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A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder

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Abstract

This was a 12-week, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, in 354 female patients with primary fibromyalgia, with or without current major depressive disorder. Patients (90% Caucasian; mean age, 49.6 years; 26% with current major depressive disorder) received duloxetine 60 mg once daily (QD) ($N=118$), duloxetine 60 mg twice daily (BID) ($N=116$), or placebo ($N=120$). The primary outcome was the Brief Pain Inventory average pain severity score. Response to treatment was defined as $\geq 30\%$ reduction in this score. Compared with placebo, both duloxetine-treated groups improved significantly more ($P<0.001$) on the Brief Pain Inventory average pain severity score. A significantly higher percentage of duloxetine-treated patients had a decrease of $\geq 30\%$ in this score (duloxetine 60 mg QD (55%; $P<0.001$); duloxetine 60 mg BID (54%; $P=0.002$); placebo (33%)). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Compared with patients on placebo, patients treated with duloxetine 60 mg QD or duloxetine 60 mg BID had significantly greater improvement in remaining Brief Pain Inventory pain severity and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impression of Improvement, and several quality-of-life measures. Both doses of duloxetine were safely administered and well tolerated. In conclusion, both duloxetine 60 mg QD and duloxetine 60 mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder.

Keywords: Fibromyalgia; Duloxetine; Randomized clinical trial

1. Introduction

Fibromyalgia is a chronic, often debilitating musculoskeletal pain disorder that is characterized by widespread pain and muscle tenderness, and often accompanied by fatigue, stiffness, anxiety, sleep disturbance, and depression (Hudson and Pope, 1996; Wolfe et al., 1990). Fibromyalgia is common and occurs in about 2% of the general population of the United States with more women (estimated at 3.4–10.5%) than men (0.5%) diagnosed with fibromyalgia (Neumann and Buskila, 2003; Wolfe et al., 1995).

Although the pathophysiology of fibromyalgia is unknown, central monoaminergic neurotransmission may play a role in its etiology. Dysfunction in both serotonin and norepinephrine systems has been implicated in the etiology of fibromyalgia (Legangneux et al., 2001; Russell et al., 1992a,b; Yunus et al., 1992). Both serotonergic and noradrenergic neurons have also been implicated in the mediation of endogenous pain inhibitory mechanisms via the descending inhibitory pain pathways in the brain and

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spinal cord (Clark and Proudfit, 1993; Basbaum and Fields, 1984; Millan, 2002). In pathological pain states, these endogenous pain inhibitory mechanisms may be dysfunctional, contributing to the central sensitization and hyperexcitability of the spinal and supraspinal pain transmitting pathways and manifesting as persistent pain (Coderre and Katz, 1997).

Duloxetine hydrochloride (Cymbalta®) is a selective serotonin and norepinephrine reuptake inhibitor that is relatively balanced in its affinity for both serotonin and norepinephrine reuptake inhibition. In a recent randomized, controlled, 12-week trial comparing duloxetine 60 mg twice a day (BID) with placebo in the treatment of fibromyalgia in 207 patients with and without major depressive disorder, duloxetine was found to be an effective and safe treatment for pain and many of the other symptoms associated with fibromyalgia, particularly for women (Arnold et al., 2004). The improvement in fibromyalgia symptoms with duloxetine compared with placebo was independent of comorbid major depressive disorder. Duloxetine-treated male patients did not respond significantly on any efficacy measure compared with placebo-treated male patients. The reasons for the gender difference were unclear, but may have been due to the small male subgroup (23 of 207 patients (11%)) or to possible gender differences in fibromyalgia that affect treatment response (Arnold et al., 2004).

Based on the evidence that duloxetine 60 mg BID was safe and efficacious in the treatment of fibromyalgia, particularly in women, we conducted a randomized, placebo-controlled, double-blind, parallel group study to confirm the safety and efficacy of duloxetine 60 mg BID in women with fibromyalgia. Because duloxetine was found to significantly reduce painful physical symptoms associated with major depressive disorder at 60 mg once a day (QD) (Goldstein et al., 2004), we also tested the safety and efficacy of this lower dose in fibromyalgia.

2. Methods

2.1. Overview

The multicenter study was conducted in 21 outpatient research centers in the United States. Enrollment began in November 2002, and the study was completed in October 2003. The Institutional Review Boards approved the protocol, and all patients provided written informed consent after the study was explained and their questions answered, and before study procedures were initiated. Patients were identified by physician referral or advertisement for a fibromyalgia medication trial.

2.2. Entry criteria

Patients were eligible for the study if they were female outpatients $\geq$18 years of age, met criteria for primary fibromyalgia as defined by the American College of Rheumatology (Wolfe et al., 1990), and had a score of $\geq$4 on the average pain severity item of the Brief Pain Inventory (Cleeland and Ryan, 1994) at randomization. Exclusion criteria included the following: pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; current primary psychiatric diagnosis other than major depressive disorder, a primary anxiety disorder within the past year (specific phobias allowed); substance abuse within the past year; serious suicide risk; pregnancy or breast-feeding; women who, in the opinion of the investigator, were treatment refractory or may have had an involvement in disability reviews that might compromise treatment response; severe allergic reactions to multiple medications; or prior participation in a study of duloxetine. Concomitant medication exclusions included use of medications or herbal agents with central nervous system activity; regular use of analgesics with the exception of acetaminophen up to 2 g/day and aspirin for cardiac prophylaxis up to 325 mg/day; chronic use of sedatives, antiemetics, or antispasmodics; and initiation of or change in unconventional or alternative therapies.

