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Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo

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SUMMARY

Background: Duloxetine has been approved in the United States, European Union and some Asian countries for the treatment of diabetic peripheral neuropathic pain (DPNP). We assessed the efficacy and safety of duloxetine (60 mg once daily) compared with placebo in Chinese patients suffering from DPNP. **Methods:** This was a phase 3, multicenter, randomised, double-blind, parallel, placebo-controlled, 12-week trial of the treatment of DPNP with duloxetine. Subjects were male and female outpatients ≥ 18 years of age with DPNP, as assessed by the Michigan Neuropathy Screening Instrument, and had a rating of ≥ 4 on the Brief Pain Inventory-Modified Short Form-Severity weekly average pain item. The primary efficacy measure was the reduction in pain severity from baseline to 12 weeks, as measured by the weekly mean of 24-h average pain ratings recorded in the patient's diary. Mean changes from baseline in efficacy measures were analysed by a restricted maximum likelihood-based, mixed-effects model repeated measures approach and by analysis of covariance. **Results:** Of the 405 patients randomised, 203 patients were assigned to duloxetine 60 mg once daily and 202 patients were assigned to placebo. Duloxetine-treated patients showed significantly greater pain relief on 24-h average pain ratings compared with placebo-treated patients each week of the 12-week study period [week 12: least squares (LS) mean change duloxetine: −2.40, placebo: −1.97; LS mean change difference (95% confidence interval) = −0.43 (−0.82, −0.04), p = 0.030]. Compared with placebo, patients treated with duloxetine experienced higher rates of nausea (p = 0.010), somnolence (p < 0.001) and asthenia (p = 0.002). **Conclusions:** Duloxetine-treated patients showed significantly greater pain relief compared with placebo-treated patients over the 12-week study period. Duloxetine was shown in Chinese patients to have a safety profile similar to that found in previous duloxetine trials.

What's known

The efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain (DPNP) is well-documented. This treatment has been approved in the United States, Europe and some Asian countries.

What's new

The present study is the first positive registration study of the use of duloxetine in the treatment of Chinese patients with DPNP. Patients treated with duloxetine had significantly greater reduction in weekly means of 24-h average pain, 24-h worst pain and 24-h night pain relative to placebo-treated patients. A greater proportion of patients treated with duloxetine experienced 30% and 50% reductions in weekly means of 24-h average pain, compared with the placebo group. More patients treated with duloxetine (compared with placebo) reported feeling 'much better.' The safety profile in Chinese patients was similar to that in other duloxetine studies.

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Disclosures
Drs Gao, Guo, Han, Li, Yang, and Qu have no conflicts of interest. Drs Dueñas, Yue, Wang, Skljarevski, and Raskin are employees and minor shareholders of Eli Lilly and Company.

Introduction

Diabetic peripheral neuropathic pain (DPNP) is a condition resulting from nerve damage after a prolonged period of suboptimal glycemic control (1). A complication of diabetes, DPNP is associated with variable pain described as aching, tingling and burning in the feet or lower legs, and is often worse at night and therefore frequently affects sleep (2,3). A recent meta-analysis indicates that the prevalence of diabetes in China is between 4.6% and 8.0%, depending on the region, and has been sharply increasing over the last three decades (4). Up to 50% of patients with diabetes develop peripheral neuropathy (5).

The neurotransmitters serotonin and norepinephrine have been implicated in the mediation of endogenous analgesic mechanisms through the descending inhibitory pain pathways in the brain and spinal cord (6,7). Dysfunction within the endogenous pain inhibitory mechanisms may contribute to the sensitisation and hyperexcitability of pain-transmitting pathways, resulting in persistent pain (8). Duloxetine is a selective and relatively balanced reuptake inhibitor

of serotonin and norepinephrine (9) and has previously been found to be effective in the management of musculoskeletal pain (10,11) and fibromyalgia (12). For the treatment of DPNP, the efficacy of duloxetine has been established in four placebo-controlled trials (13–16). Tanenberg et al. (17) showed that duloxetine was non-inferior to pregabalin for the treatment of DPNP. In addition, maintenance of effect of duloxetine in patients with DPNP has been shown in a 6-month open-label study by Skljarevski et al. (18). Two 52-week studies (19,20) also provided evidence that duloxetine was superior to routine care for the long-term management of DPNP. A third 52-week study (21) found that duloxetine was safe and well-tolerated compared with routine care.

Currently, there is no acknowledged standard of treatment in China for DPNP. However, results from recent studies of the pharmacokinetic properties of duloxetine in healthy Chinese volunteers (22,23) are consistent with those of a previous study of duloxetine comparing Japanese and Caucasian subjects (24). Therefore, it is hypothesised that duloxetine should be effective for the treatment of DPNP in Chinese patients as it is for other studied populations.

