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# A Double-Blind, Multicenter Trial Comparing Duloxetine With Placebo in the Treatment of Fibromyalgia Patients With or Without Major Depressive Disorder

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***Objective.*** **To assess the efficacy and safety of duloxetine, a serotonin and norepinephrine reuptake inhibitor, in subjects with primary fibromyalgia, with or without current major depressive disorder.**

***Methods.*** **This study was a randomized, double-blind, placebo-controlled trial conducted in 18 outpatient research centers in the US. A total of 207 subjects meeting the American College of Rheumatology criteria for primary fibromyalgia were enrolled (89% female, 87% white, mean age 49 years, 38% with current major depressive disorder). After single-blind placebo treatment for 1 week, subjects were randomly assigned to receive duloxetine 60 mg twice a day (n = 104) or placebo (n = 103) for 12 weeks. Co–primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score (score range 0–80, with 0 indicating no impact) and FIQ pain score (score range 0–10). Secondary outcome measures included mean tender point pain threshold, number of tender points, FIQ fatigue, tiredness on awakening, and stiffness scores, Clinical Global Impression of Severity (CGI-Severity) scale, Patient Global Impression of Improvement (PGI-Improvement) scale, Brief Pain Inventory (short form), Medical Outcomes Study Short Form 36, Quality of Life in Depression Scale, and Sheehan Disability Scale.**

***Results.*** **Compared with placebo-treated subjects, duloxetine-treated subjects improved significantly more ($P = 0.027$) on the FIQ total score, with a treatment difference of −5.53 (95% confidence interval −10.43, −0.63), but not significantly more on the FIQ pain score ($P = 0.130$). Compared with placebo-treated subjects, duloxetine-treated subjects had significantly greater reductions in Brief Pain Inventory average pain severity score ($P = 0.008$), Brief Pain Inventory average interference from pain score ($P = 0.004$), number of tender points ($P = 0.002$), and FIQ stiffness score ($P = 0.048$), and had significantly greater improvement in mean tender point pain threshold ($P = 0.002$), CGI-Severity ($P = 0.048$), PGI-Improvement ($P = 0.033$), and several quality-of-life measures. Duloxetine treatment improved fibromyalgia symptoms and pain severity regardless of baseline status of major depressive disorder. Compared with placebo-treated female subjects (n = 92), duloxetine-treated female subjects (n = 92) demonstrated significantly greater improvement on most efficacy measures, while duloxetine-treated male subjects (n = 12) failed to improve significantly on any efficacy measure. The treatment effect on significant pain reduction in female subjects was independent of the effect on mood or anxiety. Duloxetine was safely administered and well tolerated.**

***Conclusion.*** **In this randomized, controlled, 12-week trial (with a 1-week placebo lead-in phase), duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major depressive disorder, particularly for**

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**women, who had significant improvement across most outcome measures.**

Fibromyalgia is a chronic musculoskeletal pain disorder of unknown etiology, characterized by widespread pain and muscle tenderness, and often accompanied by fatigue, sleep disturbance, and depressed mood (1,2). Fibromyalgia occurs in ~2% of the general population in the US and is more common in women than in men (3.4% of women and 0.5% of men) (3). There are few reported effective treatments and no Food and Drug Administration–approved treatments for fibromyalgia, which is associated with substantial morbidity and disability.

The pathophysiology of fibromyalgia is unknown, but abnormalities in central monoaminergic neurotransmission might play a role. There is evidence of dysfunction in both serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) systems in patients with fibromyalgia (4–7). Both 5-HT and NE have also been implicated in the mediation of endogenous analgesic mechanisms via the descending inhibitory pain pathways in the brain and spinal cord (8–10). Dysfunction of 5-HT– and NE-mediated descending pain-inhibitory pathways is a potential mechanism for the pain experienced by patients with fibromyalgia. Antidepressants that increase 5-HT– and NE-mediated neurotransmission are commonly used to treat fibromyalgia and other chronic pain conditions (11). Prior treatment studies with antidepressant medications suggested that inhibition of both the 5-HT and NE reuptake transporters was more effective in treating fibromyalgia than inhibition of either transporter alone (11,12). Two recent meta-analyses of trials of tricyclic medications that inhibit both 5-HT and NE reuptake found a consistent, moderate efficacy for these agents (13,14). However, many patients with fibromyalgia cannot tolerate the sedative and other adverse effects associated with tricyclic agents. As an alternative to tricyclic agents, selective serotonin reuptake inhibitors (SSRIs), which are likely to be better tolerated, have had mixed results in treatment studies of fibromyalgia (12,15–18).

Duloxetine hydrochloride is a potent 5-HT and NE reuptake inhibitor (SNRI) that is relatively evenly balanced with similar affinity for both 5-HT and NE reuptake inhibition. Duloxetine lacks significant affinity for muscarinic, histamine 1, $\alpha_1$-adrenergic, dopamine, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2C, and opioid receptors. Because of the proposed role of 5-HT and NE as key mediators of descending pain pathways, duloxetine has been studied in several animal models of persistent and neuropathic pain and found to be effective in reducing pain-related behaviors at doses that did not cause neuromuscular dysfunction (19–21). In these animal models, duloxetine was more potent than venlafaxine, amitriptyline, or desipramine and more effective than the SSRI paroxetine and the selective NE inhibitor thionisoxetine in reducing persistent pain-related behaviors in animals (20). The findings from these preclinical studies suggested that duloxetine might be an effective treatment for some forms of persistent pain in humans.

Abnormalities in 5-HT and NE neurotransmission are also involved in the pathophysiology of major depressive disorder, which is frequently comorbid with fibromyalgia (1). Patients with major depressive disorder commonly present with painful physical symptoms, such as headache, back pain, stomach aches, and poorly localized musculoskeletal pain, although it is not known whether major depressive disorder is associated with altered pain processing or whether the pain associated with major depressive disorder has an etiology similar to that of pain in fibromyalgia (22–24). Duloxetine has been shown to be a safe, tolerable, and effective antidepressant at doses of 60–120 mg/day (25–27). In a previous trial, duloxetine also significantly reduced painful physical symptoms associated with major depressive disorder (28).

