# Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan

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## ABSTRACT

**Aims/Introduction:** Duloxetine has been suggested to exert analgesic effects by activating the descending inhibitory system through inhibition of serotonin (5-HT) and noradrenaline (NA) reuptake. This randomized controlled trial investigated the efficacy and safety of duloxetine in Japanese patients with diabetic neuropathic pain (DNP).

**Materials and Methods:** Duloxetine 40 or 60 mg/day or placebo was given orally once daily for 12 weeks. The primary efficacy measure was weekly mean 24-h average pain severity score on the 11-point Numerical Rating Scale.

**Results:** At 12 weeks *vs* baseline, the 24-h average pain score (adjusted mean ± SE) was significantly improved in the combined duloxetine (−2.47 ± 0.18) and duloxetine 40 mg (−2.41 ± 0.21) and 60 mg groups (−2.53 ± 0.21) as compared with the placebo group (−1.61 ± 0.18). Duloxetine also exerted significant improvements over the placebo in nearly all secondary outcome measures including 24-h worst pain, night pain, Brief Pain Inventory (BPI) pain scores, Patient's Global Impression of Improvement (PGI-I) and health outcome measures, namely, various BPI interference scores. The incidence of adverse events (AE) was higher in the duloxetine groups than in the placebo group (duloxetine overall, 84.8%; duloxetine 40 mg, 84.7%; duloxetine 60 mg, 84.9%; placebo, 73.7%). Most AE were mild or moderate in severity, and resolved or relieved. There were no clinically significant safety concerns.

**Conclusions:** Duloxetine 40 or 60 mg/day showed superiority over the placebo at reducing pain scores in patients with DNP. Duloxetine is safe, efficacious and clinically useful in the management of DNP. This trial was registered with ClinicalTrials.gov (no. NCT-00552175). (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00073.x, 2011)

**KEY WORDS: Diabetic neuropathic pain, Duloxetine, Serotonin and noradrenaline reuptake inhibitor**

## INTRODUCTION

Recently, the number of diabetic patients in Japan has increased. It is now thought to amount to 8.9 million, or 22.1 million when including incipient diabetic individuals[1]. Among three major complications of diabetes mellitus, diabetic neuropathy seems to have the highest incidence, with 36.7% of diabetic patients reported to be suffering from this condition[2].

Diabetic neuropathic pain (DNP) is characterized by the symptomatic nature of an aching, burning, tingling or stabbing sensation[3]. DNP not only is often increased at night and affects sleep[4], but also interferes with daily life, leading to deterioration of quality of life and a depressive state in severe cases[5].

Epalrestat and mexiletine hydrochloride are approved and widely used in Japan for the indication of DNP. Drugs listed as therapeutic options for DNP in *Evidence-based Practice Guideline for the Treatment of Diabetes in Japan*[6] include epalrestat, mexiletine hydrochloride, antidepressants, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs) and sustained-release oxycodone. NSAIDs might be efficacious against mild DNP, but not against moderate and severe forms. Tricyclic antidepressants, certain anticonvulsants and opioid analgesics are recommended for the treatment DNP, but might be limited by side effects[7].

Serotonin (5-HT) and noradrenaline (NA) have been implicated in the modulation of intrinsic analgesic mechanisms through descending inhibitory neurons in the brain and spinal cord[8–11]. An imbalance in these neurotransmitter mechanisms might contribute to central sensitization and hyperexcitability, thereby leading to persistent pain in DNP[12]. Current evidence suggests that antidepressants that have been shown to have analgesic effects in pain conditions exert such analgesic effects independent of improvement in mood or anxiety[13,14]. Instead, potentiation of 5-HT and NA activity in the central nervous system (CNS) through inhibition of their reuptake has been suggested as a probable mechanism of the analgesic action of antidepressants against neuropathic pain[15,16].

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Duloxetine hydrochloride is a selective and potent 5-HT and NA reuptake inhibitor (SNRI)[17] that has been shown to be effective in animal models of persistent and neuropathic pain[18]. Recently, duloxetine at doses of 60 mg/day given once or twice daily (120 mg/day) has been shown to be efficacious for the relief of pain in patients with DNP in randomized, double-blind, placebo-controlled clinical trials[19–21]. Based on this evidence, duloxetine was approved for the indication of DNP by the FDA in 2004. Presently, duloxetine has been made available in 90 countries as a therapeutic drug for DNP, and is recommended for this purpose by a number of USA and European guidelines[22–25].

