Pain 136 (2008) 432–444

PAIN

www.elsevier.com/locate/pain

Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial ☆

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Received 25 July 2007; received in revised form 20 February 2008; accepted 21 February 2008

Abstract

The primary objectives of this study were to assess the efficacy and safety of duloxetine for reducing pain severity in fibromyalgia patients with or without current major depressive disorder. This was a 6-month, multicenter, randomized, double-blind, placebo-controlled study. In total, 520 patients meeting American College of Rheumatology criteria for fibromyalgia were randomly assigned to duloxetine (20 mg/day, 60 mg/day, or 120 mg/day) or placebo, administered once daily, for 6 months (after 3 months, the duloxetine 20-mg/day group titrated to 60 mg/day). The co-primary outcome measures were the Brief Pain Inventory (BPI) average pain severity score and Patient Global Impressions of Improvement (PGI-I) score. Safety was assessed via treatment-emergent adverse events, and changes in vital sign, laboratory, and ECG measures. Compared with placebo-treated patients, those patients treated with duloxetine 120 mg/day improved significantly more on the co-primary outcome measures at 3 months (change in BPI score [−2.31 vs −1.39, $P < 0.001$] and PGI-I [2.89 vs 3.39, $P = 0.004$]) and at 6 months (change in BPI [−2.26 vs −1.43, $P = 0.003$] and PGI-I [2.93 vs 3.37, $P = 0.012$]). Compared with placebo, treatment with duloxetine 60 mg/day also significantly improved the co-primary measures at 3 months and BPI at 6 months. Duloxetine was efficacious in patients both with and without major depressive disorder. There were no clinically significant differences between treatment groups in changes in vital signs, laboratory measures, or ECG measures. Study results demonstrated that duloxetine at doses of 60 mg/day and 120 mg/day appears to be safe and efficacious in patients with fibromyalgia.

Keywords: Fibromyalgia; Duloxetine; Efficacy and safety; Randomized clinical trial

☆ Clinical Trial Registry Number: NCT00190866, at www.clinicaltrials.gov.

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0304-3959/$34.00
doi:10.1016/j.pain.2008.02.024

1. Introduction

Fibromyalgia affects about 2% of the US general population and is characterized by chronic, widespread pain [42,43]. The American College of Rheumatology criteria for fibromyalgia include widespread pain for at least 3 months and pain on palpation in 11 of the 18 tender-point sites [26,44]. Moreover, a variety of other symptoms such as fatigue, headache, and sleep disturbance often accompany the widespread pain [44]. Mood disorders are also common, with 25–40% of patients with fibromyalgia reporting current major depressive disorder (MDD) [1,2].

Although the underlying mechanisms responsible for fibromyalgia are not well understood, dysfunction of central serotonin and norepinephrine systems may play a key role. Both serotonin and norepinephrine have been implicated in the mediation of endogenous pain mechanisms via the descending inhibitory pain pathways [3,6,28]. Dysfunction in these systems could be involved in central sensitization and in hyperexcitability of the spinal cord and supraspinal pain-transmitting pathways [3,6,28,31,32,45]. Duloxetine hydrochloride, a selective serotonin and norepinephrine reuptake inhibitor that is relatively balanced in its affinity for serotonin and norepinephrine reuptake transporters, is approved by the Food and Drug Administration (FDA) for the treatment of MDD [10,11] and generalized anxiety disorder [20,24], and for the management of diabetic peripheral neuropathic pain [29,39]. Two 12-week, double-blind, placebo-controlled studies provided support that duloxetine was efficacious in the reduction of pain and well-tolerated in patients with fibromyalgia. In the first study [1], duloxetine 60 mg twice a day (BID) was well-tolerated; however, the improvement associated with duloxetine treatment was not statistically significant on the primary pain measure in the overall study population, but was significant in the female subpopulation, which comprised 89% of the overall study population. The second study [2], which included only women, found that both 60 mg once a day (QD) and 60 mg BID were efficacious on pain and nearly all other efficacy measures, including health outcome assessments. In both studies, duloxetine was equally efficacious in female patients with or without MDD.

Based on the evidence that duloxetine 60 mg QD and 60 mg BID were well-tolerated and efficacious in the treatment of fibromyalgia, we conducted another randomized, double-blind, placebo-controlled trial to further assess the efficacy and safety of duloxetine at 20 mg/day, 60 mg/day, and 120 mg/day, administered once daily for 6 months in women and men with fibromyalgia with or without comorbid MDD. This was the first study of duloxetine for fibromyalgia of this duration. Furthermore, in addition to evaluating the efficacy of duloxetine on change in pain severity, a co-primary measure to determine the effect of duloxetine on global improvement was included. The study also included secondary measures of fatigue, mood, tender-point threshold, health-related quality of life, and functional impairment.

2. Methods

2.1. Overview

The study was conducted in 38 outpatient research centers in the USA and Puerto Rico between June 2005 and June 2007. Each clinical study site's Institutional Review Board approved the protocol, which was developed in accordance with the ethical standards of Good Clinical Practice (GCP) and the Declaration of Helsinki. Patients provided written informed consent before participation in any study-related procedures. Patients were identified by physician referral or advertisement for a fibromyalgia medication trial.

2.2. Entry criteria

Female and male outpatients at least 18 years of age who met criteria for fibromyalgia as defined by the American College of Rheumatology were recruited for this study. Patients were required to have a score $\geqslant 4$ on the average pain severity item (in the past 24 h) of the Brief Pain Inventory (BPI-modified short form) [8] at screening and at baseline. Patients with or without current MDD were included and evaluated for the presence of psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI) [35]. Training was provided to psychiatrists, psychologists, or individuals with at least 6 months of experience in the administration of psychiatric scales at site start-up meetings either in person or remotely via video conferencing. Each site was also supplied with a CD-ROM containing training for the completion of the MINI and other efficacy, health outcome, and safety measures.

Exclusion criteria included any current primary psychiatric diagnosis other than MDD; pain symptoms unrelated to fibromyalgia that could interfere with interpretation of outcome measures; regional pain syndromes; multiple surgeries or failed back syndrome; a confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or other autoimmune disease; unstable medical or psychiatric disorders; severe liver disease; current pregnancy or breast-feeding; or a history of substance abuse within the past year. Patients who were judged by the investigator to be treatment-refractory or whose response might be compromised by disability compensation issues in the opinion of the investigator were also excluded.

Prior to randomization, patients were required to discontinue any medications that might interfere with the evaluation of pain improvement, including analgesics (with the exception of up to 325 mg/day of aspirin for cardiac prophylaxis and acetaminophen up to 2 g/day for pain), antidepressants, anticonvulsants, or other medications taken for fibromyalgia or pain. Sedating antihistamines and episodic use (up to 40 total days of use during the 6 months of treatment) of chloral hydrate, zolpidem, zolpiclone, and zaleplon were allowed to facilitate sleep. Patients were encouraged not to initiate or alter

non-conventional/alternative therapies such as acupuncture, biofeedback, or cognitive-behavioral therapy for the duration of the study.

