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Duloxetine for Patients with Diabetic Peripheral Neuropathic Pain: A 6-Month Open-Label Safety Study

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ABSTRACT

Objective. Duloxetine is a relatively balanced and potent reuptake inhibitor of both serotonin and norepinephrine. Because these neurotransmitters play a role in pain inhibition, duloxetine was considered a possible treatment for diabetic peripheral neuropathic pain (DPNP). This study assessed the 6-month safety and tolerability of duloxetine in patients with DPNP; evaluation of efficacy was a secondary objective.

Design. In this 28-week, open-label study, in the clinical setting, 449 patients with DPNP were randomized (3:1) to receive duloxetine 60 mg twice daily (BID) (N = 334) or duloxetine 120 mg once daily (QD) (N = 115). Comprehensive safety evaluations including laboratory analyses and electrocardiograms were performed for all patients. Efficacy measures included the Brief Pain Inventory (BPI) and Clinical Global Impression of Severity (CGI-S) scales.

Results. Protocol completion rates were 63.8% and 62.6% for the 60 mg BID and 120 mg QD groups, respectively ($P = 0.823$). Discontinuations were primarily due to adverse events, 20.1% for 60 mg BID and 27.0% for 120 mg QD ($P = 0.149$). Heart rate increased slightly in both treatment groups ($P \leq 0.02$ in both groups). Systolic blood pressure was unaffected, while diastolic blood pressure decreased slightly in the 120 mg QD group ($P = 0.04$). Sustained elevation in blood pressure was reported for 18 (5.5%) patients in the 60 mg BID group and six (5.4%) in the 120 mg QD group. Duloxetine treatment was not associated with significant QTc prolongation. There was significant improvement at endpoint on all subscales of the BPI and CGI-S ($P < 0.001$ in both groups).

Conclusions. In this study, duloxetine 60 mg BID and 120 mg QD were safely administered and well tolerated in patients with DPNP for up to 28 weeks. There were few differences in safety or tolerability between the two dosages. At both doses, duloxetine provided clinically significant pain relief.

Key Words. Duloxetine; Diabetic Peripheral Neuropathic Pain; Pain; Antidepressant

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Introduction

According to the Centers for Disease Control, about 18.2 million people, or 6.3% of the U.S. population, have diabetes [1]. Diabetic peripheral neuropathic pain (DPNP) is an especially debilitating complication of diabetes, affecting 10% to 20% of diabetic patients [2,3]. DPNP results from nerve damage after prolonged periods of suboptimal glycemic control. Although normalization of blood glucose in diabetic patients can prevent or slow the onset of DPNP, control is difficult, and this condition remains common and difficult to treat and has a major negative impact on the quality of life in patients with diabetes. Although no drugs were approved for the treatment of DPNP at the time this study was conducted, duloxetine has been recently approved by the Food and Drug Administration for management of DPNP.

Diabetic peripheral neuropathic pain is typically associated with pain that is variable in severity but always present. It is often described as an "aching, burning, stabbing, or shooting" sensation, and the pain often affects sleep. The neurotransmitters serotonin (5-HT) and norepinephrine (NE) both have been implicated in the modulation of endogenous analgesic mechanisms via the descending inhibitory pain pathways [4–6]. There is evidence that in pathological pain states, these inhibitory pathways may be dysfunctional [7,8], and the imbalance in these inhibitory mechanisms is believed to contribute to central sensitization, which is thought to be an important factor underlying the pathophysiology of DPNP.

Although there is no cure for DPNP, treatment of painful symptoms can markedly ameliorate the quality of life of affected patients [9]. Tricylic antidepressants (TCAs) have been consistently shown to produce significant relief of neuropathic pain [10,11]. These agents prevent the reuptake of 5-HT and NE, thereby augmenting the descending supraspinal pathways involved in pain inhibition [12,13]. However, the TCAs also affect other neuroreceptors, and these actions lead to undesirable adverse effects, such as sedation, urinary retention, orthostatic hypotension, and cardiac arrhythmias, which may limit the use of these agents, particularly in elderly or debilitated patients [13,14].

Duloxetine hydrochloride (duloxetine) has been shown in preclinical studies to be a selective, balanced, and potent inhibitor of reuptake of both 5-HT and NE [15,16]. In clinical trials, duloxetine administered at doses ranging from 40 to 120 mg daily has been shown to be safe and effective in the treatment of major depression [17–21]. Because of its dual reuptake activity, duloxetine was considered a possible treatment for the management of DPNP. In two 12-week studies in nondepressed patients with DPNP, duloxetine at doses of 60 mg once daily (QD) and 60 mg twice daily (BID) was safe and effective in relieving DPNP, with statistically significant pain relief reported within 1 week of beginning treatment [22,23]. For several functional measures, there was greater improvement for patients treated with 120 mg than for those treated with 60 mg, although the differences between groups were not statistically significant.

The primary objective of this 28-week study was to evaluate the 6-month safety and tolerability of duloxetine 60 mg BID in patients diagnosed with DPNP. The secondary objective was to evaluate the safety and tolerability of duloxetine 120 mg QD, as well as the efficacy of duloxetine 60 mg BID and duloxetine 120 mg QD in patients diagnosed with DPNP. In addition, this study aimed to provide information on the relative safety and tolerability of duloxetine dosage regimens of 120 mg QD and 60 mg BID.

Methods

Study Design

This was an open-label, randomized, parallel study of outpatients diagnosed with DPNP as assessed by the Michigan Neuropathy Screening Instrument (MNSI) [24]. The study was conducted at 36 sites in Argentina, Australia, Brazil, Canada, Chile, and Taiwan. The study consisted of a 5- to 17-day Screening Phase (Weeks –2 to 0) and a 28-week Open-Label Therapy Phase (Weeks 1–28) (Figure 1). Patients visited the study site at Weeks –1 or –2 and Week 0 (Screening Phase) and at Weeks 3, 7, 11, 19, 27, and 28 (Open-Label Therapy Phase), or at early discontinuation. Patients were also interviewed by phone at Week 1. The study was conducted in accordance with Good Clinical Practices and the ethical principles that have their origin in the Declaration of Helsinki. The protocol was reviewed and approved by the appropriate ethical review boards.