The primary objective of this study was to assess the efficacy of duloxetine at a dose of 60 mg once daily compared with placebo in Chinese patients suffering from DPNP. This objective was assessed by using the change in pain severity from baseline to 12 weeks, as measured by the weekly mean of the daily pain ratings based on an 11-point Likert scale reported by the patient. Secondary objectives included further assessments of the reduction in DPNP over the 12-week treatment period, the study of patient-reported health outcomes, and the evaluation of the safety of duloxetine 60 mg once daily.

Materials and methods

Study design

This phase 3, multicenter, randomised, double-blind, parallel, placebo-controlled trial consisted of three study periods (Figure 1). In Study Period I, an assessment and screening period of up to 3-week duration, patients were evaluated for study eligibility. Patients who met entry criteria were enrolled in the treatment phase (Study Period II). Randomised (1:1) to one of two treatment groups, patients received either duloxetine 60 mg once daily or placebo once daily. Those patients randomised to duloxetine were initially treated with 30 mg once daily, then, increased to 60 mg once daily after 1 week. During this study period, patients were evaluated on efficacy and safety measures. Study Period III was a 1-week, double-blind tapering period after the 12-week treatment phase. Patients who were treated with duloxetine were given 30 mg once daily and patients treated with placebo remained on placebo for the duration of the study period.

Patients were allowed to take up to 3 g of acetaminophen daily as rescue treatment. Other analgesic agents were not allowed during the screening period. However, after the screening period, episodic use of some analgesics was allowed for pain unrelated to diabetic neuropathy (e.g. for the treatment of injuries). 'Episodic use' was defined as no more than 3 consecutive days, not to exceed 14 total days during the study. Patients were not allowed to take analgesics

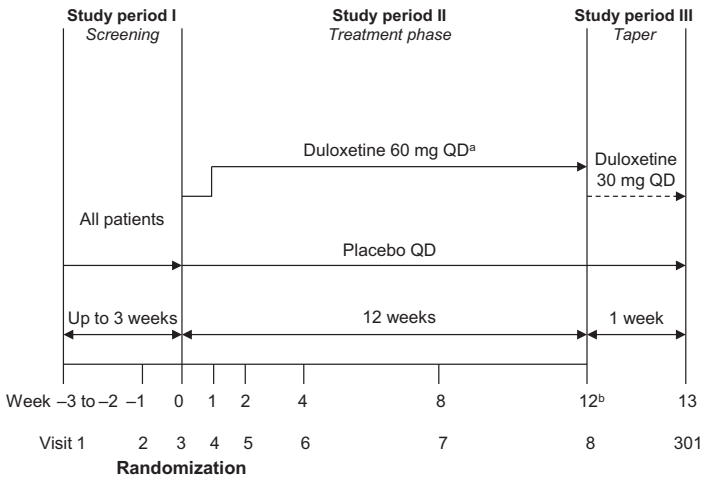

Figure 1 Study design. QD, once daily. [a]Patients randomised to duloxetine started treatment at 30 mg QD for the first week. [b]Study Period III was a required taper and began either at the patient's final visit for Study Period II (visit 8), or if a patient discontinued early after visit 4 (provided the patient was not discontinued due to suicide risk).

within 3 days prior to a scheduled visit. Any patient who exceeded the allotted use of analgesics during the study would have been discontinued. Patients taking herbal remedies/medicines started taking them at least 1 month prior to the study and continued taking them throughout the study. No changes in frequency of use, changes in dose or addition of other compounds were allowed.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its guidelines. The Ethical Review Boards at each investigative site provided written approval of the study protocol and the informed consent document. No protocol-related procedures were performed before patients signed the informed consent document.

Study population

Subjects included male and female outpatients, at least 18 years of age, who presented with bilateral DPNP that began in the feet with relatively symmetrical onset. Daily pain had to be present for at least 6 months. The diagnosis was confirmed at study entry by a score of at least three on the Michigan Neuropathy Screening Instrument. A rating of at least 4 on the Brief Pain Inventory-Modified Short Form-Severity (BPI-Severity) weekly average pain item at both screening visits was also required. Patients were excluded from the study if they had any medical or other condition that could have compromised participation in the study. These criteria included unstable glycemic control (glycosylated haemoglobin > 12%), major depressive disorder, mania, bipolar disorder, dysthymia, anxiety disorders (excluding phobias), alcohol or eating disorders, psychosis, risk for suicide, serious or unstable cardiovascular, hepatic, renal, respiratory, or haematological illness, symptomatic peripheral vascular disease, or the presence of other serious medical conditions. The first patient was enrolled in May 2011 and last patient completed the study in August 2013.

