

Safety and tolerability of duloxetine in the treatment of patients with fibromyalgia: pooled analysis of data from five clinical trials

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Abstract The purpose of this report is to describe the overall safety profile of both short- and longer-term duloxetine treatment of fibromyalgia. Data from four double-blind, randomized, placebo-controlled studies (two with 6-month open-label extension phases) and a 1-year, open-label safety study were included. Safety measures included treatment-emergent adverse events (TEAEs), adverse events leading to discontinuation, serious adverse events (SAEs), clinical laboratory tests, vital signs, and electrocardiograms. The most common TEAEs for short-term treatment with duloxetine were nausea (29.3%), headache (20.0%), dry mouth (18.2%), insomnia (14.5%), fatigue (13.5%), constipation (14.5%), diarrhea (11.6%), and dizziness (11.0%; all $p < 0.05$ vs. placebo). Most

TEAEs emerged early and were mild to moderate in severity. The profile of adverse events in patients enrolled at least 6 months, and for patients in the 1-year study, was similar to that found in the short-term treatment studies, with no new adverse events emerging at a notable rate. About 20% of patients discontinued due to adverse events in the short-term treatment studies and in the 1-year study. SAEs were uncommon, and none occurred at a significantly higher frequency for duloxetine compared with placebo. Mean changes in vital signs and weight were small. Rates of treatment-emergent potentially clinically significant (PCS) vital sign, laboratory, and electrocardiogram measures were low, with only PCS rates of alanine aminotransferase being significantly higher for duloxetine compared with placebo in the placebo-controlled treatment studies. In the 1-year study, four patients (1.1%) had suicide-related behavior. The data provided here summarize short- and long-term safety from five clinical studies in patients treated with duloxetine for fibromyalgia. In addition, postmarketing surveillance continues for adverse events reported with duloxetine in fibromyalgia, as in other indications.

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Introduction

Fibromyalgia (FM) is a chronic musculoskeletal disorder characterized by widespread pain. The overall prevalence of FM is about 2%, although rates are higher for women compared with men [1, 2]. FM is associated with substantial functional disability, work impairments, fatigue, sleep disturbances, and high rates of health care utilization [3–6].

To diagnose primary FM, pain must be evident in all four quadrants along with axial skeletal pain for at least 3 months and tenderness must be elicited on physical exam at 11 or more of 18 specified tender point sites [7]. The pain and tenderness in FM is thought by some to be due to central sensitization [8]. Consistent with this hypothesis, patients with FM have qualitatively altered nociception compared with pain-free patients [9–11]. Both serotonin and norepinephrine are believed to play a role in the modulation of pain via the descending inhibitory pain pathways in the brain and spinal cord [12, 13]. Dysfunction in pain perception is one of the proposed etiological factors in FM, although the exact pathophysiological mechanism of FM is unknown [14–17].

Duloxetine has shown efficacy in placebo-controlled trials in both psychiatric and pain disorders, including major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic peripheral neuropathic pain (DPNP), and FM [18–32]. The safety of duloxetine has been reported in individual trials and some pooled study analyses [33–36] in patients with MDD, GAD, DPNP, FM, and lower urinary tract disorders. While the safety and tolerability of duloxetine for the treatment of FM have been previously published for the individual clinical trials [18–22], a pooled analysis may offer a better overview of this topic than what individual study results can provide. Patients with fibromyalgia are often perceived as having poor tolerance for medications, perhaps related to overall heightened central sensitivity. The purpose of the current article is to present a comprehensive profile of the safety and tolerability of duloxetine during both short- (up to 6 months) and long-term (up to 60 weeks) use in patients with fibromyalgia.

Materials and methods

Study design

To evaluate the safety of duloxetine in the treatment of FM, data were drawn from five studies. Studies 1 to 4 were double-blind, randomized, placebo-controlled, multicenter efficacy studies. Study 5 was a 1-year open-label safety study without a placebo control.