In Japan, duloxetine has not yet been authorized as an approved therapeutic drug for DNP, although it is indicated for major depressive disorders. Tolerability and safety of duloxetine at dosages ≤60 mg/day have been confirmed in Japanese subjects during a phase I study[26]. In a double-blind, placebo-controlled phase II study of duloxetine ≤60 mg/day in Japanese patients with DNP, there were no safety concerns (unpublished data). Furthermore, data from phase II studies carried out in Japan and abroad[19–21] suggest that duloxetine ≥40 mg/day might improve DNP in Japanese patients.

The objective of the present study was to verify the superiority of once-daily oral dosing with the SNRI duloxetine 40 and 60 mg/day combined *vs* placebo therapy using as primary endpoint weekly mean change of 24-h average pain score on the 11-point Numerical Rating Scale[27].

## MATERIALS AND METHODS

### Patients

Patients, men and women aged 20–<80 years, had to have sustained pain for ≥6 months as a result of distal symmetric polyneuropathy caused by type 1 or type 2 diabetes mellitus. Pain was assessed on the local site of the foot, leg or hand with reference to the symptoms of an aching, burning, tingling or stabbing sensation and allodynia. Diagnosis of neuropathy was based on a revised version of the abbreviated diagnostic criteria for distal symmetric polyneuropathy proposed by the Diabetic Neuropathy Study Group in Japan (revised in 2002)[28]. The other main criteria for selection of subjects included glycated hemoglobin ($HbA_{1c}$) ≤9.4% at screening, fluctuation of $HbA_{1c}$ ≤1.0% at 42–70 days before screening, and the weekly mean of the 24-h average pain score rated by the 11-point (0–10) Numerical Rating Scale[27] collected from patient diaries over 7 days before initiation of the study drug administration being ≥4, that is, indicative of moderate or severe pain.

Main exclusion criteria were patients with psychiatric diseases, such as mania, bipolar disorder, depression, anxiety disorders and eating disorders, or patients with history of these diseases that needed any pharmacotherapy during the past year. Patients were also excluded if they had a complication that might affect assessment of DNP, such as neurological disorders unrelated to diabetic neuropathy, a skin condition in the area of the neuropathy that could alter sensation and other painful conditions. Patients were allowed to take a maximum daily dose of 1.5 g of acetaminophen, but no other drugs and therapies for DNP were allowed. Apart from insulin dose level, changes to existing diabetes treatments were prohibited.

Before randomization, an assigning table was prepared using Create Key Code 3.3. Patients were randomly assigned to duloxetine 40 or 60 mg or placebo groups in a 1:1:2 ratio by stochastic minimization allocation taking into account the following four factors: (i) weekly mean of 24-h average pain score at baseline < or ≥6; (ii) duration of diabetic neuropathy < or ≥2 years; (iii) type 1 or type 2 diabetes mellitus; and (iv) each study center.

### Study Design

Enrolment for the present study, which was carried out at 73 centers in Japan, began in December 2007 and ended in March 2009. This was a multicenter, randomized, double-blind, placebo-controlled, group-comparison phase III study in patients with DNP. The primary objective was to evaluate the efficacy of oral duloxetine 40 or 60 mg/day once daily *vs* placebo against DNP.

A screening period for 1–2 weeks during which entry criteria were evaluated without study medication was followed by a 13-week treatment period when subjects were treated with duloxetine 40 or 60 mg/day or placebo then a 1-week post-treatment period without study medication. Considering the safety of patients, a gradually titrating phase for the first 1–2 weeks initiating with 20 mg/day and increasing the dose at 20-mg weekly increments was set during the treatment period. There was also a 1-week tapering phase. Patients were seen at biweekly visits for the first 4 weeks of treatment then every 4 weeks thereafter.

The present study conforms to the principles of the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board at each center. All patients provided written informed consent before participating in any study-related procedures.

### Efficacy Evaluation

The primary efficacy measure for the present study was the reduction of the weekly mean of the 24-h average pain score as measured by the 11-point (from 0 = no pain to 10 = worst possible pain) Numerical Rating Scale recorded in a diary by patients each day. Secondary efficacy measures were pain severity for 24-h worst pain and night pain as measured by the 11-point Numerical Rating Scale, Patient's Global Impression of Improvement (PGI-I) Scale[29] recorded at weeks 2, 4, 8 and 12, and severity and interference portions of Brief Pain Inventory (BPI)[30] recorded at randomization and weeks 2, 4, 8 and 12.

