Flexible Dosed Duloxetine in the Treatment of Fibromyalgia: A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT. ***Objective***. To investigate the efficacy of flexible dose duloxetine 60–120 mg/day on changes in fibromyalgia (FM) symptoms assessed by the Patient Global Impression of Improvement (PGI-I) scale.

Methods. Outpatients ≥ 18 years of age who met American College of Rheumatology criteria for FM, and had ≥ 4 score on the Brief Pain Inventory (BPI) average pain item, were randomized to duloxetine (n = 263) or placebo (n = 267) for 24 week double-blind treatment (primary endpoint at Week 12). Key secondary measures included BPI average pain severity, patient-rated scales assessing mood, anxiety, pain, sleep, and stiffness, Clinical Global Impression of Severity (CGI-S), Multidimensional Fatigue Inventory, Cognitive and Physical Functioning Questionnaire, Beck Depression Inventory (BDI), Beck Anxiety Inventory, and Medical Outcome Study Short-Form Health Survey (SF-36).

Results. At Week 12, duloxetine-treated patients reported significantly greater global improvement with mean PGI-I scores of 2.8 compared to 3.4 in the placebo group ($p < 0.001$). Significantly more duloxetine- versus placebo-treated patients (57% vs 32%; $p < 0.001$) reported feeling "much" or "very much better" (PGI-I score ≤ 2). There was significantly greater improvement with duloxetine versus placebo treatment in BPI average pain severity, mood (including BDI total), anxiety (patient-rated only), stiffness, CGI-S, fatigue, all SF-36 domains (except role-physical and physical component summary), and being less bothered by pain or sleep difficulties. Treatment-emergent adverse events occurring significantly more frequently with duloxetine included: nausea, headache, constipation, dry mouth, dizziness, diarrhea, and hyperhidrosis.

Conclusion. Treatment with duloxetine 60, 90, and 120 mg/day was associated with feeling much better, pain reduction, being less bothered by sleep difficulties, and improvement in mood, stiffness, fatigue and functioning. (Clinical trial registry NCT00673452). (First Release Sept 15 2010; J Rheumatol 2010;37:2578–86; doi:3899/jrheum.100365)

Key Indexing Terms:
DULOXETINE FIBROMYALGIA PAIN FATIGUE FUNCTIONING

Fibromyalgia (FM) is characterized by chronic widespread musculoskeletal pain and tenderness[1]. Other symptoms commonly associated with FM include fatigue, stiffness, nonrestorative sleep, depressed mood, anxiety, and cognitive difficulties[2]. The chronicity and severity of FM symptoms negatively influence quality of life and lead to functional impairment and disability[3]. FM affects about 2%–4% of the population in the United States and is more frequently reported in women than men[4].

There is emerging evidence of the underlying mechanisms responsible for FM symptoms. Dysfunction of serotonin and norepinephrine transmission, which mediate endogenous analgesic mechanisms via the descending inhibitory pain pathways in the central nervous system, may play a key role. Individuals with dysfunctional pain inhibition often experience abnormal or heightened pain sensitivity[5], which is common in patients with FM[6]. Imbalance or deficiency in serotonin and norepinephrine is also associated with depression, anxiety, and cognitive deficits[7]. Research suggests that treatment with serotonin and norepinephrine reuptake inhibitors (SNRI) increases transmission of these neurotransmitters and improves disease states associated with serotonin and norepinephrine deficiencies[8].

Duloxetine hydrochloride (referred to as duloxetine) is a

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potent SNRI that has US Food and Drug Administration (FDA) approval for management of major depressive disorder, generalized anxiety disorder, pain due to diabetic peripheral neuropathy, and FM. Several clinical questions that were not completely answered in prior trials of duloxetine in FM included the range of optimal dosing and efficacy treating other common symptoms reported by patients with FM such as fatigue, difficulty sleeping, and cognitive impairment. Although the dosage approved by the FDA for treatment of FM is 60 mg/day, previous studies assessed 120 mg/day (administered either as 60 mg twice daily or 120 mg once daily)[9,10,11,12], and the results suggested that this dose may provide additional efficacy on some secondary measures. However, the 120 mg dose was less well tolerated, with higher dropout rates due to adverse events[10,11], suggesting that an intermediate dose (e.g., 90 mg/day) may be better tolerated. The current randomized, placebo-controlled, double-blind, parallel-group trial of duloxetine was designed to address some of these important clinically relevant questions using the Patient Global Impression of Improvement as the primary outcome measure. We report the safety and efficacy of flexible dose duloxetine 60 mg/day, 90 mg/day, and 120 mg/day in the treatment of FM from the first 12 weeks (primary endpoint) of the 24-week study. The results of the continuation phase of the study will be presented separately.

MATERIALS AND METHODS

Overview. This phase IV study was conducted under protocol FIJ-US-HMGB (trial registration NCT00673452) in 48 research centers in the United States and Puerto Rico. Enrollment began June 2, 2008, and the study was completed July 31, 2009. The institutional review boards approved the protocol, which was developed in accord with the ethical guidelines of good clinical practice and the Declaration of Helsinki. All patients provided written consent after the study was explained and their questions answered, and before study procedures were initiated. Patients were identified by physician referral or public announcements directed towards individuals with FM.