Based on the evidence from preclinical and clinical studies of duloxetine showing potential efficacy in the treatment of persistent pain symptoms and the painful physical symptoms associated with depression, we hypothesized that duloxetine would be safe and efficacious in reducing pain severity and the impact of fibromyalgia in patients with or without current major depressive disorder. To test this hypothesis on behalf of the Duloxetine Fibromyalgia Trial Group (see Appendix A), we conducted a randomized, placebo-controlled, double-blind, parallel-group study to assess the safety and efficacy of duloxetine, titrated to 60 mg twice a day, in 207 outpatients meeting the American College of Rheumatology (ACR) criteria for fibromyalgia (2) with or without current major depressive disorder. The dose of 120 mg/day was selected based on results of a previous clinical trial of fibromyalgia suggesting that patients might respond better to higher doses of antidepressants (16). This is one of the largest clinical trials ever conducted for the treatment of fibromyalgia, and, to our knowledge, the only study to include an evaluation of the impact of comorbid major depressive disorder on response to treatment.

## PATIENTS AND METHODS

**Overview.** The study was conducted in 18 outpatient research centers (5 university sites and 13 independent research centers) in the US. Enrollment began in July 2001, and the study was completed in March 2002. The Institutional Review Boards approved the protocol, and all subjects provided written informed consent after the study was explained and their questions answered, and before study procedures were initiated. Subjects were identified by physician referral or responded to an advertisement for a fibromyalgia medication trial.

**Entry criteria.** Female or male subjects were eligible for the study if they were 18 years of age or older and met the ACR criteria for fibromyalgia (2). Only subjects with primary fibromyalgia were enrolled; those with associated rheumatic or other medical disorders that contributed to the symptoms of fibromyalgia were excluded. Subjects were required to score $\geq$4 on the pain intensity item of the Fibromyalgia Impact Questionnaire (FIQ) (score range 0–10, with 10 indicating very severe pain) (29) at visits 1 (screening) and 2 (the placebo lead-in phase [see below]). Subjects were included if they were judged to be reliable and had an educational level and degree of understanding that allowed them to communicate intelligibly.

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 dysthymia, which is more treatment resistant than major depression, or primary psychiatric disorder other than major depressive disorder; substance abuse in the last year; history of psychosis; pregnancy or breast feeding; unacceptable contraception in those of childbearing potential; involvement in disability reviews that might compromise treatment response; use of an investigational drug within 30 days; prior participation in a study of duloxetine; severe allergic reactions to multiple medications; intolerance to >3 psychoactive drugs or >1 SSRI; and failure to respond to $\geq$2 adequate regimens of 2 different classes of antidepressants for depression or fibromyalgia.

Concomitant medication exclusions included use of medications or herbal agents with central nervous system activity (antidepressants required a 7-day washout prior to visit 2 except for monoamine oxidase inhibitors, which required a 14-day washout, and fluoxetine, which required a 30-day washout); regular use of analgesics with the exception of acetaminophen up to 2 grams/day and aspirin up to 325 mg/day; chronic use of sedatives, antiemetics, or antispasmodics; episodic use of anticoagulants; <3 months stable therapy with antihypertensives, hormones, antiarrhythmics, antidiarrheals, antihistamines, cough/cold preparations (excluding dextromethorphan), or laxatives; and initiation of or change in unconventional or alternative therapies.

**Study design.** The 3–30-day screening phase was followed by a 1-week, single-blind, placebo lead-in phase at visit 2. Subjects received placebo for 1 week in an attempt to obtain an unbiased evaluation of the baseline variables, including safety measures. At visit 3, subjects were randomized to 1 of the following 2 treatment groups: duloxetine or placebo in a 1:1 ratio. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive voice response system. Treatment was double-blind for 12 weeks. Subjects were evaluated weekly (visits 3–5) for the first 2 weeks of the 12-week therapy phase; thereafter, study visits were scheduled at 2-week intervals (visits 6–10). Subjects randomized to receive duloxetine underwent a double-blind forced titration from 20 mg/day to 60 mg twice a day during the first 2 weeks of the therapy phase, as follows: 20 mg every day for 5 days, 20 mg twice a day for at least 3 days, 40 mg twice a day for at least 2 days, and 60 mg twice a day for the remainder of the study beginning at visit 5. The number of placebo capsules was similarly adjusted to maintain the blinding.

**Outcome measures.** The protocol-defined co–primary outcome measures were pain severity as measured by the FIQ pain item and the FIQ total score (29). The total score reflected the impact of fibromyalgia and ranged from 0 (no impact) to 80 (maximum impact). Secondary outcome measures included the FIQ items for fatigue, morning tiredness, and stiffness (29). At the start-up meeting, study physicians or qualified study personnel were trained and certified in the performance of dolorimetry; reliability testing was not performed. For the tender point assessment, the Fischer dolorimeter (30) with a rubber disk of 1 $cm^2$ was applied at a 90° vertical angle to the 18 tender point sites defined by the ACR criteria (2), and the pressure was increased at a rate of 1 $kg/cm^2$/second until the subject indicated verbally that he/she first felt discomfort or pain (tender point pain threshold recorded in $kg/cm^2$). The mean tender point pain threshold was calculated from 18 points, and the tender point count was determined by the number of tender points that had a threshold of $\leq$4 $kg/cm^2$.

Other secondary measures included the Clinical Global Impression of Severity (CGI-Severity) scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (31), and the Patient Global Impression of Improvement (PGI-Improvement) scale, ranging from 1 (very much better) to 7 (very much worse). Subjects also completed the Brief Pain Inventory (short form) (32), which measured pain severity during the past 24 hours (from 0 [no pain] to 10 [pain as bad as you can imagine]) and 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. Multiple measures of pain were included because there is no current consensus about the evaluation of pain in fibromyalgia. The measures assessed pain during different time frames and determined the impact of pain on several functions.