### Safety Evaluation

Safety measures included spontaneously reported adverse events (AE), concomitant medications, bodyweight, vital signs (such as sitting blood pressure and heart rate) and ECG being recorded at each visit. Laboratory parameters including hematology, blood

chemistry, $HbA_{1c}$, lipids and urinalysis were generally recorded every 4 weeks. The value for $HbA_{1c}$ (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula $HbA_{1c}$ (%) = $HbA_{1c}$ (JDS) (%) + 0.4%, considering the relational expression of $HbA_{1c}$ (JDS) (%) measured by the previous Japanese standard substance and measurement methods and $HbA_{1c}$ (NGSP)[31]. For patients who discontinued the study, the aforementioned assessments were collected at their last visit.

### Statistical Analysis

The present study was planned to enrol 300 patients (150 for the placebo group and 75 each for the duloxetine 40 and 60 mg/day groups). The study would have ≥80% power to detect a difference between the combined duloxetine group and placebo group by *t*-test when the effect size of the combined duloxetine group to placebo group was taken as 0.33 and the level of significance as one-sided 0.025.

Efficacy analysis was carried out using data on all randomized patients with at least one post-baseline assessment. Efficacy analysis of the primary end-point was made by comparing the combined duloxetine group *vs* placebo group with regard to change of weekly mean of the 24-h average pain score from baseline to week 12 by incorporating all the weekly mean changes obtained at each point of the post-baseline measurements into a mixed-effects model repeated measures[32]. Secondary end-points were made by comparing the duloxetine 40 and 60 mg groups *vs* placebo group with regard to change of weekly mean of the 24-h average pain score analyzed by mixed-effects model repeated measures. Response rate defined as the percentage of patients who achieved 30 or 50% reduction of 24-h average pain score in the combined duloxetine and duloxetine 40 and 60 mg groups was compared *vs* the placebo by Fisher's exact test.

Safety was analyzed in all patients who took at least one dose of the test drugs. With regard to the incidence of each AE and each adverse drug reaction (ADR), the combined duloxetine group was compared with the placebo group by Fisher's exact test. Severity, causal relationship to study drugs, and outcome of AE and ADR were summarized by treatment group.

## RESULTS

### Patient Disposition

The disposition of patients enrolled in the study is shown in Figure 1. Of 448 screened patients, 339 patients (40 mg, $n$ = 86; 60 mg, $n$ = 86; placebo, $n$ = 167) were randomized to the study treatment. The patient population subjected to efficacy and safety analyses consisted of 338 patients, excluding one patient in the 40 mg group who did not receive the study drug and was not assessed.

### Demographics

Patients' demographics and baseline characteristics are shown in Table 1. Approximately 76% of the patients were men; the mean age was 60.8 years. Most patients (95%) had type 2 diabetes mellitus; the duration of the disease was >10 years in the majority. $HbA_{1c}$ ranged from 7.04% in the placebo group to 7.25% in the 40 mg group. Mean duration of diabetic neuropathy was 4.3 years. Weekly mean 24-h average pain score at baseline was 5.78. There was no significant difference of patient demographics and baseline characteristics among treatment groups.

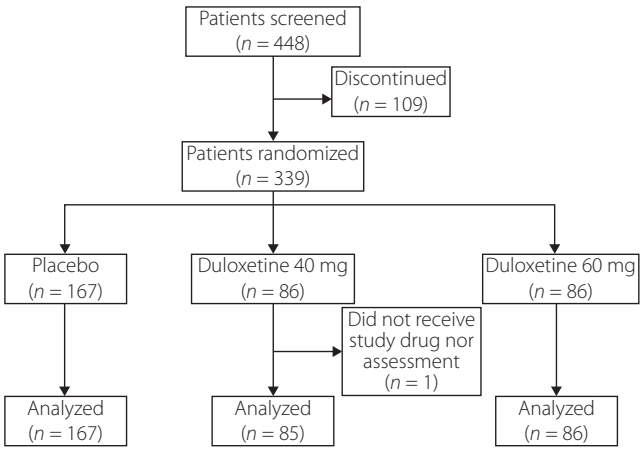


**Figure 1** | Patients' disposition.

### Efficacy

Figure 2 shows the weekly mean change of the 24-h average pain score from baseline to each point of measurement over 12 weeks. Change of this parameter (adjusted mean ± SE) from baseline to week 12 in the combined duloxetine, 40, 60 mg and placebo groups was −2.47 ± 0.18, −2.41 ± 0.21, −2.53 ± 0.21, −1.61 ± 0.18, respectively. Intergroup difference *vs* placebo for combined duloxetine was −0.87 ± 0.15 (95% confidence interval [CI], −1.17 to −0.56; $P < 0.0001$). On the basis of 95% CI of difference in each dose group *vs* placebo, the 24-h average pain score was also judged significantly improved in the duloxetine 40 and 60 mg groups as compared with the placebo (95% CI, −1.18 to −0.43 and −1.30 to −0.56, respectively). Both the combined duloxetine and 60 mg groups showed significant decreases of the 24-h average pain score compared with the placebo beginning at week 1, whereas this was observed in the 40 mg group beginning at week 2, and persisted in all three active treatment groups thereafter.

