Duloxetine Efficacy for Major Depressive Disorder in Male vs. Female Patients: Data From 7 Randomized, Double-Blind, Placebo-Controlled Trials

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Objective: A number of studies have suggested potential gender differences in the efficacy of antidepressant medications. Pooled data from double-blind, placebo-controlled studies were utilized to compare the efficacy of duloxetine in the treatment of major depressive disorder (MDD) in male and female patients.

Method: Efficacy data were pooled from 7 randomized, double-blind, placebo-controlled clinical trials of duloxetine. These studies represent all available data from U.S. acute-phase, placebo-controlled studies of duloxetine for the treatment of MDD. Patients (aged ≥ 18 years) meeting DSM-IV criteria for MDD received duloxetine (40–120 mg/day; men, N = 318; women, N = 578) or placebo (men, N = 242; women, N = 484) for up to 9 weeks. Efficacy measures included the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score, $HAM\text{-}D_{17}$ subscales (core, Maier, anxiety, retardation, sleep), the Clinical Global Impressions-Severity of Illness scale (CGI-S) and Patient Global Impression of Improvement scale (PGI-I), the Quality of Life in Depression Scale (QLDS), and Visual Analog Scales (VAS) for pain. The first patient visit was February 1, 1999, and the last patient visit was November 27, 2002.

Results: In both male and female patients, duloxetine produced significantly greater improvement in $HAM\text{-}D_{17}$, CGI-S, and PGI-I when compared with placebo ($p < .05$). Treatment-by-gender interactions did not reach statistical significance, indicating that the magnitude of duloxetine's treatment effects did not differ significantly between male and female patients. However, there was a trend for female patients to show a more robust response than male patients to both duloxetine and placebo. On the basis of VAS assessments of pain severity, duloxetine-treated female patients appeared to exhibit greater improvement than male patients, while women receiving placebo had smaller responses than placebo-treated men. Improvements in quality of life were significantly greater for both men ($p = .006$) and women ($p = .001$) receiving duloxetine than placebo and showed no significant difference by gender.

Conclusion: In this analysis of pooled data, the efficacy of duloxetine did not differ significantly in male and female patients.

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Gender differences in the prevalence, longitudinal course, and treatment response of major depressive disorder (MDD) have been the subject of numerous investigations.[1] The most consistent finding from epidemiologic studies is that the prevalence of MDD is approximately twice as high in women as in men.[2] Most recently, results from the National Comorbidity Survey Replication revealed an odds ratio for lifetime prevalence of MDD of 1.7 for women when compared with men (95% CI = 1.5 to 2.0, $p < .05$).[3] The reasons underlying this gender difference are still unclear, but most likely reflect a complex interaction of biological, psychological, and sociocultural factors.[4]

Further research has revealed other gender-related disparities in the manifestation of depressive illness. Although most studies have shown no difference in age at onset of depression, some studies suggest that women may be more likely than men to develop a chronic and recurrent course of illness.[4] In addition, depressed women have been shown to have higher rates of comorbidity when compared with depressed men,[5] most notably anxi-

ety and eating disorders. However, depressed men have a higher lifetime prevalence of alcohol and substance abuse than women.[6] Studies have also shown a higher rate of suicide attempts in depressed women, but a higher rate of completed suicide in depressed men.[7]

Presenting symptoms are generally similar in men and women, although women may report a greater number of depressive symptoms.[8] Furthermore, women appear to be more likely than men to present with atypical or reverse vegetative symptoms such as hypersomnia, increased appetite, and weight gain and to have more somatic symptoms (including fatigue, increased appetite, and sleep disruption).[4,9–11] In a study involving pairs of opposite-sex dizygotic twins meeting criteria for lifetime major depression, female twins reported experiencing significantly more fatigue, hypersomnia, and psychomotor retardation, while male twins reported more insomnia and agitation.[12]

Gender differences have also been demonstrated in the pharmacologic treatment of depression. Pharmacokinetics and pharmacodynamics of antidepressants and other psychotropic medications can show substantial differences between male and female patients.[13–19] Among other findings, studies have demonstrated higher plasma levels of antidepressants (including nortriptyline,[20] imipramine,[21] amitriptyline,[22] nefazodone,[23] clomipramine,[24] and sertraline[25]), a lower hydroxylation clearance of clomipramine,[26] and an increased volume of distribution of trazodone[27] in women than men. However, in light of the many confounding factors (e.g., body weight, fat distribution, gastric absorption and emptying, and colonic transit times) in these between-gender studies, a complete understanding of these results has remained elusive.[14] Antidepressant plasma levels may also be influenced by fluctuating hormone levels (associated with oral contraceptives,[28] the menstrual cycle,[29] and pregnancy[30]) and sex-related differences in metabolizing enzymes.[18] The majority of studies show that apparent cytochrome P450 (CYP) 3A4 activity is higher in women than in men,[16] whereas the activity of many other systems involved in drug metabolism (such as CYP2C19) may be higher in men than in women.[15] In addition, several studies have found higher plasma levels of drugs metabolized by CYP1A2 in women.[15] However, there is less evidence for any sex differences in CYP2D6 activity.

