ORIGINAL ARTICLE

A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain Due to Osteoarthritis of the Knee

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■ **Abstract**

Objective: To evaluate the efficacy and safety of duloxetine in the treatment of chronic pain due to osteoarthritis of the knee.

Methods: This was a 13-week, randomized, double-blind, placebo-controlled trial in patients meeting American College of Rheumatology clinical and radiographic criteria for osteoarthritis of the knee. At baseline, patients were required to have a ≥ 4 weekly mean of the 24-hour average pain ratings. Patients were randomized to either duloxetine 60 mg once daily (QD) or placebo. At week 7, the duloxetine dosage was increased, in a blinded fashion, to 120-mg QD in patients reporting < 30% pain reduction. The primary efficacy measure was Brief Pain Inventory (BPI) 24-hour average pain. Secondary efficacy measures included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); Clinical Global Impressions of Severity (CGI-S). Safety and tolerability was also assessed.

Results: Of the total ($n = 256$) patients, 111 (86.7%) in placebo group and 93 (72.7%) in duloxetine group completed the study. Patients treated with duloxetine had significantly ($P \leq 0.001$) greater improvement at all time points on BPI average pain and had significantly greater improvement on BPI pain severity ratings ($P \leq 0.05$), WOMAC total ($P = 0.044$) and physical functioning scores ($P = 0.016$), and CGI-S ($P = 0.009$) at the study endpoint. Frequency of treatment-emergent nausea, constipation, and hyperhidrosis were significantly higher in the duloxetine group ($P \leq 0.05$). Significantly more duloxetine-treated patients discontinued the trial because of adverse events ($P = 0.002$).

Conclusions: Treatment with duloxetine 60 mg to 120 mg QD was associated with significant pain reduction and improved function in patients with pain due to osteoarthritis of the knee. ■

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Key Words: duloxetine, acute phase therapy, chronic pain, osteoarthritis of the knee

INTRODUCTION

Osteoarthritis is the most common form of arthritis and leading cause of disability in the U.S.A.[1,2] Osteoarthritis of the knee is one of the United States' leading musculoskeletal disorders, having reported 12.1% incidence.[3] The incidence rate seems to be higher among women.[4,5] The lifetime risk of osteoarthritis of the knee is 44.7% among general population and seems to be higher in older and obese people.[6] The level of pain experienced by patients is a better predictor of the degree of disability associated with osteoarthritis compared with radiographical findings.[7] In terms of clinical management, pain reduction and functional improvement are of paramount importance in the treatment of knee osteoarthritis.[8]

To manage chronic pain due to osteoarthritis, current treatment guidelines recommend a combination of nonpharmacological and pharmacological therapies. They include acetaminophen, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids and hyaluronates, and opioid analgesics.[9] However, many of the above treatments, particularly NSAIDs and opioids, are associated with significant safety risks.

Imbalance of serotonin and norepinephrine systems within central pain pathways have been implicated in the development and maintenance of central sensitization and associated chronic pain states.[10,11] Chronic pain associated with osteoarthritis involves dysfunction of central pain pathways.[12,13]

Duloxetine is a selective and relatively balanced serotonin and norepinephrine reuptake inhibitor with central nervous system activity.[14,15] Previous studies showed that duloxetine is effective in treatment of three distinct chronic pain conditions: diabetic peripheral neuropathic pain (DPNP),[16–19] fibromyalgia,[20,21] and chronic low back pain.[22]

The current study is the second study of the two pivotal studies conducted as a regulatory requirement to assess the efficacy and safety of duloxetine in patients with chronic pain due to osteoarthritis of the knee. The findings reported in this manuscript confirm the results of the first trial.[23]

METHODS

Patients

Male and female outpatients ≥ 40 years of age who met the American College of Rheumatology clinical and radiographic criteria for the diagnosis of osteoarthritis of the knee,[24] with pain for ≥ 14 days per month during three consecutive months preceding study entry. Patients were required to have pain severity of ≥ 4 on the 24-hour average pain severity scale (0 to 10), using the mean of daily ratings from the week preceding randomization. Patients had to consent to maintain their usual activity level throughout the course of the study.