Patients

Patients were men or women at least 18 years of age who had a diagnosis of bilateral DPNP, with a score of ≥3 on the MNSI, caused by Type 1 or Type 2 diabetes mellitus. Pain was required to

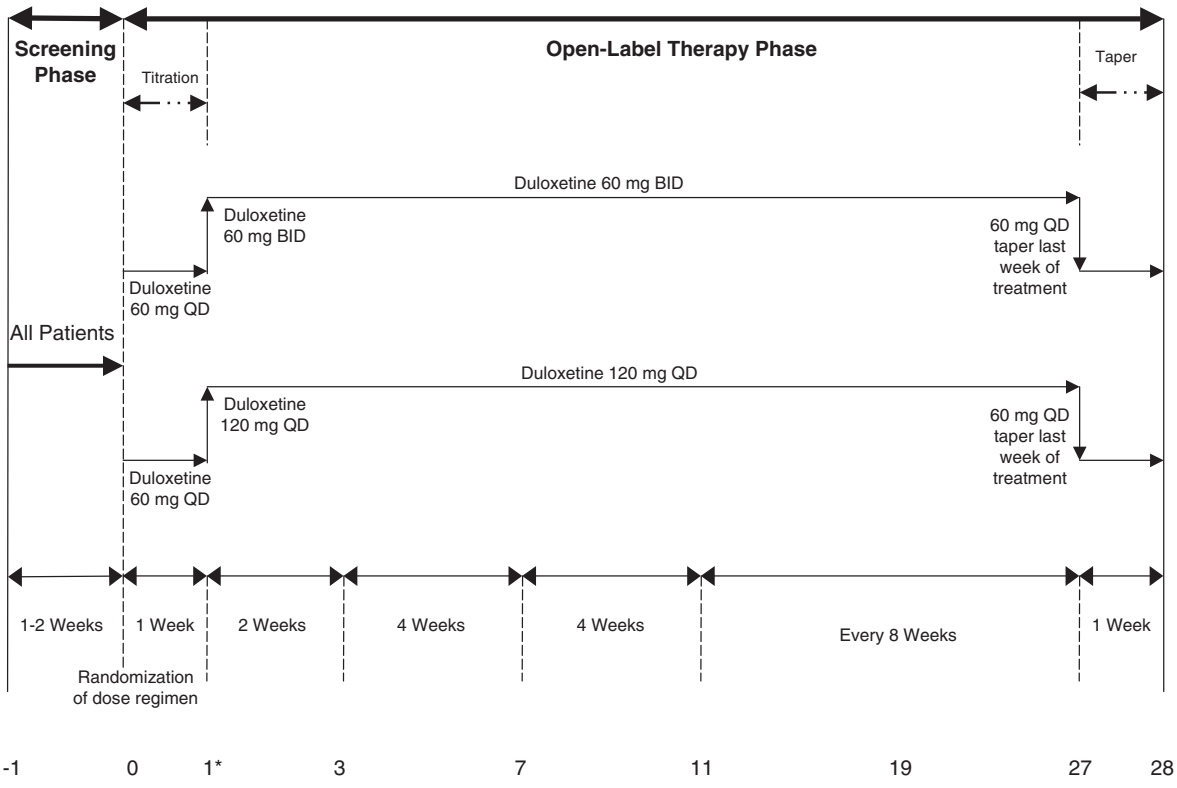

Figure 1 Study design. *The visit at Week 1 was a phone visit to assess adverse events, concomitant medications, and confirm change in dosing schedule. BID = twice daily; QD = once daily.

have begun in the feet, with relatively symmetrical onset, and to have been present daily for at least 6 months. All patients were to have stable and optimized glycemic control and a glycosylated hemoglobin (HbA_{1c}) ≤12% at screening. Patients could not have had any previous or current diagnosis of mania, bipolar disorder, or psychosis, or a history of substance abuse or dependence within the past year, and were not judged to be at risk for suicide. Patients were excluded if they had serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness; symptomatic peripheral vascular disease; or other medical or psychological conditions that would compromise study participation or be likely to lead to hospitalization during the study. Patients with alanine transaminase (ALT) levels over 1.5 times the upper limit of normal (34 U/L for women, and 43 U/L for men) or aspartate transaminase (AST) levels over 400 U/L were also disqualified, as were patients who had received a renal transplant, who were currently on renal dialysis, or who had serum creatinine levels above the upper limit of the reference range (124 mmol/L for women, and 141 mmol/L for men) at baseline. Patients who had prior exposure to drugs known to cause neuropathy or who had a medical condition that could be responsible for neuropathy were also excluded. Patients were reimbursed for travel costs, but were not otherwise compensated. All patients gave written informed consent.

Treatment

At the end of the Screening Phase, patients were randomly assigned (in a 3:1 ratio) to receive either duloxetine 60 mg BID or duloxetine 120 mg QD. Duloxetine was provided by the sponsor as 30-mg capsules. Week 1 of the Open-Label Therapy Phase was a titration week during which all patients received duloxetine 60 mg QD. During the next 26 weeks (Weeks 2–27) patients took the duloxetine dose to which they had been randomly assigned. Patients unable to tolerate their titration dose or their assigned dose were discontinued from the study. The final week of the Open-Label Therapy Phase (Week 28) was a taper week, during which all patients received duloxetine 60 mg QD. Treatment compliance was assessed by the physician through direct questioning of the patient and capsule counts at each visit. For each

visit interval, compliance was defined as taking between 80% and 120% of the study medication prescribed for that interval.