Efficacy measures

Severity of DPNP is reported here as the weekly mean of the daily pain ratings (average pain, worst pain and night pain) recorded in the patient's diary (a self-assessment of the past 24 h, based on an 11-point Likert scale, from 0 (no pain) to 10 (worst possible pain). In addition, the BPI-Severity scale (25) was reported/collected at weekly visits. Questions assessed the severity of worst pain (previous 24 h), least pain (previous 24 h), average pain (no timeframe specified) and 'pain right now.' Like the patient's pain diary, the severity ratings for the BPI-Severity scale range from 0 (no pain) to 10 (pain as bad as you can imagine). The Patient Global Impression of Improvement (PGI-Improvement) scale, a 7-point scale, was completed by the patient to measure the degree of symptom improvement at the time of assessment. A rating of 1 indicates that the patient is 'very much improved,' a rating of 4 indicates that the patient has experienced 'no change,' and a rating of 7 indicates that the patient is 'very much worse.'

Health outcomes measures

To assess patient-reported health outcomes, this study utilised the Brief Pain Inventory-Short Form-Interference (BPI-Interference) scale and the Sheehan Disability Scale (SDS) (26). The BPI-Interference was completed by patients to measure the degree to which DPNP interfered with several activities of their daily living. Seven questions assessing the interference of pain for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life were scored, ranging from 0 (does not interfere) to 10 (completely interferes). The SDS, a patient-rated instrument used to assess the functional impact of symptoms on several interrelated domains, asked patients to rate the extent to which work or school, social life and home life or family responsibilities are impaired by their symptoms. Ranging from 0 (not at all) to 10 (extremely), scores of 5 and above are associated with significant functional impairment. Patients were also asked to provide their impression of how many days were lost or rendered unproductive during the past week because of their symptoms.

Safety measures

The following safety parameters were evaluated during the study: discontinuations because of adverse events, adverse events (regardless of whether they were perceived to be related to the study drug), serious adverse events, treatment-emergent adverse events, vital signs (sitting blood pressure and pulse rate), weight, laboratory analyses, suicide-related events (behaviour and/or ideations) and the Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR) total scores (27).

Statistical analysis

Sample size was based on the primary objective to assess the efficacy of duloxetine compared with placebo, measured by the 12-week change on the weekly mean of the daily average pain. With a clinical difference of 0.6 and a likely standard deviation of 2.01, a total sample size of 400 patients (200 patients per group) was planned for 5% two-sided alpha and 90% power. An intent-to-treat principle was used in the analyses of all efficacy variables, i.e. patients were

analysed based on their randomised treatment assignment, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not follow or complete the protocol. For each efficacy variable, the analysis included all randomised patients with a baseline and at least one postbaseline observation. All randomised patients who received at least one dose of a trial treatment were included in the safety analyses (Safety Set). Investigative sites with fewer than four patients with postbaseline data were pooled for statistical analysis purposes.

Mean changes from baseline in efficacy measures, including health outcomes measures, were analysed by a restricted maximum likelihood (REML)-based, mixed-effects model repeated measures approach (MMRM) with the terms of treatment, investigative site, visit, treatment-by-visit interaction, baseline pain severity rating and baseline rating-by-visit interaction included into the model, and by analysis of covariance with the terms of treatment, investigative site, treatment-by-investigative site interaction and baseline pain severity ratings included. Mean changes from baseline to 12 weeks in health outcomes measures were analysed by analysis of covariance. Also, Fisher's exact test was used to compare the incidence rates of serious adverse events, reasons for discontinuation and treatment-emergent adverse events of duloxetine and placebo. A treatment-emergent adverse event was defined as an adverse event that first occurred or worsened during the acute treatment phase after baseline. Fisher's exact test was also used to compare frequency of usage of concomitant medications and treatment compliance.

Analysis of proportions of patients experiencing $\geq 30\%$ and $\geq 50\%$ reductions (28,29) at end-point (last observation carried forward) were carried out on the BPI-Severity of average pain and weekly means of 24-h average pain from patient diaries. Cochran Mantel Haenszel tests stratified by investigative site were performed. Finally, the number needed to treat (NNT) and the number needed to harm (NNH) were calculated.

All tests of treatment effects were conducted at a two-sided alpha level of 0.05. Analyses were conducted with SAS® Version 9.2 (The SAS Institute, Inc., Cary, NC) and run in the PC environment.