Entry criteria. Male and female outpatients were eligible for the study if they were ≥ 18 years of age, met criteria for FM as defined by the American College of Rheumatology[1], and scored ≥ 4 on the average pain item of the Brief Pain Inventory (BPI; modified short form)[13] at visit 1 (screening) and visit 2 (randomization). Patients were included if they were judged to be reliable and had a level of understanding that allowed them to communicate intelligibly and provide informed consent.

Patients were excluded if they had any of the following: current or diagnosed within the past year with any primary psychiatric disorder other than major depressive disorder (MDD) or generalized anxiety disorder (GAD) defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); clinically judged to be at serious risk of suicide; had any unstable medical illness that was likely to require intervention or hospitalization; pain symptoms unrelated to FM 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; severe liver disease; pregnant or breast-feeding; or history of substance abuse within the past year. Patients were also excluded if they had been treated with an adequate trial of duloxetine and did not respond or could not tolerate duloxetine; were judged by the opinion of the investigator to be treatment-refractory in FM; or those in whom treatment response might be compromised by disability compensation issues.

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), all antidepressants, including tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and SNRI. Patients entering the study on stable sleep medication were allowed to continue the medication during the study. Episodic use (up to 3 nights per week) of chloral hydrate, zolpidem, zopiclone, and zaleplon were allowed to facilitate sleep. Patients were encouraged not to initiate or alter ongoing nonconventional/alternative therapies such as acupuncture, biofeedback, or cognitive-behavioral therapy for the duration of the study.

Study design. This was a 24-week, multicenter, randomized, double-blind, placebo-controlled trial to confirm the efficacy of duloxetine (60 mg–120 mg once daily) on patient-rated global improvement in FM symptoms. There was a 5 to 30 day screening phase, during which patients were to wash out excluded medications prior to study entry at visit 2. A minimum of 7 days of washout was required for most medications, but monoamine oxidase inhibitors required a minimum of 14 days, and fluoxetine required 30 days. For evaluation of the primary endpoint, the acute phase was 12 weeks' duration, double-blind, and placebo-controlled. After Week 12, patients in the placebo group were transitioned to active treatment and all patients continued for an additional 12 weeks of double-blind treatment. Results of the continuation phase will be reported separately. An optional 2-week drug-tapering phase was offered at the end of the 12-week continuation phase or for patients who discontinued early after receiving at least 2 weeks of study medication.

Patients were randomly assigned 1:1 in a double-blind fashion to duloxetine 60 mg once daily (QD) or placebo by a computer-generated random sequence using an interactive voice response system (IVRS). The protocol employed a variable transition to active treatment strategy, whereby investigators and patients were told that active study drug would be initiated sometime between randomization and Week 4, thereby blinding the onset of active treatment to reduce the patient's expectations of experiencing side effects or improved symptoms. For patients randomized to duloxetine, active medication was initiated the morning after the randomization visit. Duloxetine was initiated at 30 mg QD and was escalated to 60 mg QD after 1 week. At the Week 4 and Week 8 visits, duloxetine dose was automatically escalated via IVRS by 30 mg QD for those patients who had < 50% reduction from baseline in their BPI 24-hour pain score and the investigator had endorsed a dose increase. Dose escalation/reduction was double-blind, and neither the patient nor the investigator was informed whether dose escalation/reduction had occurred. If the patient could not tolerate the dose increase, it was reduced to the pre-escalation dose via IVRS.

During the drug-tapering phase, those patients who had received duloxetine 60 mg QD experienced dosage reduction to 30 mg QD for 1 week and then received placebo for a second week. The dosage of patients who had received duloxetine 90 mg QD or 120 mg QD was reduced to 60 mg QD for 1 week, then 30 mg QD for a second week.

Efficacy measures. The protocol-defined primary outcome measure was the Patient's Global Impressions of Improvement (PGI-I)[14]. This is a categorical scale on which patients provide ratings of their overall impression of how they are feeling since treatment began with the following choices: 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, 7 = very much worse.

Secondary outcome measures included the Brief Pain Inventory (BPI; short form); the Multidimensional Fatigue Inventory (MFI)[15]; the Clinical Global Impression of Severity (CGI-S)[14]; the Patient's Global Impressions of Severity (PGI-S)[14] (assessed only at baseline); the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)[16]; the Beck Anxiety Inventory (BAI)[17]; the Beck Depression Inventory-II (BDI-II)[18]; the 36-item Medical Outcome Study Short-Form Health Survey

(SF-36)[19]; and 11-point Likert scales assessing severity of depressed mood, anxiety, stiffness, and how much the patient is bothered by sleep difficulty and pain (score range 0 = not present to 10 = extremely).

Formal cognitive assessment with standardized tests was conducted in a subset of patients at selected sites as an exploratory outcome, and these results will be presented separately.