In study 1, patients were randomly assigned to fixed dosages of duloxetine 60 mg BID (twice per day; $n=104$) or placebo ($n=103$). In study 2, patients were randomly assigned to fixed dosages of duloxetine 60 mg QD (once daily; $n=118$), duloxetine 60 mg BID ($n=116$), or placebo ($n=120$). In study 3, patients were randomly assigned to fixed dosages of duloxetine 20 mg QD ($n=79$), duloxetine 60 mg QD ($n=150$), duloxetine 120 mg QD ($n=147$), or placebo ($n=144$). After 15 weeks, patients in the 20 mg

duloxetine group were increased to 60 mg QD and continued on that dose for 13 more weeks. Patients receiving 60 mg duloxetine, 120 mg duloxetine, or placebo during the first 15 weeks were also continued on their respective treatments for 13 more weeks, for a total of 28 weeks of placebo-controlled treatment. Patients who completed the 28-week course of treatment in study 3 were eligible to participate in a further 28-week extension phase in which all patients received 120 mg QD of duloxetine. In study 4, patients were randomly assigned to 23 weeks of duloxetine treatment (8 weeks at 60 mg QD followed by 15 weeks of duloxetine continuing at 60 mg QD or increasing to 120 mg QD depending on clinical response and tolerability; $n=162$) or placebo ($n=168$). All patients who completed the initial therapy phase in study 4 were eligible to enter a 29-week double-blind extension phase at either 60 or 120 mg QD depending on dose at the end of the short-term therapy phase. Study 5 had an open-label phase of 8 weeks of duloxetine 60 mg QD treatment ($n=350$), followed by a 52-week double-blind phase in which patients were randomly assigned in a 1:2 ratio to continue at 60 mg QD ($n=104$) or 120 mg QD ($n=203$) of duloxetine, respectively. In all studies, patients assigned to doses at or above 60 mg/day were titrated briefly using doses of 20 or 30 mg/day. At study completion or discontinuation, a blinded taper phase lasting 1 or 2 weeks was implemented in all studies to prevent abrupt discontinuation of duloxetine treatment.

All patients provided written informed consent, and all study protocols were approved by the ethical review board at each investigative site. Further details about the methods and procedure of studies 1 through 5 can be found in published reports [18–22].

Patients

Patients were ≥ 18 years of age, male or female outpatients (only female for study 2), with or without MDD. All patients met the criteria for FM as defined by the American College of Rheumatology. Patients in all studies were also required to have a score of ≥ 4 on either the pain intensity item of the Fibromyalgia Impact Questionnaire [37] (study 1) or the average pain item of the Brief Pain Inventory [38] (studies 2–5). Patients were excluded from each study if they had any current primary psychiatric diagnosis other than MDD, including a current or past year diagnosis of dysthymia; had a previous diagnosis of psychosis, bipolar disorder, or schizoaffective disorder; had any anxiety disorder as a primary diagnosis within the past year; had a history of substance abuse or dependence within the past year (excluding nicotine and caffeine); or had a positive urine drug screen for any substances of abuse. Patients with an abnormal C-reactive protein level that is indicative of an

autoimmune disease, an antinuclear antibody with a dilution of $>1:320$, or a rheumatoid factor of ≥ 15 IU/mL were excluded. Patients who were pregnant or breastfeeding, were a serious suicidal risk, or had a serious medical illness were also excluded. At baseline and over the course of the studies, concomitant medications with primarily central nervous system activity were not permitted.

Safety measures

All studies evaluated safety on the basis of discontinuation rates, treatment-emergent adverse events (TEAEs); serious adverse events (SAEs); laboratory test results, including blood chemistry and hematology; vital signs; weight; and electrocardiograms (ECGs). TEAEs were assessed at each visit by recording patient responses to a general question such as, “How have you been feeling?” TEAEs were coded to Medical Dictionary for Regulatory Activities preferred terms by blinded clinical personnel. An adverse event was considered treatment emergent if it was either new or existing but worsened after initiation of study medication. The severity of each adverse event as mild, moderate, or severe was also recorded. Discontinuation-emergent adverse events were assessed during the 1–2-week tapered discontinuation phases. Suicide-related events were identified by a text string search of adverse events and investigator comments to allow for evaluation of incidences of suicidal ideation or suicidal behavior.

Vital signs consisting of supine and standing blood pressure (BP) and pulse were recorded at each visit. Laboratory tests were performed at regular visits through the treatment periods; ECGs were conducted at the final visit of the short-term phase for study 1, weeks 15 and 28 for study 3, and weeks 13 and 27 for study 4 (ECGs not conducted postbaseline in studies 2 and 5). The criteria for potentially clinically significant (PCS) ECG values were as follows: PR interval: low—any value <20 , high—any value >200 ; QRS interval: low—any value <50 , high—any value >120 ; QTcF interval: abnormal—increase ≥ 30 from baseline and postbaseline value ≥ 450 ms for males, ≥ 470 ms for females. PCS values for vital signs and weight are given in the legend of Table 6.