2.3. Study design

Women who met entry criteria following the screening phase were randomly assigned to one of three treatment groups: duloxetine 60 mg QD, duloxetine 60 mg BID (forced titration from 60 mg QD for 3 days to 60 mg BID), or placebo, with randomization in a 1:1:1 ratio. Random assignment of the patients to treatment groups was applied within two stratified groups, those with and those without current major depressive disorder. Patients were treated in a double-blind manner for 12 weeks. Patients were seen weekly for the first 2 weeks of the 12-week therapy phase; thereafter, study visits were scheduled at 2-week intervals. Patients then entered into a 1-week double-blind study-drug tapering phase at which time dosage of study drug was reduced to duloxetine 30 mg QD for duloxetine 60 mg QD-treated patients, and duloxetine 60 mg QD for duloxetine 60 mg BID-treated patients.

2.4. Outcome measures

The protocol-defined primary outcome measure was pain severity as measured by the self-reported Brief Pain Inventory (short form) (Cleeland and Ryan, 1994) average pain severity score that measures average pain severity during the past 24 h on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). Secondary outcome measures included the Brief Pain Inventory items for severity of worst pain and least pain during the past 24 h, pain right now, and pain interference (from 0 (does not interfere) to 10 (completely interferes)) with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Response to treatment was defined as $\geq$30% reduction in the Brief Pain Inventory 24-h average pain severity score. Sustained response was defined as $\geq$30% reduction from baseline to endpoint in the Brief Pain Inventory 24-h average pain severity with a 30% reduction from baseline at a week at least 2 weeks prior to the last, and with at least a 20% reduction from baseline at every week in between. Other secondary efficacy measures included the Fibromyalgia Impact Questionnaire, a self-administered questionnaire that measures components of health status most affected by fibromyalgia over the past week (Burckhardt et al., 1991). The total score, which reflected the

impact of fibromyalgia, ranged from 0 (no impact) to 80 (maximum impact). For the tender point assessment, the Fischer dolorimeter (Fischer, 1986) with a rubber disk of 1 cm^2 was applied at a 90° vertical angle to the 18 tender point sites defined by the American College of Rheumatology criteria (Wolfe et al., 1990), and pressure was applied at a rate of 1 $kg/cm^2/s$ until the patient indicated verbally when she first felt discomfort or pain (tender point threshold recorded in kg/cm^2). The mean tender point pain threshold was calculated from the 18 points, and the tender point count was determined by the number of tender points that had a threshold of ≤ 4 kg/cm^2. Other measures included the Clinical Global Impression of Severity scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (Guy, 1976), the Patient Global Impression of Improvement scale, ranging from 1 (very much better) to 7 (very much worse), and the clinician-rated, 17-item Hamilton Depression Rating Scale (score range 0 (not at all depressed)–52 (severely depressed)) (Hamilton, 1960). Patient-reported health outcomes were measured by the Quality of Life in Depression Scale (McKenna and Hunt, 1992), the Medical Outcomes Study Short Form 36 (SF-36) (Ware et al., 1993), and the Sheehan Disability Scale (Sheehan et al., 1996). The safety of duloxetine was assessed by treatment-emergent adverse events, discontinuation pattern, laboratory analysis, and vital signs.

2.5. Statistical analysis

This study required the enrollment of 345 patients to have at least 80% power to detect a treatment group difference of -1.2 points in the baseline-to-endpoint mean change on Brief Pain Inventory average pain severity score between duloxetine 60 BID and placebo. The sample size was determined using a two-sided test with $\alpha = 0.05$, assuming a common standard deviation of 2.66 and a discontinuation rate of 30%. The Brief Pain Inventory average pain severity score was chosen a priori as the primary outcome measure to test the efficacy of duloxetine in the treatment of pain associated with fibromyalgia, and thus the Type 1 error was controlled at the significance level of 0.05 for the analysis of this variable. The purpose of collecting several secondary efficacy measures was to confirm the findings on the primary measure using different instruments. A multiplicity adjustment was not performed for the secondary measures because it was not the intent of the study to assess the secondary measures at the same experimental significance level as was established for the primary variable.

All randomized patients with a baseline and at least one post-baseline visit with efficacy data were included in the efficacy analyses, while all randomized patients were included in the safety analyses. Changes from baseline to endpoint on the Brief Pain Inventory average pain severity score, and the other efficacy measures were analyzed primarily by an analysis of covariance (ANCOVA) model with the terms of treatment, investigator, and baseline score. Furthermore, for the Brief Pain Inventory average pain severity score, the area under the curve of improvement scores (postbaseline minus baseline) over visit intervals was evaluated. The greater the area under the curve, the greater the treatment effect on pain reduction over time. Due to the skewed distribution of the area under the curve, rank-transformed area under the curve scores were analyzed using an analysis of variance (ANOVA) model with the terms of treatment and investigator. As a secondary analysis, longitudinal changes from baseline on continuous efficacy measures were analyzed using a mixed-effects model for repeated measures analysis (Mallinckrodt et al., 2001). The model included the fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. The hypothesis that major depressive disorder status at baseline might have an impact on the response to duloxetine treatment was tested using an ANCOVA model as described earlier, with the addition of the major depressive disorder status at baseline and the treatment-by-subgroup interaction.

Path analysis (Retherford and Choe, 1993; Lu, 2003) was used to test the direct treatment effect on pain reduction. In this analysis, two regression models were employed to describe the following protocol-specified causal relationships: first, the treatment has an effect on pain reduction (direct effect) after accounting for the indirect effect through improvement of depressive symptoms (Model 1); second, the treatment improves depressive symptoms (Model 2). The significance of the direct treatment effect was tested by Student's *t*-test for the treatment coefficient in Model 1, where change in the Brief Pain Inventory average pain severity score was a dependent variable, and treatment, baseline, investigator, and changes in the Hamilton Depression Rating Scale total score were independent variables. In Model 2, the change in the Hamilton Depression Rating Scale total score was a dependent variable, and the treatment and baseline were used as independent variables. The indirect treatment effect was computed as the product of the coefficient for change in Hamilton Depression Rating Scale total score in Model 1 by the coefficient for the term of treatment in Model 2. The percentage of direct and indirect effects on the total treatment effect (the sum of the direct and the indirect effect) was computed and presented.

