispanic patients, duloxetine's advantage over placebo did not reach statistical significance (effect size = 0.43).

In analyses focusing on the main effect of treatment for VAS pain measures, duloxetine-treated Caucasian patients demonstrated significantly greater improvement compared with placebo on 4 of the 6 assessed outcomes (overall pain, back pain, shoulder pain, time in pain while awake). In the Hispanic group, duloxetine produced numerically greater improvement than placebo on 3 outcomes (overall pain, headache, time in pain while awake). Although none of these advantages reached statistical significance, effect sizes for improvements in pain severity were larger among Hispanic patients compared with Caucasian patients on these 3 VAS outcomes.

Safety: Discontinuation Rates

In analyses of pooled data from all 7 studies, the rate of discontinuation for any reason among Hispanic patients (48% for duloxetine vs. 37% for placebo, p = .268) was similar to that observed in Caucasian patients (46% for duloxetine vs. 37% for placebo, p = .038). Discontinuation rates due to adverse events were significantly greater for duloxetine-treated patients compared with placebo in both Hispanic patients (duloxetine 14%, placebo 3.2%, p < .031) and Caucasian patients (duloxetine 17%, placebo 5.7%, p < .001). The effect of duloxetine did not differ significantly between Hispanic and Caucasian patients (p = .671). Other events leading to early study dis-

Table 3. Summary of Efficacy Measures (focus studies)[a]

	Caucasian			Hispanic		
Measure	Duloxetine (60 mg/d, N = 202)	Placebo (N = 205)	p Value	Duloxetine (60 mg/d, N = 19)	Placebo (N = 28)	p Value
HAM-D-17 subscale score change, mean (SE)						
Core	–5.06 (0.27)	–3.23 (0.26)	< .001	–6.49 (0.87)	–3.17 (0.68)	.003
Maier	–5.81 (0.31)	–3.83 (0.30)	< .001	–7.10 (1.00)	–3.98 (0.79)	.014
Anxiety	–2.78 (0.19)	–2.19 (0.19)	.024	–3.16 (0.61)	–2.06 (0.48)	.154
Retardation	–4.05 (0.22)	–2.67 (0.22)	< .001	–5.49 (0.73)	–2.57 (0.57)	.001
Sleep	–1.69 (0.14)	–1.26 (0.14)	.024	–2.21 (0.46)	–0.37 (0.36)	.001
CGI-S score change, mean (SE)	–1.73 (0.10)	–1.25 (0.09)	< .001	–2.29 (0.31)	–1.24 (0.24)	.008
PGI-I score, mean (SE)[b]	2.59 (0.10)	3.12 (0.10)	< .001	2.15 (0.32)	3.33 (0.25)	.003
QLDS score change, mean (SD)	–8.92 (8.94)	–6.08 (9.06)	< .001	–11.29 (11.23)	–6.43 (11.13)	.803

[a]Results are from the repeated measures analysis.
[b]Lower scores represent greater improvement.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, PGI-I = Patient Global Impression of Improvement scale, QLDS = Quality of Life Depression Scale.

continuation among duloxetine-treated patients included loss to follow-up (10.0% for Hispanic patients vs. 7.1% for Caucasian patients), personal conflict (10.0% for Hispanic patients vs. 10.0% for Caucasian patients), and protocol violation (6.9% for Hispanic patients vs. 5.6% for Caucasian patients). The only adverse event leading to discontinuation in more than 1 duloxetine-treated Hispanic patient was nausea (2/58; 3.4%). The rate of discontinuation due to nausea among Caucasian patients receiving duloxetine was 2.3% (17/748). Other adverse events leading to discontinuation in both treatment groups included sedation (Hispanic patients 1.7% vs. Caucasian patients 0.1%) and somnolence (Hispanic patients 1.7% vs. Caucasian patients 0.9%).