Patients were excluded if they met any of the following criteria: body mass index > 40 kg/m^2; diagnosis of inflammatory arthritis or an autoimmune disorder; history of invasive therapies to the index knee during the past 3 months or joint replacement of the index knee at anytime; prior synovial fluid analysis indicative of a diagnosis other than osteoarthritis; nonambulatory or crutch- or walker-dependant; presence of psychiatric disorders, including major depressive disorder (identified using the Mini International Neuropsychiatric Interview); previous exposure to duloxetine; for female patients, existing pregnancy or breastfeeding; history of substance abuse or dependence; presence of serious medical condition; or history of recurrent seizures, uncontrolled narrow-angle glaucoma, acute liver injury, or severe cirrhosis; known hypersensitivity to duloxetine or any of the inactive ingredients; and frequent or severe allergic reactions to multiple medications.

Patients who entered the trial taking an NSAID or acetaminophen were allowed to continue taking it provided that the dosage was not increased during the study. Randomization of patients was stratified according to whether they were NSAID users. Patients who had taken NSAIDs at the therapeutic dose for > 14 days per month for 3 months immediately preceding study entry were identified as NSAID users. No use of any analgesics was allowed during the screening period except in NSAID users. After randomization, episodic use of short-acting analgesics was allowed for acute injury or surgery or for rescue from osteoarthritis flare-up pain. "Episodic use" was defined as ≤ 3 consecutive days and was not to exceed 20 total days during the study. Any change in or initiation of prescription or over-the-counter medications during the study required consultation with the study site personnel. Use of antidepressants and anticonvulsants or other agents used for treatment of chronic pain, except as described above, was not allowed.

Study Design

The design of this study is similar to that of the first trial[23] conducted as a requirement for regulatory

approval. The difference is the re-randomization of patients at week 7 in the first trial[23] as compared with dose-escalation at week 7 in this trial, as described below.

This multicenter, randomized, double-blind, parallel-group, placebo-controlled trial was conducted between February 27, 2007 and May 4, 2008 at 21 clinical sites in Canada, Greece, Russia, Sweden, and the U.S.A. by general practitioners and rheumatologists (Clinicaltrials.gov identifier: NCT00433290). The study was designed to assess the efficacy of duloxetine 60 mg to 120 mg once daily (QD) for 13 weeks compared with placebo on the reduction of chronic pain due to osteoarthritis of the knee. Assignment to treatment was determined by a computer-generated random sequence using an interactive voice response system to assure blinding. Each clinical study site's Institutional Review Board approved the protocol, which was developed in accordance with the ethical standards of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before the commencement of any study procedures.

This clinical trial included three study periods. Study period I was a 1-week screening phase during which patients were screened for study entry eligibility and required to discontinue any excluded medications. At visit 2 (week 0), during the beginning of study period II, eligible patients were randomly assigned to 13 weeks of double-blind treatment with duloxetine 60 mg QD or placebo in a 1:1 ratio, stratified by NSAID use. Patients randomly assigned to duloxetine 60 mg QD were started on duloxetine 30 mg QD for 1 week and then titrated up to duloxetine 60 mg QD. At visit 4 (week 7), the duloxetine (or matching placebo) dosage was increased to 120 mg QD in patients reporting < 30% pain reduction from baseline using Brief Pain Inventory (BPI) 24-hour average pain rating (referred to as the BPI average pain hereafter) and no tolerability concerns; these patients remained on the 120 mg QD dosage for the remainder of the study. The dose increase was done in a double-blind fashion. For data presentation of comparisons with placebo, patients assigned to duloxetine were treated as one treatment group regardless of the dose. Study period III (beginning at visit 5, week 13) was a 2-week taper phase to minimize discontinuation-emergent adverse events. During this phase, patients taking duloxetine 60 mg QD during the study received duloxetine 30 mg QD for 1 week and placebo for 1 week, patients taking duloxetine 120 mg QD during the study received duloxetine 60 mg QD for 1 week and then duloxetine 30 mg QD for 1 week, and patients taking placebo remained on placebo.