The response rate of 30% reduction of the 24-h average pain score in the combined, 40 and 60 mg, and placebo groups was 57.3% (98/171 patients; $P < 0.0001$ *vs* placebo), 55.3% (47/85), 59.3% (51/86) and 35.3% (59/167), respectively. The response rate of 50% reduction was 39.2% (67/171 patients; $P = 0.0001$ *vs* placebo), 37.6% (32/85), 40.7% (35/86) and 19.8% (33/167), respectively.

The results of mixed-effects model repeated measures analysis of the efficacy measures are summarized in Table 2. The combined duloxetine group produced a significantly greater

**Table 1** | Patient demographics and clinical characteristics at baseline

| | Combined duloxetine ($n$ = 171) | | 40 mg ($n$ = 85) | | 60 mg ($n$ = 86) | | Placebo ($n$ = 167) | | Total ($n$ = 338) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| Sex | | | | | | | | | | |
| Male | 127 | 74.3 | 65 | 76.5 | 62 | 72.1 | 129 | 77.2 | 256 | 75.7 |
| Female | 44 | 25.7 | 20 | 23.5 | 24 | 27.9 | 38 | 22.8 | 82 | 24.3 |
| Age (years) | | | | | | | | | | |
| 20–<30 | 1 | 0.6 | – | 0.0 | 1 | 1.2 | 1 | 0.6 | 2 | 0.6 |
| 30–<40 | 8 | 4.7 | 2 | 2.4 | 6 | 7.0 | 4 | 2.4 | 12 | 3.6 |
| 40–<50 | 16 | 9.4 | 4 | 4.7 | 12 | 14.0 | 12 | 7.2 | 28 | 8.3 |
| 50–<65 | 72 | 42.1 | 44 | 51.8 | 28 | 32.6 | 90 | 53.9 | 162 | 47.9 |
| 65–<80 | 74 | 43.3 | 35 | 41.2 | 39 | 45.3 | 60 | 35.9 | 134 | 39.6 |
| Mean ± SD | 60.9 ± 10.8 | | 62.1 ± 9.3 | | 59.7 ± 12.1 | | 60.8 ± 9.2 | | 60.8 ± 10.0 | |
| Weight (kg) | | | | | | | | | | |
| <50 | 15 | 8.8 | 10 | 11.8 | 5 | 5.8 | 14 | 8.4 | 29 | 8.6 |
| 50–<60 | 51 | 29.8 | 30 | 35.3 | 21 | 24.4 | 53 | 31.7 | 104 | 30.8 |
| 60–<70 | 62 | 36.3 | 24 | 28.2 | 38 | 44.2 | 53 | 31.7 | 115 | 34.0 |
| ≥70 | 43 | 25.1 | 21 | 24.7 | 22 | 25.6 | 47 | 28.1 | 90 | 26.6 |
| Mean ± SD | 63.9 ± 11.9 | | 62.7 ± 13.4 | | 65.1 ± 10.2 | | 64.5 ± 11.9 | | 64.2 ± 11.9 | |
| 24-h average pain score | | | | | | | | | | |
| <6 | 96 | 56.1 | 49 | 57.6 | 47 | 54.7 | 91 | 54.5 | 187 | 55.3 |
| ≥6 | 75 | 43.9 | 36 | 42.4 | 39 | 45.3 | 76 | 45.5 | 151 | 44.7 |
| Mean ± SD | 5.77 ± 1.20 | | 5.79 ± 1.23 | | 5.76 ± 1.17 | | 5.78 ± 1.17 | | 5.78 ± 1.18 | |
| Type of diabetes mellitus | | | | | | | | | | |
| Type 1 | 9 | 5.3 | 5 | 5.9 | 4 | 4.7 | 8 | 4.8 | 17 | 5.0 |
| Type 2 | 162 | 94.7 | 80 | 94.1 | 82 | 95.3 | 159 | 95.2 | 321 | 95.0 |
| Duration of diabetes (years) | | | | | | | | | | |
| <5 | 36 | 21.1 | 20 | 23.5 | 16 | 18.6 | 33 | 19.8 | 69 | 20.4 |
| 5–<10 | 32 | 18.7 | 18 | 21.2 | 14 | 16.3 | 32 | 19.2 | 64 | 18.9 |
| ≥10 | 103 | 60.2 | 47 | 55.3 | 56 | 65.1 | 97 | 58.1 | 200 | 59.2 |
| Unknown | – | 0.0 | – | 0.0 | – | 0.0 | 5 | 3.0 | 5 | 1.5 |
| Duration of diabetic neuropathy (years) | | | | | | | | | | |
| <2 | 53 | 31.0 | 26 | 30.6 | 27 | 31.4 | 51 | 30.5 | 104 | 30.8 |
| ≥2 | 118 | 69.0 | 59 | 69.4 | 59 | 68.6 | 116 | 69.5 | 234 | 69.2 |
| Mean ± SD | 4.4 ± 3.8 | | 4.6 ± 3.9 | | 4.2 ± 3.7 | | 4.2 ± 4.4 | | 4.3 ± 4.1 | |
| $HbA_{1C}$ (%) | | | | | | | | | | |
| Mean ± SD | 7.18 ± 0.88 | | 7.25 ± 0.85 | | 7.11 ± 0.90 | | 7.04 ± 0.90 | | – | |