2.3. Study design

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group study of patients with a diagnosis of fibromyalgia with or without current MDD. There was a 1-week screening phase, which was followed by 3-month (15 weeks) double-blind, randomized treatment with duloxetine (20 mg/day, 60 mg/day, or 120 mg/day) or placebo once daily, for evaluation of the primary endpoint. All remaining patients continued for an additional 13 weeks of double-blind, placebo-controlled treatment. In this paper, 6-month treatment refers to the entire 28 weeks of double-blind treatment (secondary endpoint). All patients completing the 6-month, double-blind treatment phase were eligible to enter an additional 28 weeks of treatment (this will not be reported here). A 2-week taper occurred at the end of the additional 28 weeks or for patients who discontinued after receiving at least 2 weeks of treatment.

Patients were randomly assigned in a 1:2:2:2 ratio to once daily duloxetine 20 mg/day, 60 mg/day, 120 mg/day, or placebo, respectively. Patients randomly assigned to duloxetine 60 mg/day were started at 30 mg/day for 1 week, then titrated to 60 mg/day. Patients randomly assigned to 120 mg/day were started at 30 mg/day for 1 week, then titrated to 60 mg/day for 1 week, and then to 120 mg/day. Patients randomly assigned to duloxetine 20 mg/day had their dose blindly increased to 60 mg/day after 3 months on study drug when they entered the second half of the 6-month, double-blind treatment phase (20/60 mg/day). The 20-mg/day dosage was included to help establish the minimally effective duloxetine dose. Assignment to treatment groups was determined by a computer-generated random sequence and each stratum (depressed and non-depressed) was randomly assigned within sites to achieve a relative balance across treatments.

During the taper phase, those who had received duloxetine 60 mg/day experienced dosage reduction to 30 mg/day for 1 week and then received placebo for a second week. The dosage of patients who had received duloxetine 120 mg/day was reduced to 60 mg/day for 1 week, then 30 mg/day for a second week. Patients who had received duloxetine 20 mg/day or placebo received placebo for the entire 2-week taper phase.

2.4. Outcome measures

The co-primary outcome measures were the average pain severity item of the BPI-modified short form [8] 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) and the Patient Global Impression of Improvement (PGI-I) scale [18] ranging from 1 (very much better) to 7 (very much worse). The response rate, defined as a $\geqslant$50% reduction in the average pain score from baseline to endpoint, was determined at both 3 months and 6 months. The number needed to treat (NNT) was based on the 50% response rates at 3 months and at 6 months. NNT was calculated as 1 divided by the absolute risk reduction (ARR) where the ARR was the difference between the duloxetine and placebo response rates. The numbers were then rounded up to the nearest whole number.

Secondary efficacy measures included the Fibromyalgia Impact Questionnaire (FIQ) [5], Clinical Global Impressions-Severity (CGI-S) [18], tender-point pain assessments using the Fischer dolorimeter (Pain Diagnostics and Thermography, Great Neck, NY) [13], including mean tender-point pressure pain thresholds, the Multidimensional Fatigue Inventory (MFI) [36], the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) [19], the Sheehan Disability Scale (SDS) [34], the 36-item Short-Form Health Survey (SF-36) [38], and the EuroQoL Questionnaire-5 Dimensions (EQ-5D) [23].

The safety of duloxetine was assessed through collection of spontaneously reported adverse events, vital signs, and weight that were recorded at baseline and each visit through study completion. An adverse event was considered treatment-emergent if it was new or a worsening of a pre-existing symptom upon initiation of treatment compared with the event reported at baseline. Adverse events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) version 9.1.

Centralized electrocardiograms (ECGs) and laboratory tests (hematology and clinical chemistry) were conducted at screening, at several visits throughout the study periods, and at endpoint. Urinalysis and a drug screen were undertaken during the screening phase for the evaluation of inclusion/exclusion criteria.

2.5. Statistical analyses

The *a priori*-defined primary objective of the study was to determine whether duloxetine 120 mg/day provided significant improvement compared with placebo in both co-primary outcomes at the 3-month endpoint. The study was designed to enroll 140 patients each in the duloxetine 120 mg/day and placebo groups so as to have at least 85% power to detect a treatment group difference of -1.2 points between duloxetine 120 mg/day and placebo in the change in the average pain severity score from baseline to endpoint, and at least 80% power to detect a difference in the PGI-I at endpoint of 0.68 in the same two groups for the same treatment period. Overall Type I error regarding the multiple comparisons associated with the co-primary endpoints, multiple doses of duloxetine, and multiple timepoints for assessment was maintained at the 0.05 level through implementation of a gatekeeper strategy [41].

Secondary outcomes were included to provide additional assessments of duloxetine's efficacy in treating fibromyalgia and to provide a better understanding of duloxetine's potential effect on other symptom domains associated with fibromyalgia. As such, multiplicity adjustments were not conducted for the secondary outcomes.

All analyses were conducted on an intent-to-treat basis unless otherwise specified. All randomly assigned patients were included in the safety analyses, and all patients with a baseline and at least one post-baseline measurement were included in the efficacy analyses. For continuous efficacy variables, with the exception of the PGI-I scores, treatment group differences in change from baseline to endpoint were examined using an analysis of covariance (ANCOVA) model with treatment and investigator as main effects and the baseline score as the covariate. Endpoint was defined as each patient's last observation within the respective 3- and 6-month treatment periods. The

PGI-I scores at endpoint were analyzed using an ANCOVA model with treatment and investigator as fixed effects, with the PGI-Severity (PGI-S) score [18] at baseline as a covariate. The PGI-S scale is a patient-rated measure of illness severity which is similar to the CGI-S, and that reflects the patient's impression of his/her illness severity at a given point in time. Pairwise comparisons between treatment groups were based on evaluating the difference in type II least-squares mean (LS mean) from the above ANCOVA models. Treatment-by-investigator interactions were evaluated, but the interaction term was not included in the ANCOVA model, irrespective of its statistical significance. Analysis of subgroups based on age, race, sex, and MDD status at baseline were conducted using similar ANCOVA models, with the addition of terms for the subgroup effect and treatment-by-subgroup interaction. Treatment effects between subgroups were considered to differ significantly when the treatment-by-subgroup interaction P-value was $\leqslant 0.10$.

To assess the robustness of the co-primary endpoints, a similar ANCOVA analysis in which the baseline observation was carried forward (BOCF) for all patients discontinuing early was implemented post hoc for the BPI average pain score. Similarly, for the PGI-I, mean scores at endpoint were reassessed with all discontinuing patients assigned an endpoint PGI-I score of 4, corresponding to "no change". These analyses assume no treatment benefit or deficit for patients who did not complete the 3- or 6-month acute treatment phases in the respective 3- and 6-month analyses.

Demographic and baseline disease characteristics and changes from baseline to endpoint in ECG parameters, vital signs, and weight were evaluated using a main effects analysis of variance (ANOVA) model containing terms for treatment and investigator. Unless otherwise specified, "baseline" refers to the last non-missing observation at or before the randomization visit, and "endpoint" refers to the last non-missing observation in the period of analysis (3 months or 6 months). Categorical outcomes were compared between treatment groups using Fisher's exact test. Treatment effects were evaluated based on a two-sided significance level of 0.05 and interaction effects at a significance level of 0.10. Throughout this article, the term "significant" indicates statistical significance.