Study Objectives and Measures

The primary objective of this study was to assess the efficacy of duloxetine 60 to 120 mg QD compared with placebo on the reduction of pain severity as measured by BPI average pain in patients with chronic pain due to osteoarthritis of the knee. Secondary objectives included patients' perceived improvement as measured by Patient's Global Impression of Improvement (PGI-I),[25] and the change in patients' physical function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale.[26] Additional secondary outcomes included the weekly mean of the 24-hour average pain and worst pain ratings, Clinical Global Impressions of Severity (CGI-S),[25] WOMAC pain and stiffness subscales and total score,[26] BPI-Severity (BPI-S) and BPI-Interference (BPI-I) items,[27] and response to treatment (as defined by at least 30% and at least 50% reduction of either BPI average pain administered at study visit or weekly mean of the 24-hour average pain collected through patients' daily diary). Health outcome measures included the 36-Item Short-Form Health Status Survey (SF-36) and EuroQoL: 5 Dimensions Questionnaire (EQ-5D) version of the European Quality of Life instrument.[28,29]

The direct analgesic effect of duloxetine that is independent of effects on mood or anxiety was evaluated using the BPI average pain score, the total score of the Beck Depression Inventory-II (BDI-II) and Hospital Anxiety and Depression Scale anxiety subscale (HADS-A).[30,31]

The safety and tolerability of duloxetine vs. placebo were assessed during the treatment phase of the study and were based on discontinuation rates, treatment-emergent adverse events (TEAEs), laboratory analytes, and vital signs.

Statistical Methods

All analyses were conducted on the intent-to-treat population. Treatment and interaction effects were evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons were made. A likelihood-based, mixed-effects model repeated measures (MMRM), a protocol-specified analysis, was used to analyze the primary efficacy variable (BPI average pain) and some secondary efficacy variables that were collected longitudinally. Change from baseline to endpoint was analyzed using analysis of variance (ANOVA)

model with terms of treatment and investigator for safety variables and analysis of covariance (ANCOVA) model with the stratifying variable of NSAID use and baseline values added to the above ANOVA model for efficacy variables. For categorical outcomes, Fisher's exact test was used.

Baseline is defined as the last nonmissing observation at or before the randomization visit (visit 2), and endpoint generally defined as the last nonmissing observation (last-observation-carried-forward method [LOCF]) in the treatment phase. For primary efficacy outcome, the baseline-observation-carried-forward method (BOCF) and modified BOCF method (mBOCF) were also pre-specified as additional analytic approach to define endpoint. Specifically, BOCF method assigned the baseline value as the endpoint for patients who discontinued due to any reason and mBOCF method assigned the baseline value as endpoint for patients who discontinued due to adverse event or lack of efficacy, for all other randomized patients, the last nonmissing observation was used as endpoint (LOCF).

To analyze a specific subgroup's impact, change from baseline to endpoint (LOCF) in BPI average pain were analyzed using the above ANCOVA model, with additional terms of the subgroup and the subgroup-by-treatment interaction.

Path analysis was used to test the null hypothesis that the change in the BPI average pain severity depends on the improvement on the BDI-II or HADS-A, vs. the alternative that the improvement in the BPI average pain severity is due to a direct analgesic effect of the treatment and not dependent upon the improvement in depression and anxiety symptoms.

Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Patient Disposition

Of the 256 randomized patients (duloxetine, $N = 128$; placebo, $N = 128$), 35 (27.3%) patients in the duloxetine group and 17 (13.3%) patients in the placebo group discontinued from the study ($P = 0.008$) (Figure 1). Of the 128 patients receiving duloxetine 60 mg QD, 33 (25.8%) patients were nonresponders at week 7 and had their dosages increased to 120 mg QD. Significantly more patients in the duloxetine group ($n = 24$, 18.8%) discontinued from the study due to adverse events ($P = 0.002$) than patients in the placebo group ($n = 7$, 5.5%). The treatment groups did not significantly differ in any other reasons leading to discontinuation.