Concomitant Medications

Patients were allowed to receive antiarrhythmics and most antihypertensive agents provided that the patient had been on a stable dose for a minimum of 3 months prior to study enrollment and remained on the medication for the duration of the study. Anticonvulsants, antidepressants, antimanics, and regular antipsychotic therapies were not allowed within 7 days of randomization (Week 0) or during the study. Treatment with monoamine oxidase inhibitors or fluoxetine was not permitted within 30 days of the Week 0 visit. Use of antiemetics, antipsychotics, chloral hydrate, oral and injected steroids, and hypnotics was permitted on an episodic basis. Analgesics, nonsteroidal antiinflammatory agents, and opiates excluding tramadol were allowed.

Safety Measures

Safety and tolerability were evaluated on the basis of the percentage of patients who discontinued the study early, treatment-emergent adverse events (TEAEs), vital signs (sitting blood pressure and heart rate), body weight, laboratory analytes, electrocardiogram (ECG) findings, and the frequency of hypoglycemic events [25]. TEAEs were defined as reported events that first occurred or worsened during the treatment period. Significant hypoglycemic events were defined as hypoglycemic events that required intervention of glucose, glucagon, food, drink, or assistance from another person. Consistent with the sixth report of the Joint National Committee [26], sustained elevation in blood pressure was defined as any one of the following, occurring at any time after randomization:

- Sitting diastolic blood pressure ≥85 mm Hg and an increase from baseline (defined as the highest of the screening measurements at Weeks –2 or –1 and 0) of 10 mm Hg for three consecutive visits.
- Sitting systolic blood pressure ≥130 mm Hg and increase from baseline (defined as the highest of the screening measurements at Weeks –2 or –1 and 0) of 10 mm Hg for three consecutive visits.

Data on vital signs, significant hypoglycemic events, and adverse events were collected at screening and at each visit during the Open-Label Therapy Phase. Samples for blood chemistry analyses were collected at screening and at Weeks 7, 19, and 27, or at the time of early discontinuation. Samples for HbA_{1c} and lipid profiles were collected and ECGs measured at screening and at Week 27, or at early discontinuation.

Efficacy Measures

Efficacy was evaluated using the Brief Pain Inventory (BPI) Severity and Interference scales [27] and the Clinical Global Impression of Severity (CGI-S) scale [28]. Patients rated each of the four BPI pain severity items (worst pain, least pain, average pain, current pain) on a scale of 0 (no pain) to 10 (pain as bad as you can imagine). Patients rated each of the seven BPI interference items (general activity, mood, walking ability, normal work, relations to others, sleep, and enjoyment of life) on a scale of 0 (does not interfere) to 10 (completely interferes). The CGI-S scale, which was administered by the investigator in the presence of the patient, was used to score the severity of DPNP at the time of assessment on a scale of 1 (normal) to 7 (most severe illness). The BPI and CGI have been well described [27,28] and frequently used in the assessment of pain [10,29–32]. Efficacy endpoints were assessed at screening and at Week 27 or early discontinuation.

Statistical Analyses

All analyses were conducted on an intent-to-treat basis. All data from all randomized patients were included in the statistical analyses. Unless otherwise specified, when a total score was calculated from individual items, it was considered "missing" if any of the individual items were missing. When an average score was computed from individual items, it was calculated from nonmissing values.

Baseline was defined as the last nonmissing observation of the Screening Phase, and endpoint was defined as the last nonmissing postbaseline observation at or before the Week 27 visit (last observation carried forward [LOCF]).

For both safety and efficacy variables, within-group changes from baseline to endpoint were evaluated with a Wilcoxon signed-rank procedure or Student's *t*-test. In addition, post hoc treatment group comparisons were made for selected categorical variables using the Fisher's exact test. Statistical significance was evaluated at the two-sided significance level of 0.05. The sample size of 449 patients was determined with the intent to have 300 patients exposed to the treatment for 6 months, as outlined by the International Conference on Harmonisation guidelines [33]. The

sample size was expected to uncover a common event that might occur within 6 months of exposure. With 300 subjects exposed to the treatment for 6 months, one would expect the events that occur with 1% frequency to be identified.

Results

Patients

A total of 558 patients entered the Screening Phase of the study. Of these, 449 met the entry criteria and were randomly assigned to receive duloxetine 60 mg BID (N = 334) or duloxetine 120 mg QD (N = 115). The treatment groups were similar with respect to baseline demographic and disease characteristics (Table 1). About half (47.9%) of the patients were female, and 58.1% were Caucasian. The mean ± standard deviation (SD) age was 59.9 ± 10.5 years. Most (93.8%) patients had Type 2 diabetes. The mean ± SD duration of diabetes was 12.4 ± 8.7 years, and the mean ± SD duration of DPNP was 3.2 ± 3.5 years. Secondary conditions were noted in 95.8% of patients in the duloxetine 60 mg BID group and in 96.5% of patients in the duloxetine 120 mg QD group. Hypertension, present in 62.6% of all patients, was the most common secondary condition; 5.3% of the patients in this study were known to have diabetic nephropathy.

The length of exposure to duloxetine was at least 180 days in 220 (65.9%) patients in the duloxetine 60 mg BID group and 74 (64.3%) patients in the duloxetine 120 mg QD group. Treatment compliance was 90% during Weeks 2–3 and 94% for each between-visit interval for the remainder of the Open-Label Therapy Phase up to the taper week.

A total of 195 (43.4%) patients had received drug treatment for DPNP before enrolling in the study. The medications taken most commonly for neuropathic pain were amitriptyline (16.0%), carbamazepine (10.7%), and gabapentin (8.5%). All but one patient (99.8%) reported taking at least one medication concomitantly with duloxetine. Concomitant medications used by at least 10% of the patients were metformin (36.1%), insulin (18.9%), atorvastatin (15.1%), aspirin (12.2%), glibenclamide (12.0%), and enalapril (11.8%).

