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ORIGINAL RESEARCH

Correlation between pain response and improvements in patient-reported outcomes and health-related quality of life in duloxetine-treated patients with diabetic peripheral neuropathic pain

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Objective: We assessed whether quality of life (QoL) improvement in duloxetine-treated patients with diabetic peripheral neuropathic pain (DPNP) correlates with the extent of pain relief.

Methods: Pooled data from three multicountry, double-blind, 12-week, placebo-controlled trials of duloxetine-treated (duloxetine 60 mg once daily; total number =335) patients with DPNP were analyzed. Based on improvement in 24-hour average pain scores, patients were stratified into four groups. Improvement in QoL, which was measured as the change from baseline in two patient-reported health outcome measures (Short Form [SF]-36 and five-dimension version of the EuroQol Questionnaire [EQ-5D]), was evaluated and compared among the four groups. Pearson's correlation coefficient was calculated to assess the correlation between improvement in pain scores and improvement in QoL.

Results: The group with more pain improvement generally showed greater mean change from baseline in all of the SF-36 scale scores and on the EQ-5D index. Pearson's correlation coefficients ranged from 0.114 to 0.401 for the SF-36 scale scores ($P<0.05$), and it was 0.271 for the EQ-5D ($P<0.001$).

Conclusion: Improvement in pain scores was positively correlated with improvement in QoL and patient-reported outcomes in duloxetine-treated patients.

Keywords: diabetic peripheral neuropathic pain, duloxetine, efficacy, function, quality of life

Introduction

Pain symptoms associated with diabetic peripheral neuropathic pain (DPNP) have a negative effect on functioning and quality of life (QoL).[1] Furthermore, DPNP is often unreported,[2] and although the prevalence of DPNP is high, almost one-quarter of patients with DPNP do not receive any treatment for pain symptoms.[3] Important goals in the treatment of DPNP are to not only reduce pain, but also to improve overall patient functional outcomes and QoL.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor that was approved in Japan for the management of DPNP in 2012. The pain inhibitory action of duloxetine is believed to result from potentiation of descending inhibitory pain pathways within the central nervous system.[4] Duloxetine has demonstrated efficacy and has been associated with improvement in QoL and functionality in patients with DPNP in three placebo-controlled studies.[5–8]

There are limited data on the correlation between the degree of pain response and the improvement in patient QoL for duloxetine-treated patients with DPNP. The

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purpose of these analyses is to assess whether improvements in QoL and patient-reported outcomes (PRO) in duloxetine-treated patients with DPNP correlate with the extent of pain relief.

Methods

Study designs and patients

The data used in this analysis were derived from studies that were reviewed and approved by the applicable organizational ethical review boards and were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization good clinical practice guidelines. Pooled data from three randomized, double-blind, placebo-controlled, multicountry studies of duloxetine for the management of DPNP were analyzed. Patients received either duloxetine or placebo: study 1 (total number [N]=457 [duloxetine, number [n]=342; placebo, n=115]),[5] study 2 (N=334 [duloxetine, n=226; placebo, n=108]),[6] and study 3 (N=348 [duloxetine, n=232; placebo, n=116]).[7] The treatment period for all three trials was 12 weeks; studies 2 and 3 included 1 week for drug tapering after the treatment period. Since the approved dose of duloxetine in Japan for the management of DPNP is 60 mg once daily, only patients randomized to placebo (N=330) and duloxetine 60 mg once daily (N=335) were included in the current analyses.

Patients in the three studies were aged 18 years and older and they presented with pain for at least 6 months' duration, which was due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. Pain had to start in the feet and it should have had a relatively symmetrical onset. Diagnosis was confirmed by a score ≥3 on the Michigan Neuropathy Screening Instrument. Patients also had to have a score ≥4 of average pain severity for 24 hours on an 11-point Likert scale, and they had to have stable glycemic control.

Measures

For pain, 24-hour average pain severity scores were daily recorded by the patient in a diary using an 11-point Likert scale (0 [no pain] to 10 [worst possible pain]). The weekly mean of these scores was used for the analysis.