The value for $HbA_{1C}$ (%) was estimated as an NGSP equivalent value (%) calculated by the formula $HbA_{1C}$ (%) = $HbA_{1C}$ (JDS) (%) + 0.4%.

improvement than the placebo for all pain measures including the 24-h worst pain score, night pain score, and BPI pain score with respect to the worst, least, average and right now. PGI-I score (adjusted mean ± SE) at week 12 was 2.53 ± 0.12 in the combined duloxetine group and 3.18 ± 0.12 in the placebo group. Global impression of pain improvement was significantly favorable for duloxetine *vs* the placebo ($P < 0.0001$).

Significant improvements of various individual health outcome measures were noted in the combined duloxetine group *vs* placebo including BPI average interference score ($P = 0.0095$), walking ability ($P = 0.0228$), relationship with other people ($P = 0.0076$), sleep ($P = 0.0378$) and enjoyment of life ($P = 0.0089$). However, no improvement was noted with regard to interference of general activity, mood and normal work.

### Safety

A total of 46 patients (13.6%) discontinued (combined duloxetine group, $n = 29$ [16.9%]; 40 mg group, $n = 13$ [15.1%]; 60 mg group, $n = 16$ [18.6%]; placebo group, $n = 17$ [10.2%]). Among them, 30 patients (8.8%) discontinued due to AE ($n = 21$ [12.2%], $n = 9$ [10.5%], $n = 12$ [14.0%], and $n = 9$ [5.4%], respectively).

Overall, the incidence of AE was significantly ($P = 0.0153$) higher in the combined duloxetine group (84.8%; 145/171 patients) than in the placebo group (73.7%; 123/167 patients). The incidence of AE in the 40 and 60 mg groups was 84.7% (72/85 patients) and 84.9% (73/86 patients), respectively.

AE and ADR reported during the present study are summarized in Table 3. AE that were significantly more frequently

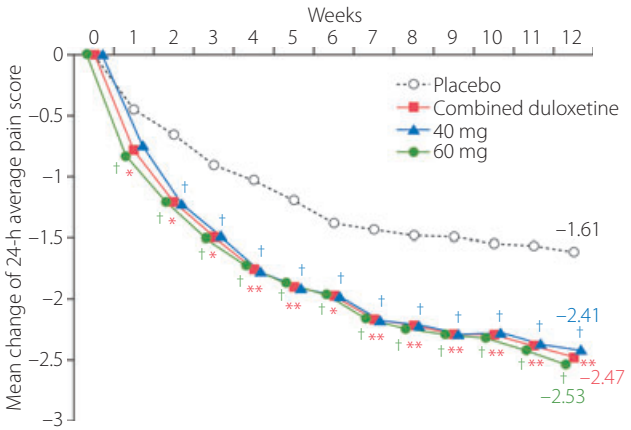


**Figure 2** | Mean weekly change of the 24-h average pain score (repeated measures analysis). *$P < 0.05$ *vs* placebo; **$P < 0.0001$ *vs* placebo; †95% confidence interval of difference *vs* placebo does not include zero.

reported in the combined duloxetine group than placebo group included somnolence ($P = 0.0007$), nausea ($P < 0.0001$) and dizziness ($P = 0.0354$). Most AE and ADR were mild or moderate in severity, and resolved or relieved. There was no noteworthy difference in the incidence, kind, severity and outcome of AE between the 40 and 60 mg groups.

