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Duloxetine in the Long-Term Management of Diabetic Peripheral Neuropathic Pain: An Open-Label, 52-Week Extension of a Randomized Controlled Clinical Trial

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ABSTRACT

Background: Duloxetine hydrochloride, a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor, is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition and is the first US Food and Drug Administration-approved prescription drug for the management of diabetic peripheral neuropathic pain (DPNP).

Objectives: The aim of this study was to determine whether management of DPNP with duloxetine interferes with the treatment of diabetes. It also examined the tolerability of long-term exposure to duloxetine with regard to the progression of diabetic complications, and assessed the impact of DPNP management with duloxetine versus routine care.

Methods: This was a 52-week, multicenter, re-randomized, open-label extension of a parallel, double-blind, randomized, placebo-controlled, acute (12-week) study. Patients who completed the duloxetine or placebo acute treatment period were randomly reassigned in a 2:1 ratio to treatment with duloxetine 60 mg BID or routine care for an additional 52 weeks. The study included male and female outpatients aged ≥18 years with a diagnosis of DPNP caused by type 1 or type 2 diabetes. Over the course of the 52-week study, visits were scheduled on the following weeks (of the extension phase of the study): 1 (via phone only), 2, 4, 8, 12, 20, 28, 40, and 52. Tolerability was assessed by review and analyses of discontinuation rates, adverse events (AEs), laboratory data, vital signs, electrocardiographic results, concomitant medications, and diabetic complications. Treatment-emergent AEs (TEAEs) were defined as AEs that appeared during therapy (were not present at baseline) or were exacerbated during treatment. Data on AEs and concomitant medications were collected at every visit. Data on blood pressure, heart rate, and significant hypoglycemic

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events were collected at every visit starting from week 2. Fasting clinical chemistry and electrolyte group laboratory assessments were done at every visit, starting from week 4. Electrocardiographic data was collected at weeks 4 and 52, and glycosylated hemoglobin and lipid profile data were collected at weeks 20 and 52. Hematology and urinalysis laboratory assessments and diabetic complication assessments were done at week 52. All safety data was assessed in cases of early discontinuation. Treatment differences on quality of life (QOL) were compared using the Short Form-36 Health Status Survey (SF-36) and the EQ-5D instrument of the European Health-Related Quality of Life Measures. This was assessed at the last visit or at early discontinuation.

Results: The open-label extension-phase study included 337 patients (duloxetine, n = 222; routine care, n = 115). For the duloxetine group, mean age was 60.2 years, 61.3% were male, and 78.4% were white. For the routine-care group, mean age was 58.9 years, 60.0% were male, and 74.8% were white. Mean weight was 95.3 kg for both groups. None of the TEAEs occurred significantly more often in the duloxetine-treated group than in the routine-care–treated group. No TEAEs were reported by >10% of patients in the duloxetine group. The TEAEs reported by >10% of patients in the routine-care group included dizziness (11.3%), somnolence (13.0%), headache (10.4%), and vomiting (10.4%). No significant differences were found between treatment groups in the occurrence of serious AEs or in the number of patients discontinuing because of AEs. Duloxetine was significantly better than routine care on the bodily pain subscale of the SF-36 (mean change: 1.5 vs –4.1; $P = 0.021$) and on the EQ-5D (mean change: –0.00 vs –0.09; $P = 0.001$).

Conclusions: Over 52 weeks of follow-up, treatment of these diabetic patients with duloxetine for peripheral neuropathic pain was associated with outcomes similar to, or significantly better than, that of routine care on most measures of tolerability, diabetic complications, and QOL. (*Curr Ther Res Clin Exp.* 2006;67: 283–304) Copyright © 2006 Excerpta Medica, Inc.

Key words: duloxetine, diabetic peripheral neuropathic pain, antidepressant, pain, serotonin, norepinephrine.

INTRODUCTION

Diabetes affects ~7% (20.8 million) of the population in the United States.[1] Diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes that affects 10% to 20% of diabetes patients.[2,3] The pain has often been described as an "aching, burning, stabbing, or tingling" sensation.[4] Although the pathophysiology of diabetic neuropathy is not fully understood, suboptimal glycemic control appears to be a major contributor to diabetic neuropathy.[5] This disease is difficult to treat, although it is possible to delay the progression of diabetic neuropathy by optimizing glycemic control.[6]

Several medications have been used for treating DPNP, including tricyclic antidepressants (eg, amitriptyline,[7] imipramine,[8] and desipramine[9]), certain anti-

convulsants (eg, gabapentin[10]), and opioid analgesics (eg, tramadol,[11] controlled-release oxycodones[12]). However, these drugs are often limited by their anticholinergic, α-adrenergic blocking, and central nervous system adverse events (AEs). Recently published data support the use of venlafaxine, pregabalin, and duloxetine in the acute treatment of DPNP.[13–15]

Other evidence suggests that endogenous inhibitory mechanisms of pain might be dysfunctional in pathologic pain states such as DPNP.[16] Serotonin (5-HT) and norepinephrine (NE) have been implicated in mediating endogenous analgesic mechanisms via the descending inhibitory pain pathways in the brain and spinal cord.[17–20]

Duloxetine hydrochloride, a dual reuptake inhibitor of 5-HT and NE, was first approved in August 2004 by the US Food and Drug Administration for the treatment of major depressive disorder (MDD), and subsequently for treatment of DPNP in September 2004.[21] Duloxetine lacks significant affinity (K_i) for muscarinic (K_i = 3000 nM), histamine$_1$ (K_i = 2300 nM), α_1-adrenergic (K_i = 8300 nM), α_2-adrenergic (K_i = 8600 nM), dopamine$_2$ (K_i = 14000 nM), 5-HT$_{1A}$ (K_i > 5000 nM), 5-HT$_{1B}$ (K_i [SD] = 3959 [810] nM), 5-HT$_{1D}$ (K_i > 3000 nM), 5-HT$_{2A}$ (K_i [SD] = 504 [87] nM), 5-HT$_{2C}$ (K_i [SD] = 916 [190] nM), and opioid receptors (K_i > 1000 nM); it also has weak affinity for the dopamine transporter (K_i [SD] = 240 [23] nM).[22]