PRO were evaluated using the Short Form (SF)-36 version 1.0,[9] the three-level, five-dimension version of the EuroQol Questionnaire (EQ-5D),[10] and the Patient Global Impression of Improvement (PGI-I) for the patient-rated global assessment of response to treatment.[11]

Assessments

To assess the efficacy of duloxetine compared with placebo to reduce pain severity in patients with DPNP, the 24-hour average pain severity scores were used. Patients were stratified into four groups (ie, ≥50%, ≥30%–<50%, ≥15%–<30%, and <15% improvement) based on the degree of pain improvement in 24-hour average pain scores. Stratification was conducted based on the percentage change at 12 weeks from baseline. Improvement in QoL and PRO measures was assessed as the change from baseline to 12 weeks on the PRO measures of the SF-36 scale scores, the EQ-5D index, and the PGI-I compared with placebo-treated patients. The correlation between the percentage improvement in 24-hour average pain scores and improvement in QoL and PRO measures was also assessed for the duloxetine group.

Statistical analysis

Post hoc analyses were conducted. Missing data were inputed according to the last observation carried forward methodology. Treatment comparison in the model was assessed using Fisher's exact test or analysis of covariance for treatment, investigator, and baseline. In the duloxetine group, Pearson's correlation coefficient was calculated for the correlation between the percentage improvements in 24-hour average pain scores and improvements in each QoL and PRO measure. A two-sided 5% significance level was used, and no adjustments were made for multiplicity.

Results

Demographics and baseline characteristics

Patient demographics and disease characteristics were similar between the duloxetine and placebo groups (Table 1).

Efficacy of duloxetine for DPNP

The distribution of patients into the four groups, based on the degree of improvement in their 24-hour average pain score, is shown in Figure 1. Significantly, more patients treated with duloxetine compared with placebo achieved ≥50% improvement (47.2% versus 27.9%, respectively; odds ratio [OR]: 2.31), ≥30% improvement (65.1% versus 43.9%, respectively; OR: 2.38), and ≥15% improvement (75.5% versus 58.8%, respectively; OR: 2.16) in 24-hour average pain scores ($P<0.001$ for all groups).

QoL and PRO measures

There were significant differences between the duloxetine and placebo groups for all SF-36 scale scores, the EQ-5D, and the PGI-I (all $P<0.05$) (Table 2).

Table 1 Patient demographics and disease characteristics at baseline

Variable	DLX 60 mg QD (N=335)	Placebo (N=330)	Total (N=665)
Sex, n (%)			
Female	141 (42.1)	152 (46.1)	293 (44.1)
Male	194 (57.9)	178 (53.9)	372 (55.9)
Age (years)			
Mean (SD)	58.9 (11.3)	60.0 (10.4)	59.4 (10.8)
Range	20.4–88.8	23.9–80.6	20.4–88.8
≥65 years, n (%)	99 (29.6)	105 (31.8)	204 (30.7)
<65 years, n (%)	236 (70.4)	225 (68.2)	461 (69.3)
Origin, n (%)			
African descent	10 (3.0)	16 (4.8)	26 (3.9)
Western Asian	3 (0.9)	0 (0.0)	3 (0.5)
Caucasian	286 (85.4)	282 (85.5)	568 (85.4)
East/Southeast Asian	4 (1.2)	2 (0.6)	6 (0.9)
Hispanic	28 (8.4)	29 (8.8)	57 (8.6)
Other	4 (1.2)	1 (0.3)	5 (0.8)
Height (cm), mean (SD)	170.8 (10.7)[a]	170.5 (10.6)	170.6 (10.6)
Weight (kg), mean (SD)	94.0 (23.2)[a]	95.2 (22.5)	94.6 (22.9)
Type of diabetes, n (%)			
Type 1	47 (14.0)	36 (10.9)	83 (12.5)
Type 2	288 (86.0)	294 (89.1)	582 (87.5)
Duration of diabetes (years), mean (SD)	12.0 (9.1)	11.9 (9.8)	11.9 (9.5)
Duration of diabetic neuropathy (years), mean (SD)	4.0 (4.2)	3.9 (3.7)	3.9 (3.9)
Baseline 24-hour average pain severity, mean (SD)	5.9 (1.5)	5.7 (1.4)	5.8 (1.5)
Michigan Neuropathy Screening score, mean (SD)	5.1 (1.5)	5.4 (1.6)[b]	5.3 (1.6)

Notes: [a]N=334. [b]N=329.
Abbreviations: DLX, duloxetine; QD, once daily; N, total number; n, sample number; SD, standard deviation.