Other secondary objectives were to determine whether the effects of duloxetine 60 mg twice a day on the FIQ pain score and total score were independent of the presence or absence of a current major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). The severity of depressive and anxiety symptoms was measured by the Beck Depression Inventory-II (33) and the Beck Anxiety Inventory (34), respectively. The impact of duloxetine compared with that of placebo on subject-reported outcomes was measured by the Medical Outcomes Study Short Form 36 (SF-36) (35), the Quality of Life in Depression Scale (36,37), and the Sheehan Disability Scale (38). The safety of duloxetine 60 mg twice a day was assessed by discontinuation pattern, treatment-emergent ad-

verse events, vital signs, electrocardiograms (EKGs), and laboratory analysis.

**Schedule of assessments.** The screening protocol (visit 1) included the medical history and the Mini International Neuropsychiatric Interview (39) to identify DSM-IV Axis I psychiatric disorders (40). Subjects also underwent a physical examination, EKG, and laboratory tests, and completed the FIQ. A digital tender point examination confirmed the diagnosis of fibromyalgia by ACR criteria (2). At the 1-week placebo lead-in phase (visit 2) and at each subsequent visit, the FIQ was completed, vital signs were checked, and adverse events and concomitant medication were reviewed. At randomization (visit 3), laboratory tests and all of the efficacy measurements were completed. From the randomization visit to the end of the study (visits 3–10), the Brief Pain Inventory was completed at each visit, and the tender point assessment, CGI-Severity scale, PGI-Improvement scale, Beck Depression Inventory-II, Beck Anxiety Inventory, and laboratory tests were completed or performed at weeks 4, 8, and 12. Additional evaluations at the final visit included a physical examination, laboratory tests, EKG, SF-36, Quality of Life in Depression Scale, and Sheehan Disability Scale.

**Statistical analysis.** This study was designed to enroll 200 patients so that it would have at least 90% power to detect a treatment group difference of 1.4 points in pain severity as measured by the pain item in the FIQ. The use of a 1.4-point difference in FIQ pain score was based on the desire to power this study to demonstrate a moderately large effect size (0.65) for duloxetine using point and variance estimates based on the results of the Arnold et al study in 2002 (16) comparing fluoxetine with placebo under similar circumstances. The present study was not powered using the FIQ total score because its higher relative variability would have required a considerably greater sample size. Analyses were also conducted to determine whether the treatment effect of duloxetine in fibromyalgia was independent of its effect on major depressive disorder. The interaction of treatment with major depressive disorder status was not included in the power calculations due to limited preprotocol information concerning this effect. We anticipated that the power for testing this interaction effect would be slightly less than that for the treatment-group-only comparisons; however, the use of a sample size that provides a high level of power (90%) based on treatment group comparisons was expected to provide reasonable power for the interaction assessment.

Longitudinal changes from baseline on continuous efficacy measures were analyzed using a mixed-effects model for repeated measures analysis (41), defined a priori in the protocol as the primary analysis. The model included the fixed, categorical effects of treatment, investigator, visit, and interaction of treatment with visit, as well as the continuous, fixed covariates of baseline and interaction of baseline with visit. An unstructured covariance matrix was used to model the within-subject errors. As a secondary analysis, changes from baseline to end point (the last observation carried forward [LOCF] method) were analyzed using an analysis of covariance (ANCOVA) model with the terms of treatment, investigator, and baseline scores. When previous use of antidepressants was not balanced at baseline between treatment groups, that subgroup was added to the ANCOVA model to assess treatment effect on the two primary measures. Furthermore, for the FIQ pain score, the area under the curve (AUC) of improvement scores (postbaseline minus baseline) over visit intervals was evaluated. The greater the AUC value, the greater the treatment effect on pain reduction. Due to the skewed distribution of the AUC, the rank-transformed AUC scores were analyzed using an analysis of variance (ANOVA) model with the terms of treatment and investigator.

The hypothesis regarding an interaction between ma-

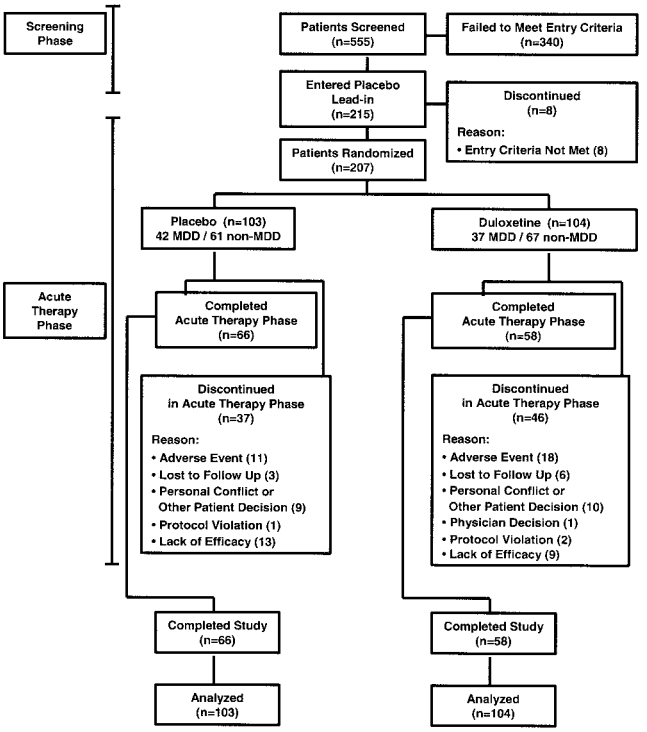


**Figure 1.** Flow of subjects through the trial. MDD = current major depressive disorder.

**Table 1.** Baseline characteristics of subjects*

| | Treatment group | |
|---|---|---|
| | Placebo (n = 103) | Duloxetine 60 mg bid (n = 104) |
| Age, mean ± SD years | 48.3 ± 11.3 | 49.9 ± 12.3 |
| Women | 92 (89.3) | 92 (88.5) |
| Race | | |
| White | 88 (85.4) | 92 (88.5) |
| African descent | 4 (3.9) | 3 (2.9) |
| Hispanic | 6 (5.8) | 5 (4.8) |
| East/southeast Asian | 2 (1.9) | 1 (1.0) |
| Western Asian | 0 (0) | 1 (1.0) |
| Other | 3 (2.9) | 2 (1.9) |
| Current major depressive episode | 42 (40.8) | 37 (35.6) |
| Previous antidepressant use | 51 (49.5) | 35 (33.7)† |

* Except where indicated otherwise, values are the number (%) of subjects. bid = twice a day.
† $P = 0.024$ versus placebo group.