Safety: Adverse Events

Treatment-emergent adverse events reported by ≥ 8% of Hispanic patients (i.e., those events occurring in 5 or more patients) are summarized in Table 4. A comparison of the incidence of these events in Hispanic and Caucasian patients is also provided. The only event that occurred at a significantly different rate in Hispanic patients compared with Caucasian patients was insomnia, where the difference appeared to be driven by a substantially higher placebo response rate in Hispanic patients. In an extension of this analysis, the incidence of all treatment-emergent adverse events that occurred in ≥ 1 patient in each treatment group was compared. Out of a total of 111 comparisons, only 1—besides insomnia—reached statistical significance (menorrhagia—Hispanic: 0.0% for duloxetine vs. 3.8% for placebo; Caucasian: 0.6% for duloxetine vs. 0.0% for placebo; Breslow-Day p = .045).

Safety: Vital Signs and Body Weights

Mean changes in vital signs and body weight are presented in Table 5. In the cohort of Caucasian patients, mean changes within the duloxetine treatment group differed significantly from those of the placebo group, whereas no significant differences were observed in the substantially smaller group of Hispanic patients. None of the treatment-by-ethnicity interactions for mean changes in vital signs or body weight achieved statistical significance.

The rate of treatment-emergent, elevated vital signs at endpoint in Hispanic patients did not differ significantly between duloxetine and placebo treatment groups (high supine systolic BP: duloxetine 0.0% vs. placebo 2.5%, p = .471; high supine diastolic BP: duloxetine 4.3% vs. placebo 7.1%, p = .664; elevated pulse: duloxetine 0.0% vs. placebo 0.0%; weight gain: duloxetine 0.0% vs. placebo 0.0%). Furthermore, the rate of sustained hypertension did not differ significantly between duloxetine- and placebo-treated Hispanic patients (sustained systolic hypertension: duloxetine 0.0% vs. placebo 0.0%; sustained diastolic hypertension: duloxetine 2.1% vs. placebo 0.0%, p = 1.00; sustained systolic or diastolic hypertension: duloxetine 2.1% vs. placebo 0.0%, p = 1.00).

Among Hispanic patients, the incidence of abnormal increases or decreases in blood pressure, heart rate, and weight at any study visit did not differ significantly between duloxetine and placebo treatment groups. Furthermore, the incidence of abnormal increases or decreases in vital signs at any study visit did not differ significantly between Hispanic and Caucasian treatment groups.

Safety: Laboratory Analyses

Small but statistically significant mean changes from baseline to last observation were observed for some laboratory analytes in Hispanic patients. In a comparison of mean changes in laboratory analytes across Hispanic and Caucasian patient groups, the treatment-by-ethnicity interaction reached statistical significance for 1 analyte—gamma glutamyl transferase (mean change = –2.34 U/L

Table 4. Treatment-Emergent Adverse Events[a,b]

Event	Duloxetine[c] N (%)	Placebo[d] N (%)	p Value Fisher Exact	p Value Breslow-Day
Nausea				
Caucasian	203 (27.1)	53 (8.9)	< .001	.254
Hispanic	17 (29.3)	3 (4.8)	< .001	
Dry mouth				
Caucasian	146 (19.5)	45 (7.6)	< .001	.085
Hispanic	12 (20.7)	1 (1.6)	< .001	
Constipation				
Caucasian	89 (11.9)	28 (4.7)	< .001	.847
Hispanic	8 (13.8)	3 (4.8)	.117	
Diarrhea				
Caucasian	88 (11.8)	41 (6.9)	.003	.830
Hispanic	7 (12.1)	5 (8.1)	.550	
Dizziness				
Caucasian	86 (11.5)	29 (4.9)	< .001	.932
Hispanic	7 (12.1)	3 (4.8)	.195	
Headache				
Caucasian	141 (18.9)	100 (16.8)	.353	.386
Hispanic	7 (12.1)	10 (16.1)	.606	
Insomnia				
Caucasian	87 (11.6)	35 (5.9)	< .001	.014
Hispanic	5 (8.6)	10 (16.1)	.274	
Fatigue				
Caucasian	94 (12.6)	25 (4.2)	< .001	.615
Hispanic	5 (8.6)	1 (1.6)	.106	

[a]Events reported by ≥ 8% of Hispanic patients.
[b]Total patient population: Caucasian, N = 1342; Hispanic, N = 120.
[c]Duloxetine-treated population: Caucasian, N = 748; Hispanic, N = 58.
[d]Placebo-treated population: Caucasian, N = 594; Hispanic, N = 62.