Statistical analyses

To assess duloxetine safety during short-term treatment, data from the 3- and 6-month placebo-controlled phases of studies 1 to 4 were pooled. Longer-term safety and tolerability of duloxetine was examined in two ways: (1) all patients that enrolled in the 60-week study (study 5) and (2) all patients continuing into the 6-month extension phases of studies 3 and 4 and all patients from study 5 maintaining enrollment for at least 6 months (to assess

safety in patients with a minimum of 6 months of drug exposure). All analyses were intent-to-treat analyses, unless otherwise specified, using all participants by the groups to which they were assigned by random allocation. Statistical significance was indicated when $p \leq 0.05$. No adjustments were made for multiplicity.

For the placebo-controlled data, comparisons of duloxetine and placebo on rates of TEAEs, reasons for discontinuation, and rates of PCS values for vital signs, weight, laboratory test results, and ECGs were performed using the Cochran–Mantel–Haenszel general association test controlling for study. For vital signs, weight, and ECGs, treatment group differences in mean change from baseline to endpoint (last observation on treatment) were analyzed using an analysis of variance model containing terms for treatment group and study. Time-to-onset and time-to-resolution of adverse events were examined using the product limit approach, and tests for significance between treatment groups were based on the log-rank test. Suicidal ideation and behavior were compared between the duloxetine and placebo groups based on exposure-adjusted Mantel–Haenszel incidence rates derived from the above-mentioned text string search.

Results

Patient characteristics

The study population of patients ($n=1,411$) receiving short-term treatment was primarily (94.8%) women. The mean age was 50.2 (SD=11.0) years, and most (87.5%) of the participants were of Caucasian origin. There were no statistically significant differences between the duloxetine- and placebo-treated patients on any of the baseline characteristics (Table 1). Duloxetine-treated patients who had at least 6 months of study participation ($n=721$) and the sample of 350 patients who participated in the longer-term (1 year) study of duloxetine had similar baseline characteristics, although the minority representation was higher in the 1-year study.

Drug exposure

For the short-term placebo-controlled studies, a total of 876 patients were exposed to duloxetine for a mean of 110 days, and 535 patients were exposed to placebo for a mean of 105 days. Of the duloxetine-treated patients in these studies, 46.7% were exposed to drug for at least 3 months (compared with 42.1% for placebo). For the sample enrolled in studies for at least 6 months, 91.3% (of 721 patients) were exposed to duloxetine for 6 months or more, and 61.9% were exposed for 1 year or more with an

Table 1 Patient characteristics

Variable	3–6-Month studies			≥6-Month exposure	1-Year study
	Placebo (N=535)	Duloxetine (N=876)	<i>p</i> ^a (duloxetine vs. placebo)	Duloxetine (N=721)	Duloxetine (N=350)
Ethnicity, <i>n</i> (%)			0.916		
African	13 (2.4%)	20 (2.3%)		5 (0.7)	3 (0.9)
Caucasian	463 (86.5%)	771 (88.0%)		560 (77.7)	214 (61.1)
East Asian	3 (0.6%)	3 (0.3%)		33 (4.6)	46 (13.1)
Hispanic	51 (9.5%)	76 (8.7%)		116 (16.1)	82 (23.4)
Nat. Amer.	1 (0.2%)	2 (0.2%)		4 (0.6)	1 (0.3)
Other	3 (0.6%)	2 (0.2%)		–	–
West Asian	1 (0.2%)	2 (0.2%)		3 (0.4)	4 (1.1)
Age, years ^b	49.61 (11.32)	50.62 (10.76)	0.147	50.48 (10.56)	48.97 (11.07)
Gender, <i>n</i> (%)			0.265		
Female	509 (95.1%)	829 (94.6%)		692 (96.0)	335 (95.7)
Height (cm) ²	163.14 (7.49)	163.32 (7.78)	0.512	161.76 (7.47)	159.44 (7.09)
Weight (kg) ²	78.15 (18.40)	79.71 (19.46)	0.582	76.84 (18.37)	69.95 (14.74)

^a Frequencies were analyzed using Cochran–Mantel–Haenszel test for general association controlling for study; means were analyzed using a type III sums of squares analysis of variance: model = treatment and study

^b Mean (SD)

average exposure period of 327 days. In the longer-term study, 350 patients were exposed to duloxetine for a mean of 298 days, with 69.1% receiving at least 6 months of exposure and 58.7% receiving at least 1 year of exposure.