The question of primary concern to clinicians and patients is whether such differences in pharmacokinetics and pharmacodynamics have any clinically relevant effects upon antidepressant response in male and female patients.[1,31] Several studies have suggested that women exhibit a poorer response to tricyclic antidepressants (TCAs; most notably imipramine) when compared with men.[32–35] Whether women respond more favorably than men to monoamine oxidase inhibitors (MAOIs)[36] and selective serotonin reuptake inhibitors (SSRIs) is the subject of considerable debate.[35,37] In a study of 635 chronically depressed outpatients,[35] women were significantly more likely to show a favorable response to sertraline than to imipramine, while men were significantly more likely to show a favorable response to imipramine than to sertraline. Differences in time to response were seen with imipramine, with women responding significantly more slowly than men.[35] Notably, the differing response rates in women were observed primarily in premenopausal women, leading to the proposal that female sex hormones may enhance response to SSRIs or inhibit response to tricyclics.[35] Similar results were observed in a head-to-head comparison of the SSRI fluoxetine with the selective-norepinephrine reuptake inhibitor (SNRI) maprotiline.[38] When the degree of baseline-to-endpoint improvement was analyzed by gender, female patients demonstrated significantly greater improvement with fluoxetine than maprotiline, while responses among male patients did not differ significantly. Furthermore, the differential efficacy was significant in women aged < 44 years, but not in those aged ≥ 44 years.[38] In a separate study of melancholic depressed patients, those aged 40 years or older, especially men, had a superior response to nortriptyline than fluoxetine while those aged 18 to 24 years, especially women, had a more favorable response to fluoxetine.[39,40] However, a number of studies have failed to find any gender differences in antidepressant treatment response. In a retrospective analysis of 11 randomized, double-blind trials involving 850 female patients, fluoxetine and TCAs were found to be equally efficacious on the basis of baseline-to-endpoint reduction in HAM-D_{17} total score.[41] In a separate meta-analysis of data from 8 double-blind, clinical trials, no significant gender-by-treatment or age-by-gender-by-treatment interactions were found for venlafaxine or SSRIs.[42] In another large study,[43] data for patients who had been treated with TCAs, MAOIs, fluoxetine, or placebo were examined in a retrospective analysis. Men and women were found to have equivalent response rates to TCAs (although older women responded better than younger women) and fluoxetine, while women had a statistically superior response to MAOIs compared with men.[43] Additional pooled analyses of data from patients receiving SSRIs, TCAs, SNRIs, or MAOIs revealed no significant gender-related differences in treatment response.[24,44–46]

Duloxetine is a dual reuptake inhibitor of serotonin (5-HT) and norepinephrine. 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.[47–52] In the present study, pooled data from 7 clinical trials were utilized to compare the efficacy of duloxetine in male and female patients. The pooled safety data from these 7 clinical trials will be discussed in a separate paper.[53]

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Table 1. Randomly Assigned Patients in 7 Placebo-Controlled Trials of Duloxetine for Major Depressive Disorder[a,b]

		Duloxetine			
Study	Placebo	40 mg/d[c]	60 mg qd	80 mg/d[d]	120 mg/d[e]
1	70 (22, 48)	…	…	…	70 (26, 44)
2	75 (25, 50)	…	…	…	82 (26, 56)
3	90 (31, 59)	91 (29, 62)	…	84 (33, 51)	…
4	89 (32, 57)	86 (38, 48)	…	91 (35, 56)	…
5	122 (39, 83)	…	123 (43, 80)	…	…
6	139 (40, 99)	…	128 (43, 85)	…	…
7	141 (53, 88)	…	141 (45, 96)	…	…
Total	726 (242, 484)		896 (318, 578)		

[a]Data from Goldstein et al.[47,48] (studies 1 and 4), Nemeroff et al.[52] (studies 2 and 3), Detke et al.[49,50] (studies 5 and 6), and Brannan et al.[51] (study 7).
[b]Data presented in the form T (M, F), where T = total number of patients, M = number of male patients, and F = number of female patients.
[c]Administered 20 mg twice daily (b.i.d.).
[d]Administered 40 mg b.i.d.
[e]Administered as a forced titration from 20 mg b.i.d. to 60 mg b.i.d.
Abbreviation: qd = every day.