Tolerability and safety measures included incidence of discontinuation due to adverse events, treatment-emergent adverse events, changes in vital signs, and changes in standard laboratory variables that included blood count, electrolytes, and liver function.

Statistical methods. The primary objective of the study was to determine whether duloxetine 60–120 mg QD provided significant improvement compared with placebo in the PGI-I at the Week 12 endpoint. The study was designed to enroll 261 patients in each treatment group in order to have at least 85% power to detect a difference of –0.4 points on the PGI-I between treatment with duloxetine versus placebo. The a priori protocol-defined difference at endpoint was estimated using a mixed-effects model repeated measures (MMRM) approach[20].

Secondary outcomes were included to provide additional assessments of duloxetine's efficacy in treating FM and to provide a better understanding of duloxetine's effect on other symptom domains associated with FM.

Analyses were done on an intent-to-treat basis. All randomized patients with a baseline and at least one post-baseline visit were included in the efficacy analyses, and all randomized patients were included in the safety analyses. All tested hypotheses were considered statistically significant if the 2-sided p value was ≤ 0.05 unless otherwise specified.

A restricted maximum likelihood-based MMRM analysis was utilized on longitudinal changes from baseline for continuous efficacy measures. The MMRM approach accounts for bias caused by non-random missing data due to early discontinuation because of adverse events or lack of efficacy better than the last observation carried forward (LOCF) method[20]. 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 score and baseline score-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors. Significance tests were based on least-squares means and Type III sum-of-squares. Efficacy results presented are from the MMRM analysis unless otherwise noted. LOCF changes from baseline to endpoint were analyzed using an analysis of covariance (ANCOVA) model with the terms of treatment, investigator, and baseline scores. Mean refers to the least-squares mean, which is the estimated mean from a specific model (MMRM or LOCF ANCOVA). Continuous baseline measures were evaluated using fixed effects (treatment, investigator) analysis of variance (ANOVA), and categorical baseline measures were evaluated using Fisher's exact test. Continuous safety measures were analyzed using MMRM, ANOVA, or ANCOVA as described above, and categorical safety measures were analyzed using Fisher's exact test. Rank-transformed laboratory analytes were analyzed using the ANOVA model to assess treatment differences.

Pain response was defined 2 ways: as at least a 30% and at least a 50% reduction from baseline to endpoint in BPI average pain score. Sustained response was defined as at least 30% reduction from baseline to LOCF endpoint, with at least 30% reduction from baseline at an earlier visit than the last visit, and remained at least a 20% reduction from baseline at every visit in between, if there were any intervening visits. In addition, response was also observed using the baseline observation carried forward (BOCF) to the endpoint approach in which endpoints were imputed with corresponding baseline values if the patients dropped out early in the study.

The influence of a specific subgroup (age, gender, ethnic origin, and baseline MDD/GAD status) on the PGI-I at endpoint was analyzed using an ANCOVA model with all the terms described above and the additional terms of the subgroup and the subgroup-by-treatment interaction. The primary statistical testing was for the treatment-by-subgroup interaction, which was tested at level 0.1 in order to identify the heterogeneity of treatment effects across subgroups. Treatment group differences were evaluated within each category of a subgroup regardless of the significance level of the treatment-by-subgroup interaction. For the subgroup of origin, all the ethnic groups that had fewer than 10% of the patients in the study were combined.

RESULTS

Patient disposition and characteristics. Patient disposition is summarized in Figure 1. A total of 824 patients were screened to enroll 530 patients who met the entry criteria and were randomly assigned duloxetine 60–120 mg/day (n = 263) or placebo (n = 267). The percentage of patients in each treatment group who completed the first 12 weeks of the study was 66.9% and 70.0% (p = 0.456), respectively. The most frequently reported reason for discontinuation was experiencing an adverse event, which was significantly more frequent in the duloxetine group (15.6%) as compared with placebo (9.0%; p = 0.024). Other reasons for discontinuation did not differ significantly between treatments.

There were no statistically significant between-treatment group differences in demographic characteristics. The majority of the patients were female (93.2%), with a mean age of 50.2 ± 11.1 years; 77.4% were Caucasian and 15.7% were Hispanic. Fewer than 20% of the study population had a diagnosis of comorbid MDD and fewer than 10% had a diagnosis of comorbid GAD. Table 1 summarizes baseline clinical assessments, which did not have significant between-treatment group differences. Overall, pain severity was moderate, with mean BPI average pain scores of 6.5 ± 1.6. Patients reported baseline stiffness and being bothered by pain and sleep difficulties. About 19% of the patients entered the study on stable sleep medications, which they could continue unchanged during the study. About 21% of patients in both the placebo and duloxetine groups took sleep medication during the study, including the patients on stable sleep medication and those who took intermittent sleep medication up to 3 nights per week after baseline. Overall, patients reported feeling mildly to moderately ill at baseline, and the clinical impression of their illness severity was moderate.

