Original Article

Additive Duloxetine for Cancer-Related Neuropathic Pain Nonresponsive or Intolerant to Opioid-Pregabalin Therapy: A Randomized Controlled Trial (JORTC-PAL08)

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Abstract

Context. Although opioids and pregabalin are widely used for cancer-related neuropathic pain (CNP), no clinical trials exist to determine which medications are effective when an opioid-pregabalin combination therapy fails.

Objectives. We investigated the efficacy of duloxetine for CNP nonresponsive or intolerant to opioid-pregabalin combination therapy.

Methods. A multicenter, randomized, double-blind, placebo-controlled trial was performed at 12 specialized palliative care services in Japan. Patients with CNP average pain scores (Brief Pain Inventory [BPI]−Item 5) ≥ 4 in the previous 24 hours and nonresponsive or intolerant to opioid-pregabalin combination therapy were eligible. Patients with chemotherapy-induced peripheral neuropathies were excluded. Patients were administered duloxetine 20 mg/day titrated to 40 mg/day or placebo for 10 days. The primary endpoint was BPI-Item 5 on Day 10. Responder analysis measured proportions of patients with 30% and 50% pain decreases.

Results. Seventy patients were enrolled. Complete case analysis revealed mean BPI-Item 5 on Day 10 of 4.03 for Group D vs. 4.88 for Group P ($P = 0.053$). Baseline observation carried forward analysis revealed mean BPI-Item 5 on Day 10 of 4.06 and 4.91 for Groups D and P, respectively ($P = 0.048$). Clinically meaningful pain improvement (≥30%) was reported by 44.1% ($n = 15$) of patients in Group D vs. 18.2% ($n = 6$) in Group P ($P = 0.02$); 32.4% ($n = 11$) vs. 3.0% ($n = 1$) of patients in Groups D and P, respectively, reported pain reduction ≥ 50% ($P = 0.002$).

Conclusion. Adding duloxetine to opioid-pregabalin therapy might have clinical benefit in alleviating refractory CNP. Further studies are needed to conclude the efficacy of adding duloxetine. J Pain Symptom Manage 2019;58:645−653. © *2019*

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Key Words
Pain, cancer-related neuropathic pain, opioid-pregabalin therapy, duloxetine, randomized controlled trial

Introduction

Cancer-related neuropathic pain (CNP) is frequently diagnosed in patients with cancer and is often resistant to optimal analgesic treatment, resulting in decreased physical, cognitive, and social function; however, clinical evidence regarding the best pharmacological treatment is limited.[1–4] According to clinical guidelines for cancer and noncancer populations with neuropathic pain (NP),[2,5–8] adjuvant analgesics such as gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants, and selective serotonin noradrenalin reuptake inhibitors combined with opioids are recommended; and gabapentinoids are among the most widely used.[9]

A recent meta-analysis[10] found a nonsignificant but favored trend that combining opioids with gabapentinoids improves cancer pain as a whole. There are no meta-analyses of pharmacological interventions to alleviate CNP, but some Phase III studies have identified moderate analgesic effects of gabapentinoids compared with placebo when administered in combination with opioids.[11,12] However, it is unclear which drugs are effective when first-line medications fail. Recently, the efficacy of duloxetine has been reported in patients with chemotherapy-induced peripheral neuropathy (CIPN) and in noncancer NP,[13,14] but no randomized trials have explored the effects on CNP refractory to first-line treatment with pregabalin. Our preliminary study revealed that 47% of patients with CNP nonresponsive or intolerant to opioid and pregabalin experienced pain reduction with duloxetine 20–40 mg/day.[15] Moreover, a systematic review and meta-analysis[16] demonstrated that the number of patients needed to treat to obtain one responder for duloxetine seems to be better than those for pregabalin.

Therefore, we conducted a randomized, double-blinded, placebo-controlled trial to test the hypothesis that addition of duloxetine to treatment regimens reduces pain intensity in patients with CNP nonresponsive or intolerant to opioid-pregabalin combination therapy.