Table 5. Mean Change in Vital Signs and Weight

Value	Mean Change (SD) Duloxetine	Mean Change (SD) Placebo	p Value Duloxetine vs. Placebo	p Value Treatment-by-Ethnicity Interaction
Supine systolic BP, (mm Hg)				
Caucasian (N = 1084)	1.6 (12.7)	–1.6 (11.8)	< .001	
Hispanic (N = 91)	–0.2 (13.7)	–0.8 (11.2)	.840	.879
Supine diastolic BP, (mm Hg)				
Caucasian (N = 1084)	1.5 (9.1)	0.1 (8.7)	.007	
Hispanic (N = 91)	2.8 (8.5)	1.7 (10.4)	.651	.278
Heart rate, (bpm)				
Caucasian (N = 1084)	1.8 (10.3)	–0.6 (9.1)	< .001	
Hispanic (N = 91)	1.0 (9.5)	1.1 (9.4)	.962	.514
Weight, (kg)				
Caucasian (N = 1083)	–0.7 (2.2)	0.3 (2.3)	< .001	
Hispanic (N = 91)	–0.3 (2.8)	–0.2 (1.6)	.821	.391

Abbreviation: BP = blood pressure.

for Caucasian patients vs. 2.67 U/L for Hispanic patients; interaction p value = .003).

The incidence of abnormal laboratory values at any study visit did not differ significantly between Hispanic and Caucasian treatment groups.

DISCUSSION

The current analysis describes efficacy and safety data from depressed Hispanic patients (N = 120) who participated in 7 clinical trials of duloxetine (40–120 mg/day) of up to 9 weeks' duration. Comparisons of treatment effects in these English-speaking Hispanic patients with those observed in majority Caucasian patients (N = 1342) did not identify clear between-group differences in either the efficacy or safety profile of duloxetine.

Effect sizes for drug-placebo differences were of similar magnitude in Hispanic and Caucasian patients for many of the comparisons conducted, although Hispanic patients tended to have somewhat larger drug and placebo responses when compared with Caucasian patients. Effect sizes increased more markedly in Hispanic than Cauca-

sian patients for the 3 efficacy measures (HAM-D-17 total score, CGI-S score, and PGI-I score) as the pooled sample was narrowed from all studies to positive studies and focus studies. However, the treatment-by-ethnicity interaction approached significance only for HAM-D-17 total score in the focus studies, which had the smallest Hispanic sample. This preliminary evidence that Hispanic patients may show a greater clinical response than Caucasian patients to 60 mg q.d. of duloxetine, the target therapeutic dose recommended in some countries, should be investigated in future studies with larger Hispanic samples.

The rate of discontinuation due to adverse events (14.0% vs. 17.0% for Hispanic and Caucasian patients, respectively) and the incidence and pattern of treatment-emergent adverse events were similar in Hispanic and Caucasian patient groups. Furthermore, treatment-by-ethnicity interactions for mean change in blood pressure, heart rate, and body weight were not statistically significant.

These findings are consistent with those of a previous study in which no differential treatment outcomes for Hispanic patients receiving long-term (52-week) duloxetine treatment were found compared with those of non-Hispanic patients.[27] Although the results suggest that data obtained from placebo-controlled trials of duloxetine within a general study population[26,28,30,31] may be equally applicable to English-speaking Hispanic patients, these results need to be interpreted with caution due to the limited sample size of Hispanic patients. Approximately 500 patients (250 per arm) would be required to yield 80% power to detect differences between duloxetine and placebo in Hispanic patients. This assumes that the true advantage of duloxetine over placebo in Hispanic patients is equivalent to an effect size of 0.25, which was in the midrange of the effect sizes seen for the various outcomes within both the Hispanic and Caucasian cohorts in the present study.

