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Maintenance of Effect of Duloxetine in Patients with Chronic Low Back Pain: A 41-week Uncontrolled, Dose-blinded Study

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Clinical Trial Registry Number: NCT00424593, at www.clinicaltrials.gov

Abstract

Objective. To assess the maintenance of the effect of duloxetine in the treatment of chronic low back pain.

Methods. Patients (N = 181) with chronic low back pain entered a 41-week extension phase after completing a 13-week placebo-controlled treatment phase. The maintenance of the effect was assessed in patients taking duloxetine 60/120 mg/day who met the response criteria (≥30% reduction in Brief Pain Inventory average pain) at the end of the placebo-controlled phase. In addition, physical function was evaluated using the Roland-Morris Disability Questionnaire, the Clinical Global Impressions-Severity of Illness, and the Brief Pain Inventory Pain Severity and Interference ratings. Quality of life, safety, and tolerability outcomes were also assessed. Finally, placebo-treated patients were switched to duloxetine 60 mg/day at the beginning of the extension phase and their response to treatment is also reported.

Results. Initial responders to duloxetine treatment demonstrated further significant improvement (within-group) in pain, physical function, and quality of life. Significant within-group improvements were also observed in the extension phase for placebo-treated patients who were switched to duloxetine. Duloxetine was well tolerated with no new safety findings reported.

Conclusions. In this study, the analgesic effect of duloxetine in patients with chronic low back pain was not only maintained for 41 weeks, but additional statistically significant improvement in pain and function was observed.

Key Words. Chronic Low Back Pain; Duloxetine; Maintenance of Effect; Efficacy and Safety

Abbreviations: DLX, duloxetine; PLA, placebo; CLBP, chronic low back pain; BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions-Severity of Illness.

Introduction

The etiology of most cases of low back pain is not known, even though the lifetime prevalence rate in the USA approaches 80% and low back pain is the primary cause of disability in people younger than 45 years of age and is one of the leading reasons for doctor visits [1,2]. Although low back pain will ameliorate in most patients within a few days to weeks, approximately 5–10% will develop chronic low back pain (CLBP). The most commonly prescribed drug treatments for low back pain include nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and muscle relaxants [3]. However, it has been noted in a recent review that neither of these treatments, nor any others for back pain, show good quality evidence for substantial benefit or, as in the case of muscle relaxants, no clinical evidence for use in CLBP [4]. There are also very few published trials with a duration of treatment lasting longer than a few weeks in length. For example, the longest trial of NSAIDs for low back pain noted in a Cochrane review was just 6 weeks [5]. A more recent review found little evidence for efficacy, and especially safety, of medications beyond 4 weeks of use [3]. Moreover, a number of treatments may have safety problems, especially if used over a long time period, including opioids (addiction), and NSAIDs (gastrointestinal events such as bleeding and ulcers as well as cardiovascular concerns).

Duloxetine has shown to be efficacious in three double-blind, placebo-controlled fibromyalgia trials (durations ranged from 12 weeks to 6 months) [6–8]. Three 12-week, double-blind, placebo-controlled studies have also shown duloxetine to be efficacious in managing pain in patients