For categorical variables, treatment group differences were evaluated using Fisher's exact test. Continuous baseline measures and safety parameters were evaluated using the ANOVA model with the terms of treatment and investigator. Laboratory values were rank-transformed prior to analysis. Treatment effects were tested at a two-sided significance level of 0.05. Interaction effects were tested at a significance level of 0.10. Throughout this article, the term 'significant' indicates statistical significance, and the 'mean change' refers to 'least-squares mean change'.

3. Results

3.1. Patient disposition

A total of 745 women were screened to enroll 354 women who met the entry criteria and were randomly assigned to one of three treatment groups: duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo. One hundred eighteen patients received duloxetine 60 mg QD, 116 patients received duloxetine 60 mg BID, and 120 patients received placebo. One hundred thirty-eight (39%) patients withdrew during the 12-week therapy phase, 41 (35%) from the duloxetine 60 mg QD group, 45 (39%) from the duloxetine 60 mg BID group, and 52 (43%) from the placebo group ($P = 0.407$) (Fig. 1). Significant differences were seen in rates of patients discontinuing due to adverse events (duloxetine 60 mg QD, 25 (21.2%, $P = 0.055$ vs.

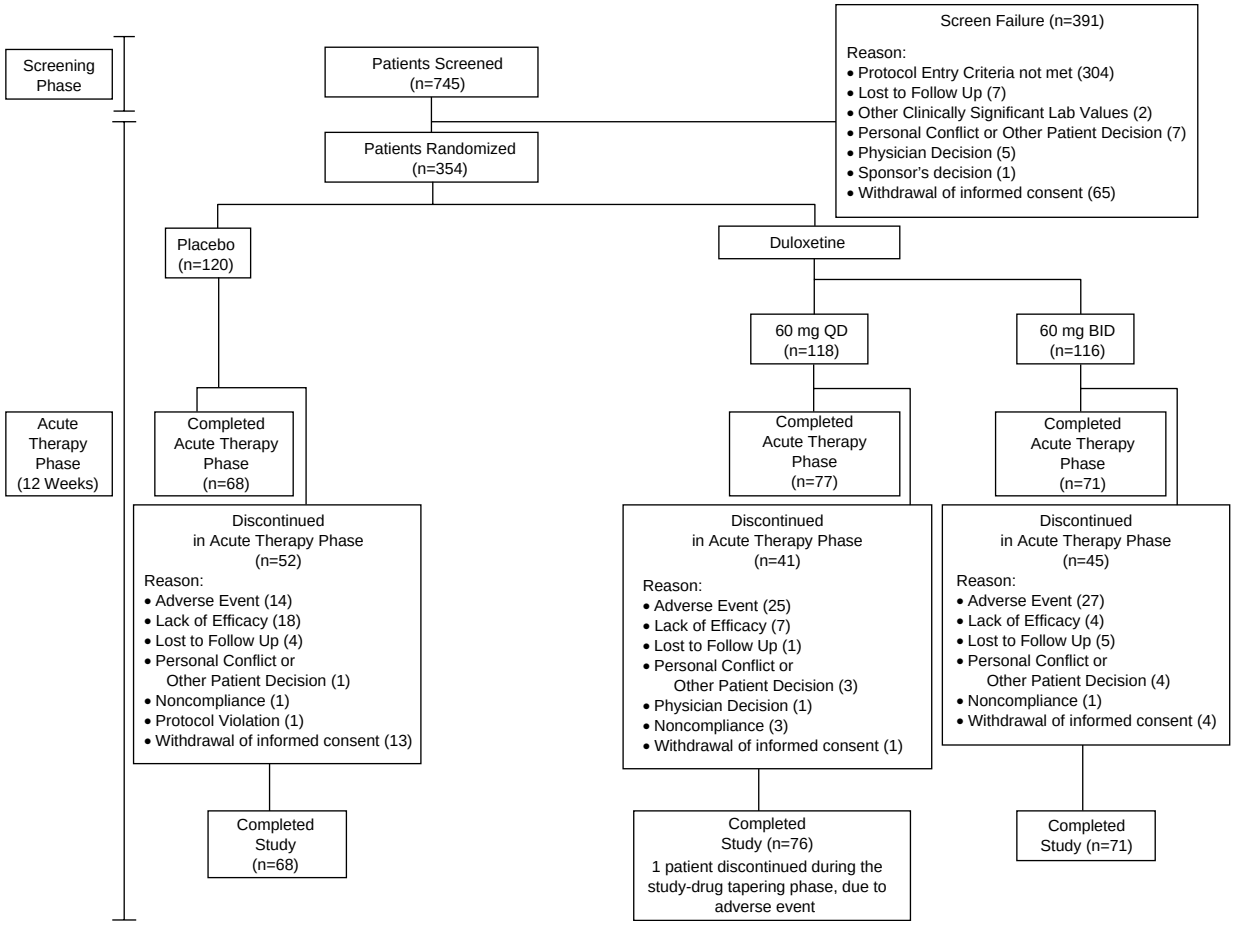

Fig. 1. Flow of patients through the trial. Duloxetine 60 mg BID = duloxetine 60 mg twice a day; duloxetine 60 mg QD = duloxetine 60 mg once a day.

placebo), duloxetine 60 mg BID, 27 (23.3%, $P = 0.025$ vs. placebo), placebo 14 (11.7%)); lack of efficacy (duloxetine 60 mg QD, 7 (5.9%, $P = 0.033$ vs. placebo), duloxetine 60 mg BID, 4 (3.4%, $P = 0.003$ vs. placebo), placebo 18 (15.0%)); and withdrawal of informed consent (duloxetine 60 mg QD, 1 (0.8%, $P = 0.001$ vs. placebo), duloxetine 60 mg BID, 4 (3.4%, $P = 0.042$ vs. placebo), placebo 13 (10.8%)).