However, assessing the power of the present analyses to detect differential efficacy across ethnic groups (i.e., the power of the interaction tests) was more difficult. Previously published literature has been inconclusive regarding the existence and magnitude of antidepressant treatment differences between Hispanic and Caucasian patients. Therefore, no basis existed for a priori specification of a particular amount by which the magnitude of duloxetine's advantage over placebo differed in Caucasian versus Hispanic patients. Ascertaining power for detecting differential efficacy was further complicated by the fact that statistical theory for assessing treatment-by-stratum interactions is not well established.[47] Therefore, it is not possible to accurately ascertain power for detecting differential efficacy of duloxetine in Caucasian versus Hispanic patients, although it is likely that such power was low. Two main factors contribute to this assertion. First, the uncertainty in estimating differential efficacy includes the uncertainty in the estimate of the treatment effects within each stratum. Therefore, the uncertainty in the estimate of differential efficacy must be greater than that within either stratum. Second, it is likely that a drug is somewhat effective in all strata. Therefore, the difference in efficacy between strata is probably smaller than the advantage of drug over placebo within each individual stratum. Consequently, tests of differential efficacy typically have considerable variability, and the magnitude of the effect is small, leading to low power even in large databases such as the one employed in the present investigation.

Baseline demographic and psychiatric profiles were similar in both treatment groups. Although Hispanic patients had a significantly higher baseline HAM-D-17 total score when compared with Caucasian patients, the difference in mean HAM-D-17 scores amounted to approximately 1 point—the clinical relevance of which is questionable. Furthermore, baseline CGI-S scores did not differ significantly. Despite the fact that Hispanic patients were significantly (approximately 6 years) younger than Caucasian patients, the number of previous depressive episodes did not show a significant between-group difference.

Efficacy results from the 3 data-pooling strategies are consistent with those obtained from an earlier study in which effect-size calculations were utilized to establish 60 mg once-daily as the optimal duloxetine dose.[26] In both Hispanic and Caucasian patients, the magnitude of drug-placebo differences in endpoint HAM-D-17 total score, CGI-S score, and PGI-I score increased progressively from all studies (40–120 mg/day) to positive studies (40–120 mg/day) to focus studies (60 mg/day). This pattern was more marked for the Hispanic than for the Caucasian patients. For example, among Hispanic patients, the endpoint advantage of duloxetine over placebo in HAM-D-17 total score was 1.1 points across all studies, 4.3 points in the positive studies, and 6.7 points in the focus studies, whereas with Caucasian patients, the corresponding duloxetine-placebo differences were 1.7 points (all studies), 2.5 points (positive studies), and 2.4 points (focus studies). This study also highlights the utility of employing several data-analytic strategies and multiple efficacy measures to obtain a clearer and more robust overall picture of treatment outcomes.

Although there were no significant differences in efficacy outcomes between ethnic groups, this English-speaking Hispanic sample appeared to demonstrate somewhat larger responses to both drug and placebo when compared with the Caucasian sample. However, the magnitude of placebo responses did not differ significantly between Hispanic and Caucasian patients. There are only a few other published reports with which to compare this finding. In a study of depressed HIV-positive patients

receiving fluoxetine therapy, Wagner et al. documented a significantly higher placebo response in Latino patients compared with Caucasian or African American patients.[24] Furthermore, in a placebo-controlled study of imipramine, Escobar and Tuason reported that 50% of Colombian patients responded to placebo (≥ 50% reduction in HAM-D total score) compared with 11% of U.S.-resident (predominantly Caucasian) patients.[23] These studies were conducted in Latin America[23] or with patients whose acculturation level was unreported,[24] raising the possibility that placebo response may be affected by acculturation. We lack information on whether factors related to acculturation, such as language fluency, affected the assessment of depression severity in our Hispanic sample, resulting in a differential placebo response relative to Caucasian patients. Research with Hispanic subgroups at different language and acculturation levels is needed to confirm the generalizability of our efficacy results to all segments of the Hispanic population.

There is growing consensus that remission, rather than response, should be the primary goal of depression treatment.[48] Remission is indicative of a more complete resolution of the wide range of depressive symptoms than is response. In addition, patients with residual depressive symptoms[49] are more likely to experience relapse than patients achieving remission.[50] Within this study, the remission rate for Hispanic patients receiving a 60-mg, once-daily dose of duloxetine (42%) was comparable with rates observed in other placebo-controlled trials.[30,31]

In this study, we found no evidence of differential rates of discontinuation due to adverse events among Hispanic and Caucasian patients. This result may be compared with those obtained in previous studies of antidepressant therapy in Hispanic patients, in which higher discontinuation rates were observed among Hispanic, compared with non-Hispanic, patient groups.[22,24,51] To date, there are no head-to-head comparisons of different antidepressants, limiting what can be said about their relative tolerability in depressed Hispanic patients.