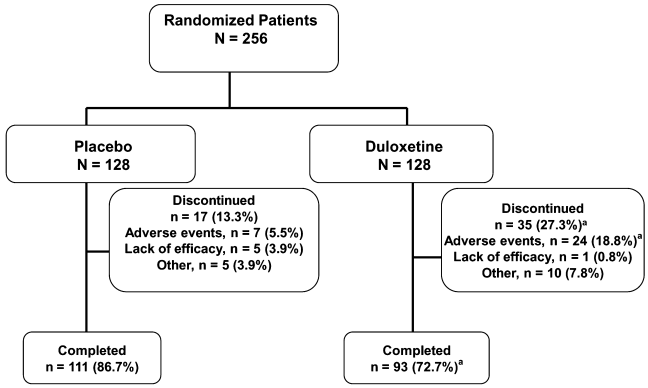

Figure 1. CONSORT diagram showing patient disposition during the treatment period. [a]$P \leq 0.01$ duloxetine vs. placebo.

Table 1. Baseline Demographics and Clinical Characteristics of All Randomized Patients with Chronic Pain due to Osteoarthritis of the Knee

Characteristics	Placebo ($N = 128$)	Duloxetine 60–120 mg QD ($N = 128$)
Age, years, mean (SD)	61.9 (9.2)	63.2 (8.8)
Ethnicity, *n* (%)		
Caucasian	124 (96.9)	126 (98.4)
African American	3 (2.3)	0 (0.0)
Other	1 (0.8)	2 (1.6)
Gender, *n* (%)		
Female	107 (83.6)	89 (69.5)*
Duration of OA since diagnosis, years, mean (SD)	5.6 (6.2)	6.2 (5.9)
Duration of OA pain since onset, years, mean (SD)	6.7 (6.6)	8.1 (7.6)
BPI average pain score, mean (SD)	6.1 (1.3)	6.1 (1.4)
Weekly 24-hour average pain severity, mean (SD)	6.1 (1.3)	6.0 (1.2)
CGI-S, mean (SD)	3.3 (1.3)	3.3 (1.2)
NSAID use, *n* (%)		
Yes	53 (41.4)	47 (36.7)

* Significantly different from placebo ($P = 0.012$).
BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions of Severity; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; QD, once daily; SD, standard deviation.

Demographics and Clinical Characteristics

With the exception of gender, the baseline demographics and clinical characteristics of patients were not significantly different between the two treatment groups (Table 1). There were significantly fewer female patients in the duloxetine group compared with the placebo group ($P = 0.012$). Most patients were white and female, did not take NSAIDs at baseline, and had similar disease characteristics in both treatment groups.

Efficacy—Pain Measures

The least squares (LS) mean changes over time from the MMRM analysis in BPI average pain rating, the primary outcome measure, are shown in Figure 2. A statistically significant ($P \leq 0.001$) reduction in the average pain rating was observed in the duloxetine group compared with the placebo group at all time points (4, 7, and 13 weeks after treatment). The BPI 24-hour average pain was also analyzed using three different methods of analyses including LOCF, BOCF, and mBOCF (Figure 3). A statistically significant pain reduction was observed between placebo and duloxetine treatment groups using all 3 methods.

The BPI average pain response rates (≥ 30% pain reduction from baseline to endpoint) were significantly higher in the duloxetine group (65.3%) compared with the placebo group (44.1%, $P \leq 0.001$; Table 2). However, the 50% response rates of BPI average pain did not significantly differ between the treatment groups (duloxetine, 43.8%; placebo, 32.3%; $P = 0.068$).