METHOD

Study Design

All 7 studies[47–52] included in these analyses were randomized, multicenter, double-blind, and placebo-controlled clinical trials. Four of the studies were active comparator–controlled clinical trials (the active comparators were fluoxetine 20 mg/day in Studies 1[47] and 2[52] and paroxetine 20 mg/day in Studies 3[52] and 4[48]). These studies represent all available data from acute-phase, placebo-controlled studies of duloxetine for the treatment of MDD carried out in the United States. Two studies performed in Eastern Europe were excluded, as prominent geographical differences may confound the results.[52] Since the current analyses focused upon duloxetine versus placebo contrasts in male and female patients, data from active comparator treatment arms were omitted from the analyses. Studies incorporated double-blind, variable-duration placebo lead-in periods to patients, and investigators were blinded to the start of active therapy. Study duration was 7 weeks (Study 7),[51] 8 weeks (Studies 1–4),[47,48,52] or 9 weeks (Studies 5[49] and 6[50]). Protocols were reviewed and approved by the ethical review board at each center in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent prior to the administration of any study procedures or study drug. The numbers of patients randomly assigned in each study are summarized in Table 1. Safety and efficacy results from Studies 1,[47] 4,[48] 5,[49] 6,[50] and 7[51] have been published separately.

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),[54] and had a 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$)[55] total score ≥ 15 and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[56(pp218–222)] score ≥ 4 at the screening and second study visits. In Study 7, patients were also required to have a Brief Pain Inventory (BPI)[57] average pain score ≥ 2 at the second study visit. 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 on a stable dose for at least 3 months prior to study entry.

Data Pooling Strategies

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");
2. Data from the 4 studies that demonstrated a significant advantage for duloxetine over placebo on the primary efficacy measure (Studies 1, 4, 5, and 6; hereafter referred to as "positive studies")—placebo: men (N = 133), women (N = 287); duloxetine: men (N = 185), women (N = 313);
3. Data from the 2 positive MDD studies in which patients received the recommended therapeutic duloxetine dose of 60 mg once daily (Studies 5 and 6; hereafter referred to as "focus studies")—placebo: men (N = 79), women (N = 182); duloxetine: men (N = 86), women (N = 165).

The design of all 7 studies was similar, and pooling of data was anticipated during protocol development. Analysis of data from all studies provided an assessment of comparative efficacy in men and women across the largest possible data set. The analysis of data from the 4 positive studies allowed differential efficacy to be studied without the potential confounding influence of non-positive data. Analyses of data from the 2 focus studies are of particular clinical relevance since they examine male

versus female treatment effects in patients receiving the therapeutic duloxetine dose.

Efficacy Measures

Efficacy was assessed using the HAM-D_{17} total score (the primary efficacy measure); HAM-D_{17} anxiety (items 10, 11, 12, 13, 15, and 17), core factor (items 1, 2, 3, 7, and 8), Maier (items 1, 2, 7, 8, 9, and 10), retardation (items 1, 7, 8, and 14), and sleep (items 4, 5, and 6) subscales; the CGI-S and the Patient Global Impression of Improvement scale (PGI-I)[56(pp313–331)]; Visual Analog Scales (VAS) for pain[58]; and the Quality of Life in Depression Scale (QLDS).[59] Patients were defined as responders if they had a decrease from baseline of at least 50% in the HAM-D_{17} total score. Patients were defined as remitters if they had a HAM-D_{17} total score ≤ 7.

Statistical Analyses

All patients who had at least 1 postbaseline assessment were included in the efficacy analyses. Within-gender longitudinal mean changes and categorical changes (estimated probabilities) were assessed using a likelihood-based repeated measures approach. Models for mean changes included investigator, visit, baseline value, and baseline-by-visit interaction. Mean changes from baseline to last observation were assessed via analysis of covariance with models that included the independent effects of investigator, gender, and therapy-by-gender interaction, with baseline score included as the covariate. The percentages of responders and remitters were also tabulated.

RESULTS

Patient Characteristics

Baseline patient demographics are summarized in Table 2. Male patients were significantly older (mean 42.6 years vs. 40.9 years, respectively; p = .015) and had significantly higher mean body weight (p < .001) than female patients. There was a significant difference in ethnic origin between male and female patients (p = .010), with a lower proportion of Caucasian women than Caucasian men and a higher proportion of Hispanic and African American female patients than male patients.