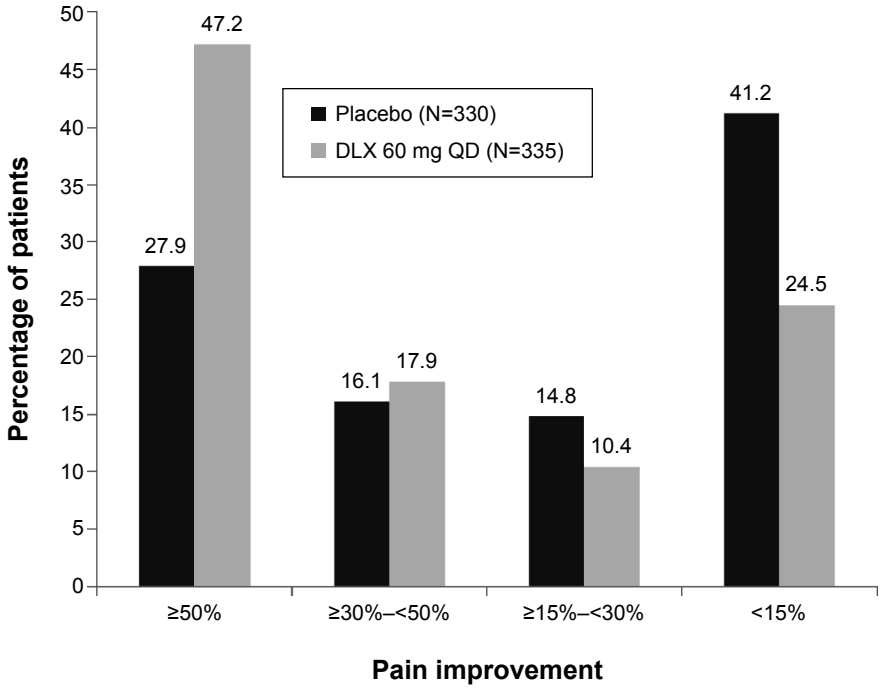

Figure 1 Percentage of patients with improvements in 24-hour average pain scores (12-week LOCF).
Notes: Patients were stratified into four groups (ie, ≥50%, ≥30%–<50%, ≥15%–<30%, and <15% improvement) for each treatment group based on the degree of pain improvement in 24-hour average pain scores (12-week LOCF) from baseline.
Abbreviations: N, total number; DLX, duloxetine; QD, once daily; LOCF, last observation carried forward.

Table 2 Change from baseline (12-week LOCF) for SF-36, EQ-5D, and PGI-I

Variable	DLX 60 mg QD		Placebo		Treatment group difference	
	n	LS mean (SE)	n	LS mean (SE)	LS mean (95% CI)	*P*-value
SF-36						
Physical functioning	316	9.02 (1.09)	309	4.28 (1.11)	4.74 (1.86–7.63)	0.001
Role–physical	315	18.52 (2.05)	308	10.81 (2.08)	7.71 (2.30–13.12)	0.005
Bodily pain	316	17.42 (1.12)	311	11.83 (1.13)	5.59 (2.65–8.52)	<0.001
General health	313	5.70 (0.88)	309	1.72 (0.89)	3.98 (1.66–6.29)	<0.001
Vitality	315	8.24 (1.01)	310	3.60 (1.02)	4.64 (1.99–7.30)	<0.001
Social functioning	316	7.15 (1.12)	311	3.77 (1.14)	3.38 (0.42–6.33)	0.025
Role–emotional	314	8.99 (1.95)	306	1.35 (1.98)	7.63 (2.48–12.78)	0.004
Mental health	315	3.79 (0.89)	310	0.12 (0.90)	3.67 (1.33–6.01)	0.002
PCS	310	5.85 (0.45)	304	3.73 (0.46)	2.12 (0.93–3.31)	<0.001
MCS	310	1.70 (0.46)	304	–0.25 (0.47)	1.96 (0.74–3.17)	0.002
EQ-5D index	311	0.13 (0.01)	309	0.08 (0.01)	0.05 (0.02–0.08)	0.002
PGI-I[a]	327	2.48 (0.07)	325	3.03 (0.07)	–0.55 (–0.74 to –0.37)	<0.001

Notes: Analysis of covariance model: change = Treatment + Investigator + Baseline. [a]Absolute value of 12-week LOCF.
Abbreviations: LOCF, last observation carried forward; SF-36, Short Form-36; EQ-5D, EuroQol five dimensions; PGI-I, Patient Global Impression of Improvement; DLX, duloxetine; QD, once daily; n, sample number; LS, least squares; SE, standard error; CI, confidence interval; PCS, physical component summary; MCS, mental component summary.