A gatekeeper strategy [41] was employed for sequentially testing secondary hypotheses and was ordered based on regulatory requirements and considerations at the time of study design. If the primary hypotheses were statistically significant at the 0.05 two-sided level, the first secondary gatekeeper hypothesis was tested. If this comparison was statistically significant at the 0.05 two-sided level, subsequent secondary hypotheses were tested in sequence until a null hypothesis in the sequence failed to be rejected. The sequential testing was conducted in the following order: the comparison between duloxetine 60 mg/day and placebo on the change from baseline to endpoint on the average pain severity score and the endpoint of the PGI-I (3-month comparison); the comparison between duloxetine 120 mg/day and placebo on the change from baseline to endpoint on the average pain severity score and the endpoint of PGI-I (6-month comparison); the comparison between duloxetine 60 mg/day and placebo on the change from baseline to endpoint on the average pain severity score and the endpoint of PGI-I (6-month comparison); the comparison between duloxetine 120 mg/day and placebo on the change from baseline to endpoint on the SDS total score (6-month comparison); the comparison between duloxetine 60 mg/day and placebo on the change from baseline to endpoint on the SDS total score (6-month comparison); the comparison between duloxetine 120 mg/day and placebo on the change from baseline to endpoint on the SDS total score (3-month comparison); and the comparison between duloxetine 60 mg/day and placebo on the change from baseline to endpoint on the SDS total score (3-month comparison).

Response profiles over time for efficacy measures were evaluated using a likelihood-based, mixed-effect repeated-measures model that contained categorical effects for treatment, visit, investigator, and treatment-by-visit interaction, as well as the continuous fixed covariates for baseline score and baseline-by-visit interaction. Visitwise treatment group comparisons were based on the difference in LS means derived from type III sums of squares.

Path analysis [30] was performed to quantify the amount of treatment benefit attributed to a direct analgesic effect as compared to the indirect effect on pain mediated through improvement in depressive symptoms. In this analysis, two regression models were employed to partition the overall treatment effect into direct and indirect components. Please see Arnold et al. [1] for statistical details of the methodology.

3. Results

3.1. Patient disposition

A total of 1010 patients were screened to enroll 520 patients who met the entry criteria and were randomly assigned to either duloxetine 20 mg/day ($N = 79$), duloxetine 60 mg/day ($N = 150$), duloxetine 120 mg/day ($N = 147$), or placebo ($N = 144$). The percentage of patients in each of the above treatment groups that completed the 3-month treatment phase was 63.3%, 64.7%, 64.6%, and 58.3% ($P = 0.645$), respectively. The most frequently reported reasons for discontinuation were adverse events, lack of efficacy, and patient decision (Fig. 1). Overall, treatment groups did not significantly differ with respect to any specific reason for discontinuation. There was a numeric trend toward increasing rates of discontinuation due to adverse events (AEs) associated with increasing duloxetine dose (duloxetine 120 mg/day [22.5%], duloxetine 60 mg/day [14.7%], duloxetine 20 mg/day [10.1%], placebo [11.8%]) with a statistically significantly higher rate of discontinuation due to AEs associated with the 120 mg/day group compared with the placebo group ($P = 0.029$). In contrast, a non-significant, inverse trend toward decreasing rates of discontinuation due to lack of efficacy was associated with increasing duloxetine dose [duloxetine 120 mg/day (4.1%), duloxetine 60 mg/day (7.3%), duloxetine 20 mg/day (10.4%), placebo (8.9%)] was demonstrated.

A total of 325 patients continued the study for 3 months. This included 49 duloxetine 20 mg/day patients, whose dose was increased to duloxetine 60 mg/day for the final 3 months. A total of 278 patients (85.5% of those entering the additional 3 months) completed the 6-month treatment phase. The percentage of patients

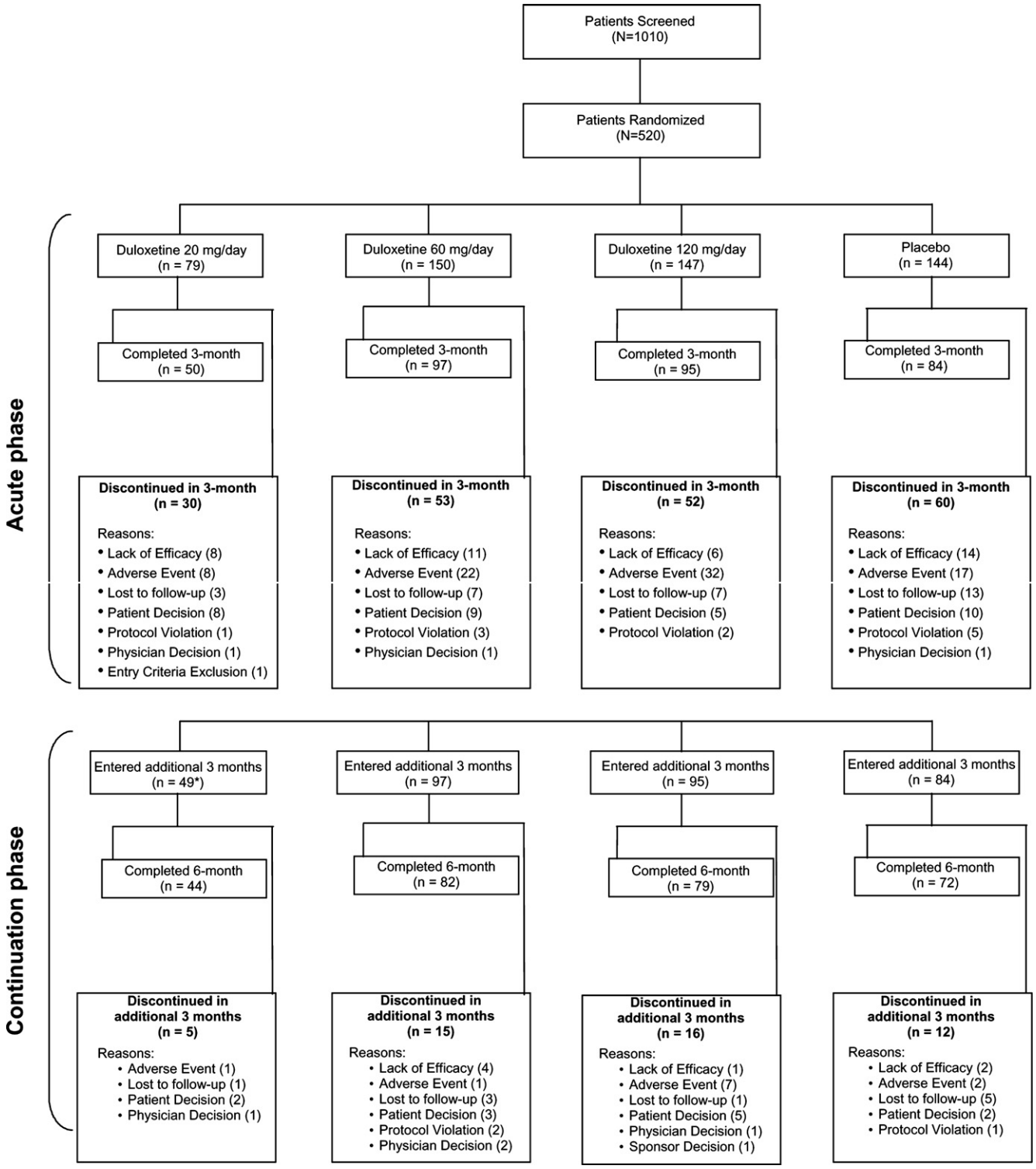

Fig. 1. Patient flow diagram. *One patient treated with duloxetine 20 mg/day that completed the acute phase decided not to enter the continuation phase.