Discontinuations

Overall, 41.4% of the duloxetine-treated patients and 42.2% of the placebo-treated patients discontinued short-term treatment (Table 2). Adverse events were the cause of early discontinuation for 19.5% of those in the duloxetine group and 11.8% in the placebo group during

short-term treatment ($p < 0.001$). Lack of efficacy was a reason for discontinuation significantly ($p < 0.001$) less often for duloxetine- compared with placebo-treated patients (7.0% and 13.5%, respectively) in the short-term studies. There were no other significant differences in other reasons for discontinuation between the duloxetine and placebo groups in the short-term studies. Among those who were enrolled for at least 6 months, 31.9% discontinued treatment, with adverse events the most common reason (Table 2). In the 1-year study, 44.9% discontinued early, with adverse events a reason for discontinuation for 21.1% of patients (Table 2).

Table 2 Reasons for study discontinuation

Primary reason for discontinuation	3–6-Month studies			≥6-Month exposure	1-Year study
	Placebo (N=535) frequency (%)	Duloxetine (N=876) frequency (%)	<i>p</i> ^a (duloxetine vs. placebo)	Duloxetine (N=721) frequency (%)	Duloxetine (N=350) frequency (%)
DC due to any reason	226 (42.2)	363 (41.4)	0.44	230 (31.9)	157 (44.9)
Adverse event	63 (11.8)	171 (19.5)	<0.001	90 (12.5)	74 (21.1)
Lack of efficacy	72 (13.5)	61 (7.0)	<0.001	24 (3.3)	29 (8.3)
Subject decision	44 (8.2)	59 (6.7)	0.16	85 (11.8)	26 (7.4)
Lost to follow-up	31 (5.8)	38 (4.3)	0.06	6 (0.8)	9 (2.6)
Protocol violation	14 (2.6)	22 (2.5)	0.99	13 (1.8)	9 (2.6)
Physician decision	2 (0.4)	9 (1.0)	0.24	10 (1.4)	8 (2.3)
Sponsor decision	0 (0)	2 (0.2)	0.24	2 (0.3)	2 (0.6)
Entry exclusion criteria	0 (0)	1 (0.1)	0.54	–	–

^a From Cochran–Mantel–Haenszel test for general association controlling for study

DC discontinuation

TEAEs

Most (59.3%) of the TEAEs reported by duloxetine-treated patients in the short-term studies were described as mild (21.1%) or moderate (38.2%) in severity. The most common TEAEs as reported by >10% of patients during short-term treatment were nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, and dizziness in the duloxetine-treated patients (Table 3). All of these, plus somnolence, hyperhidrosis, and decreased appetite, occurred significantly (all $p<0.05$) and more frequently in the duloxetine group than the placebo group. No specific adverse events led to discontinuation in the duloxetine group at a significantly higher rate than the placebo group, with the exception of somnolence ($p=0.003$; Table 4).

In the short-term studies, the common (>10%) TEAEs occurred early in treatment and had a relatively rapid resolution (Table 3). All of the most common (>10%) TEAEs associated with duloxetine had a significantly (all $p<0.05$) earlier onset for duloxetine- compared with placebo-treated patients. However, the time from onset to resolution for all of these most common duloxetine-associated TEAEs was not significantly different between duloxetine and placebo.

The same TEAEs that were common (>10%) in the short-term studies were also common among those enrolled for at least 6 months and in the 1-year study (Table 3). In addition, somnolence and hyperhidrosis occurred for more than 10% of patients. In general, the rates of adverse events among those enrolled for at least 6 months and in the 1-year study were slightly higher than in the short-term studies, but no new adverse events emerged with any frequency. In the 1-year study, rates of discontinuations due to specific adverse events were similar to the short-term studies (Table 4).

Serious adverse events

A total of 21 (2.4%) duloxetine-treated and 11 (2.1%) placebo-treated patients reported at least one SAE in the short-term studies. There were no statistically significant treatment group differences in the incidence of individual SAEs. Additionally, there was no pattern of SAEs with respect to system-organ class. No one SAE occurred at a frequency greater than others among duloxetine-treated patients. Among the 721 duloxetine-treated patients enrolled for at least 6 months, 42 (5.8%) had an SAE. Similarly, a total of 19 (5.4%) duloxetine-treated patients experienced at least one SAE in the 1-year study. No specific pattern in the incidence of specific SAEs was