The LS mean changes over time from MMRM analysis in the weekly mean 24-hour average pain rating (from the patient diaries based on the 11-point numerical scale), a secondary measure, are shown in Figure 4. A statistically significant reduction in the average pain rating was observed in the duloxetine group compared with the placebo group as early as at week 2 and remained statistically significant at all time points. Simi-

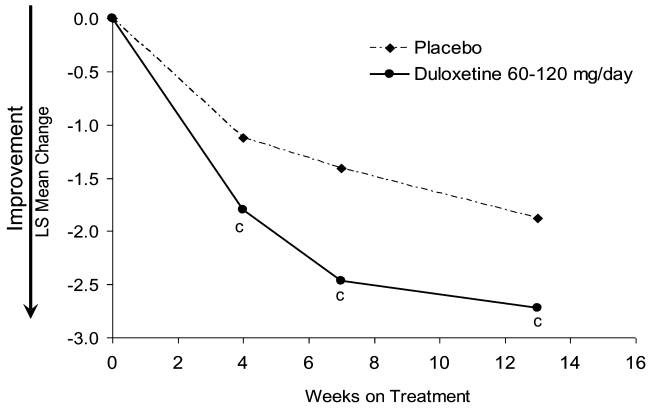

Figure 2. Changes in the Brief Pain Inventory 24-hour average pain (primary efficacy measure) in patients with chronic pain due to osteoarthritis of the knee treated with duloxetine 60 mg to 120 mg once daily or placebo for 13 weeks (mixed-effects model repeated measures). LS, least squares. $^{c}P \leq 0.001$ duloxetine vs. placebo.

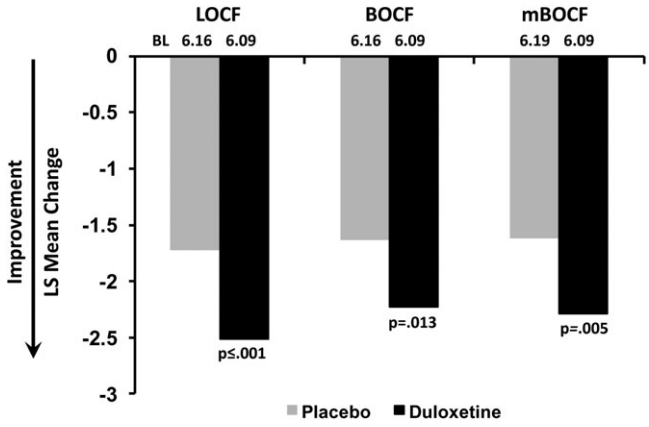

Figure 3. Changes in the Brief Pain Inventory 24-hour average pain as assessed by last-observation-carried-forward (LOCF), baseline-observation-carried-forward (BOCF), and modified baseline-observation-carried-forward (mBOCF) methods. Each bar graph represents least-squares (LS) mean changes from baseline (BL) to endpoint values. *P* values (Fisher's exact test) represent the statistical difference between placebo and duloxetine 60 mg once daily.

Table 2. Statistically Significant Changes in Secondary Efficacy Measures and Health Outcomes in Patients with Chronic Pain due to Osteoarthritis of the Knee Treated with Duloxetine or Placebo for 13 Weeks

Measures	Placebo ($N = 128$)	Duloxetine 60–120 mg QD ($N = 128$)
BPI-S ratings		
Average pain	−1.72 (0.18)	−2.51 (0.20)***
Worst pain	−1.95 (0.22)	−2.77 (0.23)**
Least pain	−1.28 (0.20)	−1.89 (0.21)*
Pain right now	−1.81 (0.20)	−2.50 (0.21)**
BPI-I ratings		
General activity	−1.66 (0.20)	−2.16 (0.21)*
Normal work	−1.31 (0.21)	−2.16 (0.22)***
BPI average pain, % response		
≥ 30%	44.1	65.3***
Weekly mean 24-hour pain-severity ratings		
Average	−1.73 (0.17)	−2.32 (0.18)**
Worst	−1.98 (0.19)	−2.45 (0.19)*
Weekly mean 24-hour average pain, % response		
≥ 30%	45.2	62.1**
≥ 50%	22.2	37.9**
CGI-S	−0.40 (0.09)	−0.70 (0.10)**
WOMAC		
Total	−13.74 (1.47)	−17.51 (1.54)*
Physical functioning	−9.43 (1.08)	−12.69 (1.15)*
SF-36		
Physical component summary	4.41 (0.81)	7.82 (0.85)***
Bodily pain	1.04 (0.17)	1.64 (0.17)**
Physical functioning	2.16 (0.38)	3.30 (0.41)*
Role-physical	0.59 (0.15)	1.13 (0.16)**

Values are least-squares mean changes from baseline to endpoint (SE) based on the ANCOVA using last-observation-carried-forward approach. Sample sizes varied for each measure and included patients with a baseline and at least 1 nonmissing postbaseline value. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ duloxetine vs. placebo.