The efficacy and tolerability of duloxetine in the short-term (12-week) management of DPNP were reported in the acute phase of the present study.[15] In that double-blind, randomized, placebo-controlled trial, treatment with duloxetine was well tolerated and significantly different from placebo on the primary and nearly all secondary efficacy measures (including 24-hour average pain severity, 24-hour worst pain score, night pain score, Brief Pain Inventory [BPI] average pain severity, BPI interference [average of 7 interference questions], BPI worst pain severity, BPI least pain severity, BPI severity pain right now, Clinical Global Impression of Severity, Patient's Global Impression of Improvement, and Short-Form McGill total score), including health-related outcomes.[15] Patients treated with duloxetine 60 mg QD and 60 mg BID had significantly greater improvement compared with placebo on the 24-hour average pain score, beginning 1 week after randomization and continuing through the 12-week trial. Efficacy was similar for duloxetine 60 mg QD and 60 mg BID in this trial (on most outcome measures), but duloxetine 60 mg QD was associated with fewer discontinuations due to AEs (duloxetine 60 mg QD = 13.2%; duloxetine 60 mg BID = 19.5%). Given the observed efficacy and tolerability in the acute management of DPNP, the present open-label study phase was conducted to assess the tolerability and health outcomes of duloxetine versus routine care in the long-term management of DPNP.

The aim of this study was to examine whether management of DPNP with duloxetine interferes with the treatment of diabetes. It also examined the tolerability of up to 52 weeks of exposure to duloxetine with regard to the progression of diabetic complications, and assessed the impact of DPNP management, with duloxetine versus routine care, on patient-reported outcomes associated with quality of life (QOL).

METHODS

Study Design

This 52-week, multicenter (23 study centers), randomized, open-label trial was an extension of a 12-week (acute phase) randomized, controlled, clinical trial consisting of patients with DPNP. In the acute phase of the study,[15] patients were randomly assigned to treatment with duloxetine 20 mg QD, 60 mg QD, 60 mg BID, or placebo. After completion of the acute phase, patients were recruited to participate in the extension phase and were randomly reassigned (2:1) to duloxetine 60 mg BID or routine care.

Study Cohort

To be enrolled in the acute phase, patients were required to experience pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus and to be ≥18 years of age. Pain had to initiate in the feet, with relatively symmetric onset. Daily pain must have been present for a minimum of 6 months. The diagnosis was confirmed by a score of ≥3 on the physical examination portion of the Michigan Neuropathy Screening Instrument (MNSI).[23] The primary efficacy measure for the acute phase of the study was the reduction in weekly mean of the 24-hour mean pain severity scores (computed from diary scores between 2 site visits), as measured by an 11-point Likert scale (0 = no pain to 10 = worst possible pain) completed daily by the patients in the diary. A reduction of ~2 points or ~30% in the pain-intensity numeric rating scale represented a clinically important difference.[24]

Patients were blinded to treatment in the acute phase. Other than receiving medications and medical care free of charge, patients were not compensated for participation in this trial.

Patients were excluded from the acute phase of the study if, over the past year, they met criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[25] for a diagnosis of Axis I depression, MDD, depression–partial remission, dysthymic disorder, generalized anxiety disorder, or alcohol or eating disorders as determined by response to the Mini International Neuropsychiatric Interview (MINI). Patients were also excluded if they reported, via the MINI, any current or past *DSM-IV* diagnosis of mania, bipolar disorder, or psychosis. Patients were excluded if they had pain that might not be clearly differentiated from DPNP or conditions that interfered with the assessment of DPNP.

The ethics committee at each site approved the entire study protocol in accordance with the principles of the Declaration of Helsinki.[26] Patients provided written informed consent before participation in any study-related procedures. Patients' consent was obtained before the acute phase and covered the extension phase of the study.

Treatments

Patients were randomly assigned to open-label treatment and received either duloxetine 60 mg BID (escalated from 40 mg BID in 3 days) or routine care. The

routine-care group was treated with therapies that the investigator and the patient believed would provide optimal benefit for the patient. The duloxetine group was allowed all treatments offered to the routine-care group with the exception of antidepressants, anticonvulsants, and antipsychotics. During the extension phase, patients in both arms were permitted to use rescue analgesics including paracetamol, NSAIDs, or opioid analgesics. Over the course of the 52-week study, visits were scheduled on the following weeks: 1 (via phone only), 2, 4, 8, 12, 20, 28, 40, and 52.

General Safety

Tolerability measures recorded at every office visit included spontaneously reported AEs, concomitant medications, vital signs, and the occurrence of significant hypoglycemic events. Patients were queried at every office visit about significant hypoglycemic events with the use of a specific questionnaire. A significant hypoglycemic event was any episode that required intervention with glucose, glucagon, food, drink, or assistance. Solicited hypoglycemic events were not entered as AEs, but were analyzed and reported separately. Data on AEs and concomitant medications were collected at every visit. Data on blood pressure, heart rate, and significant hypoglycemic events were collected at every visit starting from week 2. Fasting clinical chemistry and electrolyte group laboratory assessments were done at every visit, starting from week 4. Electrocardiographic data was collected at weeks 4 and 52, glycosylated hemoglobin (HbA_{1c} and lipid profile data were collected at weeks 20 and 52. Hematology and urinalysis laboratory assessments and diabetic complication assessments were done at week 52. All safety data was assessed in cases of early discontinuation. Mean change and the percentage of abnormal results were considered, and the magnitude of these mean changes was not considered to be of clinical significance.

Diabetic Complications

Diabetic complications were measured using the physical examination portion of the MNSI[23] (neuropathy progression), microalbumin/creatinine ratio (nephropathy progression, defined as a significant change [$P < 0.05$] in the microalbumin/creatinine ratio from baseline to end point), and ophthalmologic examination with fundus photographs (retinopathy progression). Diabetic complication assessments were done at week 52. The ophthalmologic examination assessed 4 categories of events: worsening of visual acuity, need for surgical procedures, panretinal photocoagulation, or vitrectomy. If the patient required macular laser surgery, panretinal photocoagulation, or vitrectomy, the retinopathy was judged as having progressed. If the patient did not require surgery during the trial, changes from baseline in 3-field fundus photographs were rated in terms of severity by an ophthalmologist masked to the treatment.