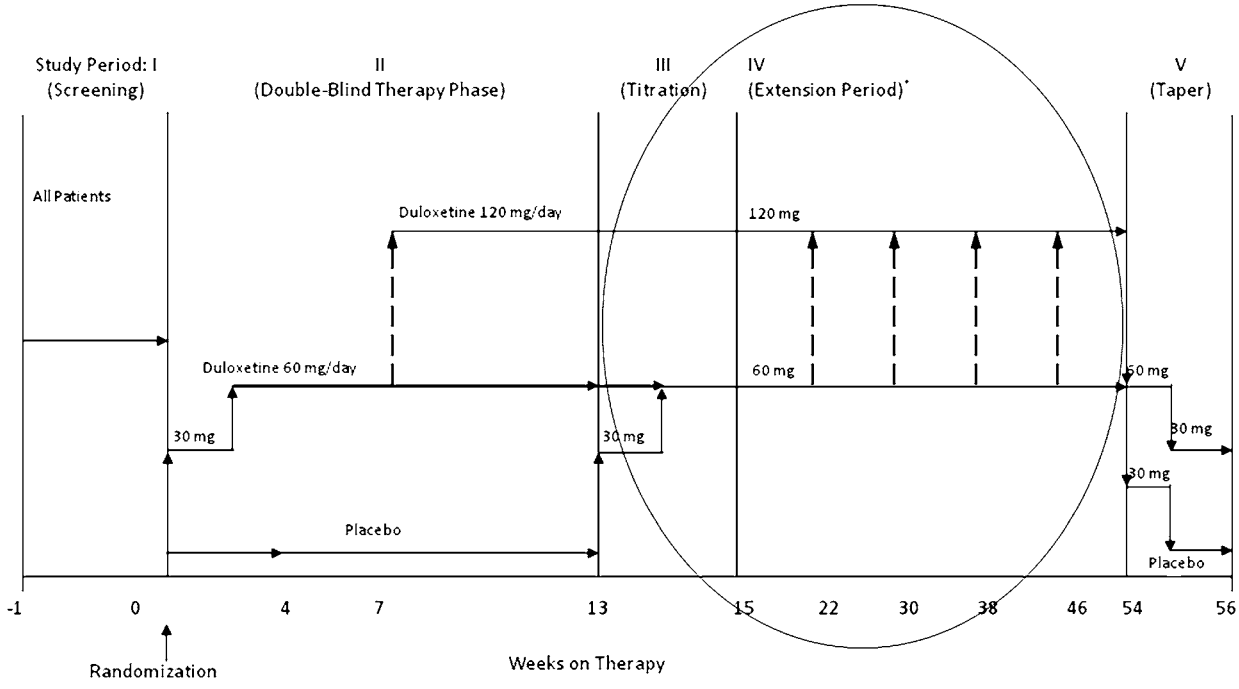

Figure 1 Study design. *The 41-week extension phase actually includes both Study Periods III and IV. After 7 weeks, patients receiving duloxetine 60 mg/day and not meeting response criteria (defined as at least 30% pain reduction on Brief Pain Inventory 24-hour average pain) were escalated to duloxetine 120 mg/day. Patients continuing on or switched to duloxetine 60 mg/day who did not meet response criteria (defined above) during the extension phase had their dose increased to 120 mg/day, beginning at week 22 and up through week 46.

with diabetic peripheral neuropathic pain (DPNP) [9–11]. Moreover, the maintenance of effect (MOE) of duloxetine has been established in both fibromyalgia (1-year study) [12] and DPNP (34-week study) [13].

A double-blind, placebo-controlled, 13-week study of duloxetine treatment in patients with CLBP was recently completed [14]. Significant improvement was observed on the primary outcome measure (pain severity) as well as most secondary outcome measures. Patients completing the initial 13 weeks of the study could then enter a 41-week, uncontrolled, dose-blinded extension phase. The main objective of the extension phase was to evaluate the MOE of duloxetine in patients with CLBP as measured by the Brief Pain Inventory (BPI) [15] 24-hour average pain ratings (referred to as BPI average pain hereafter). This report addresses this objective, as well as provides additional data on efficacy, safety, and health outcomes measures from the extension phase.

Methods

Study Design

This was the uncontrolled extension phase of a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (Figure 1). The results of the 13-week placebo-controlled treatment phase of this trial were recently published [14]. Patients (herein known as DLX/DLX group) who had received duloxetine 60 mg/day or duloxetine 120 mg/day at the end of the placebo-controlled phase remained on their respective doses. Patients who had received placebo during the placebo-controlled phase entered a 2-week titration phase. They were switched to duloxetine 30 mg/day for 1 week followed by 1 week of duloxetine 60 mg/day. These patients (herein known as PLA/DLX group) then entered a 39-week extension treatment period.

Note that all patients, regardless of the treatment group, were treated with duloxetine for up to 41 weeks (week 13 through week 54, thereafter referred to as extension phase). Patients taking duloxetine 60 mg/day during the extension phase (patients in both the DLX/DLX and PLA/DLX groups) and not meeting pre-specified response criteria (defined as at least 30% reduction on BPI average pain relative to study entry baseline) had their dose increased to 120 mg/day, beginning at week 22 (9 weeks into the extension phase) and up through week 46. Patients taking duloxetine 120 mg/day were not allowed to return to the duloxetine 60-mg/day dose. Patients who did not tolerate either duloxetine 60 mg/day or duloxetine

120 mg/day during the extension phase, and who had taken duloxetine 60 mg/day for at least 2 weeks, were entered in a 2-week taper phase to minimize discontinuation-emergent adverse events, and eventually, were discontinued. In the taper phase, patients taking duloxetine 60 mg/day during the extension phase received duloxetine 30 mg/day for 1 week and placebo for 1 week. Patients taking duloxetine 120 mg/day during the extension phase received duloxetine 60 mg/day for 1 week and then duloxetine 30 mg/day the final week.

Patients

Male and female outpatients at least 18 years of age who had CLBP as the primary painful condition were allowed to participate in this study. To be included in this study, pain must have been present in the lower back (T-6 or below) for most days the past 6 months or longer with a weekly mean of 24-hour average rating ≥4 at baseline (average values of 24-hour pain assessments were recorded in the electronic patient diary during the last week before randomization, on a 0 [no pain] to 10 [worst possible pain] scale). Eligible patients were to have pain either restricted to low back or associated with radiation to thigh proximally (Class 1 and 2 per Quebec Task Force on Spinal Disorders). Patients with clinical evidence of radiculopathy, spinal stenosis, or high grade spondylolisthesis, as well as patients with major depressive disorder were excluded. Major depressive disorder was determined using the depression module of the Mini International Neuropsychiatric Interview (MINI).