A total of seven serious AE were noted in five patients in the combined duloxetine group (four events in three patients in the 40 mg group and three events in two patients in the 60 mg group), whereas 18 serious AE occurred in six patients in the placebo group. No deaths occurred during the present study. Overall, no significant difference was noted between the combined duloxetine and placebo groups. Among serious AE reported, hypoglycemia (40 mg group) and self-injurious behavior (60 mg group) were judged as ADR, although both symptoms resolved.

At 13 weeks compared with baseline, comparable and unremarkable increases of $HbA_{1c}$ were noted in the combined duloxetine, 40, 60 mg and placebo groups (0.06, 0.03, 0.10 and 0.10%, respectively).

## DISCUSSION

To evaluate the superiority of the SNRI duloxetine 40 and 60 mg/day once daily over the placebo, a randomized, double-blind, 12-week, phase III study was carried out in Japanese patients with moderate-to-severe DNP defined as having ≥4 on the 24-h average pain score. As a result, duloxetine was shown to be significantly superior to the placebo in improving DNP as evaluated by a change of the 24-h average pain score from baseline to week 12 as the primary efficacy end-point.

**Table 2** | Mean change from baseline to endpoint (repeated measures analysis): efficacy and health outcome measures

| | Combined duloxetine ($n = 171$) | | 40 mg ($n = 85$) | | 60 mg ($n = 86$) | | Placebo ($n = 167$) | |
|---|---|---|---|---|---|---|---|---|
| | Mean baseline (SD) | Mean change (SE) | Mean baseline (SD) | Mean change (SE) | Mean baseline (SD) | Mean change (SE) | Mean baseline (SD) | Mean change (SE) |
| Weekly mean of | | | | | | | | |
| 24-h average pain score | 5.77 (1.20) | −2.47 (0.18)** | 5.79 (1.23) | −2.41 (0.21)† | 5.76 (1.17) | −2.53 (0.21)† | 5.78 (1.17) | −1.61 (0.18) |
| 24-h worst pain score | 6.58 (1.33) | −2.51 (0.19)** | 6.54 (1.33) | −2.42 (0.22)† | 6.61 (1.33) | −2.59 (0.22)† | 6.66 (1.25) | −1.55 (0.19) |
| Night pain score | 5.62 (1.59) | −2.39 (0.19)** | 5.55 (1.64) | −2.33 (0.22)† | 5.69 (1.54) | −2.45 (0.23)† | 5.50 (1.49) | −1.56 (0.19) |
| BPI pain severity | | | | | | | | |
| Worst pain | 6.6 (1.4) | −2.59 (0.21)** | 6.5 (1.4) | −2.51 (0.25)† | 6.6 (1.5) | −2.68 (0.25)† | 6.7 (1.4) | −1.62 (0.21) |
| Least pain | 4.1 (1.7) | −1.98 (0.21)** | 4.0 (1.8) | −1.92 (0.25)† | 4.2 (1.6) | −2.04 (0.25)† | 4.1 (1.8) | −1.13 (0.21) |
| Average pain | 5.7 (1.3) | −2.54 (0.20)** | 5.6 (1.3) | −2.53 (0.23)† | 5.7 (1.3) | −2.56 (0.23)† | 5.6 (1.3) | −1.54 (0.20) |
| Pain right now | 5.2 (1.7) | −2.59 (0.22)** | 5.2 (1.8) | −2.55 (0.25)† | 5.3 (1.4) | −2.62 (0.26)† | 5.1 (1.7) | −1.67 (0.22) |
| BPI interference | | | | | | | | |
| General activity | 4.5 (2.5) | −2.29 (0.24) | 4.5 (2.7) | −2.48 (0.29)† | 4.5 (2.4) | −2.10 (0.29) | 4.4 (2.4) | −1.88 (0.24) |
| Mood | 4.1 (2.5) | −2.28 (0.24) | 3.9 (2.5) | −2.18 (0.29) | 4.2 (2.5) | −2.39 (0.29) | 4.2 (2.4) | −1.91 (0.24) |
| Walking ability | 4.4 (2.6) | −2.31 (0.23)* | 4.4 (2.8) | −2.32 (0.28) | 4.3 (2.5) | −2.31 (0.28) | 4.0 (2.6) | −1.82 (0.23) |
| Normal work | 4.1 (2.5) | −1.86 (0.23) | 3.9 (2.6) | −1.84 (0.28) | 4.3 (2.5) | −1.90 (0.28) | 3.7 (2.7) | −1.49 (0.23) |
| Relationship with other people | 2.8 (2.5) | −1.32 (0.23)* | 2.7 (2.7) | −1.16 (0.27) | 2.9 (2.4) | −1.49 (0.27)† | 2.6 (2.5) | −0.77 (0.23) |
| Sleep | 4.2 (2.8) | −2.15 (0.24)* | 4.0 (2.8) | −2.26 (0.29)† | 4.3 (2.7) | −2.05 (0.29) | 3.9 (2.7) | −1.69 (0.24) |
| Enjoyment of life | 3.9 (2.6) | −2.15 (0.23)* | 3.7 (2.7) | −1.96 (0.28) | 4.0 (2.5) | −2.35 (0.28)† | 3.5 (2.5) | −1.59 (0.23) |
| Average of 7 interference scores | 3.99 (2.18) | −2.04 (0.20)* | 3.88 (2.25) | −2.00 (0.24) | 4.09 (2.13) | −2.08 (0.24)† | 3.75 (2.15) | −1.56 (0.20) |
| PGI-I | – | 2.53 (0.12)** | – | 2.53 (0.14)† | – | 2.52 (0.14)† | – | 3.18 (0.12) |