Safety

Discontinuations

Of the 449 patients treated, 213 (63.8%) patients in the duloxetine 60 mg BID group and 72 (62.6%) in the duloxetine 120 mg QD group com-

Table 1 Baseline patient demographic and disease characteristics

Characteristic	Duloxetine 60 mg BID (N = 334)	Duloxetine 120 mg QD (N = 115)	Total (N = 449)
Sex, N (%)			
Male	176 (52.7)	58 (50.4)	234 (52.1)
Female	158 (47.3)	57 (49.6)	215 (47.9)
Age (mean ± SD) (years)	60.0 ± 10.4	59.6 ± 10.9	59.9 ± 10.5
Racial origin, N (%)			
Caucasian	194 (58.1)	67 (58.3)	261 (58.1)
Eastern/Southeastern Asian	47 (14.1)	17 (14.8)	64 (14.3)
Hispanic	26 (7.8)	9 (7.8)	35 (7.8)
African descent	3 (0.9)	0	3 (0.7)
Other	64 (19.2)	22 (19.1)	86 (19.2)
Weight (mean ± SD) (kg)	82.0 ± 19.8	83.0 ± 19.7	82.2 ± 19.8
Type of diabetes mellitus, N (%)			
Type 1	18 (5.4)	10 (8.7)	28 (6.2)
Type 2	316 (94.6)	105 (91.3)	421 (93.8)
Duration of diabetes (mean ± SD) (years)	12.4 ± 8.6	12.4 ± 9.2	12.4 ± 8.7
Duration of DPNP (mean ± SD) (years)	3.1 ± 2.9	3.6 ± 4.6	3.2 ± 3.5
Significant hypoglycemic episodes (Week 0), N (%)			
No	332 (99.4)	115 (100)	447 (99.6)
Yes	2 (0.6)	0	2 (0.4)
BPI-Severity: average pain* (mean ± SD)	5.3 ± 2.0	5.4 ± 2.0	5.3 ± 2.0
BPI-Interference: average† (mean ± SD)	5.1 ± 2.3	5.2 ± 2.6	5.1 ± 2.4
CGI-S‡ (mean ± SD)	4.4 ± 1.1	4.5 ± 1.1	4.4 ± 1.1

* Pain severity was rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).
† Interference of pain on function was rated on a scale of 0 (does not interfere) to 10 (completely interferes).
‡ Severity of diabetic peripheral neuropathic pain was rated on a scale of 1 (normal) to 7 (most severe illness).
BID = twice daily; BPI = Brief Pain Inventory; CGI-S = Clinical Global Impression of Severity; DPNP = diabetic peripheral neuropathic pain; QD = once daily; SD = standard deviation.

Table 2 Reasons for study discontinuation

Reason for Discontinuation	Duloxetine 60 mg BID (N = 334) N (%)	Duloxetine 120 mg QD (N = 115) N (%)	Total (N = 449) N (%)
Adverse event*	67 (20.1)	31 (27.0)	98 (21.8)
Nausea	12 (3.6)	2 (1.7)	14 (3.1)
Dizziness	7 (2.1)	1 (0.9)	8 (1.8)
Vomiting	2 (0.6)	6 (5.2)	8 (1.8)
Protocol violation/protocol entry criteria not met	14 (4.2)	4 (3.5)	18 (4.0)
Personal conflict/patient decision/withdrawal of informed consent	14 (4.2)	4 (3.5)	18 (4.0)
Lack of efficacy	9 (2.7)	1 (0.9)	10 (2.2)
Physician decision	7 (2.1)	2 (1.7)	9 (2.0)
Lost to follow-up	4 (1.2)	1 (0.9)	5 (1.1)
Death†	3 (0.9)	0	3 (0.7)
Other clinically significant laboratory value	2 (0.6)	0	2 (0.4)
Sponsor's decision	1 (0.3)	0	1 (0.2)

* Adverse events listed are those that most frequently led to discontinuation.
† The reasons for death were cardiac arrest and hypoxic brain injury; septic shock; and acute myocardial infarction.
BID = twice daily; QD = once daily.

pleted the Open-Label Therapy Phase (the difference in completion rates between the two treatment groups was not significant; $P = 0.823$). The most commonly cited reason for discontinuation was adverse event (21.8%) (Table 2). The treatment groups did not differ significantly with respect to the reasons for discontinuation ($P \geq 0.149$). The adverse events most frequently associated with discontinuation in all patients were nausea (3.1%), dizziness (1.8%), vomiting (1.8%), fatigue (1.1%), and somnolence (1.1%). A greater number of adverse events resulting in discontinuation occurred during the initial 7 weeks of the Open-Label Therapy Phase (72 events during Weeks 0–7) than in the remaining 20 weeks (25 events during Weeks 7–27). Three patients, all in the duloxetine 60 mg BID group, died during the Open-Label Therapy Phase. The causes of death were cardiac arrest and hypoxic brain injury; septic shock; and acute myocardial infarction; none of the deaths was considered to be related to duloxetine by either the principal investigator or sponsor. The percentage of patients who discontinued because of lack of efficacy was not significantly different between the duloxetine 60 mg BID group (N = 9 [2.7%]) and the duloxetine 120 mg QD group (N = 1 [0.9%]) ($P = 0.464$).

TEAEs

At least one TEAE was reported by 96.1% of patients receiving 60 mg BID and 92.2% receiving 120 mg QD during the Open-Label Therapy Phase. The incidence of TEAEs was similar in the two treatment groups ($P = 0.129$). TEAEs for which the incidence was ≥5% are summarized for the titration and full-dose weeks of the Open-Label Therapy Phase (Weeks 1–27) and for the taper week (Week 28) in Table 3. TEAEs that were reported by 10% or more of the patients were nausea (41.0%), somnolence (34.3%), dizziness (18.7%), headache (14.7%), dry mouth (14.5%), increased sweating (13.4%), vomiting (13.1%), constipation (11.4%), insomnia (10.2%), and diarrhea (10.0%). Most TEAEs were of mild to moderate severity.

Adverse events during the taper week (discontinuation-emergent adverse events) were reported by 11.6% of patients in the 60 mg BID group and 16.2% in the duloxetine 120 mg QD group. The most frequently reported discontinuation-emergent adverse event was headache, reported in 1.4% of all patients who entered the taper week.