Vital Signs

Sitting heart rate and blood pressure were recorded at every office visit. A patient was considered to have a sustained elevation in blood pressure after random-

ization if he or she met the following criteria: sitting diastolic blood pressure ≥85 mm Hg and an increase from baseline of 10 mm Hg for 3 consecutive visits, or sitting systolic blood pressure ≥130 mm Hg and an increase from baseline of 10 mm Hg for 3 consecutive visits.

Health Outcomes

The impact of treatment on patient-reported QOL was assessed using the Short Form-36 Health Status Survey (SF-36)[27] and the EQ-5D instrument of the European Health-Related Quality of Life Measures.[28] The SF-36 is a generic instrument for rating patients' self-perceived health-related QOL[27,29] and assesses both the physical and mental dimensions of QOL. The SF-36 questionnaire is a standardized health-status profile that measures 8 categories of health,[30] including physical functioning, limitations in usual role activities due to physical health problems (physical role limit), bodily pain, general health perceptions, vitality, social functions, limitations in usual role activities due to emotional problems (emotional role limit), and mental health. The replies to individual items in each domain were added to derive a score, which was converted, using an algorithm, to a scale from 0 (poor health) to 100 (good health).

The EQ-5D self-report questionnaire is a standardized instrument used as a measure of health-related QOL.[28] Health status is defined in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension includes 3 possible levels of response (1 = "no problems," 2 = "some/moderate problems," or 3 = "extreme problems"). Respondents are asked to choose 1 level that reflects their "own health state today" for each of the 5 dimensions. An overall index measuring QOL is derived from the response to the 5 dimensions.

Statistical Analysis

All analyses were conducted on an intent-to-treat basis. All randomized patients who entered the extension phase were included in the tolerability analyses.

For measurements of diabetic complications, baseline was defined as the last value of the screening period before the acute phase of the trial. Changes from baseline in these measures were assessed using a fixed-effect analysis of variance (ANOVA) model with terms for acute treatment, extension treatment, and interaction between acute treatment and extension treatment. Categoric variables were analyzed using the Cochran-Mantel-Haenszel general association test,[31] stratified for the treatment received in the acute phase.

For all other measurements, baseline was defined as the last available value of the acute phase. Changes from baseline in continuous measures were assessed using a fixed-effect analysis of covariance model with terms for treatment, investigator, and baseline values. Categoric variables were analyzed using the Fisher exact test. Treatment-group differences in laboratory analytes (except fasting glucose) were assessed using an ANOVA model on the rank-transformed data with terms for treatment and investigator.

For all analyses, treatment effects were tested at a 2-sided significance level of 0.05. If the treatment-by-investigator interaction term was significant ($P < 0.10$), the interaction term was left in the model. Throughout this manuscript, the term *significant* indicates statistical significance ($P < 0.05$), and *mean change* refers to the least squares mean change. The least squares means presented in the manuscript are the expected treatment-group means when the outcome of interest is adjusted for the association between the outcome of interest and the dependent variables included in the ANOVA model.[32]

Statistical analysis was conducted using SAS software, version 8.0 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Baseline Characteristics

Three hundred thirty-seven (73.7%) of the 457 patients who were enrolled in the acute phase were also enrolled in the open-label, extension-phase of the study. The duloxetine group consisted of 222 patients, and the routine-care group included the remaining 115 patients (**Figure**). The demographic characteristics and baseline assessments for both treatment groups are presented in **Table I**. The majority of patients in both treatment groups had type 2 diabetes (88.4%, overall). No significant treatment-group differences were observed in baseline characteristics.

Treatment by Phase

Of the 222 patients assigned to receive duloxetine in the extension phase, 165 (74.3%) patients received duloxetine treatment in the acute phase of the study (duloxetine [acute]/duloxetine [extension]), and 57 (25.7%) patients received placebo treatment in the acute phase (placebo [acute]/duloxetine [extension]). Of the 115 patients assigned to receive routine care in the extension phase of the study, 87 (75.7%) patients received duloxetine treatment in the acute phase of the study (duloxetine [acute]/routine care [extension]), and 28 (24.3%) patients received placebo treatment in the acute phase (placebo [acute]/routine care [extension]).

Medication Use

Table II summarizes the concomitant medications used by patients in the duloxetine and routine-care groups. Medications were categorized into therapeutic categories which best described their indication for use. If many patients used a particular class (ie, statins for cholesterol lowering), then all drugs in that class were included under that category (in this case, statins). Drugs used to lower other lipids (eg, triglycerides) were included under the lipid lowering catagory. Patients in the routine-care group used gabapentin (47.8% [55/115]), venlafaxine (22.6% [26/115]), amitriptyline (22.6% [26/115]), and alpha-lipoic acid (10.4% [12/115]) most frequently for pain associated with diabetic neuropathy.