BPI, Brief Pain Inventory; BPI-I, Brief Pain Inventory-Interference; BPI-S, Brief Pain Inventory-Severity; CGI-S, Clinical Global Impressions of Severity; QD, once daily; SF-36, 36-Item Short-Form Health Status Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

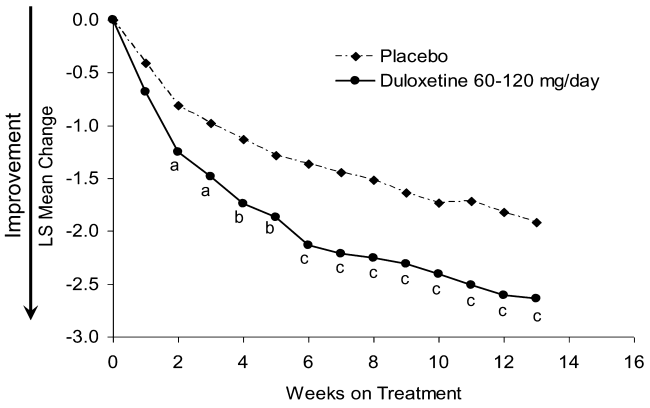

Figure 4. Weekly mean changes in the 24-hour average pain scores from patient diary in patients with chronic pain due to osteoarthritis of the knee treated with duloxetine 60 mg to 120 mg once daily (QD) or placebo for 13 weeks (mixed-effects model repeated measures). Patients received duloxetine 30 mg QD during the first week. LS, least squares. [a]$P \le 0.05$; [b]$P \le 0.01$; [c]$P \le 0.001$ duloxetine vs. placebo.

larly, the weekly mean 24-hour worst pain ratings were also significantly improved with duloxetine treatment compared with placebo (data not shown). The analysis of mean changes from baseline to endpoint by LOCF approach of the weekly mean 24-hour average pain and worst pain ratings, and the analysis of the weekly mean 24-hour average pain response rates (≥ 30% and ≥ 50% reduction in pain from baseline to endpoint) also showed significant improvement in duloxetine-treated patients compared with those treated with placebo (Table 2).

Patients treated with duloxetine compared with placebo-treated patients showed a significantly greater improvement in the mean change from baseline to endpoint analysis (LOCF) of many other secondary efficacy measures, including CGI-S, BPI-S items (average pain, worst pain, pain right now, and least pain), and BPI-I items (general activity and normal work) (Table 2). The other BPI-I items (mood, walking ability, relations with other people, sleep, enjoyment of life, and average interference) were not significantly different between the two treatment groups. No significant improvement in PGI-I was observed in the duloxetine group compared with placebo ($P = 0.164$). The mean changes from baseline to endpoint were improved significantly for WOMAC total score ($P = 0.004$) and physical functioning subscale ($P = 0.016$) in patients treated with duloxetine compared with placebo (Table 2). The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment.

The MMRM analysis of PGI-I ratings showed significant improvement in patients treated with duloxetine compared with placebo (LS means [±standard error] at week 4 [3.06 ± 0.10 duloxetine vs. 3.41 ± 0.10 placebo, $P = 0.005$], at week 7 [2.91 ± 0.11 duloxetine vs. 3.29 ± 0.11 placebo, $P = 0.008$], and at week 13 [2.77 ± 0.11 duloxetine vs. 3.07 ± 0.10 placebo, $P = 0.020$]). The MMRM analysis of WOMAC total and subscale scores also found to be significantly different between the two treatment groups at all time points (data not shown).

No significant treatment-by-subgroup interactions of clinical relevance were observed with respect to baseline demographics (age, gender, and origin) and disease characteristics (severity of osteoarthritis and duration of osteoarthritis of knee pain) using the BPI average pain. Similarly, there was no treatment-by-subgroup interaction in regard to use of NSAIDs.