Serious Adverse Events

Serious adverse events were reported by 7.5% of patients in the duloxetine 60 mg BID group and by 8.7% of the patients in the duloxetine 120 mg QD group. The investigator considered most of these events to be unrelated to duloxetine exposure. About half of these patients discontinued the study as a result of the serious adverse event. Serious adverse events reported by two or more patients are presented in Table 4.

Cardiovascular Profile

There were no significant changes from baseline to endpoint in the mean values for sitting systolic blood pressure in either treatment group or for sitting diastolic blood pressure in the duloxetine 60 mg BID group. There was a small, but statistically significant, decrease from baseline in the value

Table 3 Treatment-emergent adverse events occurring in ≥5% of patients during Open-Label Therapy Phase

	Full-Dose Therapy Period* (Weeks 1–27) Duloxetine		Taper Week (Week 28) Duloxetine	
Adverse Event	60 mg BID (N = 334) N (%)	120 mg QD (N = 115) N (%)	60 mg BID (N = 215) N (%)	120 mg QD (N = 74) N (%)
Nausea	135 (40.4)	49 (42.6)	1 (0.5)	1 (1.4)
Somnolence	112 (33.5)	42 (36.5)	0	0
Dizziness	65 (19.5)	19 (16.5)	3 (1.4)	0
Headache	52 (15.6)	14 (12.2)	1 (0.5)	3 (4.1)
Dry mouth	49 (14.7)	16 (13.9)	1 (0.5)	0
Sweating increased	44 (13.2)	16 (13.9)	0	0
Vomiting	40 (12.0)	19 (16.5)	1 (0.5)	0
Constipation	41 (12.3)	10 (8.7)	1 (0.5)	0
Insomnia	37 (11.1)	9 (7.8)	1 (0.5)	0
Diarrhea	32 (9.6)	13 (11.3)	1 (0.5)	0
Asthenia	36 (10.8)	7 (6.1)	1 (0.5)	0
Decreased appetite	30 (9.0)	12 (10.4)	0	0
Anorexia	32 (9.6)	9 (7.8)	0	0
Fatigue	28 (8.4)	13 (11.3)	2 (0.9)	1 (1.4)
Pruritus	16 (4.8)	7 (6.1)	0	0

* Week 1 (titration week) and Weeks 2–27 (full-dose therapy period).
BID = twice daily; QD = once daily.

for sitting diastolic blood pressure in the duloxetine 120 mg QD group (mean ± SD: −2.05 ± 9.99 mm Hg, $P = 0.04$), and a small, but statistically significant, increase in the heart rate in the duloxetine 60 mg BID (mean ± SD: +4.98 ± 11.26 bpm, $P < 0.001$) and 120 mg QD (mean ± SD: +2.46 ± 10.17 bpm, $P = 0.020$) groups.

A total of 18 (5.5%) patients in the duloxetine 60 mg BID group and six (5.4%) in the duloxetine 120 mg QD group met the criteria for sustained elevations in blood pressure. One (0.2%) patient (duloxetine 60 mg BID) discontinued the study because of hypertension.

Comparison of ECGs taken at screening and endpoint revealed significant decreases from baseline in the mean PR intervals in the duloxetine 60 mg BID (mean ± SD: −4.73 ± 14.46 ms, $P < 0.001$) and 120 mg QD (mean ± SD: −4.33 ± 14.26 ms, $P = 0.003$) groups, and decreases in the mean QT interval in the duloxetine 60 mg BID (mean ± SD: −10.10 ± 22.70 ms, $P < 0.001$) and 120 mg QD (mean ± SD: −10.34 ± 27.62 ms, $P < 0.001$) groups. There was also a significant decrease from baseline in the mean value for QT interval corrected for heart rate (Fridericia) (QTcF) in the duloxetine 60 mg BID group (mean ± SD: −2.33 ± 17.71 ms, $P = 0.023$). There was no significant prolongation of the QT interval corrected for heart rate using Bazett's formula (QTcB) in either treatment group.

Laboratory Analyses

The incidence of treatment-emergent blood chemistry abnormalities was low, except for fasting glucose levels. Elevated glucose values were observed at some point during the study in 16.5%

Table 4 Serious adverse events reported by two or more patients

	Duloxetine		
Serious Adverse Event	60 mg BID (N = 334) N (%)	120 mg QD (N = 115) N (%)	Total (N = 449) N (%)
Skin ulcer	3 (0.9)	0	3 (0.7)
Acute myocardial infarction	2 (0.6)	0	2 (0.4)
Cardiac failure congestive	1 (0.3)	1 (0.9)	2 (0.4)
Diabetes mellitus inadequate control	1 (0.3)	1 (0.9)	2 (0.4)
Myocardial ischemia	0	2 (1.7)	2 (0.4)
Orthostatic hypotension	1 (0.3)	1 (0.9)	2 (0.4)
Vomiting	1 (0.3)	1 (0.9)	2 (0.4)

BID = twice daily; QD = once daily.