Results

Patient disposition

Figure 2 summarises patient disposition during the screening and the 12-week treatment phase. Of the 405 patients randomised, 203 patients were assigned

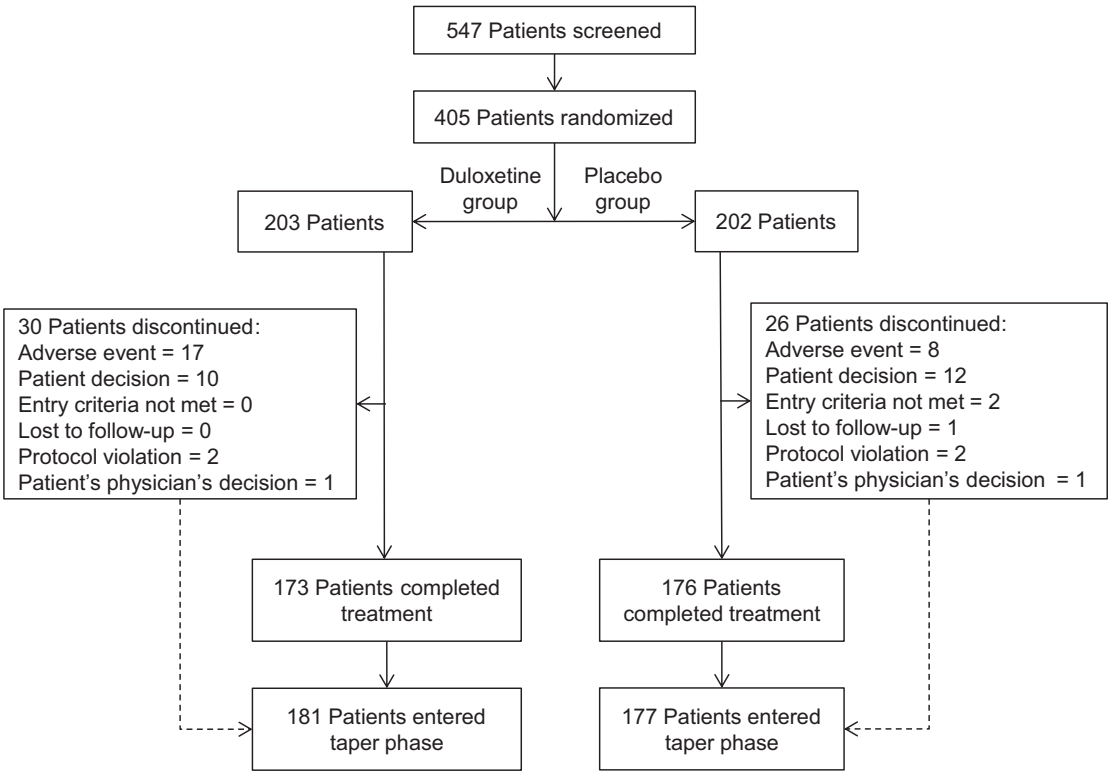

Figure 2 Subject disposition

Table 1 Demographics and baseline assessments

	Duloxetine (*N* = 203)	Placebo (*N* = 202)	Total (*N* = 405)	p-Value
Age, years, mean (SD)	61.6 (9.7)	61.2 (9.4)	61.4 (9.5)	0.431
Gender, *n* (%)				1.000
Female	112 (55.2)	111 (55.0)	223 (55.1)	
Male	91 (44.8)	91 (45.0)	182 (44.9)	
BMI, kg/m^2, mean (SD)	24.6 (3.6)	24.5 (3.2)	24.6 (3.4)	0.746
Type of diabetes mellitus, *n* (%)				1.000
Type I	3 (1.5)	3 (1.5)	6 (1.5)	
Type II	200 (98.5)	199 (98.5)	399 (98.5)	
Duration of diabetes, years, mean (SD)	11.5 (6.8)	11.4 (7.5)	11.5 (7.1)	0.943
Duration of diabetic neuropathy, years, mean (SD)	3.5 (3.9)	3.1 (3.1)	3.3 (3.6)	0.345
Weekly mean of 24-h average pain severity, mean (SD)	5.7 (1.7)	5.6 (1.7)	5.7 (1.7)	0.328
BPI-Severity average pain in the last week, mean (SD)	6.0 (1.7)	5.9 (1.6)	5.9 (1.7)	0.296
BPI-Interference average score, mean (SD)	4.4 (2.3)	4.1 (2.3)	4.2 (2.3)	0.129
SDS total score, mean (SD)	11.2 (7.6)	10.5 (7.3)	10.9 (7.5)	0.441
QIDS-SR16 total score, mean (SD)	5.6 (4.3)	4.7 (3.9)	5.2 (4.1)	0.122

Frequencies were analysed using Fisher's exact test; means were analysed using a type III sum of squares analysis of variance (investigator and treatment). BMI, body mass index; BPI-Interference, Brief Pain Inventory-Modified Short Form-Interference; BPI-Severity, Brief Pain Inventory-Modified Short Form-Severity; *N*, number of patients in group; *n*, number of affected patients; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology-Self-Rated; SD, standard deviation; SDS, Sheehan Disability Scale.

to duloxetine 60 mg qd and 202 patients were assigned to placebo. A total of 349 (86.2%) patients completed the 12-week treatment phase of this study, including 173 (85.2%) patients treated with once daily 60-mg duloxetine and 176 (87.1%) patients assigned placebo. At baseline, there were no statistically significant imbalances in demographics or disease characteristics between the two treatment groups (Table 1).