Women had a significantly higher mean baseline HAM-D_{17} total score when compared with men (p = .034), and there was a trend toward a higher mean baseline CGI-S score among women than men (p = .052). Female patients also had a significantly higher mean VAS overall pain score at baseline when compared with male patients (p < .001). With regard to psychiatric history, male patients were significantly older at onset of depression than female patients (mean 31.2 years vs. 28.2 years, respectively; p = .001), while a greater proportion of women than men had suffered a previous major depressive episode (73.7% vs. 65.4%, respectively; p = .001) and exhibited atypical features (5.0% vs. 2.6%, respectively; p = .027). There were no significant between-group differences in any other aspect of psychiatric history (including duration of current episode, number of previous episodes, or proportion of patients with melancholic features).

Table 2. Patient Baseline Demographics and Psychiatric Profile (all studies)

Variable	Men (N = 560)	Women (N = 1062)	p Value
Age, mean (SD), y	42.6 (13.1)	40.9 (13.0)	.015
Age range, y	18–82	18–80	–
Weight, mean (SD), kg	90.4 (19.4)	79.1 (21.6)	< .001
Ethnic origin, N (%)			.010
Caucasian	479 (85.5)	863 (81.3)	
Hispanic	28 (5.0)	92 (8.7)	
African American	38 (6.8)	90 (8.5)	
Asian	6 (1.0)	2 (0.2)	
East Asian	4 (0.7)	7 (0.7)	
Other	5 (0.9)	8 (0.8)	
HAM-D_{17} total score, mean (SD)	21.0 (4.0)	21.4 (4.1)	.034
CGI-S score, mean (SD)	4.27 (0.56)	4.32 (0.55)	.052
VAS overall pain score, mean (SD)	28.7 (24.0)	33.0 (25.3)	< .001

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, VAS = Visual Analog Scales.

The proportion of men and women within each treatment group did not differ significantly (duloxetine group: 64.5% women, placebo group: 66.7% women; p = .372).

Efficacy

All studies. Analyses of efficacy data from all 7 studies are presented in Table 3. Duloxetine demonstrated significant advantage over placebo in HAM-D_{17}, CGI-S, and PGI-I measures in both male and female patient groups (p < .05). Treatment-by-gender interactions were not statistically significant, indicating that the magnitude of duloxetine's treatment effects did not differ significantly between male and female patients. However, there was a trend for female patients to show a more robust response than male patients to both drug and placebo. Effect sizes across the 3 depression measures ranged from 0.19 to 0.30.

Duloxetine-treated female patients demonstrated significant improvement in VAS overall pain severity scores compared with female placebo patients (mean change = –11.27 vs. –5.66 for duloxetine and placebo, respectively; p = .001), while duloxetine's advantage over placebo was not statistically significant among male patients. However, the treatment-by-gender interaction was not statistically significant (p = .390), indicating that treatment effects in overall pain severity did not differ significantly between male and female patients. Effect sizes for VAS overall pain severity were 0.21 in female patients and 0.10 in male patients. Across the other assessed VAS pain measures, female patients receiving duloxetine demonstrated significant reduction in the severity of back pain compared with

Table 3. Summary of Efficacy Measures from 7 Randomized, Placebo-Controlled Trials of Duloxetine for Major Depressive Disorder[a]

			Placebo	Duloxetine			
Efficacy Measure	Gender	N	Mean Change (SD)	Mean Change (SD)	p Value[b]	Effect Size	p Value[c]
$HAM\text{-}D_{17}$ total score							
All studies	Male	549	–5.58 (7.02)	–7.02 (6.98)	< .001	0.21	.894
	Female	1019	–6.47 (7.51)	–8.16 (7.52)	< .001	0.22	
Positive studies[d]	Male	312	–4.81 (6.65)	–7.43 (7.11)	< .001	0.38	.992
	Female	575	–6.26 (7.24)	–8.87 (7.40)	< .001	0.36	
CGI-S							
All studies	Male	549	–0.94 (1.25)	–1.22 (1.21)	.002	0.23	.723
	Female	1021	–1.11 (1.22)	–1.35 (1.28)	< .001	0.19	
Positive studies[d]	Male	312	–0.83 (1.18)	–1.25 (1.22)	< .001	0.35	.913
	Female	577	–1.07 (1.21)	–1.43 (1.28)	< .001	0.29	
PGI-I[e]			Mean (SD)	Mean (SD)			
All studies	Male	549	3.17 (1.18)	2.93 (1.29)	.015	0.19	.284
	Female	1020	3.08 (1.34)	2.69 (1.30)	< .001	0.30	
Positive studies[d]	Male	312	3.31 (1.28)	2.90 (1.28)	.004	0.32	.552
	Female	576	3.19 (1.36)	2.69 (1.34)	< .001	0.37	

[a]Last-observation-carried-forward analysis.
[b]p Value for duloxetine versus placebo.
[c]p Value for treatment-by-gender interaction.
[d]Positive studies are those that demonstrated a significant advantage for duloxetine over placebo on the primary efficacy measure.
[e]Lower scores indicate greater improvement.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, $HAM\text{-}D_{17}$ = 17-item Hamilton Rating Scale for Depression, PGI-I = Patient Global Impression of Improvement scale.

female placebo patients (p = .003), while duloxetine did not show significant superiority to placebo on any measure for male patients. Treatment-by-gender interactions did not achieve statistical significance for any of these VAS pain measures (p > .25 in each case).