Patients regularly using therapeutic doses of NSAIDs or acetaminophen before the study entry (for ≥14 days per month for 3 months prior to study entry) were allowed to continue these therapies as long as the doses or frequency were not changed during the study. Apart from NSAIDs and acetaminophen, no medications used for treatment of chronic pain were allowed on an ongoing basis. Episodic use of short-acting analgesics (defined as no more than three consecutive days or no more than a total of 60 days during the extension phase) was allowed for the management of breakthrough CLBP (rescue therapy) or acute conditions unrelated to the lower back. Medication classes including but not limited to antidepressants, and anticonvulsants were not allowed during this study. Patients having ongoing or anticipated disability compensation or litigation issues, in the best judgment of the investigator, were excluded. Additional exclusion criteria are described in the previous publication on the placebo-controlled phase of this trial [14]. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by ethics review boards covering each site. Patients provided written informed consent before participation in any study-related procedures.

Efficacy Measures

The primary efficacy measure was the average pain severity item of the BPI-modified short form [15]. It measures average pain severity during the past 24 hours on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). The changes in the remaining BPI Pain Severity ratings (worst pain, least pain, and pain right now) and BPI Interference ratings over the 41 weeks of treatment were also assessed (see the previous publication for details of BPI scoring) [14]. Other efficacy measures included the Roland-Morris Disability Questionnaire-24 (RMDQ) to evaluate physical function [16], the Clinical Global Impressions-Severity of Illness (CGI-S) [17], 30% and 50% response rates (based on improvements in BPI average pain rating), and the Athens Insomnia Scale [18]. Patient-reported health outcomes were assessed using the 36-item Short-Form Health Status Survey (SF-36) [19], the European Quality of Life Questionnaire: 5 Dimensions (EQ-5D) [20], and the Work Productivity and Activity Impairment instrument (WPAI) [21]. Mood was evaluated using the Beck Depression Inventory-II (BDI-II) total score [22] and the Hospital Anxiety and Depression Scale (HADS) [23]. The safety of duloxetine was evaluated during the extension phase via discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, weight, and laboratory analytes.

Statistical Analyses

All analyses for the extension phase were conducted on an intent-to-treat basis. Data for the extension phase were reported by the treatment group to which patients were originally assigned (DLX/DLX and PLA/DLX); no statistical comparison between these two groups was performed. To test if the within-group change from baseline to endpoint was equal to zero, two-sided *t*-test was used for efficacy measures and the Wilcoxon signed-rank test was used for safety measures. Statistical significance was evaluated at the level of 0.05 unless specified otherwise. Baseline was defined as the last nonmissing measure before entering the extension phase, and endpoint was defined as the last nonmissing observation during the extension phase (last-observation-carried-forward).

The null hypothesis that the treatment effect of duloxetine was not maintained during the extension phase was tested by evaluating a one-sided 97.5% CI of the change from baseline to endpoint for patients in the extension phase who responded to duloxetine 60 mg/day to 120 mg/day during the placebo-controlled phase. When the upper bound of the one-sided 97.5% CI was less than or equal to the noninferiority margin of 1.5 points on BPI average pain, the null hypothesis was rejected at the significance level of 0.025. The margin of 1.5 points on the BPI average pain scale was established based on studies of minimal clinically important difference in pain ratings [24,25]. A similar analysis was also performed for patients who received duloxetine 60 mg/day during the study. For this analysis, patients who titrated from duloxetine 60 mg/day to 120 mg/day during the placebo-controlled phase were excluded, as were the observations collected after the dose titration for patients who titrated to duloxetine 120 mg/day during the extension phase.

Table 1 Patient characteristics at baseline of extension phase

Variable	DLX/DLX 60/120 mg/day N = 83	PLA/DLX 60/120 mg/day N = 98
Age, years, mean (SD)	51.2 (14.0)	52.2 (13.8)
Female, n (%)	54 (65.1)	62 (63.3)
Race, n (%)		
African descent	4 (4.8)	5 (5.1)
White	65 (78.3)	80 (81.6)
East Asian	0 (0.0)	2 (2.0)
Hispanic	13 (15.7)	10 (10.2)
Native American	1 (1.2)	1 (1.0)
Weight, kg, mean (SD)	76.7 (14.9)	75.7 (13.9)
Duration of CLBP since onset, years, mean (SD)	8.7 (8.3)	10.0 (8.7)
BPI average pain, mean (SD)	3.4 (1.9)	4.5 (2.3)
CGI-S, mean (SD)	2.2 (1.2)	2.6 (1.3)
NSAID use, n (%)	25 (30.1)	30 (30.6)
Quebec Task Force on Spinal Disorders, n (%)		
Class 1	51 (62.2)	58 (62.4)
Class 2	31 (37.8)	35 (37.6)

DLX = duloxetine; PLA = placebo; SD = standard deviation; CLBP = chronic low back pain; BPI = Brief Pain Inventory; CGI-S = Clinical Global Impressions-Severity of Illness; NSAID = nonsteroidal anti-inflammatory drug.