**Table 2.** Baseline efficacy measures*

| Efficacy measure | Treatment group | | | |
|---|---|---|---|---|
| | Placebo | | Duloxetine 60 mg bid | |
| | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD |
| FIQ total score, range 0–80 | 101 | 50.2 ± 13.3 | 103 | 48.7 ± 14.7 |
| FIQ subscores, range 0–10 | | | | |
| Pain | 102 | 7.0 ± 2.0 | 104 | 6.9 ± 2.1 |
| Fatigue | 103 | 7.4 ± 2.2 | 104 | 7.4 ± 2.1 |
| Tiredness on awakening | 103 | 7.3 ± 2.3 | 104 | 7.4 ± 2.4 |
| Stiffness | 103 | 7.1 ± 2.2 | 104 | 7.3 ± 2.3 |
| Tender points, range 0–18 | 97 | 16.6 ± 2.6 | 93 | 16.7 ± 2.2 |
| Mean tender point pain threshold, kg/cm$^2$ | 97 | 2.3 ± 0.8 | 93 | 2.3 ± 0.8 |
| CGI-Severity scale, range 1–7 | 102 | 4.3 ± 0.9 | 104 | 4.3 ± 0.8 |
| Brief Pain Inventory average pain severity, range 0–10 | 102 | 6.1 ± 1.7 | 103 | 6.1 ± 1.8 |
| Brief Pain Inventory average interference from pain, range 0–10 | 102 | 5.5 ± 2.3 | 104 | 5.5 ± 2.4 |
| Beck Depression Inventory-II total score, range 0–63 | 96 | 13.2 ± 8.9 | 99 | 12.7 ± 9.6 |
| Beck Anxiety Inventory total score, range 0–63 | 93 | 11.2 ± 8.0 | 102 | 9.9 ± 8.5 |

* There were no significant differences between the treatment groups. bid = twice a day; FIQ = Fibromyalgia Impact Questionnaire; CGI-Severity = Clinical Global Impression of Severity.

jor depressive disorder status at baseline and treatment groups was tested using an ANCOVA model as described above, with the addition of the major depressive disorder status at baseline and the interaction of treatment with subgroup. This model was also used for the subgroup analysis for the subgroups defined by other factors.

Path analysis (42) was performed to test the direct treatment effect on pain reduction. In this analysis, 3 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 or anxiety symptoms (model 1); second, the treatment improves depressive symptoms (model 2) or anxiety symptoms (model 3). In this analysis, the significance of the direct treatment effect was tested by Student's *t*-test in the first regression model (model 1), where change in the pain measure (FIQ pain score or Brief Pain Inventory average pain severity score) was a dependent variable, and treatment, baseline, investigator, and changes in the Beck Depression Inventory-II and Beck Anxiety Inventory scores were independent variables. In the other 2 regression models (models 2 and 3), for changes in Beck Depression Inventory-II and Beck Anxiety Inventory scores, respectively, the treatment and baseline were used as independent variables. The percentage of direct and indirect effects on the total treatment effect (the sum of the direct and the two indirect effects) was computed and presented.

For categorical variables, treatment group differences were evaluated using Fisher's exact test. Continuous baseline measures and continuous safety parameters were evaluated using the ANOVA model described above. 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" when presenting efficacy results.

## RESULTS

**Subject disposition.** A total of 555 subjects were screened to identify 215 subjects who met entry criteria. Of these 215 subjects, 207 were randomized to receive study treatment. This was the intent-to-treat sample, of which 104 subjects received duloxetine and 103 subjects received placebo (Figure 1). There were no significant between-group differences in subject discontinuation for any reason. Eighty-three subjects withdrew during the acute therapy phase, 46 (44%) from the duloxetine group and 37 (36%) from the placebo group ($P = 0.257$). The mean ± SD duration of treatment was 58.7 ± 32.1 days for duloxetine and 65.6 ± 28.7 days for placebo ($P = 0.116$).

**Baseline clinical and demographic characteristics.** The majority of the subjects were women (89%) and white (87%). Thirty-eight percent of the enrolled subjects had current major depressive disorder. The only significant between-group difference in any baseline characteristic (Table 1) or clinical variable (Tables 2 and 3) involved a previous history of antidepressant use for treatment of either mood or pain symptoms, which was

**Table 3.** Baseline scores for Short Form 36 (SF-36), Quality of Life in Depression Scale, and Sheehan Disability Scale*

| | Treatment group | | | |
|---|---|---|---|---|
| | Placebo | | Duloxetine 60 mg bid | |
| Outcome measure | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD |
| SF-36, range 0–100 | | | | |
| Mental subscore | 92 | 44.0 ± 10.3 | 91 | 46.3 ± 11.8 |
| Physical subscore | 92 | 30.3 ± 8.0 | 91 | 29.3 ± 8.8 |
| Bodily pain | 92 | 32.3 ± 15.0 | 92 | 31.4 ± 16.1 |
| General health perception | 92 | 49.9 ± 21.2 | 92 | 50.8 ± 22.0 |
| Mental health | 92 | 61.8 ± 17.6 | 92 | 65.5 ± 20.5 |
| Physical functioning | 92 | 45.5 ± 22.3 | 92 | 45.4 ± 22.8 |
| Role limit, emotional | 92 | 56.2 ± 42.5 | 92 | 62.0 ± 44.1 |
| Role limit, physical | 92 | 17.9 ± 29.0 | 92 | 16.0 ± 25.8 |
| Social function | 92 | 56.7 ± 21.8 | 91 | 59.8 ± 25.6 |
| Vitality | 92 | 24.1 ± 18.6 | 92 | 23.4 ± 19.1 |
| Quality of Life in Depression Scale total score, range 0–10 | 81 | 5.0 ± 6.1 | 84 | 4.9 ± 6.4 |
| Sheehan Disability Scale total score, range 0–30 | 93 | 16.1 ± 7.2 | 91 | 15.6 ± 7.9 |

* There were no statistically significant differences between the treatment groups. bid = twice a day.

more common in the placebo group. Female and male subjects were similar in demographics, baseline variables, and major depressive disorder status with the exception of the two tender point assessments. Compared with male subjects, female subjects had significantly more tender points (mean ± SD 16.88 ± 1.97 versus 14.87 ± 3.84; $P < 0.001$) and significantly lower mean tender point pain thresholds (mean ± SD 2.21 ± 0.71 versus 2.68 ± 1.04; $P < 0.001$).