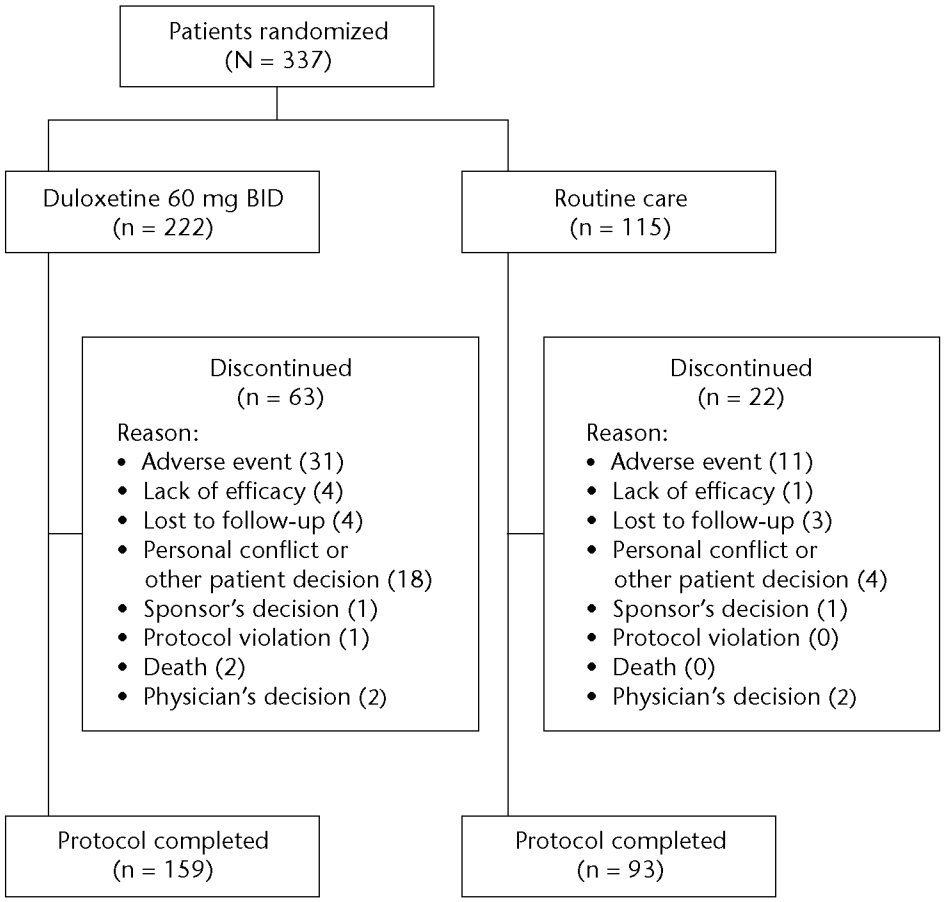

Figure. Flow chart representing study completion and reasons for discontinuation in study patients with diabetic peripheral neuropathic pain (N = 337) randomized (2:1) into 2 treatment groups.

The concomitant medications used by ≥50% of patients in the duloxetine-treated group were oral hypoglycemics (75.2% [167/222]), NSAIDs (64.4% [143/222]), and antihypertensive agents (63.5% [141/222]). Concomitant medications used by ≥50% of patients in the routine-care group were oral hypoglycemics (76.5% [88/115]), NSAIDs (68.7% [79/115]), antihypertensive agents (63.5% [73/115]), and diet supplements (55.7% [64/115]).

Safety Profile

Reasons for Discontinuation

Sixty-three (28.4%) of 222 duloxetine-treated patients and 22 (19.1%) of 115 routine-care–treated patients discontinued treatment. No significant difference

Table I. Demographic characteristics and baseline assessments for study patients with diabetic peripheral neuropathic pain (N = 337).

Variable	Duloxetine (n = 222)	Routine Care (n = 115)
Age, mean (SD), y	60.2 (10.7)	58.9 (11.3)
Sex, no. (%)		
Male	136 (61.3)	69 (60.0)
Female	86 (38.7)	46 (40.0)
Race or origin, no. (%)*		
White	174 (78.4)	86 (74.8)
Hispanic	24 (10.8)	13 (11.3)
Black	16 (7.2)	12 (10.4)
East/Southeast Asian	3 (1.4)	2 (1.7)
Western Asian	4 (1.8)	0
Other	1 (0.5)	2 (1.7)
Height, mean (SD), cm	171.0 (11.1)†	172.3 (10.3)
Weight, mean (SD), kg	95.2 (19.9)	95.4 (23.6)
Type of diabetes mellitus, no. (%)		
Type 1	26 (11.7)	13 (11.3)
Type 2	196 (88.3)	102 (88.7)
Duration of diabetes, mean (SD), y	12.1 (10.3)	10.6 (8.7)
Duration of diabetic neuropathy, mean (SD), y	3.8 (3.8)	3.5 (4.0)
MNSI score, mean (SD)	5.1 (1.5)	5.4 (1.5)
24-Hour average pain score,‡ mean (SD)	5.9 (1.6)	5.9 (1.6)

MNSI = Michigan Neuropathy Screening Instrument.[19]
*Totals may not add to 100% due to rounding.
†n = 221.
‡Measured by an 11-point Likert scale (0 = no pain to 10 = worst possible pain).

was found in overall rates of discontinuation. The total numbers of patients discontinuing by week of treatment during the extension phase of the study (based on treatment in the acute phase) are shown in **Table III**. Rates of discontinuation due to AEs were not significantly different between the duloxetine (14.0% [31/222]) and routine-care (9.6% [11/115]) groups. No significant differences were found between treatment groups with regard to any single reason for discontinuation. The most frequently reported AEs associated with discontinuation for both treatment groups together were myocardial infarction (duloxetine, 0.9% [2/222]; routine care, 2.6% [3/115]) and hypertension (duloxetine, 0.9% [2/222]; routine care, 0.9% [1/115]).

Adverse Events

Of the 337 enrolled patients, 296 (87.8%) reported ≥1 treatment-emergent AEs (TEAEs). Significantly more events of vomiting (duloxetine, 3.2%; routine care, 10.4%;

Table II. Concomitant medications used by >5% of patients in either group with diabetic peripheral neuropathic pain randomly assigned to treatment with duloxetine 60 mg BID or routine care for 52 weeks. Values are expressed as no. (%).