Efficacy. After 12 weeks of treatment, patients who received duloxetine versus placebo had significantly reduced (improved) mean PGI-I scores (2.8 vs 3.4; p < 0.001). Significant between-treatment differences in the mean PGI-I scores began with the visit that followed treatment initiation, and these differences continued to be significant at each subsequent visit to endpoint (Figure 2). At endpoint, the percentage of patients treated with duloxetine who felt "much better" (PGI-I score of 2) to "very much better" (PGI-I score of 1) was significantly greater than among patients treated with placebo (57% vs 32%; p < 0.001). Treatment-by-subgroup interaction on the average LOCF endpoint PGI-I was not significant for age (p = 0.315), sex (p = 0.468), race (p = 0.461), comorbid depression (p = 0.621), or comorbid anxiety (p = 0.405).

Improvement in secondary efficacy measures was signif-

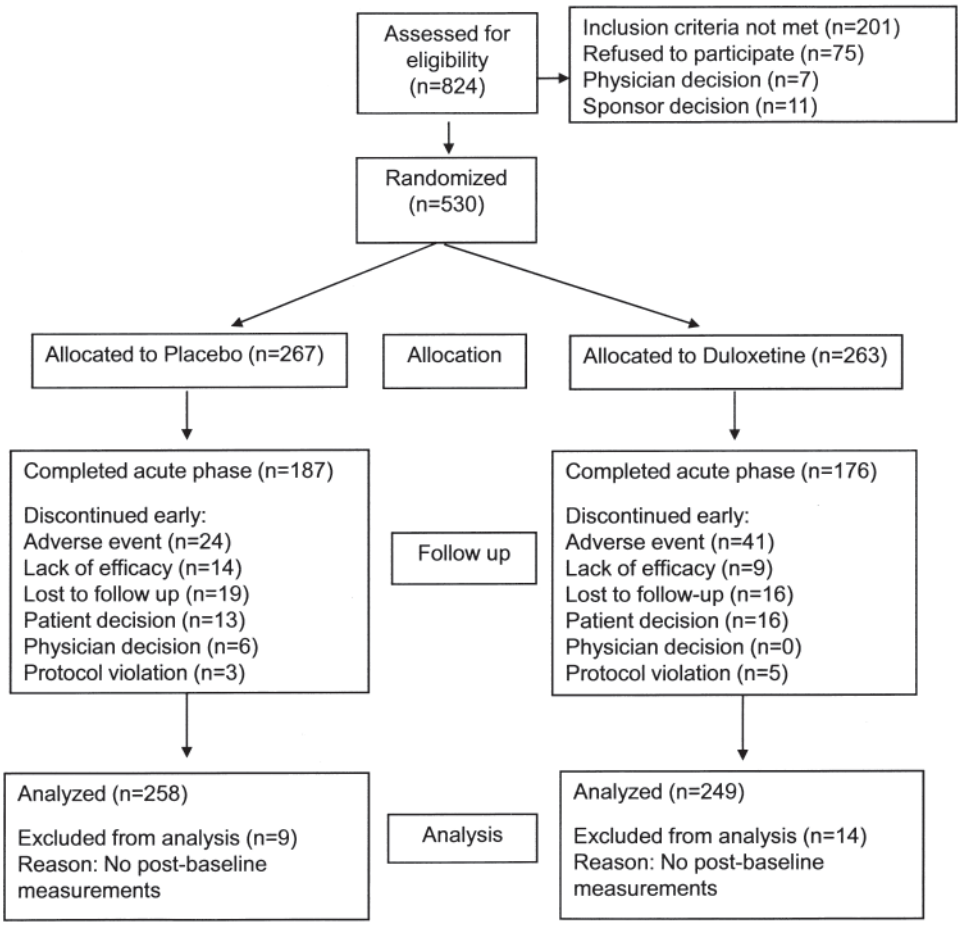

Figure 1. Patient disposition and characteristics.

icantly greater in patients treated with duloxetine compared to placebo for CGI-S, all MFI subscales, BPI pain severity (Table 2) and average pain interference scores (Figure 3), and BDI total scores for depression severity (Table 3). In addition, patients treated with duloxetine versus placebo had significantly greater mean changes in improvement from baseline on Likert scale scores rating severity of depressed mood, anxiety, and stiffness, and being bothered by pain and sleep difficulties (Figure 4). Throughout the study, 21% of the patients took concomitant sleep medication.

Duloxetine treatment was also associated with significant improvement on the SF-36 mental component summary and the following domains: bodily pain, general health, mental health, physical functioning, role-emotional, social functioning, and vitality (Table 3).

Cognitive and physical functioning assessed by the CPFQ total score at baseline revealed that patients in both treatment groups on average had moderately diminished functioning (Table 1). After 12 weeks of treatment, endpoint scores had improved to "minimally diminished" in both groups, and between-treatment differences were not significant (Table 2).