Table 5 Mean (±standard deviation) change from baseline to endpoint in laboratory values for patients treated with duloxetine 60 mg BID or duloxetine 120 mg QD

	Duloxetine (60 mg BID)				Duloxetine (120 mg QD)			
	N	Baseline	Endpoint	Change	N	Baseline	Endpoint	Change
Alkaline phosphatase (U/L)	321	83.16 ± 29.49	89.86 ± 33.51	6.70 ± 23.50†	110	81.45 ± 31.09	88.72 ± 38.60	7.26 ± 26.18†
ALT/SGPT (U/L)	320	23.61 ± 12.44	28.18 ± 38.03	4.57 ± 37.47	109	24.37 ± 17.32	26.89 ± 23.62	2.52 ± 20.69
AST/SGOT (U/L)	318	20.67 ± 8.00	22.76 ± 15.90	2.09 ± 14.93	109	21.36 ± 11.48	22.65 ± 14.66	1.29 ± 12.38
Total bilirubin (μmol/L)	320	8.20 ± 4.68	7.92 ± 4.41	–0.28 ± 3.21	109	8.05 ± 3.73	7.80 ± 3.76	–0.24 ± 2.68
Cholesterol (mmol/L)	321	5.00 ± 1.09	5.19 ± 1.21	0.19 ± 0.83†	110	5.01 ± 1.25	5.30 ± 1.34	0.29 ± 1.22†
GGT (U/L)	321	34.37 ± 40.08	40.50 ± 63.84	6.13 ± 47.54*	110	32.61 ± 23.68	40.52 ± 79.64	7.91 ± 77.32
Glucose (mmol/L)	320	9.54 ± 3.84	10.73 ± 4.28	1.18 ± 4.51†	109	10.10 ± 4.27	10.42 ± 4.57	0.33 ± 5.23
HDL cholesterol (mmol/L)	294	1.18 ± 0.31	1.21 ± 0.32	0.03 ± 0.19*	99	1.18 ± 0.33	1.21 ± 0.35	0.03 ± 0.21
Hemoglobin A_{1C}	296	0.082 ± 0.015	0.083 ± 0.017	0.002 ± 0.012*	105	0.081 ± 0.16	0.083 ± 0.018	0.002 ± 0.012
LDL cholesterol (mmol/L)	269	2.82 ± 0.96	2.98 ± 1.02	0.16 ± 0.67†	87	2.70 ± 0.80	2.87 ± 0.86	0.16 ± 0.75*
Triglycerides (mmol/L)	298	2.19 ± 1.34	2.23 ± 1.40	0.04 ± 1.15	104	2.73 ± 4.41	2.70 ± 2.48	–0.03 ± 3.28

* Significant change from baseline to endpoint; $P \leq 0.05$ (Wilcoxon signed-rank test).
† Significant change from baseline to endpoint; $P \leq 0.001$ (Wilcoxon signed-rank test).
ALT/SGPT = alanine transaminase/serum glutamate pyruvate transaminase; AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase; BID = twice daily; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; QD = once daily.

of patients in the 60 mg BID and 24.7% of patients in the 120 mg QD groups. Both treatment groups experienced a statistically significant mean increase in alkaline phosphatase, and the duloxetine 60 mg BID group experienced a statistically significant increase in gamma-glutamyl transferase. In both groups, there were sporadic treatment-emergent abnormalities in AST, ALT, alkaline phosphatase, and gamma-glutamyl transferase. These changes were transient and generally of low magnitude. In three cases, transaminase increases were associated with increases in bilirubin. One patient experienced epigastric pain and nausea after 19 weeks of treatment with duloxetine 60 mg BID, and her hepatic enzymes were found to be elevated 2 days later. Duloxetine treatment was discontinued, and ALT and total bilirubin levels had returned to normal limits within 2 weeks after discontinuation. The elevations in hepatic enzymes in this patient may have been related to a residual common bile duct calculus, later confirmed by surgery. A second patient had elevated hepatic enzymes related to congestive heart failure and cardiac arrest, both of which were judged to be unrelated to study drug. In the third patient, who was on pioglitazone and had been diagnosed with hepatitis B, ALT decreased from 40 U/L at baseline to 38 U/L at study completion. Bilirubin, which was 20 μmol/L at baseline, remained under 20 μmol/L until study completion when it increased to 22 μmol/L. This patient completed the study without serious sequelae.

Statistically significant, but numerically and clinically insignificant, within-group mean changes from baseline to last observation were observed in high-density lipoprotein cholesterol in the duloxetine 60 mg BID group (mean: +0.03 mmol/L, $P \leq 0.05$) and in low-density lipoprotein cholesterol in the 60 mg BID group (mean: +0.16 mmol/L, $P \leq 0.001$) and in the 120 mg QD group (mean: +0.16 mmol/L, $P \leq 0.05$) (Table 5).

Significant Hypoglycemic Episodes

Significant hypoglycemic episodes were reported for two (0.6%) patients in the duloxetine 60 mg BID group and none in the 120 mg QD group during the week prior to the Week 0 visit and for 14 (4.2%) patients in the duloxetine 60 mg BID group and six (5.2%) in the 120 mg QD group during the first week of treatment. Thereafter, the numbers of significant hypoglycemic episodes reported between study visits ranged from one to five in the duloxetine 60 mg BID group and none to one in the 120 mg QD group. These episodes did not follow any temporal pattern. Five incidents of low blood glucose (glucose <50 mg/dL) were reported, three (1.2%) in the duloxetine 60 mg BID group at Week 19, and two (2.6%) in the duloxetine 120 mg QD group at Week 27. A statistically significant ($P = 0.009$), but clinically insignificant (increase of less than 0.01), within-group mean change from baseline to last observation was observed in HbA_{1c} in the duloxetine 60 mg BID group.

Body Weight

Mean body weights decreased significantly from baseline to endpoint in both the duloxetine 60 mg BID (mean ± SD: –0.51 ± 3.28 kg, $P < 0.001$) and 120 mg QD (mean ± SD: –0.62 ± 4.1 kg, $P = 0.023$) groups.

Efficacy

Both treatment groups showed improvement from baseline to endpoint on all subscales of the BPI and on the CGI-S ($P < 0.001$ for both). Within each treatment group, the mean scores for each aspect of the BPI at the endpoint were significantly less than at baseline, reflecting significant improvement in all aspects of pain severity and decreased interference of function as a result of pain. The mean changes from baseline to endpoint in average pain and average interference of pain with function are shown in Figure 2. Similarly, the scores for the CGIs of pain severity improved during treatment as indicated by mean decreases from baseline to endpoint in the mean CGI-S measures in both treatment groups ($P < 0.001$ for both groups) (Figure 2).