Efficacy

Figure 3 displays the change from baseline in weekly mean of 24-h average pain severity (from patient diaries) for both treatment groups after 12 weeks of therapy. Duloxetine-treated patients showed significantly greater pain relief (as measured by the weekly mean of the daily pain ratings recorded in patients' diaries) compared with placebo-treated patients beginning 1 week after randomisation and continuing through the 12-week treatment phase [week 12: LS mean change (SE) duloxetine: −2.40 (0.14), placebo: −1.97 (0.14); LS mean change difference (95% confidence interval) = −0.43 (−0.82, −0.04), p = 0.030] (Table 2). In addition, a greater proportion of patients treated with duloxetine experienced a reduction in the weekly mean of their 24-h average

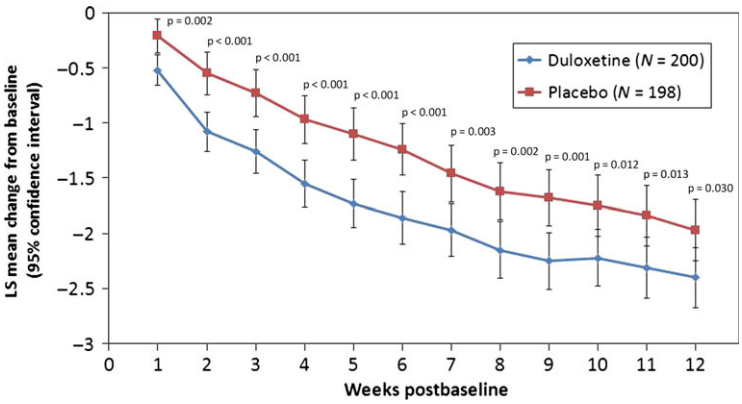

Figure 3 Change from baseline in weekly mean of 24-h average pain severity for all randomised patients over 12 weeks of double-blind therapy. LS, least squares; *N*, number of patients in group. Repeated measures analysis model: Variable = Treatment + Investigator + Week + Baseline + Treatment × Week + Baseline × Week

Table 2 Least squares mean or mean change (week 12) in efficacy and health outcome measures

	Duloxetine		Placebo			
	N	LS mean or change (SE)	*N*	LS mean or change (SE)	LS mean difference (95% CI)	Between-groups p-value
Weekly mean score from patient's diary						
24-h average pain*	172	−2.40 (0.14)	173	−1.97 (0.14)	−0.43 (−0.82, −0.04)	0.030
24-h worst pain	172	−2.80 (0.16)	173	−2.25 (0.17)	−0.55 (−1.00, −0.10)	0.017
24-h night pain	172	−2.65 (0.15)	173	−2.11 (0.15)	−0.54 (−0.95, −0.14)	0.008
BPI-Severity						
Average pain	173	−2.50 (0.15)	175	−2.00 (0.15)	−0.50 (−0.90, −0.09)	0.016
Worst pain	173	−2.86 (0.17)	175	−2.36 (0.17)	−0.51 (−0.97, −0.04)	0.032
Least pain	173	−1.97 (0.14)	175	−1.41 (0.14)	−0.55 (−0.94, −0.17)	0.004
Pain right now	173	−2.76 (0.16)	175	−2.35 (0.16)	−0.41 (−0.84, 0.02)	0.061
BPI-Interference						
Average score	173	−2.42 (0.13)	176	−1.82 (0.14)	−0.60 (−0.96, −0.24)	0.001
General activity	173	−2.80 (0.17)	176	−2.35 (0.18)	−0.45 (−0.91, 0.01)	0.054
Mood	173	−2.32 (0.15)	176	−1.77 (0.16)	−0.55 (−0.96, −0.13)	0.010
Walking ability	173	−2.76 (0.17)	176	−1.94 (0.17)	−0.82 (−1.26, −0.37)	<0.001
Normal work	173	−2.50 (0.16)	176	−1.97 (0.17)	−0.53 (−0.97, −0.10)	0.016
Relations with people	173	−1.63 (0.14)	176	−1.24 (0.14)	−0.39 (−0.76, −0.02)	0.037
Sleep	173	−2.63 (0.17)	176	−2.04 (0.17)	−0.59 (−1.04, −0.14)	0.011
Enjoyment of life	173	−2.20 (0.15)	176	−1.69 (0.16)	−0.50 (−0.91, −0.10)	0.016
PGI-Improvement	173	2.44 (0.07)	176	2.65 (0.07)	−0.21 (−0.40, −0.02)	0.034
SDS total score	172	−6.36 (0.40)	175	−5.09 (0.42)	−1.26 (−2.33, −0.20)	0.020