Treatment-emergent adverse events most frequently reported by Hispanic patients during this study were nausea, dry mouth, constipation, diarrhea, dizziness, and headache. This adverse-event profile was very similar to that reported by Caucasian patients, and only 1 significant difference in the incidence of adverse events was noted between the 2 ethnic groups, due to a higher rate of placebo-induced insomnia among Hispanic patients. Previous studies have reported overall rates of adverse events in Hispanic patients that were lower, higher, or equal to those in non-Hispanic patients, depending on the particular study.[25,52] A comparison of treatment-emergent adverse-event profiles for Hispanic and non-Hispanic patients participating in an open-label study of duloxetine revealed significant differences in the incidence of certain events.[27] However, it was unclear to what extent these differences were manifestations of pharmacologic differences between ethnic groups, as opposed to cultural and language differences.

Mean baseline-to-endpoint changes in blood pressure and heart rate in both Hispanic and Caucasian patients were small (≤ 3 mm Hg and ≤ 2 bpm, respectively) and not considered to be clinically relevant, given the low incidence of abnormal values. Treatment-by-ethnicity interactions were not statistically significant for any cardiovascular assessment (mean change or incidence of abnormal values). The small mean increase in heart rate may be associated with the pharmacologic mechanism of action of duloxetine, involving reuptake inhibition of both 5-HT and NE.

Mean baseline-to-endpoint changes in body weight for Hispanic and Caucasian patients reflected a small weight loss (approximately 0.5 kg) during the acute treatment period (8–9 weeks) and are consistent with observations from other acute-phase, placebo-controlled studies of duloxetine.[26,28–31] Data from a long-term, open-label study of duloxetine revealed a similar degree of weight loss in the first few weeks of duloxetine treatment, followed by a return to baseline weight and an eventual small weight gain (1.1 kg) after 52 weeks of therapy.[53]

A number of limitations should be considered when interpreting results from this study. First, although the comparison of ethnic subgroups was specified a priori in each study protocol, the specific pooling strategies and analyses conducted herein were not defined prior to the unblinding of the data. Therefore, the current findings should be viewed as the result of post hoc analyses. Second, the ratio of sample sizes in the Hispanic and Caucasian cohorts was approximately 1:10. This may have limited the power to detect significant ethnicity-by-treatment interactions. In addition, the sample size within the 2 focus studies was very small (< 20 duloxetine-treated Hispanic patients); as a result, these findings should be considered preliminary. Nonetheless, they are consistent with the results from the other 2 pooling strategies. Third, the studies were of 7 to 9 weeks' duration; additional studies will be required to extend the current results to longer term treatment of MDD. Finally, the term "Hispanic" is a somewhat general description of an ethnically diverse population. Although this was the term chosen by the patients as best describing their ethnicity within the options provided, it may not fully reflect the diversity of this broad patient population. The effect of nativity, language fluency, socioeconomic status, and level of acculturation were not examined in this dataset, which included only English-speaking subjects and may conceal clinical and other between-patient differences within the Hispanic group.

In conclusion, results from this analysis of pooled data suggest that the magnitude of symptom improvement in duloxetine-treated, English-speaking Hispanic patients

(assessed using HAM-D-17, CGI-S, and PGI-I scales) does not differ significantly from that observed in majority Caucasian patients. The overall safety and tolerability profile for duloxetine in Hispanic patients was very similar to that in a comparator group of Caucasian patients. Discontinuation rates and mean changes in vital signs, weight, and laboratory analytes showed few between-group differences. The incidence and pattern of treatment-emergent adverse events was similar in Hispanic and Caucasian patients. The results from these analyses provide supportive evidence for the efficacy and safety of duloxetine in the treatment of MDD in Hispanic patients. Future studies that examine the effect of nativity, acculturation, socioeconomic status, and language fluency on the efficacy and tolerability of duloxetine should be performed to extend these analyses to all segments of the Hispanic population.

Drug names: duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others).

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