3.2. Baseline clinical and demographic characteristics

The majority of the patients were Caucasian (89.5%), followed by Hispanic (8.2%), African descent (2.0%) and East/Southeast Asian (0.3%). The mean (SD) age of the enrolled patients was 49.6 (10.9) and 26% of the enrolled patients had current major depressive disorder. No significant differences among treatment groups were observed in any of the patient demographics or clinical characteristics including origin, age, gender, height, weight, primary diagnoses of major depressive disorder, or secondary diagnosis of anxiety. No significant differences among treatment groups were observed for the baseline clinical variables (Table 1) or for baseline scores on the SF-36, Quality of Life in Depression Scale, or Sheehan disability Scale (Table S1 in Appendix).

3.3. Efficacy

The changes in the Brief Pain Inventory average pain severity score over time are illustrated in Fig. 2. Compared with the placebo group, the duloxetine 60 mg QD group and the duloxetine 60 mg BID group had a significantly greater improvement in the Brief Pain Inventory average pain severity score, beginning at week 1 and continuing through week 12. There were no significant differences in pairwise comparisons between duloxetine 60 mg QD and 60 mg BID. When comparing the area under the curves on the Brief Pain Inventory average pain severity score, both duloxetine 60 mg QD (mean of area under the curve = 152.2 (median = 122.0)) and duloxetine 60 mg BID (mean of area under the curve = 160.5 (median = 139.5)) were statistically superior ($P < 0.001$) to placebo (mean of area under the curve = 79.8 (median = 61.25)). An analysis of the changes in the Brief Pain Inventory average pain severity score in patients who completed the study demonstrated results similar to those observed in the intent-to-treat analysis.

Table 1
Baseline measures for the Brief Pain Inventory average pain severity score, Brief Pain Inventory average interference from pain score, Fibromyalgia Impact Questionnaire, Hamilton Depression Rating Scale, Clinical Global Impression of Severity, and Tender Point Assessments

	Placebo		Duloxetine 60 mg QD		Duloxetine 60 mg BID	
Measure (score range)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Brief Pain Inventory average pain severity (0–10)	120	6.5 (1.5)	118	6.4 (1.4)	116	6.4 (1.6)
Brief Pain Inventory average interference from pain (0–10)	120	6.0 (2.1)	118	5.8 (2.1)	116	6.0 (2.4)
Fibromyalgia Impact Questionnaire Score (0–80)	117	53.1 (12.4)	116	51.4 (12.2)	115	52.5 (12.7)
Hamilton Depression Rating Scale (0–52)	119	11.5 (6.5)	117	11.2 (6.2)	115	11.4 (6.4)
Clinical Global Impression-Severity (1–7)	120	4.2 (0.9)	118	4.0 (0.9)	116	4.1 (0.8)
Tender point number (0–18)	109	17.0 (2.3)	111	17.0 (2.2)	110	17.1 (2.0)
Mean tender point threshold (kg/cm^2)	109	2.2 (0.9)	111	2.1 (0.7)	110	2.1 (0.8)

There were no significant differences between the treatment groups; QD, once a day; BID, twice a day; SD, standard deviation; N, number of randomized patients.

Compared with patients on placebo who completed the study, those who completed the study on duloxetine 60 mg QD had a significant ($P<0.001$) improvement in the Brief Pain Inventory average pain severity score (difference, −1.44 (95% CI: −2.16, −0.72)), and patients who completed the study on duloxetine 60 mg BID also had a significant ($P<0.001$) improvement in the Brief Pain Inventory average pain severity score (difference, −1.31 (−2.05, −0.58)). There were no significant differences in pairwise comparisons between duloxetine 60 mg QD and duloxetine 60 mg BID in patients who completed the study.

The changes in the Fibromyalgia Impact Questionnaire total score over time are illustrated in Fig. 3. Significant treatment-group differences between placebo and both duloxetine 60 mg QD and duloxetine 60 mg BID were observed beginning 1 week after randomization and continuing through week 12. There were no significant differences in pairwise comparisons between duloxetine 60 mg QD and duloxetine 60 mg BID.

Duloxetine 60 mg QD was statistically superior to placebo on all other secondary efficacy measures except for the mean tender point pain threshold and number of tender points with a low threshold. Duloxetine 60 mg BID was statistically superior to placebo on all secondary measures except for Hamilton Depression Rating Scale score (Table 2). There were no significant differences between duloxetine 60 mg BID and duloxetine 60 mg QD. The repeated measure analyses demonstrated results similar to those observed in the mean change analyses.

Analysis of the Brief Pain Inventory average pain severity score response rates (defined as ≥30% reduction from baseline to endpoint) revealed significant differences for both duloxetine 60 mg QD (55% (64/116); $P<0.001$) and duloxetine 60 mg BID (54% (61/114); $P=0.002$) compared with placebo (33% (39/118)). The 50% response rate at endpoint in the Brief Pain Inventory average pain severity score revealed significant differences for both duloxetine 60 mg QD (41% (48/116); $P=0.003$) and