Relationship between QoL, PRO measures, and pain improvement

Baseline data were similar among the duloxetine-treated patients in the four pain improvement categorized groups for all of the SF-36 scale scores and the EQ-5D. For the SF-36 scale scores (Figure 2) and the EQ-5D (Figure 3), a group with more pain improvement generally showed a greater mean change from baseline. The ≥50% improvement group demonstrated the greatest change from baseline (improvement) among the four groups. For the PGI-I, a group with more pain improvement generally demonstrated a lower (better) mean score among the four groups (Figure 4).

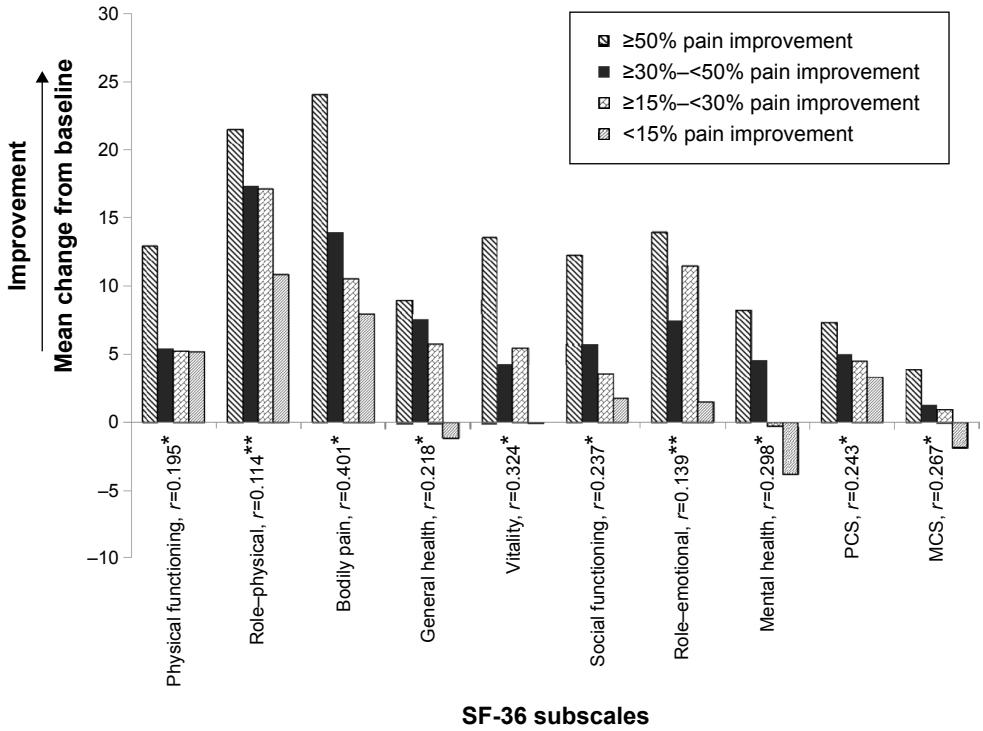

Figure 2 Mean change (12-week LOCF) from baseline in the SF-36 subscale scores in patients receiving duloxetine 60 mg per day in the four pain improvement categorized groups.
Notes: Pearson's correlation coefficient was calculated for the correlation between the percentage improvements in 24-hour average pain scores and SF-36 subscale scores (12-week LOCF). *r*-value represents the Pearson's correlation coefficient; *$P<0.001$, **$P<0.05$. Ns for pain improvement groups: ≥50%=150–151; ≥30%–<50%=57–59; ≥15%–<30%=34–35; and <15%=69–71.
Abbreviations: PCS, physical component summary; MCS, mental component summary; SF-36, Short Form-36; LOCF, last observation carried forward; N, total number.