Repeated measures analysis model: Variable = Treatment + Investigator + Week (or Visit) + Baseline + Treatment × Week (or Visit) + Baseline × Week (or Visit). BPI-Interference, Brief Pain Inventory-Modified Short Form-Interference; BPI-Severity, Brief Pain Inventory-Modified Short Form-Severity; LS, least squares; *N*, number of patients in group; PGI-Improvement, Patient's Global Impression of Improvement; SDS, Sheehan Disability Scale; SE, Standard Error. *See also Figure 3, Week 12.

pain at end-point compared with patients treated with placebo (≥ 30% reduction: 61.5% vs. 49.0%, p = 0.014, NNT=8.0; ≥ 50% reduction: 42.0% vs. 28.8%, p = 0.006, NNT=7.6). The other weekly mean ratings of 24-h pain ['worst pain' (p = 0.017) and 'night pain' (p = 0.008)] were significantly more improved (decreased) during the 12-week treatment with duloxetine compared with placebo-treated patients (Table 2) as well.

The BPI-Severity measures of 'average pain' [LS mean change (SE) for duloxetine: −2.50 (0.15); placebo: −2.00 (0.15) p = 0.016], 'worst pain' (p = 0.032), and 'least pain' (p = 0.004) were also significantly more improved (decreased) compared with placebo, while improvement in 'pain right now' was not statistically different between the two groups (Table 2). A greater proportion of patients treated with duloxetine (compared with patients treated with placebo) experienced a reduction in pain as measured on the BPI-Severity average pain at end-point (≥ 30% reduction: 63.0% vs. 46.7%, p = 0.003, NNT=6.1; ≥ 50% reduction: 46.0% vs. 29.4%, p = 0.001, NNT = 6.0).

Significant improvements for patients treated with duloxetine (compared with placebo) were also shown in PGI-Improvement (p = 0.034). Categorical analysis of patient responses on the PGI-Improvement scale indicated an overall statistically significant difference between treatment groups (p = 0.0084; Figure 4). More duloxetine-treated patients (47.2%) responded with 'much better' than placebo-treated patients (33.9%), while more placebo-treated patients (18.2%) responded with 'the same' than duloxetine-treated patients (7.1%). Patients in both treatment groups had similar proportionate responses for 'very much better,' 'a little better,' 'a little worse' and 'much worse.'

Health outcomes

Health outcomes results are shown in Table 2. The improvement in the BPI-Interference average score was significantly greater in the duloxetine-treated vs. the placebo-treated group (p = 0.001). All of the BPI-Interference individual items showed a statistically significantly decrease with duloxetine patients (compared with placebo) except for 'general activity.'

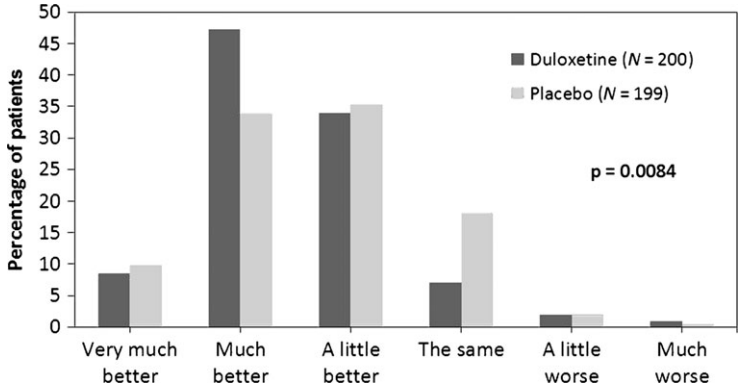

Figure 4 Categorical analysis of patient responses on the Patient Global Impression of Improvement scale (duloxetine vs. placebo). *N*, number of patients in group. Frequencies were analysed using Fisher's exact test

Significant improvements for patients treated with duloxetine (compared with placebo) were also shown in the SDS total score (p = 0.020).