Drug Type	Duloxetine (n = 222)	Routine Care (n = 115)
Oral hypoglycemic	167 (75.2)	88 (76.5)
NSAID	143 (64.4)	79 (68.7)
Antihypertensive	141 (63.5)	73 (63.5)
Insulin	99 (44.6)	47 (40.9)
Diet supplement	97 (43.7)	64 (55.7)
Statin	83 (37.4)	48 (41.7)
Antibiotic	71 (32.0)	48 (41.7)
Diuretic	62 (27.9)	46 (40.0)
Gastrointestinal	44 (19.8)	29 (25.2)
Topical, other	39 (17.6)	13 (11.3)
Antihistamine	33 (14.9)	16 (13.9)
Other	32 (14.4)	23 (20.0)
Lipid-lowering	26 (11.7)	12 (10.4)
Sex steroid	26 (11.7)	13 (11.3)
Cardiac	24 (10.8)	14 (12.2)
Steroid	24 (10.8)	14 (12.2)
Hormone, other	21 (9.5)	6 (5.2)
Antiplatelet	18 (8.1)	7 (6.1)
Opiate	18 (8.1)	14 (2.2)
Muscle relaxant	17 (7.7)	3 (2.6)
Analgesic, topical	15 (6.8)	4 (3.5)
Genitourinary	10 (4.5)	9 (7.8)
Anticoagulant	9 (4.1)	13 (11.3)
Decongestant	7 (3.2)	7 (6.1)
Bronchodilator	7 (3.2)	6 (5.2)
Expectorant	6 (2.7)	11 (9.6)
Antidiarrheal	4 (1.8)	7 (6.1)
SSRI	3 (1.4)	8 (7.0)
Tricyclic antidepressant	1 (0.5)	41 (35.7)
Gabapentin	0	55 (47.8)
SNRI, other	0	43 (37.4)

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

Table III. Total patients (no. [%]) with diabetic peripheral neuropathic pain discontinuing treatment by visit during the 52-week extension phase of the study.

	Treatment Group (Acute-Phase Treatment/Extension-Phase Treatment)											
	Duloxetine/Duloxetine (n = 165)			Duloxetine/Routine Care (n = 87)			Placebo/Duloxetine (n = 57)			Placebo/Routine Care (n = 28)		
Reason for Discontinuation*	Week 4	Week 20	Week 52	Week 4	Week 20	Week 52	Week 4	Week 20	Week 52	Week 4	Week 20	Week 52
AE	4 (2.4)	15 (9.1)	19 (11.5)	2 (2.3)	5 (5.7)	9 (10.3)	5 (8.8)	10 (17.5)	12 (21.1)	1 (3.6)	2 (7.1)	2 (7.1)
Death	0	1 (0.6)	2 (1.2)	0	0	0	0	0	0	0	0	0
Lost to follow-up	0	2 (1.2)	3 (1.8)	0	1 (1.1)	2 (2.3)	0	0	1 (1.8)	1 (3.6)	1 (3.6)	1 (3.6)
Patient's decision	1 (0.6)	6 (3.6)	13 (7.9)	0	1 (1.1)	3 (3.4)	1 (1.8)	2 (3.5)	5 (8.8)	0	1 (3.6)	1 (3.6)
Sponsor's decision	0	1 (0.6)	1 (0.6)	1 (1.1)	1 (1.1)	1 (1.1)	0	0	0	0	0	0
Physician's decision	0	1 (0.6)	1 (0.6)	1 (1.1)	2 (2.3)	2 (2.3)	0	1 (1.8)	1 (1.8)	0	0	0
Lack of efficacy	0	4 (2.4)	4 (2.4)	0	0	1 (1.1)	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0	1 (1.8)	1 (1.8)	0	0	0
Total	5 (3.0)	30 (18.2)	43 (26.1)	4 (4.6)	10 (11.5)	18 (20.7)	6 (10.5)	14 (24.6)	20 (35.1)	2 (7.1)	4 (14.3)	4 (14.3)

AE = adverse event.
*Discontinuations were recorded during treatment in the extension phase of the study.

P = 0.011), pain in foot (duloxetine, 0.9%; routine care, 5.2%; P = 0.021), nail fungal infection (duloxetine, 0.5%; routine care, 3.5%; P = 0.048), hyperglycemia (duloxetine, 0%; routine care, 3.5%; P = 0.013), cataract extraction (duloxetine, 0%; routine care, 2.6%; P = 0.039), conjunctivitis (duloxetine, 0%; routine care, 2.6%; P = 0.039), diabetic retinopathy (duloxetine, 0%; routine care, 2.6%; P = 0.039), and sinus congestion (duloxetine, 0%; routine care, 2.6%; P = 0.039) occurred in the routine-care–treated group than in the duloxetine-treated group. There were no events that the duloxetine patients had statistically significantly more of compared with the routine-care patients. Overall, proportionally more routine-care patients experienced TEAEs compared with duloxetine patients (92.2% vs 85.6%) (P = NS). In the duloxetine group there was no TEAE that was reported by ≥10% patients. TEAEs reported by ≥5% of patients in this group were dizziness (9.0% [20/222]), fatigue (9.0% [20/222]), headache (7.7% [17/222]), nausea (7.7% [17/222]), somnolence (6.8% [15/222]), increased sweating (5.9% [13/222]), upper respiratory tract infection (5.4% [12/222]), constipation (5.4% [12/222]), hypertension (5.4% [12/222]), dry mouth (5.4% [12/222]), falls (5.4% [12/222]), back pain (5.0% [11/222]), diarrhea (5.0% [11/222]), and arthralgia (5.0% [11/222]). TEAEs reported by ≥10% of patients in the routine-care group were somnolence (13.0% [15/115]), dizziness (11.3% [13/115]), headache (10.4% [12/115]), and vomiting (10.4% [12/115]). TEAEs reported by ≥5% of patients in the routine-care group were fatigue (9.6% [11/115]), nausea (9.6% [11/115]), upper respiratory tract infection (9.6% [11/115]), arthralgia (8.7% [10/115]), hypertension (7.0% [8/115]), nasopharyngitis (7.0% [8/115]), chest pain (7.0% [8/115]), pain in the limb (6.1% [7/115]), urinary tract infection (6.1% [7/115]), influenza (6.1% [7/115]), dry mouth (5.2% [6/115]), back pain (5.2% [6/115]), diarrhea (5.2% [6/115]), muscle cramp (5.2% [6/115]), skin ulcer (5.2% [6/115]), cellulitis (5.2% [6/115]), and pain in the foot (5.2% [6/115]).