BPI, Brief Pain Inventory; PGI-I, Patient's Global Impression of Improvement.
*$P < 0.05$ *vs* placebo; **$P < 0.0001$ *vs* placebo; †95%CI of difference *vs* placebo does not include zero.

**Table 3** | Incidence of adverse events reported by ≥5% patients in any group and adverse drug reactions

| Preferred term | Adverse events | | | | | | | | Adverse drug reactions | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined duloxetine (*n* = 171) | | 40 mg (*n* = 85) | | 60 mg (*n* = 86) | | Placebo (*n* = 167) | | Combined duloxetine (*n* = 171) | | 40 mg (*n* = 85) | | 60 mg (*n* = 86) | | Placebo (*n* = 167) | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Somnolence | 37 | 21.6* | 16 | 18.8 | 21 | 24.4 | 14 | 8.4 | 37 | 21.6* | 16 | 18.8 | 21 | 24.4 | 13 | 7.8 |
| Nausea | 24 | 14.0** | 10 | 11.8 | 14 | 16.3 | 3 | 1.8 | 24 | 14.0** | 10 | 11.8 | 14 | 16.3 | 3 | 1.8 |
| Nasopharyngitis | 24 | 14.0 | 10 | 11.8 | 14 | 16.3 | 24 | 14.4 | – | 0.0 | – | 0.0 | – | 0.0 | – | 0.0 |
| AST increased | 13 | 7.6 | 5 | 5.9 | 8 | 9.3 | 6 | 3.6 | 7 | 4.1 | 3 | 3.5 | 4 | 4.7 | 4 | 2.4 |
| Constipation | 11 | 6.4 | 6 | 7.1 | 5 | 5.8 | 9 | 5.4 | 9 | 5.3 | 5 | 5.9 | 4 | 4.7 | 6 | 3.6 |
| Diarrhea | 11 | 6.4 | 4 | 4.7 | 7 | 8.1 | 6 | 3.6 | 7 | 4.1 | 4 | 4.7 | 3 | 3.5 | 3 | 1.8 |
| Dizziness | 10 | 5.8* | 6 | 7.1 | 4 | 4.7 | 2 | 1.2 | 7 | 4.1 | 4 | 4.7 | 3 | 3.5 | 2 | 1.2 |
| ALT increased | 10 | 5.8 | 5 | 5.9 | 5 | 5.8 | 6 | 3.6 | 6 | 3.5 | 3 | 3.5 | 3 | 3.5 | 4 | 2.4 |
| Malaise | 9 | 5.3 | 3 | 3.5 | 6 | 7.0 | 3 | 1.8 | 9 | 5.3 | 3 | 3.5 | 6 | 7.0 | 3 | 1.8 |
| Vomiting | 9 | 5.3 | 4 | 4.7 | 5 | 5.8 | 2 | 1.2 | 8 | 4.7* | 4 | 4.7 | 4 | 4.7 | 1 | 0.6 |
| WBC increased | 9 | 5.3 | 4 | 4.7 | 5 | 5.8 | 4 | 2.4 | 1 | 0.6 | – | 0.0 | 1 | 1.2 | 1 | 0.6 |
| GGT increased | 7 | 4.1 | 2 | 2.4 | 5 | 5.8 | 5 | 3.0 | 4 | 2.3 | 1 | 1.2 | 3 | 3.5 | 2 | 1.2 |
| LDH increased | 7 | 4.1 | 2 | 2.4 | 5 | 5.8 | 4 | 2.4 | 3 | 1.8 | 1 | 1.2 | 2 | 2.3 | 3 | 1.8 |
| CK increased | 6 | 3.5 | 6 | 7.1 | – | 0.0 | 6 | 3.6 | 1 | 0.6 | 1 | 1.2 | – | 0.0 | 3 | 1.8 |
| $HbA_{1c}$ increased | 6 | 3.5 | 1 | 1.2 | 5 | 5.8 | 4 | 2.4 | 4 | 2.3 | – | 0.0 | 4 | 4.7 | 3 | 1.8 |