The percentages of patients meeting response criteria during the extension phase were reported using three definitions based on the change from baseline to endpoint in BPI average pain rating: 1) ≥30% reduction; 2) ≥50% reduction; and 3) sustained response, defined as a ≥30% reduction at the end of the extension phase, with a ≥30% reduction at an earlier visit than the last visit, remaining at a ≥20% reduction in all the nonmissing visits in between. For this analysis, baseline was defined as the last nonmissing observation before randomization. SAS® software version 9 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses.

Results

Patient Demographic and Clinical Characteristics at Baseline

The baseline demographics and clinical characteristics for the DLX/DLX group (i.e., patients on duloxetine 60/120 mg/day in the placebo-controlled and extension phases) and the PLA/DLX group (patients on placebo in the placebo-controlled phase and titrated to duloxetine in the extension phase) are shown in Table 1. The mean age of patients in this study was approximately 52 years with most being women (64.1%) and white (80.1%).

Prior Medication Use

Medications used by at least 1% of the patients (includes all patients from baseline of placebo-controlled phase) [14] in the previous 2 years included diclofenac (9.3%), paracetamol (3.4%), ibuprofen (3.0%), celecoxib (1.7%), tramadol (1.7%), gabapentin (1.3%), naproxen (1.3%), tilidine (1.3%), and ultracet (1.3%). There were no statistically significant differences in the prior use of these medications between treatment groups.

Patient Disposition

Fifty-five of the 83 (66.3%) patients in the DLX/DLX group and 62 of the 98 (63.3%) patients in the PLA/DLX group completed the extension phase (Figure 2). The most common reason for discontinuation during the extension phase was "patient decision" (12.0%) for the DLX/DLX group and "adverse events" (13.3%) for the PLA/DLX group.

Exposure

The mean duration of duloxetine exposure during the extension phase was 35 weeks (median of 41 weeks) for the DLX/DLX group and 32 weeks (median of 40 weeks) for the PLA/DLX group. In the extension phase, 106 patients received duloxetine 60 mg/day, with 46 patients continuing on that dose from the placebo-controlled phase and 60 switching from placebo. Seventy-five patients stayed on duloxetine 120 mg/day, with 25 patients continuing from the placebo-controlled phase, 12 titrating from 60 mg/day (placebo-controlled phase treatment) to 120 mg/day, and 38 switching from placebo.

Efficacy

A total of 58 DLX/DLX patients met the response criteria after the 13-week placebo-controlled treatment phase

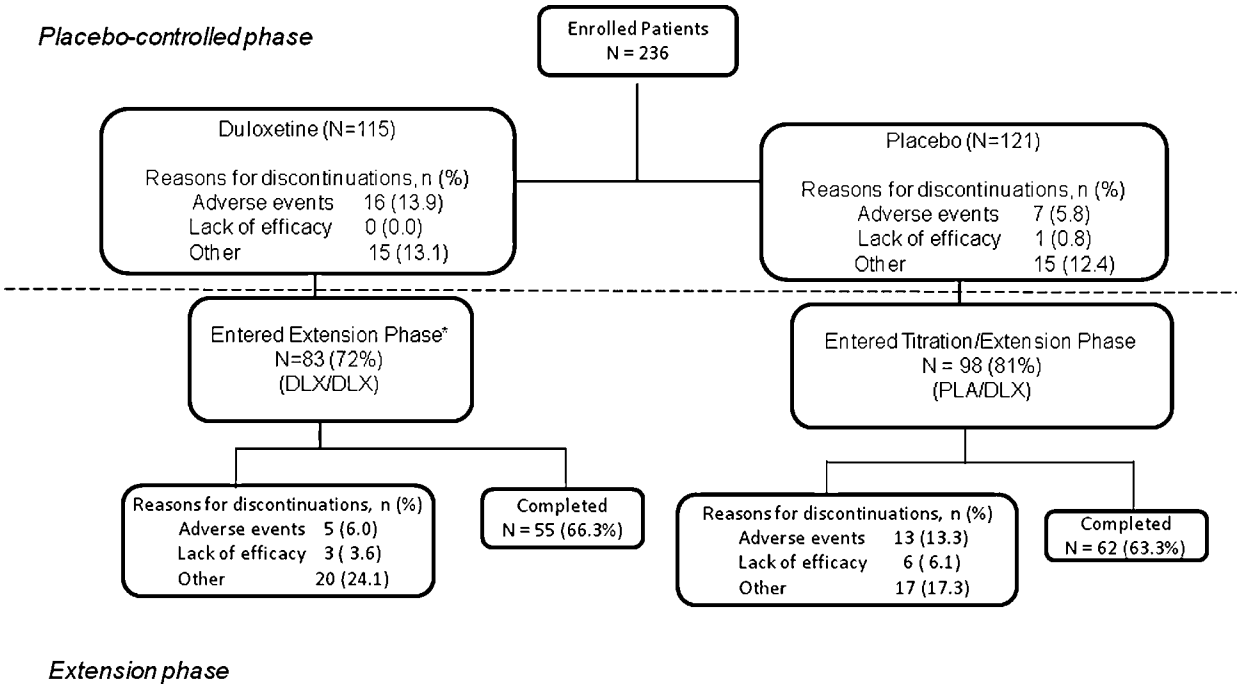

Figure 2 Patient disposition flowchart. *One patient completed the placebo-controlled phase but did not continue into the extension phase. PLA = placebo; DLX = duloxetine.