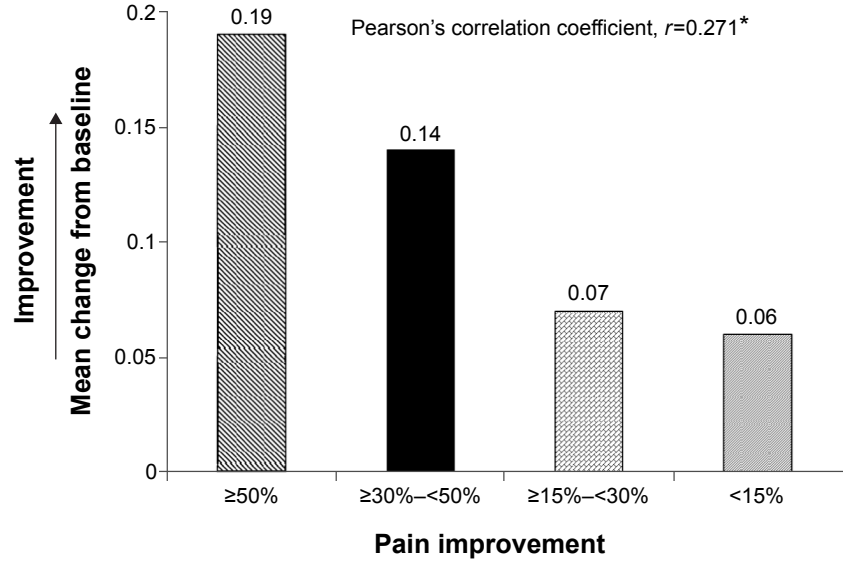

Figure 3 Mean change (12-week LOCF) from baseline on the EQ-5D index in patients receiving duloxetine 60 mg per day in the four pain improvement categorized groups.
Notes: Pearson's correlation coefficient was calculated for the correlation between the percentage improvements in 24-hour average pain scores and the EQ-5D index (12-week LOCF). *r*-value represents the Pearson's correlation coefficient; *$P<0.001$. Ns for the pain improvement groups: ≥50%=149; ≥30%–<50%=57; ≥15%–<30%=35; <15%=70.
Abbreviations: LOCF, last observation carried forward; EQ-5D, EuroQol five dimensions; N, total number.

Pearson's correlation coefficients ranged from 0.114 to 0.401 for the SF-36 scale scores ($P<0.05$) (Figure 2); the correlation coefficient was 0.271 for the EQ-5D ($P<0.001$) (Figure 3) and −0.565 for the PGI-I ($P<0.001$) (Figure 4).

Discussion

Studies have reported that DPNP is associated with poor QoL outcomes.[1] Duloxetine is effective in reducing pain and has been associated with significant improvement in health outcome measures in the management of DPNP.[5–8] In the current study, patients treated with duloxetine had superior improvement in pain and all QoL and PRO measures examined compared with placebo-treated patients. As in other duloxetine trials for chronic pain treatment,[12] a consistent relationship was seen between an average of 0 and 10 numeric rating scale scores for pain intensity and PGI-I.

However, the correlation between the degree of pain response and the improvement in patient QoL in