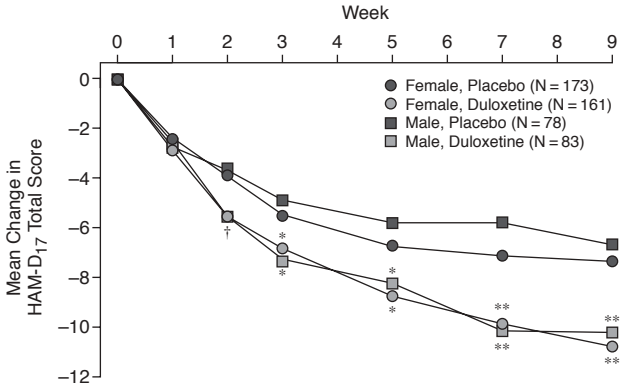
Positive studies. Analysis of pooled efficacy data from the 4 positive studies (Studies 1, 4, 5, and 6) yielded results similar to those observed from all studies (Table 3). Duloxetine demonstrated significant advantage (p < .005) over placebo in both male and female patient groups, but treatment-by-gender interactions were not statistically significant for $HAM\text{-}D_{17}$, CGI-S, or PGI-I. Female patients appeared to exhibit a more robust treatment response to both duloxetine and placebo than male patients. Effect sizes for depression outcomes were somewhat larger than those observed in the analysis of all studies, and ranged from 0.29 to 0.38.

Focus studies. In the 2 focus studies (Studies 5 and 6), both male and female patients receiving duloxetine (60 mg q.d.) demonstrated significantly greater improvement than those who received placebo on $HAM\text{-}D_{17}$ (Figure 1), CGI-S (men, p = .003; women, p < .001), and PGI-I (men, p = .003; women, p < .001). In the case of the $HAM\text{-}D_{17}$ total score, effect sizes were 0.50 in male patients and 0.49 in female patients. Mean changes from baseline to endpoint in the 5 assessed $HAM\text{-}D_{17}$ subscales are summarized in Figure 2.

Plots of estimated probabilities of response and remission are presented in Figure 3. At endpoint (week 9), estimated probabilities of response for male patients were 59% vs. 30% for duloxetine and placebo, respectively (p = .007), while the corresponding probabilities of response among female patients were 64% vs. 35%, respectively (p < .001). Estimated probabilities of remission at endpoint for male patients were 43% vs. 15% for duloxetine and placebo, respectively (p = .004), while the probabilities of remission for duloxetine- and placebo-treated female patients were 45% vs. 24%, respectively (p = .003).

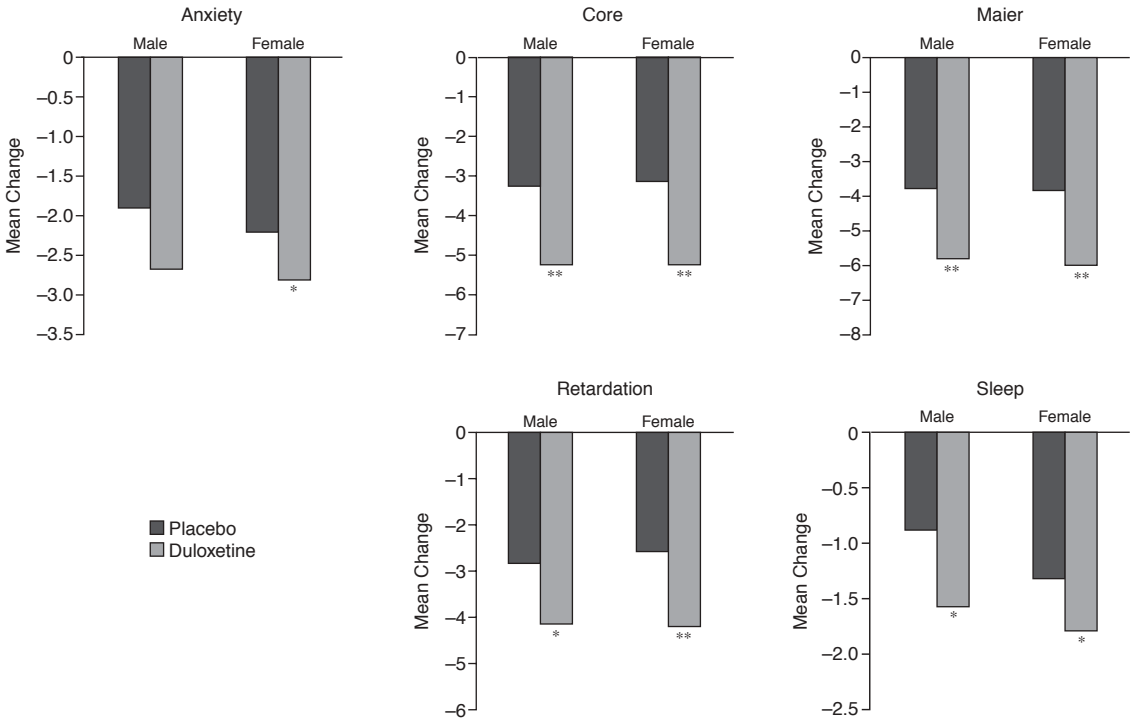
In analyses focusing on the main effect of treatment for VAS pain measures (pooled data from all visits),