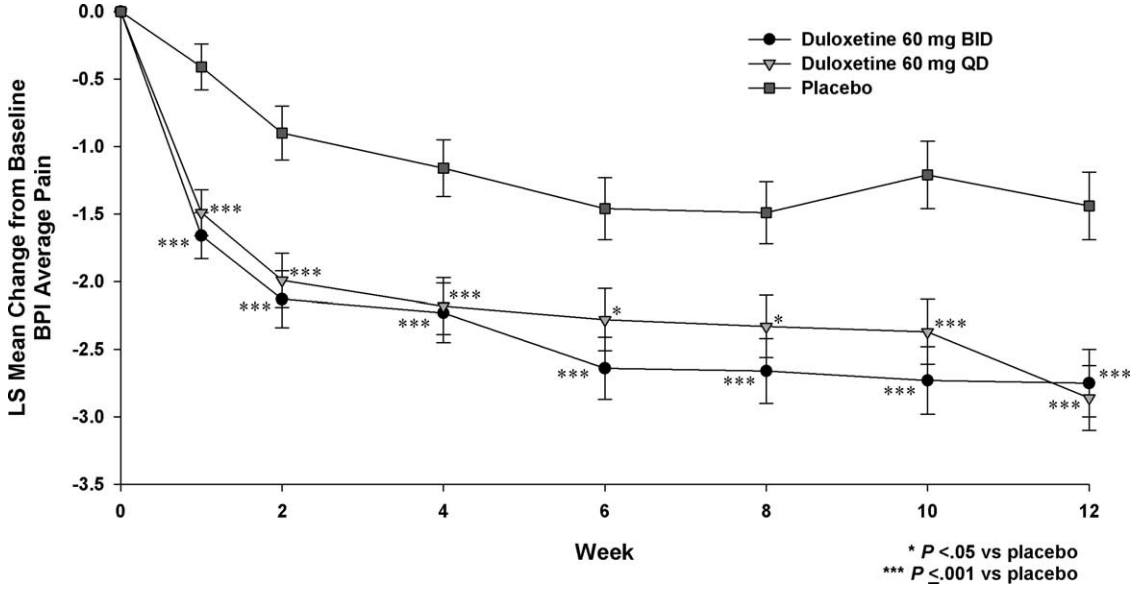

Fig. 2. Least-squares (LS) mean change from baseline in Brief Pain Inventory (BPI) average pain severity score for all randomized patients. Duloxetine 60 mg BID = duloxetine 60 mg twice a day; duloxetine 60 mg QD = duloxetine 60 mg once a day.

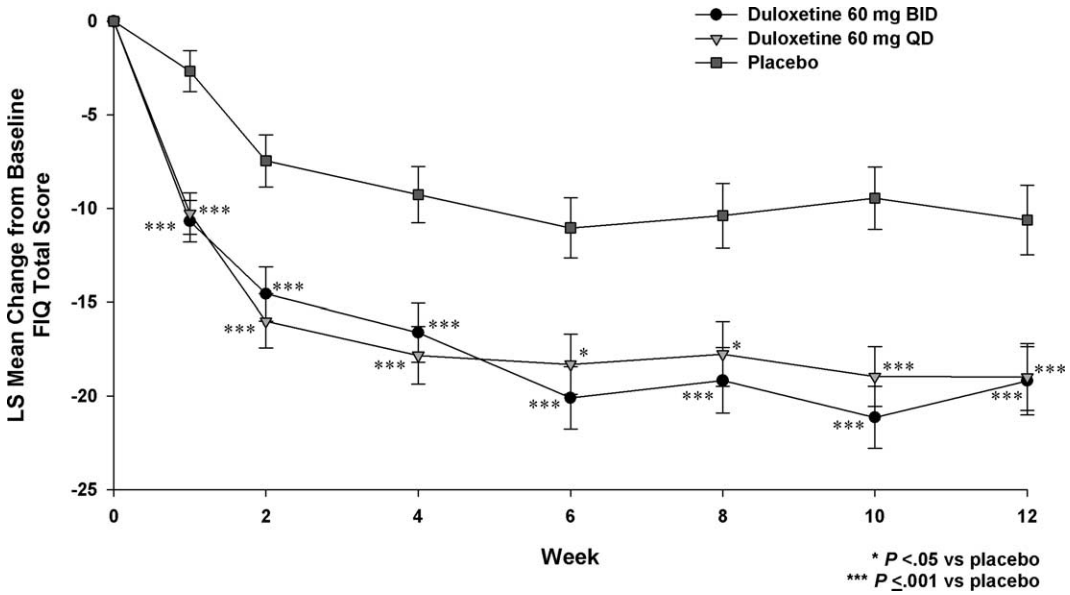

Fig. 3. Least-squares (LS) mean change from baseline in the Fibromyalgia Impact Questionnaire (FIQ) total score for all randomized patients. Duloxetine 60 mg BID = duloxetine 60 mg twice a day; duloxetine 60 mg QD = duloxetine 60 mg once a day.

duloxetine 60 mg BID (41% (47/114); $P = 0.003$) compared with placebo (23% (27/118)). Analysis of the Brief Pain Inventory average pain severity score sustained response showed that significantly more patients achieved sustained response over time on both duloxetine 60 mg QD (44%) and 60 mg BID (43%) doses compared with placebo (19%) ($P < 0.001$ vs. both duloxetine doses). No treatment-by-major depressive disorder interaction was observed for the primary efficacy measure ($P = 0.294$) (Brief Pain Inventory average pain severity score), suggesting that the effect of duloxetine on reduction of pain was similar in patients with or without major depressive disorder.

The path analysis for the Brief Pain Inventory average pain severity score showed that, for both duloxetine treatment groups, the direct treatment effect of duloxetine on pain accounted for the major portion of the total effect. The direct effect of duloxetine 60 mg QD on the reduction of the Brief Pain Inventory average pain severity score accounted for 75.6% of the total treatment effect ($P = 0.006$); the indirect treatment effect through improvement in depressive symptoms accounted for 24.4% of the total treatment effect. The direct effect of duloxetine 60 mg BID on the reduction of the Brief Pain Inventory average pain severity score accounted for 86.9% of the total treatment effect ($P = 0.0007$); the indirect treatment effect through improvement in depressive symptoms accounted for only 13.1% of the total treatment effect. In the subgroup that was defined by diagnosis of major depressive disorder (MDD), patients with a current diagnosis of MDD ($N = 91$) demonstrated significant differences between duloxetine treatment groups and placebo ($P = 0.005$ for duloxetine 60 QD, $P = 0.003$ for duloxetine 60 BID) on reduction in Brief Pain Inventory average pain severity score. Patients without a current diagnosis of MDD ($N = 257$) also demonstrated significant differences between duloxetine treatment groups and placebo ($P = 0.004$ for duloxetine 60 QD, $P = 0.005$ for duloxetine 60 BID) on reduction in Brief Pain Inventory average pain severity score. There was no significant therapy-by-subgroup interaction observed ($P = 0.294$).