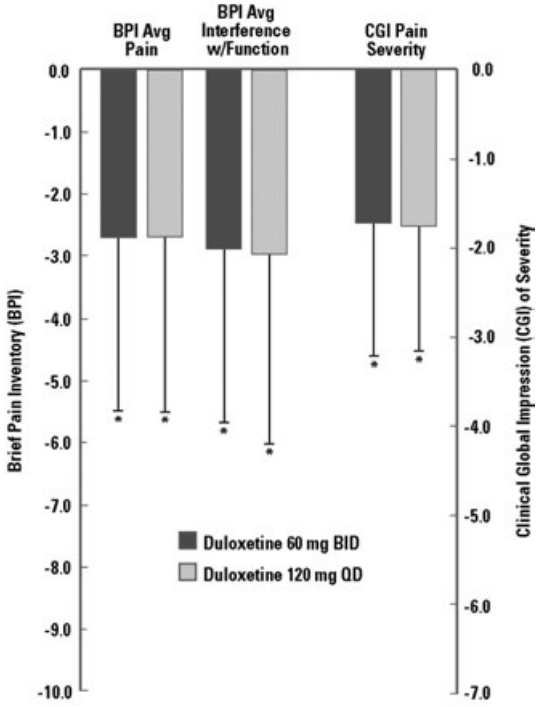

Figure 2 Mean (standard deviation) change from baseline to endpoint in scores for the Brief Pain Inventory and Clinical Global Impression of Severity in patients treated with duloxetine 60 mg twice daily (BID) or duloxetine 120 mg once daily (QD) for 28 weeks. Pain severity was rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine); interference of pain on function was rated on a scale of 0 (does not interfere) to 10 (completely interferes); and severity of diabetic peripheral neuropathic pain was rated on a scale of 1 (normal) to 7 (most severe illness). *Significant change from baseline to endpoint ($P < 0.001$, Student's *t*-test).

Discussion

Duloxetine at doses of 60 mg BID and 120 mg QD was safely administered and well tolerated in this open-label, 28-week study in patients with DPNP. Most TEAEs were of mild to moderate severity. The TEAEs most commonly reported by the patients in this study were nausea, somnolence, and dizziness. The incidence of TEAEs was similar in the two treatment groups. The number of adverse events that led to discontinuation was greater in the initial 7 weeks of the study than in the remaining 20 weeks, suggesting that such events were most common during the first weeks of treatment and decreased over time.

The types of TEAEs reported in this study were consistent with those observed in the double-blind, placebo-controlled studies of duloxetine in patients with DPNP [22,23] and in patients with major depressive disorder [17–19,21,34]. In our study, however, the incidence of some of these events and the rates of discontinuation were higher than those reported in the previous studies. Several factors likely contribute to this difference. Our study, which was 6 months in duration, was considerably longer than previous studies in depression, which were 8–9 weeks in duration [17–19,21] and previous studies in DPNP, which were 12 weeks in duration [22,23]. Also, in our study, the dose was titrated to 120 mg after 1 week; perhaps a slower titration would have increased tolerability. In addition, the patients in this study were older than those in the studies in patients with major depression. The mean age of the patients in this study was nearly 60 years, whereas the mean age of the patients in the depression studies was approximately 41 years [17–19,21]. All of the patients in our study had a significant medical illness (diabetes) for which all but one were receiving medication treatment. Diabetes placed these patients at increased risk of serious complications, including nephropathy and coronary and peripheral arterial disease. Also, the high percentages of patients with comorbid conditions (96%) and patients receiving concomitant medical treatments may have been a factor in the higher rate of adverse events and discontinuation. Additionally, it is possible that psychiatrists and depressed

patients are more familiar with and tolerant of the adverse events caused by serotonergic and noradrenergic agents than patients with diabetes and their physicians. In addition, it has been our experience that the incidence of adverse events tends to be higher in open-label, uncontrolled studies [20,35]. Sexual dysfunction, which is a concern in patients with diabetes and patients taking antidepressants, was not specifically assessed in this study because of its open-label design; however, sexual side effects were reported by fewer than 5% of the patients in this study and were not a reported as reason for discontinuation.

The lower rate of discontinuation due to adverse events in the 60 mg BID arm (20.1%) relative to the 120 mg QD arm (27.0%) suggests that the 60 mg BID regimen may have been better tolerated. Many studies in which the incidences of TEAEs and discontinuation rates were lower than in our study used smaller doses than in our study [17,18,21–23]. In addition, unlike in our study, other studies escalated doses gradually in a titration regimen [19] or had a provision for patients to lower their dose temporarily if necessary [17,18]. It is important to note that the total daily duloxetine dose of 120 mg/day in this study is the highest duloxetine dose studied in duloxetine efficacy clinical trials and is twice the duloxetine 60 mg/day dose, the usual dose for DPNP. As a consequence, the safety and tolerability profile of duloxetine 120 mg/day observed in this study implies that duloxetine 60 mg/day would be at least as safe and even better tolerated.

Mean increases in blood pressure were noted in this study; however, these changes were not considered clinically significant. In this long-term study, 5.5% of patients in the duloxetine 60 mg BID group and 5.4% in the duloxetine 120 mg QD group met the criteria for sustained elevation in blood pressure. Several factors unrelated to duloxetine treatment may account for these rates, which were higher than those observed in the analysis by Nemeroff et al. [34] of seven 8- to 14-week studies of duloxetine. As noted above, this study was longer than previous studies, and the patients were older and may have been more medically unstable. Also, at study entry, 5.3% of the patients in this study were known to have diabetic nephropathy, which would have predisposed them to elevated blood pressure, and most (62.6%) had hypertension as a secondary condition. As diabetes is an important risk factor for hypertension, it is possible that the increases in blood pressure seen in this study were a complication associated with the natural course of the disease. Most importantly, the blood pressure limits considered to be indicative of elevated blood pressure were set lower in this trial than in trials of duloxetine in depression [17–20,34] or trials of venlafaxine [36] as individuals with diabetes have greater risk associated with smaller elevations in blood pressure [26]. The sustained elevations in blood pressure observed in this study were generally not perceived to be clinically relevant as only one (0.2%) patient (duloxetine 60 mg BID) discontinued the study because of hypertension.