Figure 1. Mean Change in $HAM\text{-}D_{17}$ Total Score for Male and Female Patients Receiving Placebo or Duloxetine (60 mg q.d.)[a]



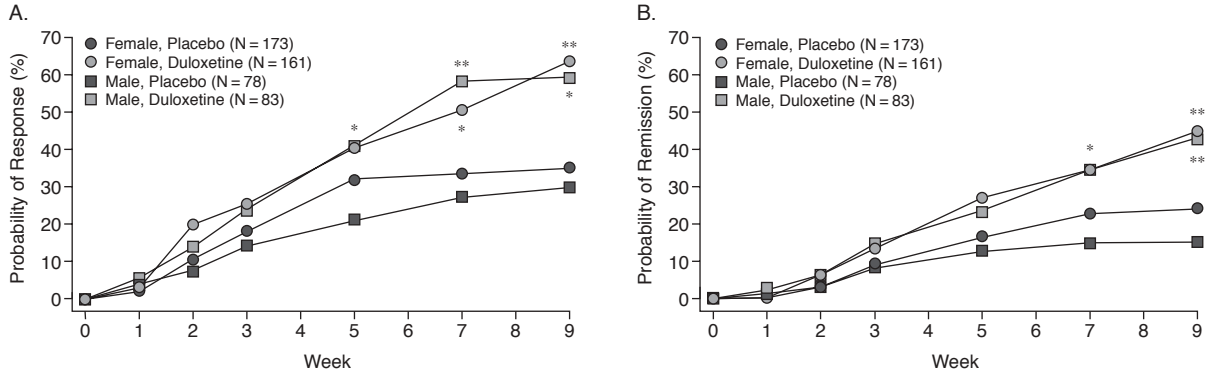
[a]Patient numbers for each treatment group represent those with at least 1 postbaseline assessment.
†Male, duloxetine: p = .023 vs. male, placebo; female, duloxetine: p = .005 vs. female, placebo.
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.

Figure 2. Mean Change in HAM-D_{17} Subscale Scores for Male and Female Patients Receiving Placebo or Duloxetine (60 mg q.d.)



*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.

Figure 3. Estimated Probability of (a) Response and (b) Remission for Male and Female Patients Receiving Placebo or Duloxetine (60 mg q.d.)[a]