and were included in the MOE analysis. The mean change in BPI average pain in the extension phase was –0.97, and the upper bound of the one-sided 97.5% confidence interval (CI) was –0.45, which was significantly lesser than the pre-specified, noninferiority margin of 1.5 points ($P < 0.001$). This result indicates that the treatment effect of duloxetine 60 mg/day to 120 mg/day on pain reduction in placebo-controlled phase duloxetine responders was maintained throughout the extension phase. Moreover, the upper limit of the one-sided 97.5% CI was less than zero, demonstrating a statistically significant reduction in pain for DLX/DLX patients with CLBP during the extension phase when compared with pain severity at the end of the placebo-controlled phase.

The MOE was also assessed for patients ($N = 49$) receiving duloxetine 60 mg/day during the placebo-controlled and extension phases of this study. The mean change in BPI average pain in the extension phase was –0.59, and the upper bound of the one-sided 97.5% CI was 0.05, which was, again, less than the pre-specified, noninferiority margin of 1.5 points ($P < 0.001$).

Figure 3 shows the change from baseline of the placebo-controlled phase through the end of the extension phase in the BPI average pain rating in all patients who entered the extension phase. There was a continuous pain reduction for patients with CLBP during the extension phase for both PLA/DLX and DLX/DLX groups.

The 30%, 50%, and sustained response rates were on average about 10% higher for the DLX/DLX group than for the PLA/DLX group (Figure 4). Fifty-five of 58 (94.8%) of placebo-controlled phase duloxetine responders still met response criteria at the end of the 41-week extension phase.

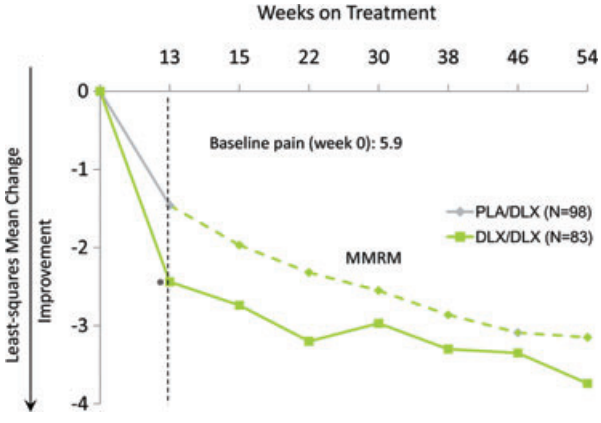

Figure 3 Mean change in BPI average pain rating for patients who entered the extension phase. *$P \leq 0.05$ duloxetine completers compared with placebo completers at the end of the placebo-controlled phase (week 13). BPI = Brief Pain Inventory; PLA = placebo; DLX = duloxetine; MMRM = mixed-effects model repeated measures.

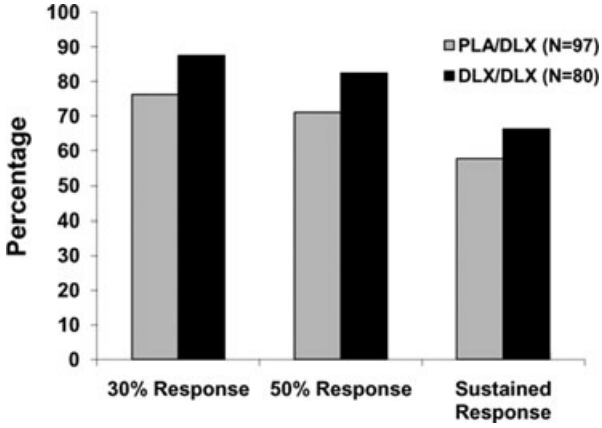

Figure 4 Response rates at the end of the extension phase. The response rates were based on the change from baseline to endpoint in BPI average pain rating and were defined as a ≥30% reduction (response), ≥50% reduction, and sustained response (i.e., defined as a ≥30% reduction at the end of the extension phase). BPI = Brief Pain Inventory; PLA = placebo; DLX = duloxetine.

The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both the DLX/DLX and PLA/DLX treatment groups (Table 2). Both treatment groups also showed significant improvement on the RMDQ and CGI-S measures as well as most of the health outcome assessments. No significant change was observed in the BDI total score and HADS depression score.