Consistent with the inhibition of NE uptake associated with duloxetine, a small increase in mean heart rate was observed in both treatment groups. Duloxetine treatment was not associated with any significant QTc prolongation. The absence of significant cardiovascular changes due to duloxetine therapy in the patients in this study suggests that patients with diabetes mellitus do not require more intensive assessment of their cardiovascular status when treated with duloxetine than they require for their underlying diabetes. Duloxetine's favorable cardiac safety profile is a strong attribute. Other antidepressants, especially the TCAs, may have deleterious effects on patients with compromised heart function, including precipitation or worsening of cardiac arrhythmias, angina, or heart failure [37,38], that may limit the use of these agents in some patients.

Duloxetine did not appear to adversely affect glycemic control or lipid profiles. Although patients showed changes in chemistry, HbA_{1c}, and lipid profile laboratory assessments, these changes were of low magnitude and were not considered clinically relevant. In three cases, transaminase increases were associated with increases in bilirubin. In two of these cases, the increases were associated with comorbid conditions unrelated to treatment, and in the third, the patient experienced no serious untoward sequelae. Because of the presence of confounding variables, the etiology of these increases cannot be determined with certainty, and duloxetine cannot be excluded as a contributing factor.

In this study, mean body weights decreased significantly from baseline to endpoint in both treatment groups. In a pooled analysis of studies of up to 12 weeks of treatment with duloxetine, patients experienced a mean weight loss of 0.54 kg [34], a change that was significantly different from that in placebo-treated patients who gained an average of 0.25 kg (0.56 lb). In the acute phase of a study in depressed patients by Detke et al. [39], the mean

changes in weight in the duloxetine group did not differ significantly from that in the placebo group. In a 1-year study of duloxetine in major depressive disorder, patients experienced a mean weight increase of 2.4 kg (5.3 lb) (mean change was 1.1 kg [2.4 lb] based on a LOCF analysis) [20]. The findings from our study suggest that long-term treatment with duloxetine has little effect on body weight in patients with DPNP. The effect of treatment on body weight is an important consideration, especially in patients with diabetes, as weight gain is a risk factor for poor glycemic control. However, these results may be confounded by the fact that weight gain is associated with a number of medications frequently prescribed to patients with diabetes, including rosiglitazone [40,41], pioglitazone [40], and insulin [42].

The recommended duloxetine dose for the management of DPNP is 60 mg QD. The duloxetine dose of 120 mg/d has also been demonstrated to be safe and effective, although less well tolerated than 60 mg QD. The twice-daily 60-mg dosage regimen has been shown in earlier studies in DPNP to be slightly, although not statistically significantly, more efficacious than the once-daily dose, particularly with respect to functional measures [22,23]. Two dosing regimens, 60 mg BID and 120 mg QD, were evaluated in this study to assess the safety and tolerability of this higher dosage and whether there is a difference in safety between the two regimens. In addition, we evaluated the higher dosage to provide further information on the safety margin of the 60 mg QD dose used to treat most patients.

Other agents have also demonstrated efficacy in the treatment of patients with DPNP. The safety profiles of these other agents vary widely depending on the doses administered, the duration of exposure, and the age and health of the patient population. The TCAs are used as first-line treatment for neuropathic pain [43,44]. The rates of discontinuations due to adverse events in studies of TCAs have been generally less than in our study [45–48]. However, the risk of adverse cardiovascular events associated with TCAs is a serious concern, especially in older patients [44,49]. The anticonvulsant gabapentin has also been shown to be effective in patients with DPNP, with rates of withdrawal due to adverse events lower than those seen with TCAs [30]. In studies of TCAs and gabapentin, the patients have been younger and the treatment duration shorter than in our study, precluding comparisons across studies. Also, the doses studied were not higher than the recommended dose, as in our study. In one open-label parallel study comparing amitriptyline and gabapentin in DPNP, the mean age of the 25 patients enrolled was 71 years, and the patients were treated for 12 weeks [50]. In this study in older patients, side effects prevented escalation to an effective dose (or attainment of the maximum allowed dose in the absence of efficacy in one patient) in 33% of the patients treated with amitriptyline and in 23% of those treated with gabapentin; this is in sharp contrast to the higher than recommended doses of duloxetine used in our trial. Additional study in older patient populations is needed to determine the relative long-term tolerability of the different treatments currently used for DPNP.

In our open-label, uncontrolled trial, both duloxetine 60 mg BID and duloxetine 120 mg QD showed significant improvement from baseline to endpoint on all subscales of the BPI and on the CGI-S, reflecting improvement in all aspects of pain severity and interference of pain with function. Although patients with DPNP are often treated with TCAs or anticonvulsant medications [51–53], duloxetine has been approved by some regulatory agencies for the management of DPNP; thus, these findings are important to patients with DPNP and those caring for them.

As with any open-label, uncontrolled study, these results must be interpreted appropriately. The lack of blinding may have influenced the evaluation of adverse events and efficacy by both the investigator and patients. Also, as there was neither a placebo nor an active treatment control for comparison, evaluations of safety and efficacy endpoints obtained after treatment with duloxetine were limited to comparisons with baseline. This study also utilized doses that are twice the recommended therapeutic dose for DPNP. At the time the study was conducted, the recommended dose for DPNP, ultimately determined to be 60 mg daily, was not known. The study used the 120 mg daily dose, but not the 60 mg daily dose, because it was believed that if a 120 mg dose was well tolerated, a dose of 60 mg would be well tolerated as well.

Conclusions

The findings of this 28-week, open-label study, together with the results of the two previous placebo-controlled, 12-week studies in patients with DPNP, support the view that treatment with duloxetine at either 60 mg BID or 120 mg QD is

well tolerated and efficacious for the management of DPNP. There were few differences in safety between the two dosages.

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