completing the entire 6 months of treatment was 57.0% (45/79) for the duloxetine 20/60 mg/day group, 54.7% (82/150) for the duloxetine 60 mg/day group, 53.7% (79/147) for the duloxetine 120 mg/day group, and 50.0% (72/144) for the placebo group.

3.2. Baseline clinical and demographic characteristics

Most of the patients were women (94.8%), white (84.2%), and, on average, 51 years of age. There were no significant differences between treatment groups in

demographics or baseline disease characteristics (Table 1).

3.3. Efficacy and health outcomes

3.3.1. Three month treatment phase

Unlike patients receiving duloxetine 20 mg/day, patients treated with duloxetine 60 mg/day and duloxetine 120 mg/day experienced significantly greater improvement in pain severity compared with placebo-treated patients, as measured by the change from baseline in the average pain severity score (Table 2). The mean endpoint PGI-I score was significantly lower (better) in patients treated with duloxetine for each of the three doses compared with patients treated with placebo.

Significant improvement in the average pain severity score (Fig. 2) and in the PGI-I score (Fig. 3) occurred as early as 1 week after starting treatment for both the duloxetine 60 mg/day and 120 mg/day treatment groups. In addition, duloxetine-treated patients showed similar improvement in the average pain severity score and PGI-I score compared with placebo regardless of the presence or absence of MDD at baseline (Table 2).

For secondary measures, both duloxetine 60 mg/day- and duloxetine 120 mg/day-treated patients demonstrated significantly greater improvements compared with placebo-treated patients in the CGI-S score, FIQ total score, SF-36 mental component score, and some of the MFI domains, but did not achieve significance on the other secondary efficacy and health outcome measures (Table 2). In addition, the BOCF analysis for the average pain severity score demonstrated significant improvement in pain severity in the duloxetine 120 mg/day (-2.25, $P < 0.001$) and 60 mg/day (-1.92, $P = 0.027$) groups but not in the 20 mg/day group (-1.86, $P = 0.102$) compared with the placebo group (-1.34). The PGI-I at endpoint assessments assuming a value of 'no change' for discontinuing patients were consistent with the above findings: duloxetine 120 mg/day (3.39, $P = 0.004$), 60 mg/day (3.40, $P = 0.007$), duloxetine 20 mg/day group (3.45, $P = 0.052$) compared with the placebo group (3.69).

No significant treatment-by-investigator interactions were observed during either 3 months or 6 months of treatment for the average pain severity score, PGI-I score, SDS Global Functioning score, and those measures and timepoints relating to the primary and secondary gatekeeper objectives.

Response rates, defined as a $\geqslant 50\%$ improvement from baseline to the 3-month endpoint in the average pain severity score, were significantly greater for duloxetine 120 mg/day (40.1%; $P = 0.003$), but not for duloxetine 60 mg/day (34.0%; $P = 0.067$) or for duloxetine 20 mg/day (32.5%; $P = 0.200$) compared with placebo (23.7%). Post hoc analyses also showed that response rates defined by $\geqslant 30\%$ reduction from baseline to 3-month endpoint in the average pain severity score were significantly higher for duloxetine 120 mg/day (52.1%; $P = 0.008$) and for duloxetine 60 mg/day (50.7%; $P = 0.016$), but not for duloxetine 20 mg/day (46.8%; $P = 0.147$) compared with placebo (36.0%). The number needed to treat (95% CI) for duloxetine 20 mg/day, 60 mg/day, and 120 mg/day was 12 (4.6, ∞), 10 (4.8, ∞), and 7 (3.7, 18.1), respectively.

The path analysis demonstrated that the direct analgesic effect of duloxetine 60 mg/day on the reduction in the average pain severity score accounted for 62.2% ($P = 0.183$) of the total treatment effect at 3 months. The indirect treatment effect through improvement in

Table 1
Baseline characteristics of patients

Variable	Duloxetine			Placebo
	20 mg/day ($N = 79$)	60 mg/day ($N = 150$)	120 mg/day ($N = 147$)	($N = 144$)
Women, *n* (%)	77 (97.5)	136 (90.7)	143 (97.3)	137 (95.1)
Age, mean years (SD)	50.9 (11.4)	51.8 (10.6)	51.1 (10.8)	50.3 (10.9)
Race, *n* (%)				
White	66 (83.5)	127 (84.7)	126 (85.7)	119 (82.6)
African descent	4 (5.1)	3 (2.0)	4 (2.7)	5 (3.5)
Hispanic	9 (11.4)	16 (10.7)	17 (11.6)	20 (13.9)
Other	0 (0.0)	4 (2.7)	0 (0.0)	0 (0.0)
MDD diagnosis, *n* (%)	22 (27.9)	35 (23.3)	34 (23.1)	35 (24.3)
BPI average pain severity score, mean (SD)	6.8 (1.6)	6.5 (1.4)	6.4 (1.6)	6.6 (1.7)
CGI-severity, mean (SD)	4.4 (0.9)	4.3 (0.8)	4.4 (0.8)	4.5 (0.9)
FIQ total score, mean (SD)	54.0 (11.4)	51.7 (11.8)	51.7 (14.1)	53.0 (11.2)
Mean tender-point threshold, mean (SD)	2.1 (0.7)	2.3 (1.0)	2.1 (0.9)	2.2 (0.8)
$HAMD_{17}$ total score, mean (SD)	10.6 (5.8)	9.9 (6.1)	9.9 (6.1)	10.6 (5.8)
MDD patients	15.1 (4.9)	15.4 (5.8)	16.3 (4.4)	15.3 (4.5)
Non-MDD patients	8.9 (5.1)	8.2 (5.1)	8.1 (5.2)	9.1 (5.3)

Abbreviations: MDD, major depressive disorder; BPI, Brief Pain Inventory; CGI-Severity, Clinical Global Impressions-Severity; FIQ, Fibromyalgia Impact Questionnaire.No significant between-group differences were found.