Safety

No deaths occurred during the extension phase or tapering phase. Four DLX/DLX patients each experienced one serious adverse event (SAE), which was acute tonsillitis, osteoarthritis, syncope, and tonsillitis. A total of 7 SAEs were experienced by 5 patients in the PLA/DLX group, including one incidence each of accidental overdose (duloxetine), angiopathy, back pain, femur fracture, hand fracture, road traffic accident, and suicidal ideation. Regarding the suicidal ideation, an elderly female patient experienced suicidal thoughts and was discontinued from the study, although the study investigator stated that this SAE was not related to the study drug.

The proportion of patients who discontinued the extension phase due to adverse events was 6.0% in the DLX/DLX group and 13.3% in the PLA/DLX group. No adverse event leading to discontinuation occurred in more than 1 patient within either treatment group, except for upper abdominal pain in 2 patients in the PLA/DLX group.

Treatment-emergent adverse events (TEAEs) experienced by at least 5% of patients in either treatment group during the extension phase are presented in Table 3. Overall, a greater percentage of patients in the PLA/DLX group (76.5%) experienced a TEAE than in the DLX/DLX group (68.7%). The most common TEAEs in both treatment groups were headache, nausea, and upper abdominal pain.

Results of pulse, blood pressure, and weight assessments in the extension phase are summarized in Table 4. There was a small but statistically significant mean weight gain in the DLX/DLX group (1.4 kg). No cases of sustained elevation in diastolic blood pressure occurred in either treatment group, but three patients (4.0%) experienced sustained elevations in systolic blood pressure in the DLX/DLX group.

Mean changes in both fasting and random glucose levels were not statistically significant within both treatment groups. Of these patients (n = 130), the majority had no change (51.5%) or a small (<1.5 mmol/liter) change (42.3%) from baseline to endpoint in fasting glucose. The remaining 6.1% of the patients (eight patients) had a greater than 1.5 mmol/liter increase from baseline to endpoint in fasting glucose. Of relevance to this finding is that four of these eight patients had either a preexisting condition of diabetes mellitus, abnormally high baseline fasting glucose, or both. Findings for other chemistry analytes, including liver function tests, due to the magnitude and/or direction of change, were considered not clinically relevant.

Discussion

Patients who were responders during the placebo-controlled phase benefited from continuing treatment with duloxetine 60 mg to 120 mg/day in the 41-week extension phase of the study. The MOE was demonstrated in patients taking duloxetine 60 mg to 120 mg/day (DLX/DLX group) but also in the subgroup of those patients who remained on 60 mg/day in both the placebo-controlled and the extension phases of the study. Statistically significant within-group improvements occurred in the DLX/DLX group for the BPI Pain Severity and Interference measures and in the physical functional measure (RMDQ). The PLA/DLX group showed significant within-group improvements on nearly all efficacy, physical function, and quality-of-life measures, which is consistent with results in fibromyalgia studies.

The safety and tolerability profile of duloxetine was comparable with that observed in previous studies of duloxetine for other indications. For those patients who took duloxetine in both the placebo-controlled and extension phases of the study (DLX/DLX), the incidence of discontinuations due to adverse events was low and the adverse event profile was consistent with what is typically observed with the use of duloxetine, indicating that there is no increased risk with taking duloxetine for long-term treatment.

Approximately two-thirds of the patients in both groups completed the extension phase. This rate is similar to

Table 2 Summary of secondary outcome measures during the extension phase

	DLX/DLX		PLA/DLX	
	60/120 mg/day (N = 80)		60/120 mg/day (N = 97)	
Measure	Baseline	Mean Change (SD)	Baseline	Mean Change (SD)
BPI average pain	3.4 (1.9)	–1.1 (1.8)***	4.5 (2.3)	–1.4 (2.2)***
BPI worst pain	4.5 (2.1)	–1.3 (2.4)***	5.7 (2.4)	–1.8 (2.6)***
BPI least pain	2.4 (2.0)	–0.8 (1.7)***	3.3 (2.6)	–0.9 (2.2)***
BPI pain right now	2.8 (2.0)	–0.8 (2.0)***	4.1 (2.6)	–1.3 (2.5)***
BPI average interference	2.3 (1.9)	–0.7 (1.4)***	3.3 (2.3)	–1.1 (2.0)***
RMDQ	7.8 (5.8)	–1.1 (3.5)*	9.6 (6.1)	–2.4 (5.3)***
CGI-S	2.2 (1.2)	–0.2 (0.8)*	2.6 (1.3)	–0.5 (1.1)***
Athens Insomnia	5.4 (4.4)	–0.4 (4.3)	6.7 (5.1)	–1.1 (4.5)*
BDI-II	5.9 (7.2)	–0.6 (4.0)	7.7 (9.0)	–1.0 (6.6)
HADS anxiety	3.7 (3.7)	–0.1 (2.3)	4.3 (3.7)	–0.6 (2.4)*
HADS depression	3.3 (3.3)	–0.1 (2.2)	3.7 (3.4)	0.1 (3.1)
EQ-5D UK index	0.7 (0.3)	0.0 (0.2)***	0.6 (0.3)	0.1 (0.3)***
EQ-5D US index	0.8 (0.2)	0.0 (0.1)***	0.7 (0.2)	0.1 (0.2)***
SF-36 MCS	52.6 (10.0)	0.6 (8.6)	49.5 (11.4)	1.0 (10.3)
SF-36 PCS	39.8 (10.6)	2.8 (8.7)**	37.6 (9.6)	5.6 (9.2)***
SF-36 bodily pain	7.3 (2.2)	0.8 (2.1)**	6.6 (2.1)	1.5 (2.2)***
WPAI absenteeism	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
WPAI presenteeism	0.2 (0.2)	–0.1 (0.2)	0.3 (0.3)	–0.1 (0.2)***
WPAI work productivity loss	0.2 (0.2)	–0.0 (0.2)	0.3 (0.3)	–0.1 (0.2)***
WPAI activity impairment	0.3 (0.2)	–0.1 (0.2)*	0.5 (0.3)	–0.2 (0.2)***