Safety and tolerability

Overall, there were few significantly different rates of serious adverse events between the two treatment groups. No deaths occurred during the study. A total of five (1.2%) patients experienced five serious adverse events during treatment phase, which included three (1.5%) duloxetine-treated patients (one asthenia, one diabetes mellitus, one nodal arrhythmia), and two (1.0%) placebo-treated patients (one cholecystitis chronic, one non-Hodgkin's lymphoma). Asthenia was possibly related to blinded study drug, but not related to protocol procedures; others were not related to the blinded study drug or protocol procedures at the investigators' discretion. Of 202 patients treated with duloxetine, 17 (8.4%) discontinued because of adverse events and of 202 patients treated by placebo, 8 (4.0%) discontinued because of adverse events (p = 0.097).

In addition, there were no suicide-related events (behaviour or ideation) reported. Compared with placebo, patients treated with duloxetine experienced statistically significantly higher rates of the following treatment-emergent adverse events: nausea (p = 0.010, NNH = 14.5), somnolence (p < 0.001, NNH = 12.7) and asthenia (p = 0.002, NNH=20.0) (Table 3). Nausea associated with duloxetine was most often characterised as 'mild' [*n* = 19 (two patients experienced nausea twice)], but there were also cases of 'moderate nausea' (*n* = 4). All of the instances of nausea associated with placebo were characterised as 'mild' (*n* = 7). For the duloxetine group, two patients (1.0%) discontinued because of nausea, zero patients discontinued because of somnolence, and two patients (1.0%) discontinued because of asthenia. No placebo-treated patients discontinued because of these adverse events. Although not statistically significant, more duloxetine-treated patients (8.4%) discontinued the study because of any adverse event compared with placebo-treated patients (4.0%) in this study.

Table 3 Adverse events (treatment phase) in ≥ 5% of duloxetine-treated patients or that were statistically different between duloxetine and placebo

	Duloxetine (*N* = 202), *n* (%)	Placebo (*N* = 202), *n* (%)	p-Value
Patients with ≥ 1 TEAE	94 (46.5)	72 (35.6)	0.034
Nausea	21 (10.4)	7 (3.5)	0.010
Dizziness	17 (8.4)	9 (4.5)	0.155
Decreased appetite	11 (5.4)	8 (4.0)	0.639
Somnolence	17 (8.4)	1 (0.5)	< 0.001
Constipation	10 (5.0)	4 (2.0)	0.172
Fatigue	10 (5.0)	4 (2.0)	0.172
Asthenia	10 (5.0)	0	0.002

Frequencies were analysed by Fisher's exact test. *N*, number of patients in group; *n*, number of affected patients; TEAE, treatment-emergent adverse event.

There were no significant LS mean changes from baseline for duloxetine for blood pressure, heart rate or weight. Also, QIDS-SR16 total scores (LS mean change, week 12) were not significantly different between treatment groups.

Concomitant medications

Almost all of the patients in this study (97.3%) were taking concomitant medications. The most commonly used drugs (≥ 10% of patients) were metformin (37.8%), acarbose (31.9%), mecobalamin (17.5%), Chinese medicine (16.5%), human mixtard

Table 4 Percentage use of concomitant paracetamol, by visit

	Duloxetine	Placebo	Total	p-Value
Paracetamol (visit 3 – baseline)				
N	202	202	404	0.543
Yes, *n* (%)	7 (3.5)	4 (2.0)	11 (2.7)	
No, *n* (%)	195 (96.5)	198 (98.0)	393 (97.3)	
Paracetamol (visit 4)				
N	200	198	398	0.371
Yes, *n* (%)	1 (0.5)	3 (1.5)	4 (1.0)	
No, *n* (%)	199 (99.5)	195 (98.5)	394 (99.0)	
Paracetamol (visit 5)				
N	191	191	382	1.000
Yes, *n* (%)	2 (1.0)	3 (1.6)	5 (1.3)	
No, *n* (%)	189 (99.0)	188 (98.4)	377 (98.7)	
Paracetamol (visit 6)				
N	184	187	371	0.724
Yes, *n* (%)	3 (1.6)	5 (2.7)	8 (2.2)	
No, *n* (%)	181 (98.4)	182 (97.3)	363 (97.8)	
Paracetamol (visit 7)				
N	178	181	359	0.215
Yes, *n* (%)	1 (0.6)	5 (2.8)	6 (1.7)	
No, *n* (%)	177 (99.4)	176 (97.2)	353 (98.3)	
Paracetamol (visit 8)				
N	174	176	350	1.000
Yes, *n* (%)	2 (1.1)	3 (1.7)	5 (1.4)	
No, *n* (%)	172 (98.9)	173 (98.3)	345 (98.6)	

Frequencies were analysed by Fisher's exact test. *N*, number of patients in group; *n*, number of affected patients.