**Efficacy.** The changes in the FIQ total score and pain score over time are illustrated in Figures 2 and 3. Compared with the placebo group, the duloxetine group had a significantly greater improvement in the FIQ total score at the last visit of the acute therapy phase (week 12), as well as at week 4. The treatment group difference in FIQ pain score was not significant at week 12 ($P = 0.130$); however, it was significant at early visits of the study (weeks 1, 2, and 4). Results are summarized in Table 4.

Most of the secondary outcome measures improved significantly more in the duloxetine group compared with the placebo group (Table 4). The Brief Pain Inventory interference items that improved significantly were general activity, mood, walking ability, normal work, sleep, and enjoyment of life.

The duloxetine group had significantly greater improvement (by ANCOVA) in the FIQ total score, with a difference of −4.52 (95% confidence interval [95% CI] −8.86, −0.17) ($P = 0.042$), and marginally significant improvement in the FIQ pain score, with a difference of −0.71 (95% CI −1.42, 0.01) ($P = 0.052$), after accounting for the significant group difference in prior antidepressant use at baseline. When comparing the AUCs on the FIQ pain score, duloxetine treatment demonstrated a significant superiority over placebo (median AUC 75.5 versus 27, respectively; $P = 0.041$). The LOCF results on secondary outcome measures were similar to the findings obtained by the primary

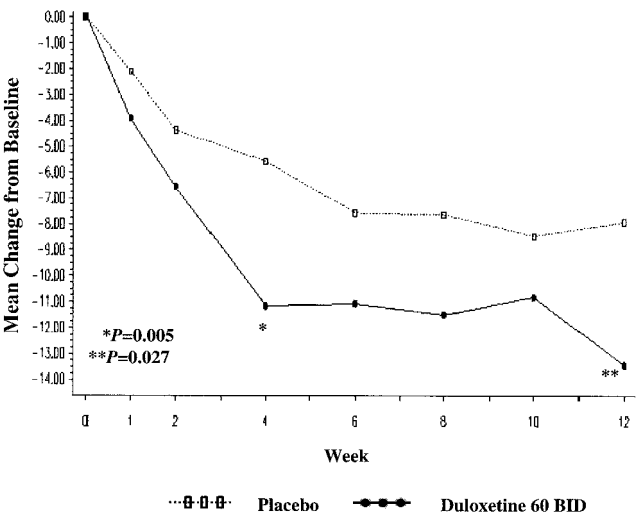


**Figure 2.** Mean change from baseline in Fibromyalgia Impact Questionnaire (FIQ) total score for all randomized subjects. Duloxetine 60 BID = duloxetine 60 mg twice a day.

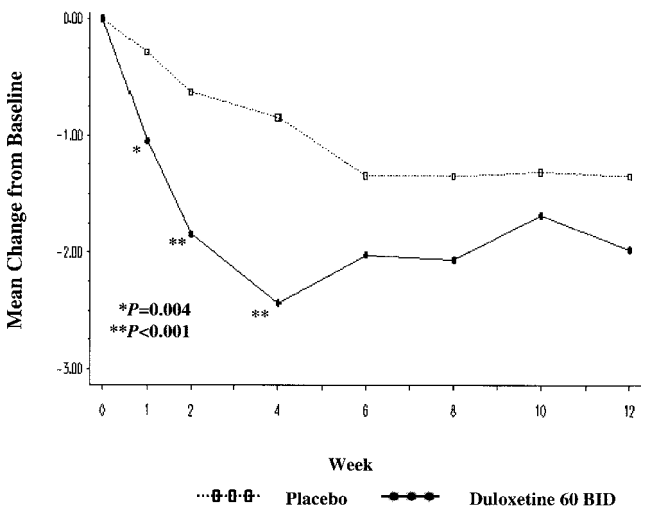


**Figure 3.** Mean change from baseline in FIQ pain score for all randomized subjects. See Figure 2 for definitions.

analysis. Other outcome measures improved significantly more in the duloxetine group than in the placebo group (Table 5).

The response rates, defined as a reduction of at least 50% in the FIQ pain score at end point, were 27.7% and 16.7% for the duloxetine and placebo groups, respectively ($P = 0.06$). No interaction of treatment with major depressive disorder was observed for the primary efficacy measures ($P = 0.862$ for FIQ total score and $P = 0.677$ for FIQ pain score), suggesting that the effect of duloxetine on reduction of fibromyalgia symptoms was similar in subjects with or without major depressive disorder.

**Efficacy analysis on female subjects.** The interaction of treatment with sex approached the significance level of 0.1 for the FIQ total score ($P = 0.101$) and FIQ pain score ($P = 0.121$). Compared with placebo-treated female subjects, duloxetine-treated female subjects had significantly greater improvement in both the FIQ total score ($P = 0.029$) and FIQ pain score ($P = 0.035$). A significantly higher percentage of duloxetine-treated women than placebo-treated women had a decrease of $\geq$50% in the FIQ pain score (30.3% versus 16.5%; $P = 0.035$). The interaction of treatment with sex was significant for two secondary measures, the Brief Pain Inventory average pain score ($P = 0.046$) and the Sheehan Disability Scale total score ($P = 0.007$). Duloxetine-treated female subjects improved significantly more than placebo-treated female subjects on all of the secondary efficacy measures that demonstrated treatment group differences for all randomized subjects. The male subjects receiving duloxetine did not respond significantly on primary or secondary efficacy measures.