Table 2
Summary of primary and secondary efficacy outcomes: 3-month and 6-month treatment phases

Variable	Duloxetine			Placebo
	20 mg/day ($N = 79$) LS mean change (SE)	60 mg/day ($N = 150$) LS mean change (SE)	120 mg/day ($N = 147$) LS mean change (SE)	($N = 144$) LS mean change (SE)
3-Month double-blind treatment phase				
BPI average pain severity score				
Overall	−1.92 (0.27)	−1.99 (0.20)*	−2.31 (0.20)***	−1.39 (0.20)
With MDD[a]	−2.45 (0.50)	−2.49 (0.44)	−2.69 (0.46)	−1.60 (0.43)
Without MDD	−1.70 (0.32)	−1.86 (0.24)	−2.21 (0.24)**	−1.30 (0.24)
PGI-I[b]				
Overall	2.85 (0.17)**	3.04 (0.13)*	2.89 (0.13)**	3.39 (0.13)
With MDD	2.84 (0.31)	2.64 (0.27)	2.46 (0.28)*	3.28 (0.26)
Without MDD	2.89 (0.22)*	3.15 (0.16)	3.02 (0.16)*	3.44 (0.16)
FIQ total score	−14.60 (1.83)*	−15.41 (1.40)**	−14.50 (1.38)*	−10.05 (1.42)
MFI general fatigue	−1.73 (0.42)	−2.20 (0.32)	−2.34 (0.32)	−1.88 (0.33)
MFI physical fatigue	−1.70 (0.42)	−1.62 (0.32)	−1.80 (0.32)	−0.99 (0.33)
MFI mental fatigue	−1.64 (0.44)	−2.38 (0.34)**	−2.07 (0.33)	−1.21 (0.34)
MFI reduced motivation	−0.32 (0.43)	−1.41 (0.33)*	−1.42 (0.33)*	−0.32 (0.33)
MFI reduced activity	−1.82 (0.44)*	−1.30 (0.34)	−1.77 (0.33)**	−0.61 (0.34)
CGI-S	−0.96 (0.12)	−1.06 (0.10)**	−1.10 (0.09)***	−0.70 (0.10)
Mean tender-point threshold	0.51 (0.11)	0.52 (0.08)	0.42 (0.08)	0.33 (0.08)
SDS global functioning	−5.41 (0.86)	−5.69 (0.66)	−5.02 (0.66)	−4.37 (0.68)
EQ-5D	0.18 (0.03)*	0.18 (0.03)	0.16 (0.02)	0.09 (0.03)
SF-36 mental component summary	2.44 (1.22)	5.18 (0.93)**	5.28 (0.92)**	1.78 (0.95)
SF-36 physical component summary	4.87 (1.09)	4.64 (0.83)	4.07 (0.83)	3.60 (0.85)
	20/60 mg/day ($N = 79$) LS mean change (SE)	60 mg/day ($N = 150$) LS mean change (SE)	120 mg/day ($N = 147$) LS mean change (SE)	Placebo ($N = 144$) LS mean change (SE)
6-Month double-blind treatment phase				
BPI average pain severity score				
Overall	−2.22 (0.28)*	−1.98 (0.21)*	−2.26 (0.21)**	−1.43 (0.21)
With MDD	−2.58 (0.53)	−2.35 (0.46)	−2.56 (0.48)*	−1.35 (0.45)
Without MDD	−2.16 (0.34)	−1.93 (0.25)	−2.20 (0.25)*	−1.48 (0.25)
PGI-I[b]				
Overall	2.79 (0.17)**	3.08 (0.13)	2.93 (0.13)*	3.37 (0.13)
With MDD	2.85 (0.33)	2.96 (0.29)	2.41 (0.30)*	3.28 (0.28)
Without MDD	2.76 (0.22)*	3.07 (0.16)	3.04 (0.16)	3.37 (0.16)
FIQ total score	−14.77 (1.88)	−12.28 (1.44)	−13.86 (1.41)	−10.42 (1.46)
MFI general fatigue	−1.79 (0.44)	−1.83 (0.34)	−2.12 (0.33)	−1.69 (0.34)
MFI physical fatigue	−2.09 (0.42)	−1.67 (0.32)	−2.10 (0.32)*	−1.10 (0.33)
MFI mental fatigue	−2.37 (0.44)*	−2.29 (0.34)*	−2.37 (0.33)**	−1.14 (0.34)
MFI reduced motivation	−0.64 (0.43)	−1.04 (0.33)	−1.93 (0.33)***	−0.50 (0.34)
MFI reduced activity	−1.75 (0.45)	−1.26 (0.35)	−1.93 (0.34)*	−0.77 (0.35)
CGI-S	−0.97 (0.13)*	−1.07 (0.10)**	−1.14 (0.10)***	−0.66 (0.10)
Mean tender-point threshold	0.54 (0.12)	0.52 (0.09)	0.54 (0.09)	0.42 (0.09)
SDS global functioning	−5.63 (0.86)	−5.38 (0.66)	−5.23 (0.65)	−4.85 (0.68)
EQ-5D	0.20 (0.03)*	0.12 (0.03)	0.15 (0.02)	0.12 (0.03)
SF-36 mental component summary	2.56 (1.28)	3.68 (0.97)	4.41 (0.97)*	1.75 (1.00)
SF-36 physical component summary	4.82 (1.11)	4.94 (0.84)	4.43 (0.84)	4.01 (0.87)

Abbreviations: LS, least-squares; SE, standard error; MDD, major depressive disorder; BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions-Severity; EQ-5D, EuroQoL Questionnaire-5 Dimensions; FIQ, Fibromyalgia Impact Questionnaire; MFI, Multidimensional Fatigue Inventory; PGI-I, Patient's Global Impressions of Improvement; SDS, Sheehan Disability Scale; SF-36, The 36-item Short-Form Health Survey.

[a] The percentage of patients with MDD was 24.2%.

[b] The scores for PGI-I indicate LS mean at endpoint.

* $P \leqslant 0.05$.

** $P \leqslant 0.01$.

*** $P \leqslant 0.001$ vs placebo.

depressive symptoms accounted for 37.8% ($P = 0.017$) of the total treatment effect. The direct effect of duloxetine 120 mg/day on the reduction in the average pain severity score accounted for 79.0% ($P = 0.045$) of the total treatment effect at 3 months. The indirect treatment effect through improvement in depressive symptoms accounted for 21.0% ($P =$ NS) of the total treatment effect.

The treatment-by-subgroup interactions on the average pain severity score for sex ($P = 0.774$), age

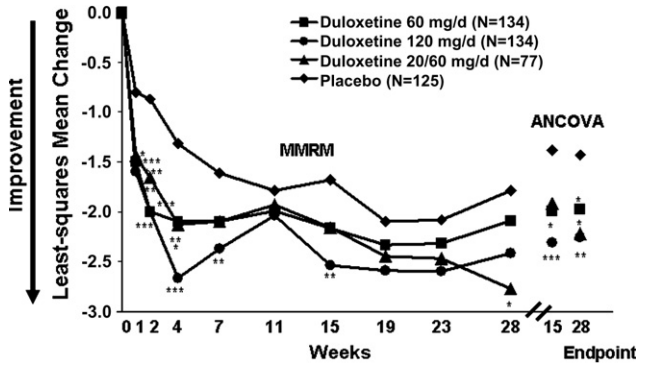

Fig. 2. BPI average pain severity score: LS mean change from baseline to each visit: 6-month double-blind treatment phase. *Abbreviations:* LS, least-squares; MMRM, mixed-effect repeated-measures analysis; ANCOVA, analysis of covariance. $^{*}P \leqslant 0.05$, $^{**}P \leqslant 0.01$, $^{***}P \leqslant 0.001$ vs placebo.