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ (within-group comparisons).
DLX = duloxetine; PLA = placebo; SD = standard deviation; BPI = Brief Pain Inventory; RMDQ = Roland-Morris Disability Questionnaire; CGI-S = Clinical Global Impressions-Severity of Illness; BDI-II = Beck Depression Inventory-II; HADS = Hospital Anxiety and Depression Scale; EQ-5D = European Quality of Life Questionnaire: 5 Dimensions; SF-36 = 36-Item Short Form Health Survey; SF-36 MCS = SF-36 Mental Component Summary; SF-36 PCS = SF-36 Physical Component Summary; WPAI = Work Productivity and Activity Impairment questionnaire.

completion rates in patients with fibromyalgia in studies lasting up to 1 year [12]. In another study, 68% of the patients randomly assigned to 60 mg/day of duloxetine after a short open-label period of 8 weeks on that same dose, completed 52 weeks of double-blind treatment [26]. Completion rates of greater than 70% were found in a study of patients with peripheral diabetic neuropathy receiving 60 mg/day of duloxetine, although the extension phase was of shorter duration (26 weeks) [13]. Therefore, most patients, regardless of pain condition, remain on duloxetine treatment for time periods of 6 months and longer. In contrast, there are very few trials lasting more than 1 month with other treatments for CLBP.

According to a recent review of the literature, the longest trial of acetaminophen treatment for CLBP was 4 weeks and the longest trial of any NSAID for the same indication was 6 weeks [3]. This review suggests that NSAIDs are moderately effective for short-term relief of CLBP but there is little clinical evidence for use of these medications in long-term use of pain relief. This conclusion was based

Table 3 Treatment-emergent adverse events during the extension phase

Adverse Event, n (%)	DLX/DLX 60/120 mg/day (N = 83)	PLA/DLX 60/120 mg/day (N = 98)
≥1 event	57 (68.7)	75 (76.5)
Headache	9 (10.8)	13 (13.3)
Nausea	6 (7.2)	11 (11.2)
Upper abdominal pain	4 (4.8)	9 (9.2)
Hyperhidrosis	3 (3.6)	8 (8.2)
Back pain	2 (2.4)	6 (6.1)
Diarrhea	3 (3.6)	5 (5.1)
Fatigue	0 (0.0)	6 (6.1)

* Adverse events occurring at a rate ≥5% in either treatment group.
DLX = duloxetine; PLA = placebo.

Table 4 Vital signs and weight during the extension phase

	DLX/DLX 60/120 mg/day (N = 83)		PLA/DLX 60/120 mg/day (N = 98)	
Measure	Baseline	Mean Change (SD)	Baseline	Mean Change (SD)
Pulse, beats per minute	75.0 (10.2)	–2.5 (10.5)	71.0 (7.6)	1.5 (7.5)
Diastolic BP, mm Hg	81.5 (8.2)	–2.0 (9.4)	79.7 (8.7)	0.5 (8.0)
Systolic BP, mm Hg	127.0 (14.1)	–1.4 (14.4)	127.1 (15.0)	0.8 (13.0)
Sustained elevation in BP, n (%)*	3 (4.0)		0 (0.0)	
Weight, kg	76.6 (14.6)	1.4 (3.3)***	75.3 (13.4)	–0.4 (2.5)

*** $P \leq 0.001$ (within-group comparisons).

* Sustained elevation = diastolic BP ≥90 mm Hg and increase from baseline (defined as the highest of the measures at all the visits before randomization) of ≥10 mm Hg for 3 consecutive visits, or systolic BP ≥140 mm Hg and increase from baseline (defined as the highest of the measures at all the visits before randomization) of ≥10 mm Hg for 3 consecutive visits.