**Table 4.** Summary of results for the FIQ, tender point assessments, CGI-Severity scale, Patient Global Impression of Improvement (PGI-Improvement) scale, Brief Pain Inventory, Beck Depression Inventory-II, and Beck Anxiety Inventory*

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Placebo | | Duloxetine 60 mg bid | | | |
| Measure | No. of subjects | Change, mean ± SEM | No. of subjects | Change, mean ± SEM | Between-group difference at end point (95% CI) | *P* |
| FIQ total score, range 0–80 | 102 | −7.93 ± 1.73 | 101 | −13.46 ± 1.82 | −5.53 (−10.43, −0.63) | 0.027 |
| FIQ subscores, range 0–10 | | | | | | |
| Pain | 103 | −1.35 ± 0.29 | 101 | −1.98 ± 0.3 | −0.63 (−1.45, 0.19) | 0.130 |
| Fatigue | 103 | −0.88 ± 0.28 | 101 | −1.30 ± 0.29 | −0.42 (−1.2, 0.36) | 0.287 |
| Tiredness on awakening | 103 | −0.95 ± 0.28 | 101 | −1.42 ± 0.30 | −0.47 (−1.27, 0.33) | 0.246 |
| Stiffness | 103 | −1.51 ± 0.29 | 101 | −2.33 ± 0.30 | −0.82 (−1.64, −0.01) | 0.048 |
| Tender points, range 0–18 | 97 | 0.11 ± 0.26 | 93 | −1.06 ± 0.26 | −1.17 (−1.88, −0.45) | 0.002 |
| Mean tender point pain threshold, kg/cm$^2$ | 97 | −0.04 ± 0.07 | 93 | 0.29 ± 0.07 | 0.33 (0.13, 0.53) | 0.002 |
| CGI-Severity scale, range 1–7 | 97 | −0.39 ± 0.12 | 95 | −0.72 ± 0.12 | −0.33 (−0.65, 0.00) | 0.048 |
| PGI-Improvement scale, range 1–7 | 99 | 3.53 ± 0.17 | 95 | 3.02 ± 0.17 | −0.51 (−0.99, −0.04) | 0.033 |
| Brief Pain Inventory average pain severity, range 0–10 | 102 | −0.94 ± 0.23 | 100 | −1.83 ± 0.24 | −0.89 (−1.55, −0.23) | 0.008 |
| Brief Pain Inventory average interference from pain, range 0–10 | 102 | −0.95 ± 0.26 | 101 | −2.01 ± 0.27 | −1.06 (−1.78, −0.34) | 0.004 |
| Beck Depression Inventory-II total score, range 0–63 | 89 | −1.02 ± 0.83 | 88 | −3.32 ± 0.85 | −2.30 (−4.62, 0.02) | 0.052 |
| Beck Anxiety Inventory total score, range 0–63 | 86 | −1.39 ± 0.69 | 93 | −2.60 ± 0.69 | −1.21 (−3.12, 0.69) | 0.209 |

* 95% CI = 95% confidence interval (see Table 2 for other definitions).

**Table 5.** Summary of results for SF-36, Quality of Life in Depression Scale, and Sheehan Disability Scale*

| Variable | Treatment group: Placebo No. of subjects | Placebo Change, mean ± SEM | Duloxetine 60 mg bid No. of subjects | Duloxetine 60 mg bid Change, mean ± SEM | Between-group difference (95% CI) | *P* |
|---|---|---|---|---|---|---|
| SF-36, range 0–100 | | | | | | |
| Mental subscore | 92 | 0.52 ± 1.05 | 91 | 2.98 ± 1.04 | 2.46 (−0.47, 5.39) | 0.099 |
| Physical subscore | 92 | 2.53 ± 0.80 | 91 | 5.49 ± 0.81 | 2.97 (0.79, 5.14) | 0.008 |
| Bodily pain | 92 | 5.67 ± 1.90 | 92 | 15.32 ± 1.89 | 9.65 (4.52, 4.79) | <0.001 |
| General health perception | 92 | 3.86 ± 1.43 | 92 | 7.88 ± 1.42 | 4.02 (0.16, 7.88) | 0.041 |
| Mental health | 92 | 2.86 ± 1.77 | 92 | 8.24 ± 1.74 | 5.39 (0.48, 10.29) | 0.032 |
| Physical functioning | 92 | 3.82 ± 1.69 | 92 | 8.44 ± 1.68 | 4.61 (0.05, 9.18) | 0.048 |
| Role limit, emotional | 92 | −2.88 ± 4.41 | 92 | 6.77 ± 4.34 | 9.65 (−2.57, 21.86) | 0.121 |
| Role limit, physical | 92 | 11.41 ± 3.29 | 92 | 15.48 ± 3.28 | 4.07 (−4.82, 12.96) | 0.368 |
| Social function | 92 | 4.37 ± 2.19 | 91 | 9.78 ± 2.18 | 5.41 (−0.69, 11.51) | 0.082 |
| Vitality | 92 | 4.40 ± 1.88 | 92 | 9.57 ± 1.87 | 5.17 (0.09, 10.25) | 0.046 |
| Quality of Life in Depression Scale total score, range 0–10 | 81 | 0.11 ± 0.54 | 84 | −1.52 ± 0.53 | −1.63 (−3.10, −0.17) | 0.029 |
| Sheehan Disability Scale total score, range 0–30 | 93 | −1.28 ± 0.64 | 91 | −4.18 ± 0.63 | −2.90 (−4.67, −1.13) | 0.001 |

* 95% CI = 95% confidence interval (see Table 3 for other definitions).

The path analysis for the FIQ pain score and the Brief Pain Inventory average pain severity score, performed as a secondary analysis to further evaluate treatment effect on pain reduction in the female subjects, showed that, for both measures, the direct treatment effect on pain accounted for a major portion of the total effect. The direct effect of duloxetine on the reduction of the FIQ pain score accounted for 61.1% of the total treatment effect ($P = 0.313$); the indirect treatment effect through improvement in depressive symptoms accounted for 38.5% of the total treatment effect, and improvement in anxiety accounted for only 0.5% of the total treatment effect. The direct effect of duloxetine on the reduction of the Brief Pain Inventory average pain severity score accounted for 83.3% of the total treatment effect ($P = 0.015$); the indirect treatment effect through improvement in depressive symptoms accounted for 15.3% of the total treatment effect, and improvement in anxiety accounted for 1.5% of the total treatment effect. The path analysis also suggested that there was more indirect effect from change in depressive symptoms than anxiety symptoms, but neither effect was significant.