*$P < 0.05$ *vs* placebo; **$P < 0.0001$ *vs* placebo.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphokinase; GGT, γ-glutamyltransferase; $HbA_{1c}$, glycosylated hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cell count.

Recently, Farrar *et al.*[27,33] pooled data from placebo-controlled studies that investigated relationships between changes of Numerical Rating Scale pain ratings and quantifiable PGI-I scale. Their findings showed that a reduction of approximately 2 points from baseline on an 11-point pain rating scale, equivalent to a 30% reduction on pain score from baseline, corresponds to a clinically meaningful improvement. Subjects with 30–50% reduction in the assessment scale as compared with baseline are considered to be responders in guidelines on clinical investigation of medicinal products intended for the treatment of neuropathic pain[34]. In the present trial, the rate of responders was significantly higher in the combined duloxetine group than the placebo group. Taking into consideration that the present study was carried out in patients with moderate or severe DNP, duloxetine might contribute favorably to the treatment of such individuals.

Excluded from participating in the present study were patients complicated with psychiatric diseases including depression. Thus, the present findings support the argument that dual inhibition of reuptake of 5-HT and NA in the CNS contributes to the independent analgesic effect of duloxetine.

DNP is typically characterized by the manifestation of peripheral pain in the extremities, which causes unbearable distress to patients. The most important matter for those with DNP must be to lessen the pain as early as possible. Duloxetine was found to significantly improve the 24-h average pain score *vs* the placebo as early as 1 week after starting treatment. Therefore, duloxetine might be useful for treating patients with DNP because of its early manifestation of an analgesic effect.

DNP is not only often increased at night and affects sleep[4], but also interferes with daily life, leading to a lack of appetite and a depressive state in severe cases[5,35], and eventually to the deterioration of quality of life. Another important finding in the present study was that a significant improvement in health outcome measures was noted in the combined duloxetine group over the placebo for BPI average interference score as well as BPI interference of walking ability, relationships with other people, sleep and enjoyment of life. These clinical findings suggest that duloxetine might be helpful to improve patients' quality of life.

From the practical point of view, dosing frequency is an important clinical consideration. A systematic review of associations between dosing frequency and medication compliance showed that the latter is inversely related to the former[36]. The dosing frequency of epalrestat and mexiletine hydrochloride, which are widely used for the treatment of DNP in Japan, is thrice daily, whereas that of pregabalin, which is approved and used in the USA and European-approved pregabalin, is twice daily. Because we observed a significant improvement of DNP with the once-daily regimen, this suggests that adherence to treatment with duloxetine might be less of a clinical concern.

Incidence of AE/ADR was significantly higher in the combined duloxetine group than the placebo group, whereas that in the 40 and 60 mg groups was similar. In contrast, most AE and

ADR reported in the combined duloxetine group were mild or moderate in severity and resolved or relieved. Because no clinically problematic findings were noted, it is considered that there are no safety concerns with duloxetine in the setting of DNP.

Our safety data are comparable to those observed in a previous clinical trial carried out overseas[19,21], where the incidence of AE on duloxetine was 87.7% (498/568 patients); major AE were nausea (23.6%; $n = 134$ patients), somnolence (15.5%; $n = 88$), dizziness (13.4%; $n = 76$), constipation (11.3%; $n = 64$) and insomnia (10.2%; $n = 58$). Therefore, the type and incidence of AE in Japanese patients are similar to those in non-Japanese patients. Furthermore, there was little difference in change of $HbA_{1c}$ between each duloxetine treatment group and the placebo, as was observed in studies carried out overseas; 13-week treatment with duloxetine does not appear to adversely affect glycemic control.

In conclusion, the superiority of once-daily dosing with the SNRI duloxetine *vs* placebo in improving DNP was shown in Japanese patients. Both 40 and 60 mg daily dosages of duloxetine were safe and well tolerated.

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