($P = 0.581$), and race ($P = 0.374$) were not significant. In men, the LS mean changes from baseline to endpoint during the 3-month treatment period were similar to the overall results although the number of men in each treatment group was small (duloxetine 120 mg/day [$n = 4$], −2.18; duloxetine 60 mg/day [$n = 14$], −2.17; duloxetine 20 mg/day [$n = 2$], 0.70; placebo [$n = 7$], −0.68). The LS mean changes were similar between patients 65 years and younger (duloxetine 120 mg/day [$n = 129$], −2.39; duloxetine 60 mg/day [$n = 129$], −2.03; duloxetine 20 mg/day [$n = 68$], −1.90; placebo [$n = 131$], −1.37) and patients older than 65 years (duloxetine 120 mg/day [$n = 13$], −1.07; duloxetine 60 mg/day [$n = 15$], −2.10; duloxetine 20 mg/day [$n = 9$], −1.97; placebo [$n = 8$], −2.08). Similar results were found among racial groups.

Post hoc evaluations of changes in $HAMD_{17}$ total score in patients diagnosed with MDD at study entry found LS mean changes of −4.8 for placebo ($n = 30$), −6.0 for duloxetine 20 mg/day ($n = 22$), −6.6 for duloxetine 60 mg/day ($n = 30$) and −7.8 for 120 mg/day ($n = 29$). Only the latter group demonstrated statistically significant improvement compared with placebo ($P = 0.022$).

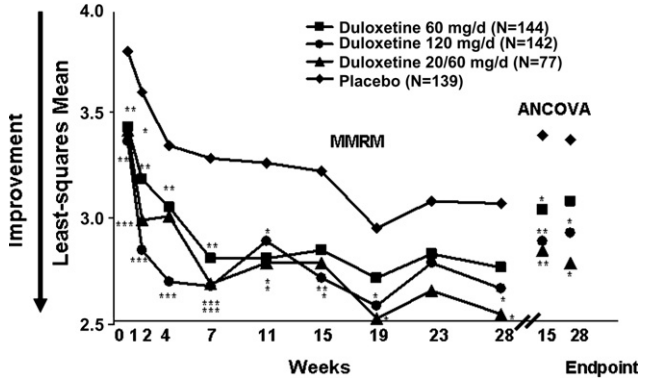

Fig. 3. PGI-I LS mean score at each visit: 6-month double-blind treatment phase. *Abbreviations:* LS, least-squares; MMRM, mixed-effect repeated-measures analysis; ANCOVA, analysis of covariance. $^{*}P \leqslant 0.05$, $^{**}P \leqslant 0.01$, $^{***}P \leqslant 0.001$ vs placebo.

3.3.2. Six month treatment phase

At the 6-month endpoint, patients treated with duloxetine 20/60 mg/day, duloxetine 60 mg/day, and duloxetine 120 mg/day all experienced significantly greater improvement in change from baseline in the average pain severity score compared with patients receiving placebo (Table 2). The mean endpoint PGI-I score was significantly lower (better) in the duloxetine 20/60 mg/day and duloxetine 120 mg/day groups, but not the duloxetine 60 mg/day group, compared with the placebo group. Duloxetine-treated patients showed similar improvement in the average pain severity score and PGI-I compared with placebo-treated patients regardless of whether they had comorbid MDD.

For secondary measures, all the duloxetine treatment groups demonstrated significant improvement compared with the placebo group in the CGI-S and MFI mental fatigue domain. The other efficacy and health outcome measures that achieved significance in the duloxetine treatment groups compared with the placebo group included the MFI physical fatigue domain and EQ-5D (duloxetine 20/60 mg/day) and the MFI physical fatigue, reduced motivation, and reduced activity domains, as well as SF-36 mental component score (duloxetine 120 mg/day).

Response rates, defined as a $\geqslant 50\%$ improvement from baseline to the 6-month endpoint on the average pain score, were significantly greater for duloxetine 20/60 mg/day (36.4%; $P = 0.025$), duloxetine 60 mg/day (32.6%; $P = 0.045$), and duloxetine 120 mg/day (35.9%; $P = 0.009$) compared with placebo (21.6%). Post hoc analyses also showed that response rates defined by $\geqslant 30\%$ reduction from baseline to 6-month endpoint in the average pain severity score were significantly higher for duloxetine 20/60 mg/day (51.9%; $P = 0.045$), but not for duloxetine 60 mg/day (47.2%; $P = 0.118$) or duloxetine 120 mg/day (49.3%; $P = 0.054$) compared with placebo (37.4%). The number needed to treat (95% CI) for duloxetine 20/60 mg/day, 60 mg/day, and 120 mg/day was 10 (4.7, 148.6), 7 (4.1, 26.6), and 7 (3.6, 42.7), respectively.

The path analysis demonstrated that the direct analgesic effect of duloxetine 60 mg/day on the reduction in the average pain severity score accounted for 69.1% ($P = 0.250$) of the total treatment effect at 6 months. The indirect treatment effect through improvement in depressive symptoms accounted for 30.9% ($P =$ NS) of the total treatment effect. The direct effect of duloxetine 120 mg/day on the reduction in the average pain severity score accounted for 82.3% ($P = 0.060$) of the total treatment effect at 6 months. The indirect treatment effect

through improvement in depressive symptoms accounted for 17.7% ($P = \text{NS}$) of the total treatment effect.

The treatment-by-subgroup interactions on the average pain severity score for sex ($P = 0.353$), age ($P = 0.922$), and race ($P = 0.685$) were not significant. In men, the LS mean changes from baseline to endpoint were similar to the overall results although the number of men in each treatment group was small (duloxetine 120 mg/day [$n = 4$], −2.02; duloxetine 60 mg/day [$n = 14$], −2.41; duloxetine 20 mg/day [$n = 1$], 1.35; placebo [$n = 7$], −0.46). The LS mean changes were similar between patients 65 years and younger (duloxetine 120 mg/day [$n = 129$], −2.29; duloxetine 60 mg/day [$n = 129$], −1.98; duloxetine 20/60 mg/day [$n = 68$], −2.20; placebo [$n = 131$], −1.42) and older than 65 years (duloxetine 120 mg/day [$n = 13$], −1.91; duloxetine 60 mg/day [$n = 15$], −2.31; duloxetine 20/60 mg/day [$n = 9$], −2.77; placebo [$n = 8$], −1.90). Similar results were found among racial groups.

In patients diagnosed with MDD at study entry, LS mean changes in $HAMD_{17}$ total score at 6 months were −4.8 for placebo ($n = 30$), −5.2 for duloxetine 20/60 mg/day ($n = 22$), −6.9 for duloxetine 60 mg/day ($n = 30$) and −7.2 for 120 mg/day ($n = 29$). Treatment group differences were not statistically significant when compared with placebo.