**Safety.** Of the 207 randomized subjects, 94 duloxetine-treated subjects (90.4%) and 77 placebo-treated subjects (74.8%) reported at least one treatment-emergent adverse event ($P = 0.003$). A total of 29 subjects discontinued during the therapy phase due to adverse events, with no statistically significant differences between treatment groups (18 in the duloxetine group [17.3%] and 11 in the placebo group [10.7%]; $P = 0.229$) (Figure 1). Duloxetine-treated subjects reported insomnia, dry mouth, and constipation significantly more frequently than did placebo-treated subjects. Most treatment-emergent adverse events were of mild or moderate severity. There were no significant treatment group differences in the percentage of severe treatment-emergent adverse events.

Duloxetine-treated subjects had small, but significant, increases from baseline to end point in heart rate (mean ± SD change 3.53 ± 11.56) ($P = 0.005$). Duloxetine-treated subjects also experienced small, nonsignificant increases in systolic and diastolic blood pressure (mean ± SD changes of 1.26 ± 15.31 mm Hg and 0.58 ± 8.36 mm Hg, respectively). Three subjects (2 randomized to the duloxetine group and 1 randomized to the placebo group) experienced sustained hypertension, but the treatment group difference was not statistically significant. Mean change in weight was not statistically different between treatment groups.

Compared with placebo-treated subjects, duloxetine-treated subjects experienced small, but significant, increases from baseline to end point in levels of aspartate transaminase, creatine phosphokinase, and cholesterol, and significant decreases in levels of calcium and chloride. These mean differences were within normal reference ranges and were not considered clinically relevant. No subject experienced elevated corrected QT intervals during the study.

## DISCUSSION

In this randomized, double-blind, 12-week trial, duloxetine had significantly greater efficacy than placebo on most outcome measures in the treatment of subjects with ACR-defined primary fibromyalgia at a fixed dose of 60 mg twice a day. This is the first medication trial of fibromyalgia to use a structured psychiatric interview to identify comorbid DSM-IV–defined major depressive disorder and to include subjects with and without current major depressive disorder. In the subgroup analysis, the improvement in fibromyalgia symptoms with duloxetine compared with placebo was independent of the presence or absence of major depressive disorder. The effect on mood was measured by the Beck Depression Inventory-II, which showed marginal improvement in the duloxetine group compared with the placebo group ($P = 0.052$). Duloxetine demonstrated a direct effect on pain reduction in female subjects that was significantly greater than the indirect effect attributed to improvement in mood and anxiety symptoms. Therefore, the effect of duloxetine on the reduction of pain associated with fibromyalgia appears to be independent of its effect on mood. These results confirm the findings from prior studies of fibromyalgia with the tricyclic agents amitriptyline and cyclobenzaprine, and with the SSRI fluoxetine, which found no significant relationship between improvement in fibromyalgia symptoms and change in depression scores, although none of these prior studies evaluated the impact of currently diagnosed major depressive disorder (12,16,43).

The pathophysiology of fibromyalgia remains unknown. Duloxetine, a potent SNRI, may correct a functional deficit of 5-HT and NE neurotransmission. Although the pathophysiology of major depressive disorder and fibromyalgia may share abnormalities in central monoaminergic neurotransmission, the independent effect of duloxetine on reduction in pain suggests that pain-modulating effects in the spinal and supraspinal pathways are not dependent on the modulation of mood. Consistent with this hypothesis, previous fibromyalgia trials of tricyclic medications have used doses that are subtherapeutic for major depressive disorder, making it unlikely that their moderate effects on reduction of pain were due to antidepressant properties (13,14).

Compared with placebo-treated female subjects, duloxetine-treated female subjects improved significantly on most efficacy measures, while duloxetine-treated male subjects did not respond significantly on any efficacy measure compared with placebo-treated male subjects. The reasons for the sex differences in response are unclear. Because the male subgroup was small (23 of 207 subjects [11%]), reflecting the much higher prevalence of fibromyalgia in women (3), the results of the study may not be generalizable to all men with fibromyalgia. Studies of larger samples of men with fibromyalgia are needed to reexamine the efficacy of duloxetine in men. There may also be sex differences in fibromyalgia that affect treatment response. Notably, female subjects had significantly more tender points and lower mean tender point pain thresholds at baseline than did male subjects. Other studies of fibromyalgia clinical features found that women had significantly more tender points than men, as well as more fatigue, sleep disturbance, irritable bowel syndrome, and "pain all over" (44). The disparate presentations of fibromyalgia in women and men suggest that there might be sex differences in the pathophysiology of fibromyalgia that could affect response to treatment, but more study is needed.

The improvement in tender point measures in duloxetine-treated subjects compared with placebo-treated subjects was the most significant change of the efficacy measures, and improvement was evident in both women and men. The significant improvement in the number of tender points and in the tender point pain threshold in the duloxetine group compared with the placebo group is notable, because previous fibromyalgia studies using tricyclic antidepressants found minimal improvement in tender point measures (13,14). These results suggest that duloxetine improves pain and tenderness, the hallmark characteristics of fibromyalgia. The dolorimeter method of tender point assessment used in the present study is more quantitative and might be a more reliable technique than manual assessments for monitoring change over time in a clinical trial. Dolorimetry provides an objective measure of the pressure pain threshold that is relatively independent of distress and less influenced by psychological factors than are manual tender point counts (45,46).

Duloxetine was safely administered and well tolerated. Significantly more duloxetine-treated subjects than placebo-treated subjects reported treatment-emergent adverse events, most commonly insomnia, dry mouth, and constipation, but these events were generally mild or moderate in severity. There were no significant differences between treatment groups in subject discontinuation due to treatment-emergent adverse events. The safety findings are in general agreement with the findings in other studies of duloxetine in patients with major depressive disorder (25–27).