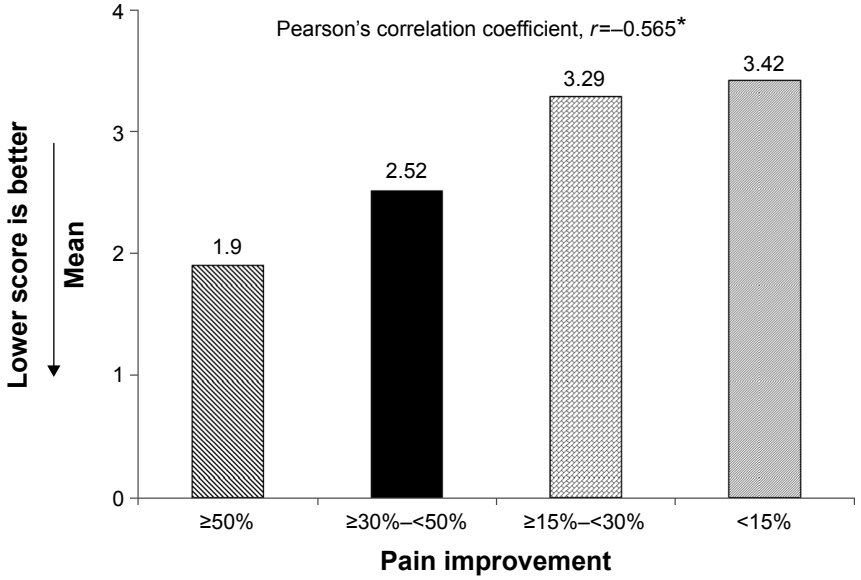

Figure 4 Mean (12-week LOCF) PGI-I in patients receiving duloxetine 60 mg per day in the four pain improvement categorized groups.
Notes: Pearson's correlation coefficient was calculated for the correlation between the percentage improvements in 24-hour average pain scores and PGI-I (12-week LOCF). *r*-value represents the Pearson's correlation coefficient; *$P<0.001$. Ns for pain improvement groups: ≥50%=156; ≥30%–<50%=60; ≥15%–<30%=34; <15%=77.
Abbreviations: LOCF, last observation carried forward; PGI-I, Patient Global Impression of Improvement; N, total number.

duloxetine-treated patients with DPNP has not been investigated in detail. In the current analyses, the group with more pain improvement generally showed greater mean change from baseline (improvement) for all QoL and PRO measures. The correlation between pain relief and QoL improvement was strong, particularly in the SF-36 subscale scores of bodily pain (correlation coefficient, r=0.401) and vitality (r=0.324), and in the PGI-I (r=–0.565).

Regarding the SF-36 scale scores, in the ≥50% improvement group, the physical component summary score numerically improved more than the mental component summary score, and the greatest change from baseline (improvement) was seen in the bodily pain and role–physical subscale scores. Similar results were also seen for the EQ-5D and the PGI-I, where the greatest improvement was seen in the ≥50% improvement group. Overall, patients achieving ≥50% pain improvement at the end of the study reported some SF-36 scale scores that were comparable with the general US population: vitality, mean baseline: 47.1, mean endpoint: 60.6, US norm: 60.9; social functioning, mean baseline: 72.3, mean endpoint: 84.5, US norm: 83.3; role–emotional, mean baseline: 70.4, mean endpoint: 84.3, US norm: 81.3; mental health, mean baseline: 71.4, mean endpoint: 79.7, US norm: 74.7; and general health: mean baseline: 49.2, mean endpoint: 58.1, US norm: 72.0.[13] Similar results were seen in a study of pregabalin, which also reported that improvement in functional outcomes and QoL correlated with the amount of pain relief (mental health was not described in the discussion).[14]

The 0.19 change seen in the EQ-5D associated with duloxetine treatment represents a considerable improvement that is well in excess of the minimally important difference reported for this instrument (0.074).[15] The EQ-5D endpoint score of 0.78 in the ≥50% improvement group is higher than that of a previous report of patients with diabetes having an EQ-5D score of 0.668.[16]

Higher levels of pain correspond with decreases in physical and mental functioning,[17] and patients with diabetes score poorly on QoL measures.[18] This current study shows that among duloxetine-treated patients, the greatest improvement was seen in the group with ≥50% improvement in the SF-36 scale scores, the EQ-5D, and the PGI-I. For the SF-36 scale scores, the greatest change from baseline was seen in the bodily pain and role–physical scale scores, both of which are subscales within the physical component summary of the SF-36 model. In this 12-week study, improvement in QoL and PRO in duloxetine-treated patients with DPNP was correlated with the extent of pain relief.

Limitations

Some limitations to these analyses need to be considered when interpreting the findings. This was a post hoc analysis. The results are based on an acute treatment duration of 12 weeks and may not be generalizable to longer periods of treatment. In addition, the generalizability of the results to all patients with DPNP may be affected by the inclusion and exclusion criteria of the individual trials. Finally, the SF-36 and EQ-5D are general health-related QoL instruments that are not specific for DPNP.

Conclusion

In the current results, significantly more patients treated with duloxetine compared with placebo achieved improvement in 24-hour average pain scores. Patients with the greatest improvement in pain scores had the greatest improvement in functionality, QoL, and PRO.

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Author contributions

All authors participated in the drafting, critical revision, and approval of the final version of the manuscript. SF conducted the data analysis, and all authors were involved in the interpretation of the data. All authors critically revised the manuscript for important intellectual content and approved the final version.

Disclosure

This manuscript was sponsored by Eli Lilly Japan K.K. KO, SF, and LA are employees of Eli Lilly Japan K.K. WM is an employee of Eli Lilly Australia Pty Ltd. SF and LA are minor stockholders of Eli Lilly and Company. The authors report no other conflicts of interest in this work.

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