3.4. Safety and tolerability

The safety and tolerability of the duloxetine groups were compared with the placebo group across the entire 6-month treatment period. The proportions of patients who discontinued due to an adverse event during the 6-month study period were significantly different across treatment groups: duloxetine 20/60 mg/day (11.4%), duloxetine 60 mg/day (15.3%), duloxetine 120 mg/day (27.2%), and placebo (13.2%, $P = 0.005$). Despite this global difference, there were no significant differences in the incidence of any specific adverse event among any of the duloxetine treatment groups as compared with the placebo group.

Fifteen treatment-emergent adverse events occurred in at least one of the duloxetine groups at a frequency greater than 5% and twice the rate of the placebo group (Table 3), with nausea consistently reported as the most common treatment-emergent adverse event in all of the treatment groups. A total of 20 patients reported at least one serious adverse event. Serious adverse events were infrequent and did not demonstrate any pattern with respect to the system organ class designation. Only asthma (1 placebo patient and 1 duloxetine 60 mg/day patient) and suicidal ideation (1 placebo patient and 1 duloxetine 120 mg/day patient) were reported by more than 1 patient during the 6-month study period.

Mean changes in heart rate and supine systolic and diastolic blood pressure for the duloxetine treatment groups did not differ significantly from those for the placebo group, except for systolic blood pressure (duloxetine 60 mg/day, 3.0 mm Hg; placebo, −1.1 mm Hg, $P = 0.019$). A total of 10 patients met criteria for sustained elevation in blood pressure (supine diastolic blood pressure $\geqslant 90$ mm Hg and an increase from baseline of $\geqslant 10$ mm Hg for at least 3 consecutive visits, or supine systolic blood pressure $\geqslant 140$ mm Hg and an increase from baseline of $\geqslant 10$ mm Hg for at least 3 con-

Table 3
Treatment-emergent adverse events during 6 months of therapy[a]

Adverse event, *n* (%)	Duloxetine			Placebo
	20/60 mg/day ($N = 79$)	60 mg/day ($N = 150$)	120 mg/day ($N = 147$)	($N = 144$)
Nausea	18 (22.8)	36 (24.0)*	46 (31.3)***	19 (13.2)
Dry mouth	11 (13.9)*	20 (13.3)*	31 (21.1)***	7 (4.9)
Constipation	10 (12.7)*	15 (10.0)	30 (20.4)***	6 (4.2)
Somnolence	9 (11.4)	12 (8.0)	25 (17.0)***	6 (4.2)
Fatigue	9 (11.4)	21 (14.0)*	12 (8.2)	8 (5.6)
Insomnia	6 (7.6)	14 (9.3)	21 (14.3)*	8 (5.6)
Dizziness	5 (6.3)	16 (10.7)	17 (11.6)	8 (5.6)
Decreased appetite	4 (5.1)	11 (7.3)**	12 (8.2)**	1 (0.7)
Hyperhidrosis	5 (6.3)**	8 (5.3)**	11 (7.5)***	0 (0.0)
Cough	7 (8.9)*	6 (4.0)	5 (3.4)	2 (1.4)
Pharyngolaryngeal pain	4 (5.1)	2 (1.3)	9 (6.1)	4 (2.8)
Tremor	1 (1.3)	5 (3.3)	15 (10.2)***	0 (0.0)
Myalgia	4 (5.1)	6 (4.0)	6 (4.1)	1 (0.7)
Rash	3 (3.8)	4 (2.7)	9 (6.1)	2 (1.4)
Weight increased	2 (2.5)	6 (4.0)	9 (6.1)*	1 (0.7)

[a] All events that occurred in $\geqslant 5\%$ of duloxetine patients and twice the rate of placebo during the 6-month treatment phase.
* $P \leqslant 0.05$.
** $P \leqslant 0.01$.
*** $P \leqslant 0.001$, compared with placebo.

secutive visits), including 6 (4.2%) on duloxetine 60 mg/day, 2 (1.4%) on duloxetine 120 mg/day, and 2 (1.4%) on placebo. Neither the incidence of sustained elevation in blood pressure nor the incidence of hypertension, reported as a spontaneous adverse event, differed significantly between any of the duloxetine groups when compared with the placebo group. The mean change in weight over the 6 months of therapy was less than 1 kg for all of the treatment groups. Additionally, no significant differences occurred between the duloxetine groups and the placebo group in mean change from baseline to endpoint in the QTc interval or in the incidence of treatment-emergent abnormal ECG values including heart rate, QTcB, and QTcF.

Statistically significant differences (all $P < 0.05$) were observed in mean change from baseline to endpoint between the duloxetine and placebo groups for some clinical laboratory values and included the following: alkaline phosphatase (Units/L) (duloxetine 20/60 mg/day, 3.13; duloxetine 60 mg/day, 2.58; placebo, 0.44); chloride (mmol/L) (duloxetine 20/60 mg/day, −0.49; duloxetine 60 mg/day, −0.17; duloxetine 120 mg/day, −0.32; placebo, 0.41); cholesterol (mmol/L) (duloxetine 60 mg/day, −0.03; duloxetine 120 mg/day, −0.04; placebo, −0.27); γ-glutamyl transferase (Units/L) (duloxetine 20/60 mg/day, −2.15; placebo, 0.86); sodium (mmol/L) (duloxetine 20/60 mg/day, −0.66; placebo, 0.07); eosinophils (tril/L) (duloxetine 120 mg/day, 0.02; placebo, −0.01); hematocrit (actual count) (duloxetine 20/60 mg/day, 0.00; placebo, −0.01); hemoglobin (mmol/L) (duloxetine 20/60 mg/day, −0.16; duloxetine 60 mg/day, −0.13; duloxetine 120 mg/day, −0.17; placebo, −0.25); mean cell hemoglobin (femtomole) (duloxetine 60 mg/day, 0.00; duloxetine 120 mg/day, 0.00; placebo, −0.02); mean cell volume (femtoliter) (duloxetine 120 mg/day, 0.66; placebo, −0.12); monocytes (bill/L) (duloxetine 20/60 mg/day, 0.05; placebo, 0.01); and platelet count (bill/L) (duloxetine 120 mg/day, 10.48; placebo, −1.10). However, these differences in mean changes between treatment groups were small and not considered to be clinically relevant. No significant differences in the percentage of patients exhibiting treatment-emergent abnormal chemistry or hematology analytes at any time were observed, with the exception of creatine kinase (higher levels) in the duloxetine 20/60 mg/day (15.3%, $P = 0.038$) and duloxetine 120 mg/day (13.6%, $P = 0.036$) treatment groups compared with the placebo group (5.7%). However, the mean change in creatine kinase levels was not significantly different between the active treatment groups and placebo.

4. Discussion

In this randomized, double-blind trial, both duloxetine 60 mg/day and 120 mg/day had significantly greater efficacy, compared with placebo, on reduction in pain severity after 3 months and 6 months of treatment in patients with fibromyalgia. Compared with placebo, duloxetine at both doses significantly reduced pain beginning in the first week of therapy. Global improvement, as assessed by the patient (PGI-I) and the clinician (CGI-S), was significantly improved after 3 months in the duloxetine groups and maintained through 6 months of treatment compared with the placebo group (except 60 mg/day group for PGI-I). The FIQ total score and SF-36 mental component summary were significantly improved at 3 months in both duloxetine groups compared with the placebo group.