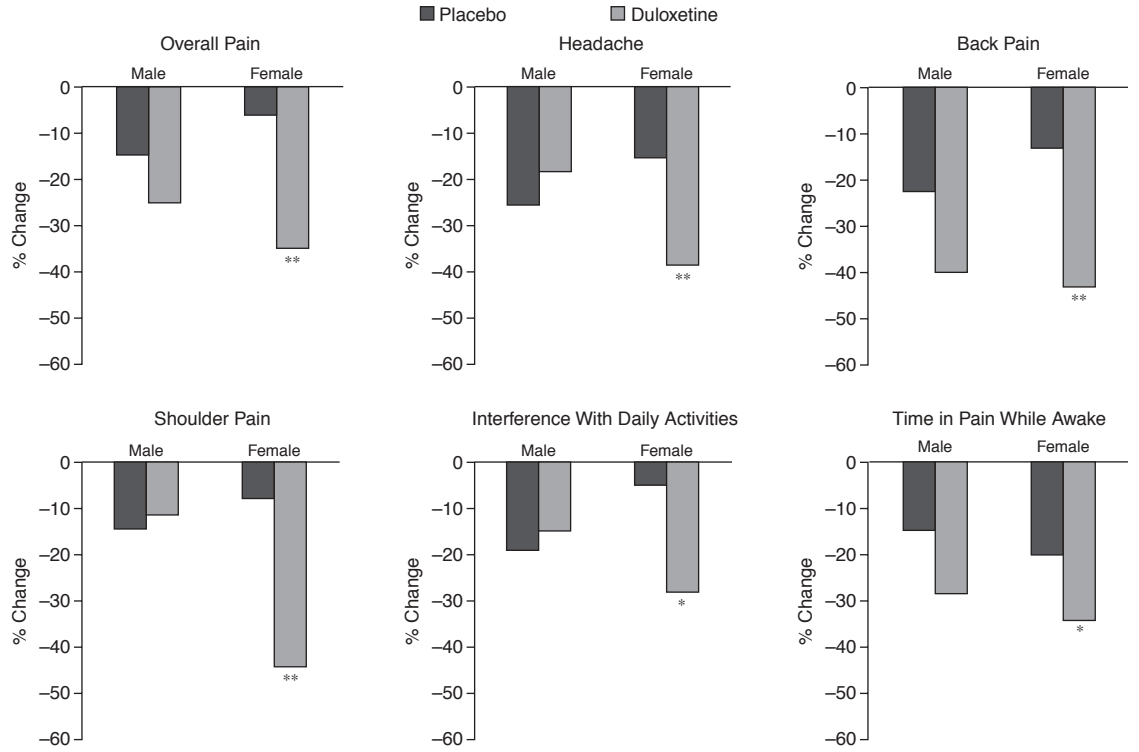


[a]Patient numbers for each treatment group represent those with at least 1 postbaseline assessment.
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.

duloxetine-treated female patients demonstrated significantly greater improvement compared with female placebo patients on all 6 assessed outcomes ($p < .05$; Figure 4). In male patients, duloxetine did not show a significant advantage over placebo on any of the VAS pain measures. In general, duloxetine-treated female patients exhibited more robust improvements in pain severity compared to male patients, while female patients receiving placebo had smaller responses compared with placebo-treated male patients. Effect sizes across the 6 VAS for pain outcomes ranged from 0.17 to 0.33 for female patients, and from 0.07 to 0.18 in male patients. A visitwise plot of mean changes in overall pain severity in male and female patients is shown in Figure 5.

Additional exploratory analyses of the VAS for pain outcomes in the focus studies assessed gender differences

Figure 4. Percentage Change in VAS Pain Severity for Male and Female Patients Receiving Placebo or Duloxetine (60 mg q.d.) (main effect of treatment, pooling all visits)



*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.
Abbreviation: VAS = Visual Analog Scales.

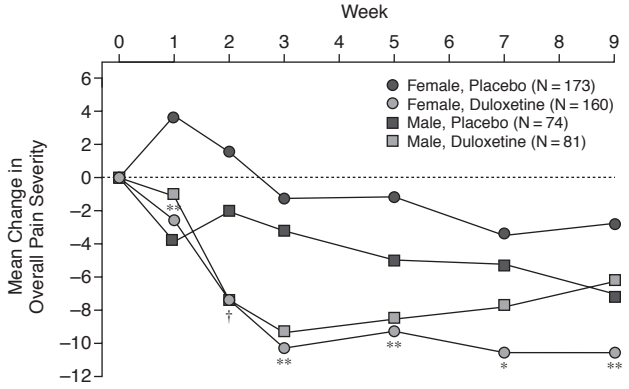
after adjusting for differences in baseline pain severity. After adjusting for baseline differences, the treatment-by-gender interaction was statistically significant ($p < .05$) for headaches and shoulder pain, and approached significance for overall pain ($p < .10$). However, after applying a Bonferroni correction (.05/6 = .008) to adjust for multiple comparisons, none of the interactions were considered to be statistically significant. Further analyses of pain results in the focus studies included only those patients with baseline pain severity of 20 or greater, as measured by the VAS overall pain item. In these analyses, the advantage of duloxetine over placebo tended to be greater for both men and women than in the all-patient analyses, and the treatment-by-gender interaction did not significantly influence outcomes.

Improvements in mean QLDS score were significantly greater with duloxetine than placebo in both male and female patients ($p = .006$ for men; $p = .001$ for women), while the treatment-by-gender interaction was not significant ($p = .940$).