Table 3 Treatment-emergent adverse events

Event ^a	3–6-Month studies			Time to Onset (days) PBO	DLX	Time to Resolution (days) PBO	DLX	≥6-Month exposure	1-Year study
	PBO (N=535) %	DLX (N=876) %	p^b (duloxetine vs. placebo)					Mdn	Mdn
Nausea	11.4	29.3	<0.001	10.5	1.0	9.0	6.0	30.2	40.6
Headache	12.0	20.0	<0.001	14.0	9.0	9.0	8.0	26.1	29.4
Dry mouth	5.2	18.2	<0.001	13.0	4.0	32.0	73.0	22.2	17.1
Insomnia	9.2	14.5	0.003	26.0	8.0	43.0	34.0	16.4	19.7
Fatigue	7.1	13.5	<0.001	26.0	7.0	39.0	54.0	12.2	11.1
Constipation	3.6	14.5	<0.001	16.0	10.0	74.0	47.0	18.3	17.4
Diarrhea	7.9	11.6	0.018	14.0	3.0	5.0	4.0	14.3	12.9
Dizziness	6.7	11.0	0.011	10.5	6.0	7.5	7.5	15.5	18.9
Somnolence	2.8	9.6	<0.001	2.0	3.0	59.0	50.5	11.8	14.0
Hyperhidrosis	1.1	6.8	<0.001	31.5	22.0	33.0	49.0	13.7	11.4
Decreased appetite	0.6	6.5	<0.001	7.0	2.0	68.0	32.0	5.7	4.6

Estimates of median times for the adverse events are based on the first new occurrence after initiation of treatment for the subsample of patients who experienced each event.

PBO placebo, DLX duloxetine, Mdn median

^a Event list comprises those treatment-emergent adverse events in the 3–6-month studies for which the rate for duloxetine was $\geq 5.0\%$ and significantly higher than placebo

^b Cochran–Mantel–Haenszel test for general association, controlling for study

Table 4 Discontinuations due to adverse events

Event ^a	3–6-Month studies			1-Year study
	Placebo (N=535) %	Duloxetine (N=876) %	<i>p</i> ^b (duloxetine vs. placebo)	Duloxetine (N=350) %
Nausea	0.7	1.9	0.074	1.4
Insomnia	0.7	1.1	0.411	2.6
Fatigue	0.2	1.3	0.073	0.6
Diarrhea	0.2	0.8	0.077	1.4
Dizziness	0.6	0.7	0.672	1.4
Somnolence	0	1.5	0.003	0.3
Vomiting	0.2	0.5	0.390	2.0

^a Event list comprises any adverse events that led to discontinuation in >1% of patients in either the 3–6-month studies or the long-term study

^b Cochran–Mantel–Haenszel test for general association, controlling for study

observed in the 1-year study, and no deaths occurred in any of the five studies.

Suicidality

Three cases of suicide ideation (one on duloxetine, two on placebo; $p=0.86$) were identified during the short-term, placebo-controlled studies. An exposure-adjusted analysis of these rates of suicide ideation also revealed no significant ($p=0.29$) difference between duloxetine and placebo. In the 1-year study, there were four patients (1.1%) who had suicide-related behavior (three suicidal ideations and one suicide attempt).

Vital signs and weight

Mean changes from baseline to endpoint of short-term treatment in the 3–6-month studies for all vital signs were relatively small for duloxetine (Table 5). With the large

sample sizes, differences between duloxetine and placebo were statistically significant, with duloxetine evidencing slight increases in pulse, systolic BP, and diastolic BP, and a slight decrease in body weight, relative to placebo. For the sample of patients enrolled for 6 months or more and the 1-year study, there were similar small mean changes in vital signs from baseline to endpoint (Table 5).

Rates of treatment-emergent PCS values for vital signs and weight changes were low in the short-term studies (Table 6). No significant differences between the duloxetine and placebo groups were evident for pulse, sitting systolic BP, sitting diastolic BP, body weight, or the incidence of sustained elevation in BP (for systolic BP, 1.3% in the duloxetine group and 1.1% in the placebo group had a sustained elevation, $p=0.74$; for diastolic BP, 0.7% of the duloxetine group and 0.2% of the placebo group had a sustained elevation, $p=0.17$).