DLX = duloxetine; PLA = placebo; SD = standard deviation; BP = blood pressure.

both on the paucity of clinical trial data as well as safety concerns with long-term treatment. The longest trials to date for opioids include 13- and 16-week trials [27,28]. These trials showed moderate pain relief but do not allow extrapolation to time periods longer than 4 months. Moreover, this class of drugs has the potential of abuse and has not shown to be safe for long-term treatment in clinical trials [29]. Trials of benzodiazepines for CLBP have also been disappointing [3,30]. Clinical trials for low back pain using antidepressants, anti-epileptics, skeletal muscle relaxants, and other alternative treatments were of short duration, lasting from a few days to a few weeks [3].

A meta-analysis by Staiger *et al*. [31] found that the four antidepressants (three tricyclic and one tetracyclic), which demonstrated mild to moderate effectiveness in reducing low back pain, inhibited norepinephrine reuptake. In contrast, two antidepressants that did not improve back pain did not inhibit norepinephrine reuptake (paroxetine and trazodone). Venlafaxine, a serotonin norepinephrine reuptake inihibitor (SNRI), has been shown to improve neuropathic pain [32,33] and pain associated with osteoarthritis [34] and fibromyalgia [35]. However, these were primarily small studies. Another SNRI, milnacipran, has been shown to be efficacious in the management of pain in patients with fibromyalgia [36,37]. Published studies in other chronic pain conditions, including low back pain, were not found. One would expect that venlafaxine and milnacipran should also be effective for CLBP, but appropriately designed studies are needed to confirm that hypothesis.

The continued significant improvement in pain measures was somewhat surprising as tolerance or tachyphylaxis is common with treatments, in particular opioids, for CLBP [4]. In addition, prolonged use of opioids may lead to hyperalgesia. However, improvements or minimal worsening in pain measures were noted in the 6-month extension phases in duloxetine studies of patients with fibromyalgia [12]. Pain improvement was also maintained in patients with diabetic peripheral neuropathy for up to 26 weeks of continued treatment after 8 weeks of acute therapy [13]. Thus, the results from the present study, and studies in other chronic pain conditions, are encouraging inasmuch that duloxetine may be efficacious in controlling CLBP for extended periods of time.

Ideally, to assess the MOE, one needs a random withdrawal study which randomizes the acute treatment responder to either continue on treatment or switch to placebo for a period of time (6 month to 1 year). At the end of the randomization phase, if the percentage of patients who lost the treatment effect (returning toward the study baseline value) is greater in the placebo group compared with the drug group, then MOE could be declared. However, placebo-controlled studies in pain are always of limited duration due to ethical considerations. In our study, as there is no placebo control in the extension phase, the MOE was assessed at the group mean level and compared with the pre-specified clinically meaningful value. In other words, we averaged the mean change of pain severity for DLX/DLX acute responders who entered the extension phase and observed a one-point reduction compared with the end of the placebo-controlled phase. Because the upper limit of the mean difference was lower than the pre-specified cut-off value, we reached the conclusion that the pain reduction from the treatment obtained at the end of the initial 13 weeks was maintained during the subsequent 41-week extension treatment phase. From the individual patient level, we found that out of 58 acute DLX/DLX treatment responders, 55 of them maintained ≥30% pain reduction during the extension phase. Moreover, very few patients discontinued due to lack of efficacy during the 41-week extension phase (three out of 83 patients treated with duloxetine in the placebo-controlled phase). Therefore, we believe that duloxetine does have a positive MOE profile for up to at least 54 weeks in patients with CLBP.

The safety profile of duloxetine long-term treatment in patients with CLBP is consistent with that observed in long-term studies of duloxetine for fibromyalgia [12] and

DPNP [38]. Duloxetine was well tolerated and no new safety concerns were noted in the extension phase. The results of cardiovascular assessments, including blood pressure and pulse, were similar to those noted in a review of 42 placebo-controlled studies of duloxetine [39]. Changes in chemistry and hematology analytes, including glucose levels and liver function tests, were also clinically unremarkable.

The strengths of this study include the treatment duration of 41 weeks, which makes it one of the few studies in CLBP lasting more than 12 weeks, as well as the relatively large number of patients who completed the extension phase. One study limitation is that only a small number of patients who were not white were included in the study. In addition, exclusion criteria prevented many patients from entering the trial so results should be extrapolated with care to the general population. Notably, patients with chronic pain often have major depression, but these patients were excluded from the study. Patients with ongoing or anticipated disability compensation or litigation issues were excluded from the study based on the judgment of the investigator. Because the disability and workers compensation status of patients have been found to have a significant impact on the efficacy of a variety of treatments for low back pain, this could affect the results in clinical practice. Finally, there was no control group in the extension phase.

Conclusions

The findings from this study demonstrate that patients with CLBP maintained the improvement in pain measures that occurred in the 13-week placebo-controlled phase, and actually showed additional improvement, during 41 weeks of continued treatment with duloxetine. Moreover, duloxetine was well tolerated and demonstrated a safety profile similar to that observed in previous clinical trials.

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