Methods

Trial Design

This is a multicenter, double-blinded, randomized, placebo-controlled, two-parallel group trial (the DIRECT study; registration number UMIN 000017647) performed at specialized palliative care services across Japan. The study was performed according to the Helsinki Declaration and the Japanese ethical guidelines for clinical research. Written informed consent was obtained from all participants. The protocol was approved by the Japanese Organization for Research and Treatment of Cancer (JORTC) Protocol Review Committee and the institutional review boards at each study site. The JORTC independent data monitoring committee reviewed modifications to the protocol, progress, and safety. The study design has been reported previously.[17]

Participants

The study setting included nine hospital palliative care teams and three palliative care units. Adult patients with cancer suffering from neuropathic or neuropathic/nociceptive pain were enrolled if they were nonresponsive or intolerant to opioid-pregabalin combination therapy. Primary responsible palliative care specialists made a diagnosis of NP based on the International Association for the Study of Pain algorithm,[18] and patients with definite or probable NP were enrolled in this study. We did not use diagnostic measurement instruments because of lack of validated scales to diagnose NP in patients with cancer. Other inclusion criteria were expected survival $\geq$ 1 month, Brief Pain Inventory (BPI)—Item 5 (average pain) score $\geq$ 4 in the last 24 hours,[19,20] and Hospital Anxiety and Depression Scale total score $<$ 20.[21,22] Exclusion criteria included contraindication for duloxetine; CIPN (diagnosed by palliative care specialists); spinal cord compression; use of any types of antidepressants; and a change in medications or dosages of opioids, coanalgesics (such as anticonvulsants, steroids, antiarrhythmic agents, and *N*-methyl-D-aspartate receptor antagonists), or antipsychotics within two days of study enrollment.

Interventions

Preintervention Treatment. All patients had received opioid-pregabalin combination therapy, and pregabalin was used in all patients because of an approved license from the national health care insurance. Opioid doses were initially optimized, that is, the opioid dose was titrated up to the dosage until poor analgesic responses or intolerance to opioid-induced side effects was observed in the patients. Pregabalin was then

added, with a starting dose of 25−150 mg/day and titrated up to at least 300 mg based on individual patient condition. Patients reporting inadequate pain relief with opioid-pregabalin combination therapy thus included 1) nonresponsive patients (patients taking pregabalin ≥ 300 mg/day but with an average pain score ≥ 4) and 2) intolerant patients (patients for whom the pregabalin dosage could not be increased because of side effects, such as somnolence, dizziness, or peripheral edema).[11,23]

Study Protocol. Study medications were provided as identical capsules containing duloxetine or lactose (placebo). The medications were administered orally, starting with one capsule per day (duloxetine 20 mg or placebo) on Day 1. On Day 3, the degree of pain relief was evaluated using the Pain Relief Scale[17]; patients who reported complete or substantial relief continued to receive the same dose (one capsule). The dose was increased to two capsules (duloxetine 40 mg) for the remaining patients. The dose tested was determined in our preliminary study.[15] If severe nausea/vomiting continued despite antiemetic treatment, the dose was reduced or the treatment was discontinued. Administration of previous analgesics (i.e., opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, and/or all coanalgesics) remained unchanged throughout the study. Immediate-release opioids were available for breakthrough pain.

Recruitment, Randomization, Masking, and Follow-up

On enrollment and after obtaining written informed consent, patients were randomly allocated to either the duloxetine group (Group D) or the placebo group (Group P) with the VIEDOC 3 Web-based central randomization system (PCG Solutions, Uppsala, Sweden) using minimization methods with a 1:1 allocation ratio. Patients were stratified by the following factors: intensity of average pain on Day 0 (≤7, ≥8); response to pregabalin (nonresponsive or intolerant); total Hospital Anxiety and Depression Scale score (≤10, ≥11); treatment setting (inpatient or outpatient); study site; and underlying cause of pain (spinal cord infiltration or others, determined by palliative care specialists). Treatment was started within 1 week after randomization. All patients, clinicians responsible for treatment, and investigators were blinded to the administration of duloxetine or placebo, except for a clinical trial pharmacist who the generated capsules and was not involved in direct patient care.