(15.6%), insulin glargine (14.6%), acetylsalicylic acid (13.6) and repaglinide (10.6%). The only drug used by at least 5% of patients and whose rate of use was different between treatment groups was glimepiride (duloxetine: 11.3%; placebo: 5.4%; $p = 0.047$). No more than 2.7% of patients had taken paracetamol on any visit (duloxetine group, no more than 3.5%; placebo group, no more than 2.8%), and no statistically significant differences between treatment groups in use of paracetamol were observed on any visit (Table 4).

Discussion

Assessing the efficacy of duloxetine in Chinese patients with DPNP, the results of this double-blind, placebo-controlled trial show that duloxetine-treated patients reported significantly greater pain relief compared with placebo-treated patients over the 12-week study period. In support of this conclusion, a greater proportion of patients treated with duloxetine (compared with patients treated with placebo) experienced ≥ 30% and ≥ 50% reductions in weekly mean of 24-h average pain and BPI-Severity (average pain) at end-point. In addition, more duloxetine-treated patients indicated they were 'much better' on the PGI-Improvement scale, compared with placebo.

For response rates, as mentioned above, compared with placebo, a greater proportion of patients treated with duloxetine experienced ≥ 30% and ≥ 50% pain reductions. Improvements of ≥ 30% corresponded to patients feeling 'a little better' and improvements of ≥ 50% corresponded to patients feeling 'a lot better' (30) in previous duloxetine DPNP studies. These cut-offs are also consistent with the recommendation from IMMPACT (the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) (28). That is, ≥ 30% pain decrease indicates moderately important improvement, while ≥ 50% pain decrease indicates substantial improvement. NNT is a straightforward way to help physicians understand the likelihood that a patient will be helped by a medication. Smaller NNTs indicate greater efficacy. The NNTs for ≥ 30% and ≥ 50% pain reductions (range: 6–8) were similar. Thus, compared with a control group, for every 6–8 patients treated, one patient will achieve a ≥ 30% or ≥ 50% reduction in pain, which is clinically meaningful.

It is worth noting that pain relief occurs and is appreciated by individuals differently. Therefore, the magnitude of a statistically significant group mean change may bear little relation to an important improvement for the person with pain (28). In clinical practice, individual level assessment is very important to determine and adapt the individual treatment strategy. It is for these reasons that we included response rates as a secondary objective in this study.

For BPI-Severity average pain, the reduction in pain with duloxetine treatment was similar to other studies on DPNP with duloxetine treatment (13–16). Although this 12-week trial does not allow for assessment of long-term use of duloxetine for DPNP patients, one 6-month and three 52-week studies assessing the long-term management of DPNP and safety of duloxetine provide support for the use of duloxetine in the long-term management of DPNP (18–21).

A recent clinical trial of duloxetine for the treatment of DPNP in Chinese patients studied the efficacy of duloxetine for the management of DPNP in this population (31). Although the difference between treatment groups on the primary outcome measure of that study (mean change in BPI-Severity average pain) was not statistically significant, secondary results supported the efficacy of duloxetine in this patient population. The authors attributed the negative result possibly to a generally higher placebo response rate in Asian, compared with Western,

studies using subjective outcome measures. They also cited the inclusion of patients with major depressive disorder in the study population as problematic, as 50% of antidepressant trials fail to demonstrate a difference between study drug and placebo (32). They also cited factors relating to subjective outcomes measures and pain fluctuation associated with DPNP. In the current study, measures were taken to address factors that may have influenced outcomes in previous studies. For example, the primary outcome measure of the present study was not used as an inclusion criterion. Instead, the BPI-Severity was used to screen patients for severity of DPNP. In addition, we excluded from the present study those patients with major depressive disorder.

The overall safety profile found in this study was similar to previous studies of duloxetine. Reasons for discontinuation were not significantly different between treatment groups. Adverse event was the most cited reason for discontinuation, but still accounted for only 8.4% of duloxetine-treated patients.

Conclusion

In this study conducted in China, duloxetine-treated patients showed significantly greater pain relief compared with placebo-treated patients over the 12-week study period. Duloxetine 60 mg once daily was shown to have a similar safety profile presented in other duloxetine trials. Results from this study showed Chinese patients have similar levels of pain reduction with duloxetine treatment for the management of DPNP to that observed in other countries.

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Author contributions

Authors VS and JR were critical in the design of the study. Authors YG, XHG, PH, QML, GYY and SQ were involved in data acquisition. C-NW performed the statistical analysis. All authors participated in analysis and interpretation of the data and drafting and/or critical revision of the manuscript. All authors approved the final version of the manuscript.

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