Path analysis demonstrated that 95.48% of the effect of duloxetine on the BPI average pain ratings was a direct analgesic effect; this effect was significant ($P = 0.002$). The effect of duloxetine was not dependent upon the improvement in depression (BDI-II, 3.93%) or anxiety (HADS-A, 0.59%) symptoms.

Efficacy—Health Outcomes

Both the U.K. and the U.S. indexes of EQ-5D did not change significantly in patients treated with duloxetine as compared with placebo but numerical improvement was observed. Physical component summary and three of the subscales of SF-36 (bodily pain, physical functioning and role-physical) were significantly improved in duloxetine group compared with placebo (Table 2). However, the other SF-36 items (mental component summary, general health, mental health, role-emotional, social functioning, and vitality) were numerically, but not significantly, improved with duloxetine treatment compared with placebo.

Safety

No deaths occurred during the study. No statistically significant differences between treatment groups were observed in the occurrence of serious adverse events. A total of 5 (2.0%) patients experienced five serious adverse events, including two patients in the placebo group (atrial fibrillation and acute pyelonephritis) and three patients in the duloxetine group (drug intolerance, memory impairment, and supraventricular tachycardia).

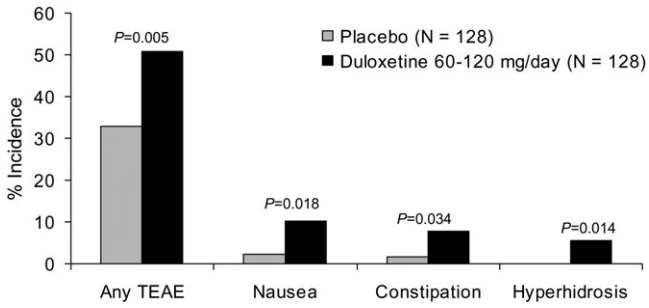

Figure 5. Treatment-emergent adverse events with ≥ 5% incidence in any treatment arm in all randomized patients. TEAE, treatment-emergent adverse event.

A total of 107 (41.8%) patients reported one or more TEAEs during the treatment phase. As illustrated in Figure 5, significantly more duloxetine-treated patients experienced TEAEs than patients in the placebo group ($P = 0.005$). Compared with placebo, significantly more duloxetine-treated patients experienced nausea ($P = 0.018$), constipation ($P = 0.034$), and hyperhidrosis ($P = 0.014$).

A statistically significant treatment difference in mean change (±SD) from baseline to endpoint was observed in alkaline phosphatase (ALKPH) (duloxetine, 2.38 ± 15.74 vs. placebo, –3.43 ± 14.56, $P \leq 0.001$), aspartate transaminase (AST) (duloxetine, 1.44 ± 8.32 vs. placebo, –1.37 ± 7.26, $P = 0.010$), and gamma glutamyl transaminase (GGT) (duloxetine, 5.33 ± 20.40 vs. placebo, –2.10 ± 19.12, $P = 0.023$). All three laboratory tests were expressed as units/liter. The magnitude of the mean changes that were statistically significant was small and not clinically meaningful. The percentages of patients with treatment-emergent abnormally high laboratory results (> 1X) were not statistically significantly different between placebo and duloxetine for those laboratory tests that showed statistically significant difference in the mean change analysis: ALKPH, 3/124 (2.4%) placebo vs. 3/117 (2.6%) duloxetine, $P > 0.999$; AST, 7/116 (6.0%) placebo vs. 12/113 (10.6%) duloxetine, $P = 0.238$; and for GGT, 12/113 (10.6%) placebo vs. 18/111 (16.2%) duloxetine, $P = 0.244$. These treatment differences in laboratory analytes were considered not clinically relevant since the treatment groups did not significantly differ in changes in any of the other liver function tests including bilirubin level.