3.4. Health outcomes

Both duloxetine treatment groups were significantly superior to placebo on several SF-36 subscales, including the mental subscore, bodily pain, mental health, role limit emotional, role limit physical, and vitality, as well as the Quality of Life in Depression total score, and the Sheehan Disability Scale total score and subscores for work, social life, and family life. In addition, duloxetine 60 mg QD was superior to placebo on the SF-36 subscale of social function and duloxetine 60 mg BID was superior to placebo on the SF-36 subscale of physical functioning (Table S2 in Appendix).

3.5. Safety

Of the 354 randomly assigned patients, 95 placebo-treated (79.2%), 109 duloxetine 60 mg QD-treated (92.4%; $P = 0.005$ vs. placebo), and 105 duloxetine 60 mg BID-treated (90.5%; $P = 0.018$ vs. placebo) patients reported at least one treatment-emergent adverse event. Patients in the duloxetine 60 mg QD and 60 mg BID groups reported nausea, dry mouth, constipation, decreased appetite and anorexia significantly more frequently than did placebo-treated patients (Fig. 4). Additionally, diarrhea and nasopharyngitis were reported by patients treated with

Table 2
Summary of results for the Brief Pain Inventory (BPI) severity and interference scores, Fibromyalgia Impact Questionnaire (FIQ), Tender Point assessments, Clinical Global Impression (CGI) of Severity, Patient Global Impression (PGI) of Improvement, and Hamilton Depression Rating Scale ($HAMD_{17}$) for all randomized patients

Measure	Placebo		Duloxetine 60 mg QD			Duloxetine 60 mg BID		
	n	Mean change (SE)	*n*	Mean change (SE)	Between-group difference (95% CI at endpoint)	*n*	Mean change (SE)	Between-group difference (95% CI at endpoint)
BPI severity (0–10)								
Average pain	118	−1.16 (0.21)	116	−2.39 (0.22)	−1.23 (−1.82,−0.64)***	114	−2.40 (0.22)	−1.24 (−1.83,−0.65)**
Worst pain	118	−1.35 (0.24)	115	−2.53 (0.25)	−1.18 (−1.85, −0.5)***	114	−2.37 (0.25)	−1.02 (−1.69,−0.34)**
Least pain	118	−0.58 (0.20)	116	−1.77 (0.20)	−1.19 (−1.73, −0.65) ***	114	−1.76 (0.20)	−1.18 (−1.72,−0.63)***
Pain right now	118	−1.15 (0.23)	116	−2.40 (0.23)	−1.24 (−1.87,−0.61) ***	114	−2.33 (0.23)	−1.17 (−1.81,−0.54)***
FIQ total score (0–80)	115	−8.35 (1.53)	114	−16.72 (1.53)	−8.38 (−12.58,−4.17) ***	112	−16.81 (1.54)	−8.46 (−12.68,−4.25)***
Mean tender point pain threshold	109	0.06 (0.08)	111	0.22 (0.08)	0.16 (−0.06, 0.37)	110	0.39 (0.08)	0.33 (0.11, 0.55)**
Tender points number (kg/cm^2)	109	−0.39 (0.26)	111	−0.42 (0.25)	−0.03 (−0.73, 0.67)	110	−1.11 (0.25)	−0.71 (−1.42,−0.01)*
CGI severity	111	−0.44 (0.10)	112	−0.84 (0.10)	−0.4 (−0.68,−0.12)**	111	−0.84 (0.10)	−0.4 (−0.68,−0.12)**
PGI improvement[a]	111	3.71(1.50)	114	3.11(1.77)	−0.66 (−1 1.−0.2)**	111	3.06 (1.73)	−0.68 (−1.13,−0.22)**
$HAMD_{17}$	109	−2.24 (0.45)	111	−3.79 (0.44)	−1.55 (−2.78,−0.32)*	110	−2.97 (0.45)	−0.73 (−1.96, 0.50)
BPI-interference								
General-activity	118	−1.27 (0.24)	116	−2.53 (0.25)	−1.26 (−1.94,−0.58)***	114	−2.34 (0.25)	−1.07 (−1.76,−0.39)**
Mood	117	−1.46 (0.24)	116	−2.94 (0.24)	−1.48 (−2.14,−0.82)***	114	−2.87 (0.24)	−1.42 (−2.08,−0.75)***
Walking ability	118	−1.12 (0.23)	115	−2.01 (0.24)	−0.89 (−1.53,−0.24)**	114	−2.53 (0.24)	−1.41 (−2.06,−0.76)***
Normal work	118	−1.20 (0.23)	116	−2.57 (0.23)	−1.36 (−2.00,−0.73)***	114	−2.47 (0.24)	−1.26 (−1.91,−0.62)***
Relationship with people	118	−1.31 (0.21)	116	−2.49 (0.21)	−1.18 (−1.77,−0.58)***	113	−2.49 (0.21)	−1.18 (−1.77,−0.59)***
Sleep	118	−1.71 (0.28)	116	−2.67 (0.29)	−0.96 (−1.74,−0.18)*	114	−2.69 (0.29)	−0.98 (−1.76,−0.20)*
Enjoyment of life	118	−1.68 (0.25)	116	−2.90 (0.26)	−1.22 (−1.92,−0.52)***	114	−2.89 (0.26)	−1.21 (−1.91,−0.51)***
Average of seven questions	118	−1.43 (0.21)	116	−2.57 (0.22)	−1.14 (−1.74,−0.54)***	114	−2.58 (0.22)	−1.15 (−1.75,−0.55)***

SE, standard error; CI, confidence interval; *n*, number of patients with a baseline and a non-missing postbaseline observation on the specific variable; **P*-value $<.05$ vs. placebo, ***P*-value $<.01$ vs. placebo, ****P*-value $<.001$ vs. placebo.