Treatment with duloxetine versus placebo was associated with significantly greater response rates defined as a 30% and a 50% improvement from baseline in BPI 24-hour average pain severity utilizing both LOCF and BOCF methods (Table 4). In addition, treatment with duloxetine versus placebo was associated with significantly more patients who experienced at least a 2 point decrease from baseline to the 12-week endpoint (LOCF) in BPI 24-hour average pain severity, but there was no between-treatment significance on this measure with BOCF analysis. The number of patients who sustained a 30% improvement in BPI 24-hour average pain to endpoint (LOCF) was significantly greater in duloxetine- versus placebo-treated patients.

The final dose distributions of duloxetine at Week 12 were: 60 mg, n = 137 (52.1%); 90 mg, n = 62 (23.6%); and 120 mg, n = 64 (24.3%). Mean BPI 24-hour average pain scores and PGI-I scores reported by patients before and after dose increase are summarized in Table 5. Overall, there was a significant improvement in pain severity for patients who were escalated to and stayed on the 90 mg dose. Significant improvement in pain was also seen for patients who were escalated to 120 mg. PGI-I scores improved from feeling

Table 1. Baseline demographics and illness severity measures. Values are mean (SD) unless otherwise indicated. There were no significant between-treatment differences in these measures.

Characteristic	Duloxetine, n = 263	Placebo, n = 267
Age, yrs	50.7 (11.3)	49.6 (10.8)
Female, n (%)	244 (92.8)	250 (93.6)
Caucasian, n (%)	204 (77.6)	206 (77.2)
Hispanic, n (%)	37 (14.1)	46 (17.2)
MDD diagnosis, n (%)	44 (16.7)	53 (19.9)
GAD diagnosis, n (%)	19 (7.2)	24 (9.0)
BDI, total score (0–63)	16.2 (10.4)	16.2 (10.4)
BAI, total score (0–63)	12.8 (9.3)	13.2 (9.8)
PGI-S	3.9 (1.2)	3.7 (1.4)
CGI-S	4.2 (0.9)	4.2 (1.0)
Mood, Likert scale (0–10)	3.8 (2.8)	4.0 (2.8)
Anxiety, Likert scale (0–10)	3.7 (2.8)	4.1 (2.9)
Bothered by pain, Likert scale (0–10)	7.3 (1.9)	7.5 (1.8)
Stiffness, Likert scale (0–10)	7.0 (2.0)	7.1 (1.8)
Bothered by sleep difficulties, Likert scale (0–10)	6.7 (2.6)	6.8 (2.7)
Use of sleep medication, n (%)	45 (17.1)	54 (20.2)
BPI 24-h average pain severity (0–10)	6.5 (1.5)	6.5 (1.6)
BPI average pain interference (0–10)	6.0 (2.0)	6.0 (2.1)
MFI general fatigue (4–20)	17.1 (2.9)	17.2 (2.9)
Physical fatigue (4–20)	13.3 (4.2)	13.0 (4.3)
Mental fatigue (4–20)	15.5 (3.5)	15.4 (3.6)
Reduced activity (4–20)	13.8 (4.1)	13.6 (3.9)
Reduced motivation (4–20)	12.4 (3.7)	12.6 (3.7)
CPFQ, total score (7–42)	26.6 (6.4)	26.6 (6.4)
SF-36 mental component summary (0–100)	43.3 (12.3)	42.9 (12.6)
SF-36 physical component summary (0-100)	31.0 (7.8)	31.3 (8.2)

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; CGI-S: Clinician Global Impression of Severity; CPFQ: Cognitive and Physical Functioning Questionnaire; GAD: generalized anxiety disorder; MDD: major depressive disorder; MFI: Multidimensional Fatigue Inventory; PGI-S: Patient Global Impression of Severity; SF-36: Medical Outcome Study Short-form Health Survey.

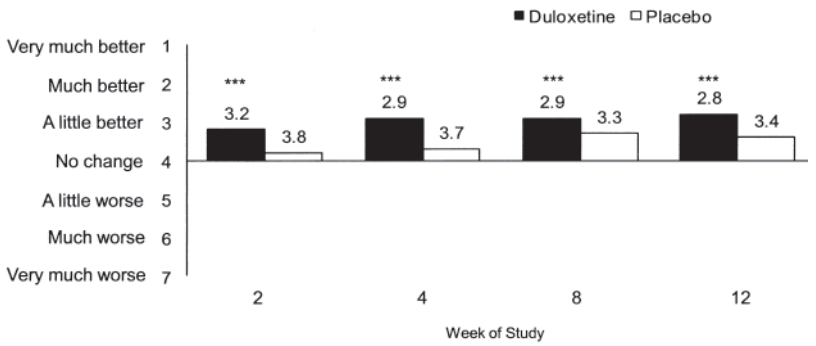

Figure 2. PGI-I scores at each visit after initiating treatment with duloxetine or placebo. ***p < 0.001 vs placebo.

"better" to "much better" after dose escalation to 90 mg, but scores remained the same after dose escalation to 120 mg.