There is a statistically significant difference in the mean change (±standard deviation [SD]) from baseline to endpoint in pulse rate between placebo and duloxetine-treated patients (duloxetine, 2.38 ± 0.69 vs. placebo, –0.07 ± 0.67 beats per minute; $P = 0.005$). No significant differences were observed between the two treatment groups in either diastolic or systolic blood pressure, sustained elevation of blood pressure, or orthostatic hypotension. The mean body weight (±SD, in kilograms) change from baseline to endpoint significantly ($P \leq 0.001$) decreased in the duloxetine group (–0.65 ± 0.20) as compared with the placebo group (0.43 ± 0.19).

DISCUSSION

In this study, patients treated with duloxetine, compared with those taking placebo, showed statistically significantly greater pain reduction based on the primary efficacy analysis of BPI average pain, using the MMRM as well as LOCF, BOCF, and mBOCF methods. Significant pain reduction was evident at all time points measured during the 13-week treatment period. Similarly, this study demonstrated significant improvement on secondary efficacy measures, including weekly mean of the 24-hour average pain and worst pain scores, WOMAC, BPI-S, BPI-I, and CGI-S. These findings provide significant evidence for the efficacy of duloxetine to improve pain in patients with osteoarthritis of the knee. Further, the improvement in patients' pain status was related to their improved function, as evidenced by the health outcomes assessments, including SF-36 physical component summary and several subscales. These findings are consistent with and confirm the findings of the recently published first study of duloxetine treatment of patients with chronic pain due to osteoarthritis of the knee.[23] The study designs of these two studies are similar except that in the first trial at week 7, patients were randomly assigned to 60 mg/day or 120 mg/day in a 1:1 ratio.[23]

A number of recently completed path analyses have shown that reduction in pain was due to a direct analgesic effect and was independent of improvement in mood and anxiety.[32–34] The current study supports these findings that are consistent with the previously discussed role of serotonin and norepinephrine in the mediation of endogenous pain inhibitory pathways,[10] which is the presumed mechanism of action of duloxetine's analgesic effect.

Duloxetine is a centrally acting compound, like opioids, but with a distinctly different mechanism of action and a different adverse event profile. The results of this study are consistent with previous studies of duloxetine in DPNP, fibromyalgia and chronic low back pain.[17,18,20,22,35] These findings together further support

the notion that duloxetine can effectively treat chronic pain, regardless of origin, at the central pain inhibitory level.

The analyses of subgroups did not show significant differences for patients with different duration and severity of osteoarthritic pain. This finding suggests that duloxetine was equally efficacious regardless of duration or severity of the pain at baseline. Further, no significant differences in treatment interaction by subgroups with regard to age, gender, and origin were found.

Patients who did not take NSAIDs at baseline experienced significantly greater reduction in the BPI average pain after duloxetine treatment compared with placebo, whereas there was only a numerical difference between treatment groups in the subgroup of patients who were using NSAIDs at baseline. However, there was no significant treatment-by-NSAIDs-use interaction.

The safety profile of duloxetine in this study, in general, is favorable compared with profiles reported in earlier pain studies.[17,18,20,22,35] The occurrence of TEAEs was low in both treatment groups in this study. Using the data from duloxetine studies in various patient populations, including major depressive disorder, generalized anxiety disorder, fibromyalgia, urinary incontinence, and DPNP, a pooled analysis of all patients treated with duloxetine[36] showed that 75% of patients reported one or more TEAEs as compared with only 50% of patients who reported one or more TEAEs in the current study. This difference between our study and that of Gahimer et al.[36] may be due to the current study's inclusion of 40% patients using NSAIDs and acetaminophen at baseline. NSAID-associated adverse events, including nausea, diarrhea, constipation, dizziness, and headache are also associated with duloxetine treatment and therefore were less likely to be reported as TEAEs during the study's duloxetine treatment phase. For example, nausea occurred in approximately 24.8% of patients in the pooled analysis, as compared with only 10.2% of patients in the current study.[36] Additionally, the lower nausea rate in this study may be of the result of combining two dosing strategies—1-week up-titration of duloxetine 30 mg QD then to 60 mg QD and administration of the medication with food, which in fact has been shown to reduce nausea rate.[37]

This study demonstrates efficacy and tolerability of duloxetine in patients with chronic pain due to osteoarthritis of the knee.

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