Within the sample of duloxetine-treated patients who were enrolled for 6 months or more, treatment-emergent

Table 5 Mean baseline and change (to endpoint) on vital signs and weight

		3–6-Month studies			≥6-Month exposure	1-Year study
		Placebo (N=527)	Duloxetine (N=855)	<i>p</i> ^a (duloxetine vs. placebo)	Duloxetine (N=721)	Duloxetine (N=350)
Pulse	Baseline	73.3 (9.9)	73.7 (9.7)		74.2 (9.5)	75.2 (8.7)
	Change	−0.4 (9.5)	1.2 (10.6)	0.003	2.3 (11.0)	1.9 (10.4)
Sitting diastolic BP	Baseline	76.7 (9.2)	76.4 (8.9)		77.0 (9.2)	76.9 (9.3)
	Change	−1.2 (8.9)	1.0 (9.2)	<0.001	0.8 (9.5)	−0.2 (9.6)
Sitting systolic BP	Baseline	122.5 (14.9)	122.3 (15.3)		122.4 (15.8)	120.1 (14.8)
	Change	−1.6 (13.2)	0.9 (14.7)	0.003	0.2 (13.9)	−0.1 (14.4)
Weight (kg)	Baseline	77.9 (18.2)	79.9 (19.5)		76.8 (18.4)	69.9 (14.7)
	Change	0.3 (2.4)	−0.4 (4.2)	0.002	0.6 (5.0)	0.7 (4.3)

^a From analyses of variance with study and treatment as effects

BP blood pressure

Table 6 Vital signs and weight: treatment-emergent potentially clinically significant values

Abnormality	3–6-Month studies			<i>p</i> ^a (duloxetine vs. placebo)	≥6-Month exposure	1-Year study
	Placebo (<i>N</i> =535) <i>n</i> / <i>N</i> (%)	Duloxetine (<i>N</i> =876) <i>n</i> / <i>N</i> (%)	Duloxetine (<i>N</i> =721) <i>n</i> / <i>N</i> (%)		Duloxetine (<i>N</i> =350) <i>n</i> / <i>N</i> (%)	
Pulse	High	1/527 (0.2)	4/855 (0.5)	0.308	1/721 (0.1)	2/347 (0.6)
	Low	2/519 (0.4)	3/846 (0.4)	0.900	0/716 (0)	0/348 (0)
Sitting diastolic BP	High	1/522 (0.2)	6/847 (0.7)	0.159	1/712 (0.1)	8/342 (2.3)
	Low	3/523 (0.6)	3/852 (0.4)	0.607	2/718 (0.3)	3/346 (0.9)
Sitting systolic BP	High	1/525 (0.2)	3/848 (0.4)	0.415	3/715 (0.4)	6/347 (1.7)
	Low	3/517 (0.6)	2/845 (0.2)	0.525	1/708 (0.1)	11/340 (3.2)
Weight (kg)	Gain	2/499 (0.4)	10/823 (1.2)	0.126	55/719 (7.6)	28/348 (8.0)
	Loss	6/499 (1.2)	18/823 (2.2)	0.173	29/719 (4.0)	17/348 (4.9)

Criteria for PCS values: systolic low (≤ 90 and decrease from baseline ≥ 20), systolic high (≥ 180 and increase from baseline ≥ 20), diastolic low (≤ 50 and decrease from baseline ≥ 15), diastolic high (≥ 105 and increase from baseline ≥ 15), pulse low (≤ 50 and decrease from baseline ≥ 15), pulse high (≥ 120 and increase from baseline ≥ 15), weight low (decrease from baseline $\geq 10\%$), high (increase from baseline $\geq 10\%$)

N number of patients at risk of having potentially clinically significant (PCS) values at baseline, *n* number of patients with a PCS postbaseline measurement

^a Cochran–Mantel–Haenszel test for general association, controlling for study

PCS increases in weight were evident for 7.6% of individuals; 4.0% had PCS decreases in weight. Rates for treatment-emergent values for vital signs were very low (0% to 0.4%). Similar results were evident in the 1-year study (Table 6).

A total of 2.2% (16 of 721) of patients enrolled for 6 months or more had a sustained elevation in systolic BP; 2.1% (15 of 721) had a sustained elevation in diastolic BP. In the 1-year study, sustained elevations in systolic BP occurred for five (1.4%) patients and sustained elevations in diastolic BP occurred for 10 (2.9%) patients.

Electrocardiogram

There were no significant treatment group differences in the incidence of PCS values for any ECG parameters in the 3–6-month pooled study data. PCS rates for duloxetine and placebo were as follows: PR interval (high)—1.1%, 2.3%, $p=0.19$; PR interval (low)—3.0%, 1.4%, $p=0.09$; QRS (high)—1.3%, 1.2%, $p=0.68$; QRS interval (low)—0%, 0%; QTcF (abnormal)—0.4%, 0.3%, $p=0.79$. Mean changes from baseline to endpoint in ECG intervals for duloxetine and placebo, respectively, were as follows: PR (−3.3 ms, 1.0 ms, $p<0.001$), QRS (−0.3 ms, 0.4 ms, $p=0.32$), QT (−5.3 ms, 1.7 ms, $p<0.001$), QTcB (4.8 ms, 1.9 ms, $p=0.06$), and QTcF (1.3 ms, 1.9 ms, $p=0.26$).