TEAEs were also reported based on the patients' previous treatment in the acute phase of the study. TEAEs reported by >10% of patients in the duloxetine (acute)/routine-care (extension) group were somnolence (14.9% [13/87]); dizziness (12.6% [11/87]); headache, pain in extremity, and vomiting (11.5% [10/87], for each event); and peripheral edema (10.3% [9/87]). In the placebo (acute)/duloxetine (extension) group, TEAEs reported by >10% of patients were somnolence (17.5% [10/57]); nausea and dizziness (14.0% [8/57], for each event); fatigue and hyperhidrosis (12.3% [7/57], for each event); and influenza, erectile dysfunction, and back pain (10.5% [6/57], for each event). In the placebo (acute)/routine-care (extension) group, TEAEs reported by >10% of patients were fatigue (17.9% [5/28]); upper respiratory tract infection, hypertension, and dry mouth (14.3% [4/28], for each event); and nausea, pain in extremity, nasopharyngitis, back pain, arthralgia, and skin ulcer (10.7% [3/28], for each event). There was no TEAE that was reported by >10% of patients in the duloxetine (acute)/duloxetine (extension) group (N = 165).

During the study, 54 (16.0%) of 337 patients experienced serious AEs, which were defined as any study-related AE resulting in one of the following outcomes (or was significant for any other reason): death, initial or prolonged

inpatient hospitalization, a life-threatening experience, severe or permanent disability, or congenital anomaly. Serious AEs occurring in >1% of patients in either group included myocardial infarction (duloxetine, 2.7% [6/222]; routine care, 4.3% [5/115]), cellulitis (duloxetine, 1.4% [3/222]; routine care, 1.7% [2/115]), cerebrovascular accident and chest pain (routine care, 1.7% [2/115], for each event), pneumonia (routine care, 1.7% [2/115]), and acute renal failure (routine care, 1.7% [2/115]). No significant treatment-group differences were found in the occurrence of any serious AE. Two deaths were reported in the duloxetine treatment group: 1 patient with severe sepsis and 1 patient after myocardial infarction. The principal investigator and sponsor considered both deaths to be unrelated to the study medication.

Hypoglycemic Events

The number of patients who had ≥1 significant hypoglycemic episode between 2 visits (those requiring intervention with glucose, glucagon, food, drink, or assistance) did not differ significantly between treatment groups (week 1: no episode; week 2: duloxetine, 9.3% [20/216] vs routine care, 9.6% [11/115]; week 4: duloxetine, 9.4% [20/212] vs routine care, 10.7% [12/112]; week 8: duloxetine, 16.3% [34/208] vs routine care, 13.0% [14/108]; week 12: duloxetine, 12.8% [25/196] vs routine care, 15.4% [16/104]; week 20: duloxetine, 19.1% [36/188] vs routine care, 17.5% [18/103]; week 28: duloxetine, 16.3% [29/178] vs routine care, 19.4% [19/98]; week 40: duloxetine, 13.5% [23/170] vs routine care, 25.8% [25/97]; and week 52: duloxetine, 16.5% [27/164] vs routine care, 15.1% [14/93]). Significantly fewer duloxetine-treated patients (13.5% [23/170]) than routine-care–treated patients (25.8% [25/97]) had experienced hypoglycemic episodes by week 40 of the extension phase ($P = 0.020$).

Laboratory Data

Mean changes from baseline to end point in several chemistry analytes differed significantly between treatment groups (**Table IV**). In order to have data included in the analyses of laboratory data, patients had to have results at both baseline and end point. Some patients had missing values at baseline, end point, or both, and were thus not included in the analyses. The duloxetine group had a significant increase in fasting glucose and a significant decrease in sodium compared with the routine-care–treated group ($P = 0.021$ and $P = 0.001$, respectively). The routine-care group had significant increases in creatinine and chloride ($P = 0.025$ and $P < 0.001$, respectively), and significant decreases in aspartate aminotransferase, alanine aminotransferase, and total cholesterol ($P = 0.019$, $P = 0.026$, and $P = 0.002$, respectively) compared with the duloxetine group.

With the exception of low-density lipoprotein cholesterol (LDL-C), no significant differences were observed between treatment groups at end point in HbA_{1c} or lipid-profile changes (**Table V**). Although both treatment groups had mean decreases in LDL-C, the mean change was significantly smaller for the duloxetine group than for the routine-care group ($P = 0.001$).

Table IV. Laboratory values: changes from baseline to end point for patients with diabetic peripheral neuropathic pain treated with duloxetine 60 mg BID or routine care (N = 332). Values are expressed as mean (SD).

Parameter	Duloxetine (n = 218)	Routine Care (n = 114)	*p**
Albumin, g/L	–0.4 (2.7)	–0.2 (3.0)	0.532
Alkaline phosphatase, U/L	5.2 (21.9)	2.2 (18.3)	0.254
ALT/SGPT, U/L	0.3 (11.0)	–1.8 (8.9)	0.026
AST/SGOT, U/L	0.2 (7.0)	–2.2 (10.2)	0.019
Bicarbonate, HCO_3, mmol/L	–0.03 (2.5)	–0.1 (2.7)	0.601
Bilirubin, total, µmol/L	–0.3 (3.5)	–0.4 (3.3)	0.342
Calcium, mmol/L	0.02 (0.1)	0.01 (0.1)	0.614
Chloride, mmol/L	1.2 (3.3)	3.0 (4.0)	<0.001
Cholesterol, total, mmol/L	0.002 (1.0)	–0.4 (1.2)	0.002
Creatine phosphokinase, U/L	2.8 (68.8)	14.0 (199.3)	0.567
Creatinine, µmol/L	2.6 (11.5)	6.3 (14.6)	0.025
GGT, U/L	–0.2 (19.1)	–5.1 (27.2)	0.545
Glucose, fasting, mmol/L	1.0 (4.7)	–0.6 (5.0)	0.021
Inorganic phosphorus, mmol/L	0.04 (0.2)	0.01 (0.2)	0.332
Potassium, mmol/L	–0.02 (0.4)	0.00 (0.4)	0.504
Protein, total, g/L	0.0 (4.2)	–0.3 (4.0)	0.673
Sodium, mmol/L	–0.7 (2.7)	0.4 (3.5)	0.001
Urea nitrogen, mmol/L	0.3 (1.8)	0.7 (1.9)	0.345
Uric acid, µmol/L	–5.3 (61.7)	10.8 (61.9)	0.051

ALT/SGPT = alanine aminotransferase/serum glutamate pyruvate transaminase; AST/SGOT = aspartate aminotransferase/serum glutamate oxaloacetate transaminase; GGT = gamma-glutamyl transferase.
**P* values determined using an analysis of variance model on the rank-transformed data with terms for treatment and investigator.