DISCUSSION

The current analysis describes efficacy data from depressed male and female patients who participated in 7 clinical trials of duloxetine (40–120 mg/day) of up to 9 weeks' duration. This represents all available data from acute-phase, placebo-controlled studies of duloxetine for the treatment of MDD carried out in the United States. Comparisons of treatment effects revealed that the magnitude of depressive symptom improvements (as assessed using HAM-D_{17}, CGI-S, and PGI-I scales) did not differ significantly between male and female patients, i.e., treatment-by-gender interactions were not significant for any of the 3 efficacy measures. Although drug-placebo differences were of similar magnitude in both patient groups, female patients tended to have somewhat larger drug and placebo responses when compared with male patients (i.e., women appeared to have a greater nonspecific response than men in these studies). Responses in pain severity suggested some potential gender-related differences, with women exhibiting greater benefit from duloxetine treatment than men. Considering the main effect of treatment, duloxetine-treated women had greater improvement compared with duloxetine-treated men in all 6 assessed VAS pain measures. In contrast, on 5 of the 6 pain measures, placebo-treated men had greater improvement than placebo-treated women. However, these results must be considered with a degree of caution, given the post hoc nature of the comparisons and the fact that

Figure 5. Mean Change in VAS Overall Pain Severity for Male and Female Patients Receiving Placebo or Duloxetine (60 mg q.d.)[a]



[a]Patient numbers for each treatment group represent patients with at least 1 postbaseline assessment.
†Male, duloxetine: not significant vs. male, placebo; female, duloxetine: $p < .001$ vs. female, placebo.
*$p \leq .05$ vs. placebo.
**$p \leq .005$ vs. placebo.
Abbreviation: VAS = Visual Analog Scales.

significance of the treatment-by-gender interactions was not maintained after adjustment for multiple comparisons. Nevertheless, the pattern of results in pain outcomes for men versus women stands as an interesting contrast to those of the traditional depression outcomes used in this study (HAM-D, CGI, PGI) in which no evidence of gender differences was found.

Baseline severity of depression, as assessed using the HAM-D_{17} total score, was significantly higher in women compared with men, although the between-group difference was only 0.4 points. On the CGI-S scale, there was a trend toward greater severity of baseline depressive symptoms in women compared with men, but again the between-group difference was of doubtful clinical relevance. These data are consistent with most literature reports suggesting that depressed men and women present with similar severity of illness.[1] However, baseline severity of painful physical symptoms (as assessed using the self-rated VAS measure of overall pain) was found to be significantly higher in women compared with men ($p < .001$). These data are consistent with previous findings that depressed female patients have a higher prevalence of pain complaints when compared with male patients[60] and report significantly higher levels of bodily pain.[11] While the current data do not allow a comparison of the number of painful physical complaints reported in each group at baseline, they do suggest that, at least in terms of severity of painful symptoms, female patients show a marked difference from male patients. The difference in severity of baseline pain between genders also appeared to influence treatment response. Female patients had greater benefit from duloxetine treatment than male patients. However, after accounting for differences in baseline pain severity and excluding patients with very low baseline pain, the benefit from duloxetine treatment in pain outcomes did not differ significantly between men and women.

It is unclear whether previously reported gender differences in antidepressant response are related to mechanism of action. Women appear to have a more favorable response to serotonergic agents, in particular the SSRIs, and this effect is most pronounced in premenopausal women.[35,38] Older women, and also men, appear to respond equally well to both serotonergic and noradrenergic agents.[38] Consistent with these findings, there do not appear to be any gender differences in efficacy for venlafaxine, which inhibits reuptake of both 5-HT and norepinephrine at higher doses.[42] However, women have shown a poor response to imipramine, which is also a dual-reuptake inhibitor of 5-HT and norepinephrine.[35]

In both clinician- and self-rated scales, female patients had a somewhat larger placebo response when compared with male patients. There are very few literature reports examining gender differences in placebo responses in antidepressant clinical trials. In one previous retrospective evaluation, men were found to be slightly more responsive to placebo than were women,[61] while a separate study found that placebo response did not vary by gender.[62]

On the HAM-D_{17} anxiety subscale, male patients receiving duloxetine in this study did not show a significant advantage over male placebo patients, while duloxetine-treated female patients did exhibit significantly greater improvement compared with female patients receiving placebo. However, this difference appears to be a result of variation in sample sizes, since the drug-placebo difference in male patients was actually larger than that observed in female patients.

A number of limitations should be considered when interpreting results from this study. Firstly, this was a post-hoc analysis of pooled data. Secondly, 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. Thirdly, data concerning the menopausal status of female patients were not collected, thus precluding any investigation of relative efficacy in premenopausal and postmenopausal women. Fourthly, patients with serious or unstable secondary medical conditions were excluded from the trials, possibly limiting the generalizability of the current results to clinical practice.

CONCLUSION

In this study of duloxetine for the treatment of MDD, the magnitude of improvement in depressive symptoms did not differ significantly between male and female pa-

tients. However, women appeared to demonstrate a more robust improvement in some aspects of pain severity.

Drug names: clomipramine (Anafranil and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

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