Chemistry and hematology

Rates of treatment-emergent PCS laboratory values were low in all studies. In the short-term studies, there was a

significantly ($p<0.05$) higher incidence of alanine aminotransferase (ALT) values >5 times upper limit of normal (PCS criteria) among duloxetine-treated patients (0.6%) compared with placebo-treated patients (0%). There were no significant differences between duloxetine and placebo in the rates of treatment-emergent PCS values for aspartate aminotransferase, bilirubin, calcium, cholesterol, creatine phosphokinase, creatinine, gamma-glutamyltransferase (GGT), inorganic phosphorus, sodium, total protein, urea nitrogen, or uric acid (all rates $<1.2\%$). For those patients enrolled for 6 months or more, treatment-emergent PCS values occurred at a rate $>1\%$ only for high cholesterol (1.6%, 11 of 706; PCS criteria = total cholesterol greater than 7.76 mmol/L). In the 1-year study, two treatment-emergent PCS values occurred at a rate $>1\%$: high cholesterol (2.1%) and high GGT (1.5%; PCS criteria for GGT = greater than 135,000 U/L for women and greater than 195,000 U/L for men).

There were no significant differences in the incidence of hepatic-related treatment-emergent adverse events and hepatic-related serious adverse events for duloxetine compared with placebo in the short-term studies. No patients in the short-term studies, 1-year study, or the sample that was enrolled for 6 months or more met Hy's rule (Hy's rule is defined as an ALT value greater than three times the upper limit of normal together with a total bilirubin greater than two times normal and reflects the presence of hepatocellular injury) [39]. There was a significantly ($p<0.05$) higher incidence of duloxetine-treated patients (0.6%) who discontinued due to a hepatic-related adverse event compared with placebo-treated patients (0%). There was no evidence

that longer-term treatment added to the risk of discontinuation due to a hepatic-related adverse event: 0.6% of the 350 patients in the 1-year study discontinued due to a hepatic-related adverse event.

Discussion

This comprehensive safety analysis revealed that the most common TEAEs seen during duloxetine treatment of FM were similar to those seen during duloxetine treatment of other indications, including MDD, GAD, and DPNP. Most TEAEs were mild to moderate in severity and were transient. In the short-term 3- and 6-month studies, adverse events leading to discontinuation varied, with no one event responsible for more than 2% of patients discontinuing. Overall, 19.5% discontinued due to an adverse event.

Duloxetine-treated patients had significantly larger increases in BP and heart rates, compared with placebo-treated patients, in short-term 3- and 6-month studies. These increases, however, were not of clinical significance. Furthermore, there was no evidence of higher rates of PCS abnormal laboratory values, ECG parameters, vital signs, or changes in body weight, for duloxetine-treated patients compared with placebo-treated patients during 3–6-month treatment, with one exception: A significantly higher incidence of ALT values >5 times upper limit of normal was found for duloxetine-treated patients (0.6%) compared with placebo-treated patients (0%).

Over the course of 1-year open-label of treatment with duloxetine, there was a somewhat higher total incidence of certain adverse events and PCS values on laboratory parameters. In the absence of a comparator, it seems most likely that these increased rates were due to the longer observation period compared with the 3- and 6-month studies. Overall, instances of PCS laboratory values were very low in the sample enrolled for 6 months or longer, as well as in the 1-year study, with no discernable clinical pattern suggestive of a specific body system or disease state.

While the overall pattern of adverse events during duloxetine treatment was similar for the FM studies compared with other disorders, the base rate of such adverse events appears somewhat higher in FM. In the treatment of MDD, for example, the incidence of common adverse events has been reported to be generally lower for both placebo and duloxetine than found here [40]. Although initial occurrences of adverse events tend to occur early in treatment, the shorter duration (8–9 weeks) of the MDD trials may account in part for this apparent difference. Discontinuations due to adverse events occurred in about 20% of patients in both the short-term 3- and 6-month studies and the 1-year study. This rate is somewhat

higher than the discontinuation rate due to adverse events of 11% reported in a review of 19 studies of short-term treatment (duration, 8–26 weeks) of MDD with serotonin reuptake inhibitors [41]. Rates of 9–10% for discontinuation due to adverse events were found across six studies of venlafaxine, a serotonin and norepinephrine reuptake inhibitor of similar class to duloxetine, and four studies of duloxetine, in the short-term treatment of MDD [42]. These findings suggest that patients with FM report slightly more adverse events and have somewhat higher rates of discontinuation due to adverse events compared with other disorders for which duloxetine has been studied, whether on drug or placebo. Nevertheless, clinicians need to be aware of the risk of discontinuation due to adverse events with duloxetine in the treatment of fibromyalgia and balance this risk against the likelihood of treatment response.