The results of this study showing improvement in pain, FIQ scores, and patient-rated global improvement in fibromyalgia patients on duloxetine are similar to previously published results [1]. Improvement in mean tender-point threshold was not significantly different between duloxetine- and placebo-treated patients in this study, but was significantly improved at the 120 mg/day dosage, compared with placebo, in the two earlier duloxetine studies [1,2]. Significant improvement in tender-point threshold appears to be a difficult outcome to achieve [28]. Recent clinical trials of fibromyalgia have not included tender-point assessments as an efficacy measure [9,15,22,33,37], and the usefulness of the tender-point evaluation in clinical practice is the subject of debate [7,25].

Fatigue is a common, disabling symptom reported by patients with fibromyalgia [27]. While duloxetine did not significantly improve the MFI general fatigue score compared with placebo at the 3-month or 6-month endpoints, all doses of duloxetine at the 6-month endpoint significantly improved the MFI mental fatigue domain compared with placebo. Because the mental fatigue domain consists of four questions relating to attention/concentration, it is possible that treatment with duloxetine may improve some of the cognitive dysfunction often reported by patients with fibromyalgia [27].

Consistent with the previous duloxetine studies in fibromyalgia, patients experienced an improvement in pain regardless of the presence of MDD [1,2]. Both in prior studies and in the present study, path analysis showed that the majority of duloxetine's effect on pain is direct rather than mediated through improvement in MDD symptoms. Whereas it is important to note that improvement in pain of duloxetine-treated patients with fibromyalgia was not dependent on mood improvement, the antidepressant effect of duloxetine may be quite relevant in this disorder where many patients have comorbid mood disorders. Additionally, effect sizes [21] for improvements in $HAMD_{17}$ scores in patients with MDD who where randomized to duloxetine 60 mg/day or 120 mg/day, were 0.45 and 0.63 for the 3-month phase, respectively, and 0.42–0.53 for the 6-month treatment phase, respectively, which is indicative of a clinically significant antidepressant effect [4,12].

Unlike a previous study in fibromyalgia [1], male and female patients treated with duloxetine showed similar improvement in the average pain severity score after both 3 months and 6 months of treatment. Consistent improvement was also found in patients <65 and ⩾65 years of age and by race. The treatment-by-subgroup interactions for sex, age, and race were all not significant, a finding that supports the consistency of duloxetine's effect across each of these subgroups when taking the positive within-group treatment effects into consideration.

The duloxetine 20 mg/day dosage was included in this study to determine the ineffective or minimally effective dose for the treatment of fibromyalgia. The 20 mg dose did not significantly improve the average pain severity score compared with placebo, making it the highest ineffective dose in this study. A study of duloxetine in diabetic neuropathic pain using the same doses also established 20 mg as the highest ineffective dose [16].

The safety and tolerability findings in this study were consistent with what has been found with duloxetine in other patient populations, including the previous fibromyalgia studies. The most common treatment-emergent adverse events, such as nausea, headache, and dry mouth, occurred almost entirely within the first 3 months of the study. A pooled analysis of nearly 24,000 duloxetine patients from 64 studies found that the large majority of the most commonly reported treatment-emergent adverse events occur early in treatment and were mild or moderate in severity [14]. Moreover, an analysis of eight pooled double-blind duloxetine studies found that the most common treatment-emergent adverse event, nausea, which presents in the first few weeks of treatment, tends to resolve within a few days to a week [17]. In support of the relatively benign cardiovascular findings in this study, a recent analysis of more than 8500 duloxetine-treated patients from 42 placebo-controlled studies found no increased cardiovascular risk associated with this medication [40].

Several limitations of this study should be considered. Although this is one of the longest trials of a medication treatment for fibromyalgia that has been published, the results may not generalize to treatment periods greater than 6 months. Additionally, the results of the study may not generalize to patients with excluded or unstable psychiatric or medical disorders, or comorbid pain disorders. No active comparator was included because this study was intended to confirm and extend the previous findings of safety and efficacy of duloxetine compared with placebo in the treatment of fibromyalgia. There may have been variability in whether patients were potentially treatment-refractory because the interpretation relied on the investigator's judgment. The lack of significance between treatment groups in some safety measures could be attributed to the study not being sufficiently powered to detect these differences. Also, because this was a monotherapy medication trial, patients were required to discontinue medications used to treat fibromyalgia before enrollment, which may have deterred patients with more severe illness from enrolling. Finally, given the relatively large number of safety, tolerability and secondary efficacy assessments included in this trial, the presence or absence of statistical significance in these outcomes should be regarded as supportive or exploratory data and considered in conjunction with established levels of clinically significant improvement, wherever possible.

This study provides further evidence that duloxetine at dosages of 60 mg/day and 120 mg/day for up to 6 months appears to be safe and efficacious in the treatment of fibromyalgia in patients with or without MDD. Because most published drug studies in fibromyalgia and other pain conditions are of 3 months' duration or shorter, the finding of positive results at 6 months provides a more robust assessment of duloxetine's efficacy.

Acknowledgements

This work was sponsored by Eli Lilly and Company and Boehringer Ingelheim GmbH. For potential conflict of interest relationships of different authors, please see Supplementary Materials. All authors accept full responsibility for the conduct of this trial, were given full access to all data from the trial, and participated in the decision to publish the data. The authors thank the many patients for their voluntary participation in this clinical trial, as well as the principal investigators including: Lesley Arnold MD, Andre Barkhuizen MD, Mira Baron MD, Elizabeth Barranco Santano MD, Patricia Buchanan MD, Maryann Colvard MD, Adnan Dahdul MD, Patricia Daly MD, Nizar El-Khalili MD, John Farrar MD, Frances Gallagher MD, Donald Garcia, Jr. MD, Gary Gerard MD, Jeffrey Gitt DO, David Hart MD, Rakesh Jain MD, Lissette Jimenez MD, Louis Kirby MD, James Knutson MD, Wendy Lee MD, Frank Maggiacomo DO, Philip Mease MD, Kenneth Miller MD, DJ Muniak MD, Russell Pet MD, Julie Poludniak MD, John Prater DO, H. Malin Prupas MD, Bruce Rankin DO, Robert Reade MD, Randall Ricardi MD, Grissel Rios MD, I. Jon Russell MD, Martin Schuster MD, Eric Sheldon MD, Timothy Smith MD, Cynthia Strout MD, Haydn Mikel Thomas MD, Bridget Walsh DO, and Richard Weinstein MD. We also thank Deborah D'Souza, PhD, for critical review of the manuscript, and Jessica Pitrelli, BA, and Tania Miles for formatting assistance.

Appendix A. Supplementary data

For potential conflict of interest relationships of different authors, please see Supplementary Materials. Supplementary data associated with this article can be

found, in the online version, at doi:10.1016/j.pain.2008.02.024.

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