Safety. Of the 530 randomly assigned patients, significantly more patients treated with duloxetine (n = 218, 82.9%) reported having at least one adverse event as compared with placebo-treated patients (n = 191, 71.5%; p = 0.002). Most of these events (73.1% of 409 events) were mild to moderate in severity. Patients in the duloxetine versus placebo group reported significantly more nausea (31.6% vs 9.7%; p < 0.001), headache (17.1% vs 9.0%; p = 0.006), constipation (13.3% vs 4.1%; p < 0.001), dry mouth (11.8% vs 4.5%; p = 0.002), dizziness (9.9% vs 5.2%; p = 0.049), diarrhea (10.3% vs 4.5%; p = 0.012), hyperhidrosis (8.7% vs 1.5%; p < 0.001), hot flush (4.9% vs 0.7%; p = 0.003), vomiting

Table 2. Least squares (LS) mean change from baseline in secondary efficacy measures.

Measure	Duloxetine n	Duloxetine LS Mean Change (SE)	Placebo n	Placebo LS Mean Change (SE)	MMRM p
CGI-S	172	–1.2 (0.1)	180	–0.8 (0.1)	< 0.001
BPI 24-h average pain	188	–2.3 (0.2)	199	–1.5 (0.2)	< 0.001
24-h worst pain	188	–2.5 (0.2)	199	–1.7 (0.2)	0.003
24-h least pain	188	–1.7 (0.2)	199	–1.1 (0.2)	0.002
Pain right now	188	–2.3 (0.2)	199	–1.5 (0.2)	0.002
Average interference	188	–2.6 (0.2)	197	–1.7 (0.2)	< 0.001
CPFQ total score	187	–5.3 (0.5)	198	–4.2 (0.4)	0.051

BPI: Brief Pain Inventory; CGI-S: Clinician Global Impression of Severity; CPFQ: Cognitive and Physical Functioning Questionnaire; MFI: Multidimensional Fatigue Inventory; MMRM: mixed-effects model repeated measures analysis; SE: standard error.

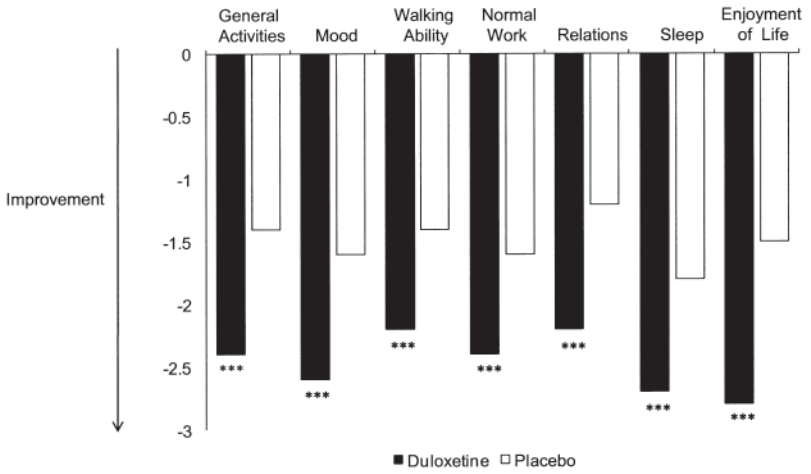

Figure 3. Mean change from baseline in Brief Pain Inventory Pain Interference items after 12 weeks of treatment (LOCF analysis). ***p < 0.001 vs placebo.

(4.6% vs 0.7%; p = 0.006), feeling jittery (2.7% vs 0%; p = 0.007), and middle insomnia (1.9% vs 0.0%; p = 0.030). Among these events, those that were severe and significantly greater with duloxetine treatment included constipation (n = 6, 2.3% vs n = 0 in the placebo group; p = 0.015) and hyperhydrosis (n = 5, 1.9% vs n = 0 in the placebo group; p = 0.030).

There were no significant treatment group differences in the rate of serious adverse events (SAE). In the duloxetine group, one SAE (0.4%) was reported: an intervertebral disc protrusion. In the placebo group, there were 6 SAE reported: chest pain (n = 1, 0.4%), muscle spasms (n = 1, 0.4%), myocardial infarction (n = 1, 0.4%), non-cardiac chest pain (n = 1, 0.4%), pancreatitis (n = 1, 0.4%), and suicidal ideation (n = 1, 0.4%).

There were statistically significant between-treatment differences in mean change in weight over the 12 weeks, which were less than 1 kg in either treatment group (duloxetine, –0.62 kg; placebo, 0.21 kg; p < 0.001). These changes were not considered clinically relevant.

Mean changes in heart rate were significantly different between the duloxetine and placebo groups (1.76 bpm vs –0.20 bpm; p = 0.003), but mean changes in systolic and diastolic blood pressure did not differ statistically between treatment groups. One patient in each of the treatment groups met criteria for sustained elevation in diastolic blood pressure (supine diastolic blood pressure ≥ 90 mm Hg and an increase from baseline of ≥ 10 mm Hg for at least 3 consecutive visits). One patient in the placebo group met criteria for sustained systolic blood pressure (supine systolic blood pressure ≥ 140 mm Hg and an increase from baseline of ≥ 10 mm Hg for at least 3 consecutive visits).