Diabetic Complications

Michigan Neuropathy Screening Instrument

No significant treatment-group differences were observed in the mean changes in the MNSI score from baseline (last value prior to acute phase) to end point (difference, –0.20 [95% CI, –0.57 to 0.16]).

Retinopathy Progression

No significant treatment-group differences were found in the proportion of patients with worsening of visual acuity (right eye: duloxetine, 5.7% [9/158] vs routine care, 7.4% [6/81]; left eye: duloxetine, 4.4% [7/158] vs routine care, 2.4% [2/82]). No significant treatment-group differences were noted in changes in retinopathy (right eye: duloxetine, 11.0% [11/99] vs routine care, 6.5% [3/46]; left eye: duloxetine, 10.0% [10/100] vs routine care, 8.7% [4/46]). No significant

Table V. Lipid profiles and glycosylated hemoglobin (HbA_{1c}): changes from baseline to end point for patients with diabetic peripheral neuropathic pain treated with duloxetine 60 mg BID or routine care. Values are expressed as mean (SD).

	Duloxetine			Routine Care			
Parameter	No. of Patients	Baseline	Change to End Point	No. of Patients	Baseline	Change to End Point	*P**
LDL-C, mmol/L	193	2.911 (0.755)	–0.066 (0.785)	103	3.089 (0.909)	–0.321 (0.852)	0.001
HDL-C, mmol/L	212	1.157 (0.279)	0.103 (0.182)	112	1.173 (0.312)	0.067 (0.187)	0.127
Triglycerides, mmol/L	212	2.406 (1.680)	0.093 (1.600)	112	2.575 (2.187)	–0.172 (1.908)	0.488
HbA_{1c}	210	0.078 (0.016)	0.005 (0.014)	111	0.079 (0.017)	0.003 (0.014)	0.092

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
**P* values determined using an analysis of variance model on the rank-transformed data with terms for treatment and investigator.

treatment-group differences were found for required ophthalmologic surgical procedures, reasons for panretinal photocoagulation, or reasons for vitrectomy.

Microalbumin/Creatinine Ratio

No significant treatment-group difference was observed in the change in microalbumin/creatinine ratio (mean change [SE]: duloxetine, 0.04 [0.03] vs routine care, 0.08 [0.04]).

Vital Signs and Electrocardiographic Results

The difference in the mean change in sitting heart rate at end point was significant between the groups (**Table VI**). Twenty-one (9.6%) of 219 duloxetine-treated patients and 12 (10.4%) of 115 routine-care–treated patients had an increase in heart rate of <5 bpm from baseline, which is unlikely to be of clinical significance. Forty-one (18.7%) duloxetine patients and 27 (23.5%) routine-care patients had an increase in heart rate of ≥5 bpm but <10 bpm; 119 (54.3%) duloxetine-treated patients and 50 (43.5%) routine-care patients had an increase in heart rate of ≥10 bpm. These changes could be clinically meaningful in some patients, and the frequency of such changes is slightly higher in the duloxetine-treated group. Weight and blood pressure changes were not significantly different between the duloxetine and routine-care groups.

One case (0.5%) of sustained blood pressure elevation occurred in the duloxetine group and none in the routine-care group. There were statistically significant mean decreases in QT and PR for duloxetine-treated patients compared with routine-care–treated patients. No significant differences were noted between treatment groups in mean changes in corrected QT intervals using either the Fridericia or Bazett correction.

Health Outcomes

Compared with the routine-care group, patients in the duloxetine group had a significantly greater increase from baseline on the SF-36 bodily pain subscale score ($P = 0.021$). On the EQ-5D, the duloxetine group had a significantly smaller decrease from baseline than the routine-care group, and a significant treatment-by-investigator interaction was found ($P = 0.001$ and $P = 0.003$, respectively). Mean changes on the SF-36 and EQ-5D are summarized in **Table VII**.

DISCUSSION

In this 52-week, multicenter, open-label study of the management of DPNP, duloxetine appeared to be as well tolerated as routine care in the population studied. No significant between-group differences were found in the reasons for discontinuing treatment or the occurrence of serious AEs. However, some AEs were significantly more frequent in the routine-care group than in the duloxetine group.

Laboratory data analyses revealed some significant differences between duloxetine treatment and routine care treatment. Although statistically signifi-

Table VI. Vital signs and weight: Changes from baseline to end point for patients with diabetic peripheral neuropathic pain treated with duloxetine 60 mg BID or routine care. Values are expressed as mean (SD).

	Duloxetine			Routine Care			
Parameter	No. of Patients	Baseline	Change to End Point	No. of Patients	Baseline	Change to End Point	*P**
Weight, kg	205	94.61 (19.90)	0.11 (4.56)	107	95.77 (24.04)	0.79 (5.91)	0.261
Sitting heart rate, bpm	219	77.15 (11.20)	1.93 (12.31)	115	77.92 (11.55)	–1.78 (12.27)	0.009
Sitting systolic blood pressure, mm Hg	219	132.51 (14.30)	0.48 (15.56)	115	132.75 (16.70)	1.13 (16.20)	0.686
Sitting diastolic blood pressure, mm Hg	219	77.23 (9.66)	0.61 (9.42)	115	78.05 (9.56)	–0.44 (10.16)	0.357
QT interval, ms	216	387.85 (32.29)	–3.43 (21.79)	113	384.90 (33.14)	8.39 (31.25)	<0.001
QTcB, ms	216	428.17 (20.31)	4.78 (18.48)	113	428.17 (23.16)	2.19 (22.66)	0.267
QTcF, ms	216	414.31 (19.89)	1.81 (15.31)	113	413.24 (21.68)	4.35 (21.16)	0.193
PR interval, ms	211	168.77 (29.70)	–2.61 (14.46)	112	163.25 (26.81)	2.79 (12.44)	0.001

QTc = QT interval corrected for heart rate; B = the Bazett formula; F = the Fridericia formula.
**P* values determined using an analysis of variance model with terms for treatment and investigator.