The cardiovascular safety of duloxetine has been previously investigated across all conditions for which duloxetine has been studied [43]. Using a database of 42 clinical trials, plus postmarketing safety studies, this recent study found no evidence of cardiovascular risk [43]. Similarly, in the treatment of FM, no evidence of clinically significant changes in ECG parameters or sustained increases in BP was seen for duloxetine relative to placebo. Although duloxetine's noradrenergic effect suggests that it is likely to cause increases in heart rate, only 0.5% of patients in the 3- and 6-month studies, 0.1% of patients enrolled for 6 months or more, and 0.6% of patients in the 1-year study had a clinically significant increase in pulse rate. The QTc interval was prolonged to a clinically meaningful degree in 0.4% of duloxetine-treated patients compared with 0.3% of placebo-treated patients.

In the 3- and 6-month FM studies, small numbers of patients lost or gained >10% in body weight. However, among those duloxetine-treated patients who were enrolled for at least 6 months, 7.6% gained >10% in body weight and 4.0% lost >10% in body weight. Similarly, in the 1-year study, 8.0% gained >10% in body weight and 4.9% lost >10% in body weight. In the absence of a placebo or other comparator, these changes over 6 months and 1 year are difficult to interpret. A previous longer-term (1 year) open-label study of duloxetine (80–120 mg/day) for MDD found early (first few weeks) decreases in mean body weight followed by a return to baseline and then an increase on average of 1.1 kg by the end of the study [44]. This pattern is consistent with what was found here, with more patients losing >10% weight than gaining >10% weight in the 3–6 months studies, but more patients gaining >10% weight than losing >10% weight after being enrolled for 6 months or more and in the 1-year study. The overall mean change, however, was small (0.7 kg gain by endpoint of the 1-year study).

The effect of duloxetine on ALT has been previously found in other populations and is described in the product labeling. Changes in ALT do not appear to predict hepatotoxicity, and the absence of cases that met criteria for Hy's rule during either short- or long-term use supports the conclusion that the risk of hepatotoxicity associated with duloxetine in patients with FM is very low.

There has been considerable attention to the issue of suicide risk with antidepressants [45, 46]. Because rates of suicidality are typically very low, analysis of a pooled study database is a particularly useful to test for any potential drug-placebo difference. In the analyses of short-term placebo-controlled studies of FM, there were no significant differences between duloxetine and placebo in the incidence of suicidal behavior or ideation according to adverse event reporting. In the 1-year open-label study, four patients were reported to have suicide-related behavior. However, in the absence of a placebo control, these rates of suicide-related behavior in the longer-term study are difficult to interpret, particularly because elevated rates of suicide have been found for individuals with widespread pain syndromes like FM [47].

Strengths of this study include the large number of patients treated with duloxetine in the shorter-term studies ($n=876$). In addition, a broad range of safety assessments were conducted. This report on the safety of duloxetine in the treatment of fibromyalgia is limited by the fact that all patients were participants in clinical trials with extensive inclusion/exclusion criteria. In particular, patients with certain comorbidities and patients on most other centrally acting medications were excluded from the trials. In clinical practice, psychiatric and medical comorbidity and polypharmacy is common among patients with FM [48]. Thus, the generalizability of the findings to typical clinical practice patients who have psychiatric or medical comorbidities and who also receive concomitant medications is not known.

Another limitation of this pooled safety analysis includes the lack of a placebo group in the long-term safety study. However, the fact that the safety findings from the longer-term study are generally similar or show only slightly increased rates of adverse events or laboratory/vital sign values, relative to values from the 3- and 6-month studies, may provide reassurance about longer-term use of duloxetine in fibromyalgia.

In conclusion, duloxetine in dosages from 20 to 120 mg/day demonstrated a similar safety and tolerability profile in the treatment of FM to that seen in the treatment of other indications. Most patients tolerate duloxetine without clinically meaningful effects on vital signs, cardiovascular parameters, or laboratory (chemistry, hematology) analytes.

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