Statistically significant differences were observed in mean change from baseline to endpoint in patients treated with duloxetine versus placebo for some clinical laboratory values: alkaline phosphatase (1.00 vs –1.00 units/l; p < 0.001), bicarbonate (1.70 vs 1.00 mmol/l; p = 0.01), chloride (–1.00 vs 0.00 mmol/l; p < 0.001), cholesterol (0.01 vs –0.13 mmol/l; p = 0.013), glucose non-fasting (–0.30 vs 0.10 mmol/l; p = 0.007), and uric acid (–17.5 vs 0.00

Table 3. Baseline to LOCF endpoint changes in depression, anxiety, and health outcomes.

Measure	Duloxetine 60–120 mg QD, n = 263 Mean Change (SE)	Placebo, n = 267 Mean Change (SE)	ANCOVA p
BDI, total score	–5.5 (0.5)	–3.6 (0.5)	0.007
BAI, total score	–3.1 (0.5)	–3.2 (0.5)	0.907
MFI general fatigue	–2.2 (0.2)	–1.4 (0.2)	0.005
Physical fatigue	–2.1 (0.2)	–1.4 (0.2)	0.013
Mental fatigue	–2.0 (0.2)	–1.1 (0.2)	0.003
Reduced activity	–1.5 (0.2)	–0.6 (0.2)	0.005
Reduced motivation	–1.7 (0.2)	–0.7 (0.2)	< 0.001
SF-36			
Bodily pain	18.5 (1.3)	13.3 (1.3)	0.003
General health	9.3 (1.2)	2.9 (1.2)	< 0.001
Mental health	10.1 (1.2)	2.6 (1.2)	< 0.001
Physical functioning	13.5 (1.3)	8.1 (1.3)	0.002
Role-emotional	14.9 (2.6)	5.1 (2.5)	0.004
Role-physical	20.5 (2.5)	18.9 (2.5)	0.632
Social functioning	14.2 (1.5)	7.5 (1.5)	< 0.001
Vitality	12.8 (1.3)	8.5 (1.3)	0.015
Mental component summary	5.1 (0.7)	1.3 (0.7)	< 0.001
Physical component summary	6.0 (0.6)	4.8 (0.6)	0.134

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; MFI: Multidimensional Fatigue Inventory; SE: standard error; SF-36: Medical Outcome Study Short-Form Health Survey.

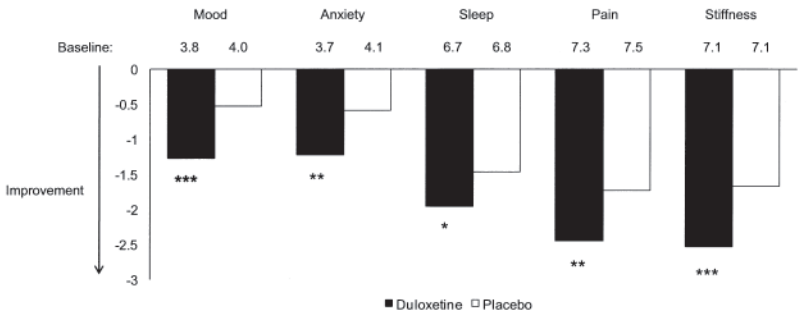

Figure 4. Mean change from baseline to Week 12 in patient-rated Likert scale scores (LOCF analysis). *p ≤ 0.05; **p ≤ 0.01; ***p < 0.001.

Table 4. Percentage of patients who responded to treatment based on changes from baseline in Brief Pain Inventory 24-hour average pain severity item score. Values are percentages.

	Duloxetine, n = 249	Placebo, n = 248	p
LOCF			
30% improvement	47.8	34.1	0.002
Sustained 30% improvement	36.1	24.0	0.004
50% improvement	33.3	21.3	0.003
2 point reduction from baseline	53.8	43.8	0.026
BOCF			
30% improvement	36.1	26.6	0.019
50% improvement	24.7	16.5	0.024
2 point reduction from baseline	40.3	32.6	0.071

LOCF: last observation carried forward; BOCF: baseline observation carried forward.

mmol/l; p < 0.001). However, differences in mean changes between treatment groups were small and not considered to be clinically relevant.

DISCUSSION

Ours is the first study of duloxetine treatment in patients with FM that assessed changes in the Patient's Global Impression of Improvement (PGI-I) as the primary measure. In this double-blind, randomized trial duloxetine 60–120 mg/day had significantly greater improvement, compared with placebo, on the PGI-I after 12 weeks of treatment. Compared with placebo, duloxetine 60–120 mg/day reduced (improved) PGI-I scores beginning with the first assessment following treatment initiation (2 weeks).

Because FM is perceived by patients to be more than a painful condition[21], assessing the global impression of

Table 5. Brief Pain Inventory (BPI) 24-hour average pain scores and patient global impression of improvement (PGI-I) scores reported before and after duloxetine dose increase.