[a] For PGI Improvement, endpoint was analyzed and the mean (SD) is provided.

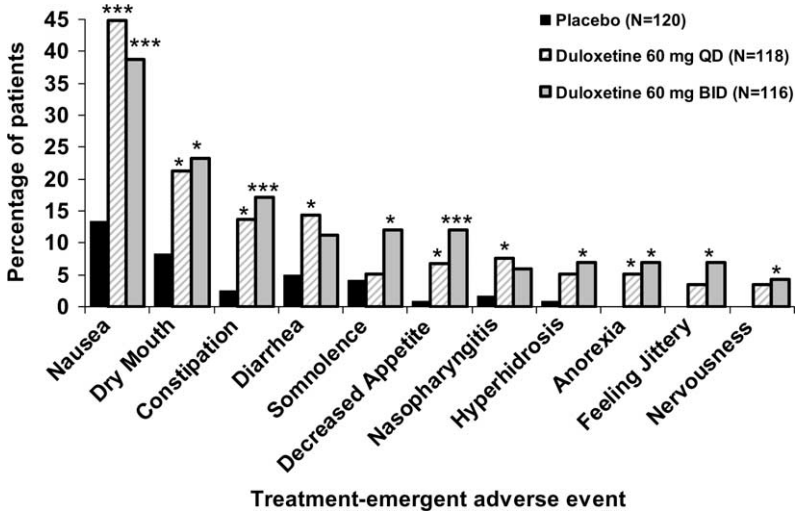

Fig. 4. Treatment-emergent adverse events that were significantly more common in the duloxetine-treated patients compared with the patients on placebo. *P-value <0.05 vs. placebo, ***P-value <0.001 vs. placebo. Duloxetine 60 mg BID = duloxetine 60 mg twice a day; duloxetine 60 mg QD = duloxetine 60 mg once a day.

duloxetine 60 mg QD significantly more frequently than patients treated with placebo. Somnolence, increased sweating, feeling jittery, and nervousness were reported significantly more frequently by patients on duloxetine 60 mg BID compared with placebo-treated patients. There were no significant treatment group differences in the percentage of serious treatment-emergent adverse events (SAE). During the study, one (0.9%) duloxetine 60 mg BID-treated patient experienced a SAE of appendicitis, and one (0.8%) duloxetine 60 mg QD-treated patient experienced a SAE of blood creatine phosphokinase increase and a hepatic enzyme increase. A total of 66 patients discontinued during the therapy phase due to adverse events, with significant differences between duloxetine 60 mg BID- and placebo-treated groups ($P=0.025$) (duloxetine 60 mg QD, 25 (21.2%); duloxetine 60 mg BID, 27 (23.3%); placebo 14 (11.7%)). Sixty-four percent of all patients who discontinued due to adverse events did so during the first 4 weeks of the study.

Compared with placebo-treated patients, both duloxetine 60 mg BID- and duloxetine 60 mg QD-treated patients experienced a slight, but significant, mean increase in alkaline phosphatase and a mean decrease in chloride. These mean differences were within normal reference ranges and were not considered clinically relevant. There was a slight but significant mean decrease in weight from baseline to endpoint for duloxetine 60 mg QD- (mean change (SD) (kg): -0.29 (2.46); $P=0.036$) and 60 mg BID- (mean change (SD): -0.44 (2.67); $P=0.009$) compared with placebo (mean change (SD): 0.38 (2.19)). There were no statistically significant treatment group differences in mean change of heart rate. For systolic and diastolic blood pressure, there was a significant difference between the duloxetine 60 mg BID and placebo groups ($P=0.03$ for both measures), with placebo-treated patients experiencing a decrease in systolic (mean change (SD): -1.57 (12.61)) and diastolic (mean change (SD): -1.23 (8.80)) blood pressure, and duloxetine 60 mg BID-treated patients experiencing an increase in systolic (mean change (SD): 1.32 (14.03)) and diastolic blood pressure (mean change (SD): 1.32 (8.95)). These changes were not considered clinically relevant. Two patients (one patient randomized to placebo, and one patient randomized to duloxetine 60 mg BID) experienced sustained elevation of blood pressure, but the treatment group differences were not significant (defined as a sitting diastolic blood pressure ≥ 90 mmHg and an increase from baseline of at least 10 mmHg, or sitting systolic blood pressure ≥ 140 mmHg and an increase from baseline of at least 10 mmHg, for 3 consecutive visits).

Among patients who continued in the 1-week study-drug tapering phase ($n=220$), 61 (27.7%) patients reported at least one discontinuation-emergent adverse event: 22 (30.6%) duloxetine 60 BID-treated patients, 30 (38%) duloxetine 60 mg QD-treated patients, and 9 (13%) placebo-treated patients ($P=0.002$). A significant treatment-group difference was observed for insomnia ($P=0.019$), with a greater number of duloxetine 60 mg QD-treated patients reporting insomnia during discontinuation compared with placebo-treated patients ($P=0.03$). In duloxetine 60 mg QD-treated patients, the discontinuation-emergent adverse events reported by $\geq 2\%$ of patients included dizziness, insomnia, headache, myalgia, nausea, diarrhea, abnormal dreams, depression, anxiety, and emotional disorder. In duloxetine 60 mg BID-treated patients, the discontinuation-emergent adverse events reported by $\geq 2\%$ of patients included dizziness, nausea, headache, diarrhea, fatigue, myalgia, abnormal dreams, depression, arthralgia, and edema peripheral.