Table VII. Mean changes in quality-of-life measures for patients with diabetic peripheral neuropathic pain treated with duloxetine 60 mg BID or routine care.*

	Duloxetine			Routine Care				
Measure†	No. of Patients	Baseline, Mean (SD)	Mean Change (SE)	No. of Patients	Baseline, Mean (SD)	Mean Change (SE)	Between-Group Difference (95% CI at End Point)	P‡
SF-36								
Mental health	204	81.4 (16.0)	–3.6 (1.2)	108	79.3 (17.5)	–6.7 (1.6)	3.0 (–0.7, 6.7)	0.106
General health perceptions	203	63.0 (20.9)	–1.6 (1.2)	108	61.1 (21.9)	–5.1 (1.6)	3.5 (–0.3, 7.3)	0.068
Bodily pain	204	63.4 (18.8)	1.5 (1.6)	108	62.2 (20.4)	–4.1 (2.1)	5.6 (0.8, 10.4)	0.021
Mental component summary	202	55.4 (8.0)	–2.5 (0.7)	107	54.6 (8.9)	–3.1 (0.9)	0.7 (–1.4, 2.7)	0.542
Physical component summary	202	40.7 (9.5)	0.7 (0.6)	107	40.1 (11.0)	–1.1 (0.8)	1.8 (–0.2, 3.7)	0.072
Vitality	204	60.5 (19.2)	–2.4 (1.3)	108	57.6 (20.5)	–5.1 (1.7)	2.7 (–1.3, 6.7)	0.186
Social functions	204	85.2 (18.8)	–4.2 (1.6)	108	82.4 (19.8)	–5.6 (2.1)	1.5 (–3.4, 6.3)	0.544
Physical role limit	203	66.4 (38.6)	–3.4 (2.9)	107	66.4 (41.2)	–9.9 (3.8)	6.5 (–2.2, 15.2)	0.142
Emotional role limit	203	83.9 (31.2)	–4.5 (2.8)	107	84.7 (32.5)	–5.5 (3.9)	1.0 (–8.4, 10.5)	0.832
Physical functioning	204	62.7 (25.4)	1.6 (1.5)	107	60.8 (27.0)	1.4 (2.0)	0.2 (–4.2, 4.7)	0.915
European Quality of Life Measures§	204	0.8 (0.2)	–0.00 (0.01)	107	0.7 (0.2)	–0.1 (0.02)	0.1 (0.03, 0.1)	0.001

SF-36 = Short Form-36 Health Status Survey.
* An increase in the mean change from baseline indicates an improvement in quality of life.
† The scores were similar at baseline ($P \geq 0.017$ for all measures).
‡ P values determined using an analysis of covariance model with terms for treatment, investigator, and baseline value.
§ Treatment-by-investigator interaction: $P = 0.003$.

cant, the mean changes were small, and none of these differences were determined to be clinically meaningful based on the judgment of the investigators. No patients discontinued treatment because of these changes. The observation that duloxetine increased fasting glucose slightly suggests a possible effect on glycemic control. No statistically significant difference was observed for HbA_{1c}, but this finding would need verification in subsequent studies before a conclusion about an effect on this parameter might be reached. The duloxetine and routine-care groups did not differ with respect to progression of neuropathy, nephropathy, or retinopathy.

The differences observed in patient LDL-C levels have potential clinical significance. Because these differences were small, it is important not to draw conclusions from 1 study. Effects on lipids are being considered by examination of a pool of 3 studies, the results of which will be published separately. Conclusions about the effects of duloxetine on lipids are deferred until that analysis has been completed.

The treatment groups did not differ significantly with regard to mean changes in weight, blood pressure, or corrected QT interval. A significant difference was found in the mean changes in heart rate: a 1.93 bpm increase was observed in the duloxetine group and a 1.78 bpm decrease was observed in the routine-care group, which was not considered to be clinically significant.

As measured by the SF-36, patients treated with duloxetine reported significantly better health status with regard to bodily pain compared with patients treated with routine care. As demonstrated by the EQ-5D, duloxetine-treated patients reported significantly smaller negative impact on their QOL compared with routine-care–treated patients. Within the health-outcome measurements analyzed, the 8 subscales of the SF-36, and the physical and mental component summaries did not suggest a treatment-by-investigator interaction. The detection of a treatment-by-investigator interaction in the EQ-5D might be spurious and is not likely to affect the overall results or conclusions.

Study Limitations

The primary objective of the present study was to determine the effects of long-term treatment of DPNP with duloxetine as compared with other options in a "real-world" clinical setting. As such, the comparison of treatment groups during the extension phase was secondary in purpose. Once patients were randomized to the duloxetine or routine-care group, treatment in the latter group was guided by the investigator's usual clinical practice and was not mandated by the protocol. It is reasonable to expect that the heterogeneity among approaches to the standard of care and the lack of blinding of physicians with regard to patients' treatment groups would introduce bias into the comparisons between treatment groups. As such, the direct comparison of duloxetine to other therapies should be approached with caution.

Other limitations apply to this study. First, it is reasonable to expect that patients entering the extension phase would continue deriving benefit because

they had a positive experience in the acute study. However, the objective of this extension study was to assess long-term treatment. Second, because this study primarily assessed the safety profile, the only duloxetine dose used was 60 mg BID, and not the recommended starting dose of 60 mg QD. Third, the study was not designed or powered to quantify individual safety parameters or statistically significant differences between AE reporting rates.

CONCLUSIONS

Over 52 weeks of open-label follow-up, treatment of these diabetic patients with duloxetine for peripheral neuropathic pain was associated with outcomes similar to, or significantly better than, that of routine care on most measures of tolerability, diabetic complications, and QOL.

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