Dose	n	Week of Increase	BPI 24-hour Average Pain Score Before, mean (SD)	BPI 24-hour Average Pain Score Endpoint*, mean (SD)	PGI-I Score Before, mean (SD)	PGI-I Score Endpoint*, mean (SD)
90 mg/day	59**	4	6.0 (1.8)	4.1 (2.3)††	3.3 (1.4)	2.7 (1.3)
120 mg/day	64†	8	6.1 (1.6)	5.4 (1.9)††	3.4 (1.0)	3.2 (1.2)

* Last observation carried forward to Week 12. ** No. of patients who had dose escalation to 90 mg and responded. † No. of patients who had dose escalation to 90 mg, but did not respond, and were escalated to 120 mg. †† Within-dose improvement, $p < 0.05$.

improvement may be a more clinically relevant measure than improvement in pain. In a post-hoc analysis of 4 clinical trials in patients with FM that had improvement in pain as a primary outcome[9,10,11,12], PGI-I outcomes of feeling "better" or "very much better" were found to be correlated with improvement in multiple symptom domains that included physical functioning, fatigue, and influence of symptoms on daily living, as well as pain[22].

In our study significantly more patients reported that they felt "much better" or "very much better" after 12 weeks of treatment with duloxetine versus placebo. Patients treated with duloxetine compared to those treated with placebo reported significant improvement in self-assessments of mood (Likert and BDI), anxiety (Likert only), stiffness, and being bothered by pain and sleep difficulties, fatigue, as well as a significant reduction in pain interference with general activity, walking ability, normal work, relations with others, sleep, and enjoyment of life. In addition, there were significant improvements in patient-rated health-related quality of life assessments for bodily pain, general health, mental health, physical functioning, role-emotional, social functioning, vitality, and the mental component summary on the SF-36.

Although cognitive dysfunction is another commonly reported symptom domain in patients with FM[21], few FM treatment trials have systematically assessed cognition. Our study explored possible outcome measures to evaluate cognitive dysfunction in patients with FM. Results from the self-report cognitive measure, the CPFQ, did not differ significantly between treatments at endpoint. The CPFQ was developed to measure cognitive and executive dysfunction in mood and anxiety disorders and has been validated in depressed outpatients[23] but not in patients with FM. In this trial, fewer than 20% of the study population had comorbid MDD and fewer than 10% had comorbid GAD. The mean CPFQ total score at endpoint indicated that cognitive functioning had improved somewhat to "minimally diminished" in both groups. These results suggest that perhaps the CPFQ is not an adequate measure of cognitive functioning in patients with FM if they are not depressed or anxious. Further, the CPFQ may be problematic as an outcome measure because patients retrospectively assess their cognitive and physical functioning over the prior month, and because the responses on the questionnaire refer to how diminished functioning has become relative to "normal," it may be difficult for patients to provide a response indicating improvement. The Multiple Ability Self-Report Questionnaire[24] has been shown to be sensitive to change in clinical trials with intervention in patients with FM[25], and may be a better assessment for perceived cognitive difficulties in this patient population, because it assesses the frequency of experiencing difficulty in performing daily cognitive tasks.

This is also the first study to explore the efficacy of duloxetine 90 mg/day in the treatment of FM. In those patients who had < 50% reduction in pain severity after 4 weeks' treatment with duloxetine 60 mg, double-blind escalation to 90 mg resulted in reduced pain severity in some patients, and on average they reported feeling "much better." Titration to higher doses of duloxetine was double-blind to reduce the expectation of improvement with a dose increase. For those patients who did not experience the expected reduction in pain severity after 4 weeks' treatment with 90 mg, their dose was increased to 120 mg, after which their pain severity decreased, and on average they reported feeling "a little better." These results may support usual clinical practice for increasing the dose of duloxetine to improve efficacy, and suggest that the duloxetine 90 mg daily would be an appropriate intermediate dosage to manage FM.

The safety and tolerability findings in our study were consistent with those reported in previous studies in FM patients treated with duloxetine 60 and 120 mg/day[9,10,11,12].

There are limitations of the acute phase of this study that should be considered. First, the use of a single patient-rated assessment of improvement in global FM symptoms cannot provide information regarding specific symptom response. Second, the instrument used to assess cognitive functioning in this study has not been validated in FM, and there remains a need to develop instruments that adequately assess this domain in FM. Third, the results of the acute phase of this study may not generalize to patients with some psychiatric comorbid disorders, unstable medical or comorbid pain disorders, or patients who were treatment-refractory or disabled, because patients with these conditions were excluded from the study.

In summary, in patients with FM, with or without MDD or GAD, duloxetine 60–120 mg/day improved patient-reported global improvement beginning after 2 weeks of treatment and continued through to the 12-week endpoint. Increasing the dose in patients with inadequate pain response was associated with further pain reduction, and suggests that duloxetine 90 mg/day may be an appropriate intermediate dosage for some patients. Duloxetine treatment resulted in improvement in function and in other common associated symptoms, including fatigue, depressive and anxiety symptoms, stiffness, and being bothered by sleep difficulties. Consistent with 4 earlier trials of duloxetine in the treatment of FM, duloxetine was safely administered, and tolerated by most patients.

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