4. Discussion

In this randomized, double-blind, 12-week trial, duloxetine 60 mg QD and 60 mg BID had significantly greater efficacy than placebo on most outcome measures in the treatment of women with American College of Rheumatology-defined primary fibromyalgia. Compared with placebo, both doses of duloxetine significantly reduced pain, as measured by the primary efficacy measure (Brief Pain Inventory average pain severity score) beginning in the first week of treatment and continuing throughout the 12 weeks of therapy. Response rates demonstrated greater pain reduction for both duloxetine groups compared with placebo, and patients in the duloxetine groups were more likely to achieve a sustained response over time. In addition, the improvement in fibromyalgia symptoms with both doses of duloxetine compared with placebo was independent of the presence or absence of major depressive disorder. Twenty-six percent of the patients had current major depressive disorder, which is consistent with community samples of adults with fibromyalgia in which about one third report major current problems with depression (White et al., 2002). The results of the present study, suggest that duloxetine is efficacious in fibromyalgia patients with or without current depression. Duloxetine also demonstrated a direct effect on pain reduction that was significantly greater than the indirect effect attributed to improvement in depressive symptoms. Therefore, the effect of duloxetine on reduction of pain associated with fibromyalgia appears to be independent of its effect on mood. Although the pathophysiology of fibromyalgia is unknown, duloxetine, a potent selective serotonin and norepinephrine reuptake inhibitor, may correct a functional deficit of serotonin and norepinephrine neurotransmission. Abnormalities of monoaminergic neurotransmission may be shared between major depressive disorder and fibromyalgia, but the independent effects of duloxetine on reduction in pain suggest that pain modulating effects in spinal and supraspinal pathways are not dependent on modulation of mood. Indeed, human experimental studies suggest that there is a complex relationship between pain and depression (Schreiber et al., 2003; Gormsen et al., 2004).

These results confirm findings from the previous study comparing duloxetine to placebo in the treatment of fibromyalgia patients with or without major depressive disorder (Arnold et al., 2004). In the present study, in which two doses of duloxetine were evaluated, there were no significant differences between the duloxetine 60 mg QD and duloxetine 60 mg BID treatment groups in efficacy outcomes. However, only the duloxetine 60 mg BID dose, compared with placebo, significantly improved the tender point assessments. These results are consistent with the previous study of duloxetine in fibromyalgia in which duloxetine 60 mg BID significantly improved the tender point measures compared with placebo (Arnold et al., 2004). A higher dosage of duloxetine might therefore be necessary to significantly improve tenderness, one of the common features of fibromyalgia. Previous fibromyalgia studies using tricyclic antidepressants found minimal improvement in tender point measures (Arnold et al., 2000; O'Malley et al., 2000), suggesting that tender points are less responsive to treatment. The dolorimeter method of tender point assessment used in the present study and in the previous trial of duloxetine (Arnold et al., 2004) offers promise as a more reliable technique than manual assessments for monitoring change over time. However, a definition of a clinically meaningful response in tender point counts and pressure pain thresholds as measured by the dolorimeter has yet to be established (Arnold, 2005). Both doses of duloxetine were well tolerated by most patients and safely administered. Significantly more duloxetine-treated patients than placebo-treated patients reported treatment-emergent adverse events, but these events were generally mild to moderate in severity. Clinical laboratory assessments, vital signs, and physical findings were stable relative to baseline and no clinically relevant differences were detected between treatment groups.

Significantly more patients in the duloxetine 60 mg BID group than the placebo group discontinued treatment due to adverse events. These findings differ from the previous trial of duloxetine 60 mg BID in the treatment of fibromyalgia, in which there were no differences between treatment groups in discontinuation due to treatment-emergent adverse events (Arnold et al., 2004). Notably, most patients in the present study who discontinued due to adverse events did so within the first 4 weeks of the study. Therefore, the difference between the studies might be explained by the slower titration of duloxetine in the previous study, in which patients were started on duloxetine 20 mg QD and underwent titration to 60 mg BID over 2 weeks. By contrast, patients in the present study were started on 60 mg QD and underwent titration to 60 mg BID over just 3 days. These results suggest that some patients would have better tolerability with a lower duloxetine starting dose and slower titration. The present study also included a 1-week discontinuation phase in which significantly more duloxetine-treated patients reported discontinuation-emergent adverse events, most commonly dizziness, than placebo-treated patients. Tapering the duloxetine dose at the end of therapy is recommended.

Several limitations of this study should be considered. First, the results are based on an acute treatment trial of 12 weeks, and the results may not generalize to a longer duration of treatment. Furthermore, about 38% of all patients did not complete the study. Future studies should evaluate the long-term efficacy of duloxetine in fibromyalgia, a chronic condition that will likely require treatment for more than 3 months. Second, the results of this study may not generalize to individuals with certain forms of psychopathology or secondary fibromyalgia, because patients with these conditions were excluded from the study. Third, this study included only women because it was

designed to confirm the results from the previous duloxetine fibromyalgia trial in which duloxetine-treated women, but not duloxetine-treated men responded significantly more than same sex placebo-treated patients on efficacy measures (Arnold et al., 2004). Therefore, the results of this study cannot be generalized to men. Studies that include men with fibromyalgia are planned to reexamine the efficacy of duloxetine in men. Finally, this study did not include an active comparator, because it was intended to confirm and extend previous findings of the efficacy of duloxetine compared with placebo in the treatment of fibromyalgia (Arnold et al., 2004). Future studies should compare the efficacy of duloxetine with other medications, such as tricyclic antidepressants that inhibit both serotonin and norepinephrine and have a consistent, moderate efficacy in fibromyalgia (Arnold et al., 2000).

In summary, this randomized, placebo-controlled study provides substantial evidence and confirms previous findings that treatment with duloxetine 60 mg BID for up to 12 weeks is safe and effective in the treatment of fibromyalgia in women with or without major depressive disorder. In addition, this study provides evidence that duloxetine at the lower dose of 60 mg QD is also safe and effective in these patients.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.pain.2005.06.031.

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