Several limitations of this study should be considered. First, the co–primary outcome measure, the FIQ pain score, did not improve significantly in the duloxetine group compared with the placebo group at the last visit of the acute therapy phase. The FIQ pain item might be problematic as an outcome measure because subjects retrospectively rate their pain over the prior week, which may be more difficult to recall than their pain over the past 24 hours. However, the AUC improvement in pain as measured by the FIQ pain score indicated that duloxetine-treated subjects had superior reduction in pain compared with placebo-treated subjects. In addition, the secondary measure of pain, the Brief Pain Inventory average pain score, improved significantly with duloxetine treatment, as did the Brief Pain Inventory measure of interference from pain. The SF-36 component for bodily pain also improved significantly in the duloxetine group compared with the placebo group. Therefore, the weight of the evidence supports improvement in painful symptoms of fibromyalgia with duloxetine treatment, especially for women, who improved significantly on all measures of pain. Furthermore, duloxetine-treated female subjects were significantly more likely than placebo-treated female subjects to have a decrease of $\geq$50% in the FIQ pain score, which represents clinically meaningful improvement. Second, because the duration of treatment was 12 weeks, the results may not be generalizable to longer treatment periods. Furthermore, ~40% of all subjects did not complete the study. Future studies should assess the long-term efficacy of duloxetine in fibromyalgia. Third, individuals with several forms of lifetime psychopathology were excluded. Thus, the results may not be generalizable to individuals with certain forms of psychopathology such as primary anxiety disorders or bipolar disorder. Individuals with secondary fibromyalgia and unstable medical or psychiatric illness were also excluded, and the results may not be generalizable to patients with these conditions. Finally, because subjects who had shown no reponse in $\geq$2 adequate antidepressant trials were excluded, the results may not be generalizable to those who are resistant to treatment with antidepressants.

In summary, in this 12-week, randomized, placebo-controlled trial, duloxetine at 60 mg twice a day was found to be efficacious on most outcome measures in subjects with primary fibromyalgia with or without major depressive disorder, particularly in women, and was safe and well tolerated.

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## REFERENCES

1. Hudson JI, Pope HG Jr. The relationship between fibromyalgia and major depressive disorder. Rheum Dis Clin North Am 1996; 22:285–303.
2. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;33:160–72.
3. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
4. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 1992;35:550–6.
5. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA. Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. J Rheumatol 1992;19:104–9.
6. Yunus MB, Dailey JW, Aldag JC, Masi AT, Jobe PC. Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study. J Rheumatol 1992;19:90–4.
7. Schwarz MJ, Spath M, Muller-Bardorff H, Pongratz DE, Bondy B, Ackenheil M. Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients. Neurosci Lett 1999;259:196–8.
8. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984;7:309–38.
9. Clark FM, Proudfit HK. The projections of noradrenergic neurons in the A5 catecholamine cell group to the spinal cord in the rat: anatomical evidence that A5 neurons modulate nociception. Brain Res 1993;616:200–10.
10. Millian MJ. Descending control of pain. Prog Neurobiol 2002;66: 355–474.
11. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305–16.
12. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996; 39:1852–9.
13. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41: 104–13.
14. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000;15:659–66.
15. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Eur J Pain 2000;4:27–35.
16. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191–7.
17. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A random-

ized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995;61:445–9.
18. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255–9.
19. Simmons RM, Li DL, Lee DH, Iyengar S. Duloxetine, a potent and balanced dual serotonin and norepinephrine reuptake inhibitor, is efficacious in animal models of persistent pain. Presented at the American Psychiatric Association annual meeting [May 5–10, 2001], New Orleans, LA.
20. Iyengar S, Ahmad L, Simmons RM. Efficacy of the selective serotonin and norepinephrine reuptake inhibitor, duloxetine, in the formalin model of persistent pain. Biol Psychiatry 2002;51(8 Suppl):75S–76S.
21. Jones CK, Peters SC, Iyengar S, Shannon HE. Duloxetine, a selective serotonergic and noradrenergic reuptake inhibitor, is efficacious in persistent and inflammatory, but not acute nociceptive, pain states in rodents. Presented at the 10th World Congress on Pain [August 17–22, 2002], San Diego, CA.
22. Fava M. Somatic symptoms, depression, and antidepressant treatment. J Clin Psychiatry 2002;63:305–7.
23. Simon GE, VonKorff M, Piccinelli M, Fullerton C, Ormel J. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999;341:1329–35.
24. Kroenke K, Price RK. Symptoms in the community: prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993; 153:2474–80.
25. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry 2002;63;225–31.
26. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63:308–15.
27. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36:383–90.
28. Goldstein DJ, Lu Y, Detke MJ, Hudson JI, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004;45:17–28.
29. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18: 728–33.
30. Fischer AA. Pressure threshold meter: its use for quantification of tender spots. Arch Phys Med Rehabil 1986;67:836–8.
31. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. US Department of Health, Education, and Welfare publication (ADM). Rockville (MD): National Institute of Mental Health; 1976. p. 218–22.
32. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
33. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–97.
34. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–7.
35. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey manual and interpretation guide. Boston (MA): The Health Institute, New England Medical Center; 1993.
36. Hunt SM, McKenna SP. The QLDS: a scale for the measurement of quality of life in depression. Health Policy 1992;22:307–19.
37. McKenna SP, Hunt SM. A new measure of quality of life in depression: testing the reliability and construct validity of the QLDS. Health Policy 1992;22:321–30.
38. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11 Suppl 3:89–95.
39. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22–33.
40. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association; 1994.
41. Mallinckrodt CH, Clark WS, David SR. Type I error rates from mixed-effects model repeated measures compared with fixed-effects ANOVA with missing values imputed via LOCF. Drug Inf J 2001;35:1215–25.
42. Retherford RD, Choe MK. Statistical methods for causal analysis. New York: John Wiley & Sons; 1993.
43. Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia: a randomized, double-blind clinical trial. Arthritis Rheum 1994;37:32–40.
44. Yunus MB, Inanici F, Aldag JC, Mangold RF. Fibromyalgia in men: comparison of clinical features with women. J Rheumatol 2000;27:485–90.
45. Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. Ann Rheum Dis 1997;56:268–71.
46. Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003;30:567–74.

## APPENDIX A: THE DULOXETINE FIBROMYALGIA TRIAL GROUP

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