Evaluations were performed at four time points: baseline (time of randomization), the day before the start of treatment (Day 0), at 3 days (Day 3), and at 10 days (Day 10). Patients were not allowed to cross from one group to another group until the end of the study, and we measured the endpoints for all patients who discontinued the treatment. Postprotocol treatment was not designated. All data were collected by the JORTC Data Center; data entry, data management, and central monitoring were performed using the VIEDOC 3 electronic data capture system.

Outcomes

The primary endpoint was average pain intensity over the last 24 hours at Day 10 similar to that in the previous studies, as measured by BPI-Item 5, an 11-point (0−10) Likert scale.[11,19,20,24] The observation periods were determined based on a previous study that demonstrated clinical benefits up to 10 days,[11] and the fact that the target study population was patients with advanced cancer with short expected survival times. We also calculated the percentages of patients with 30% and 50% pain reduction from Day 0.[14] The secondary endpoints included the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL scores,[25,26] frequency of daily rescue use, and adverse events (AEs). AEs were assessed with the Common Terminology Criteria for Adverse Events v.4.0, Japan Clinical Oncology Group version.[27,28] The European Cooperative Oncology Group Performance Status system was used for evaluation of performance status by primary physicians.[29] All patient-reported outcome measures were validated in Japanese[17] and recorded by the patients themselves using paper-based questionnaires.

Sample Size Calculation

Assuming an attrition rate of 10%, the estimated number of patients required to detect the minimum difference in average pain of 1.0 (standard deviation, 1.5) on Day 10 between groups was 70 ($n = 35$ in each group), as estimated from published data[15,30] and with significance set at 0.05 and power set at 80%.

Statistical Analysis

All statistical procedures were detailed in the statistical analysis plan before data evaluation. Comparisons of the primary endpoint of average pain on Day 10 between the groups were conducted using a one-sided *t*-test at a significance level of 5% according to the intention-to-treat principle. We adopted a one-sided *t*-test on the assumption that the placebo did not alleviate pain over the study medication, and the point estimates and 90% confidence intervals (CIs) for the differences between groups were calculated. To deal with missing data, a complete case (CC) population was used for the primary analysis of efficacy data on Day 10. We also adopted baseline observation carried forward (BOCF) for sensitivity analysis to investigate the stability of the results.[31] BOCF is based on the assumption that the pain returns to the

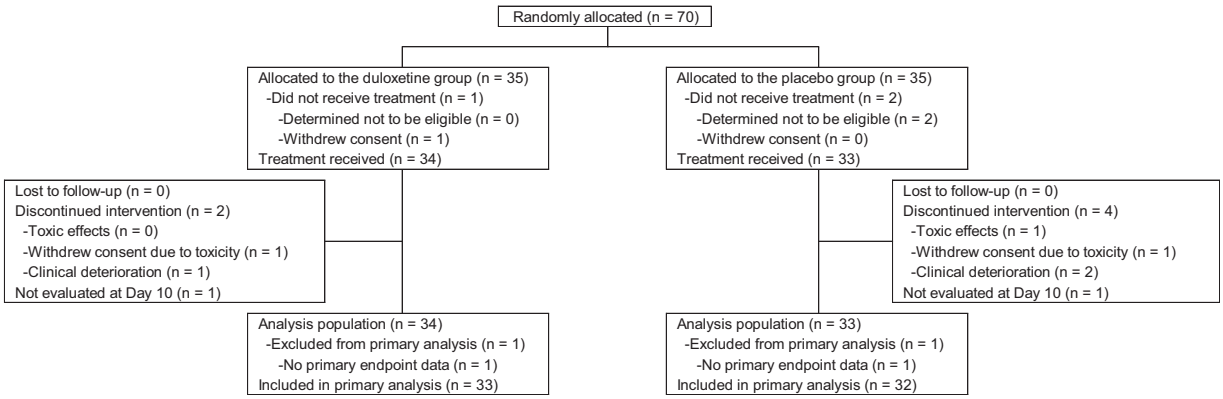

Fig. 1. Flow chart of study procedures. Participants were randomized (1:1 allocation ratio) into the duloxetine group or the placebo group. Evaluations were made at baseline (at randomization), and on Days 0, 3, and 10. BPI = Brief Pain Inventory.

baseline state if treatment is stopped because CNP is unlikely to improve in the natural course during this short period. Hence, we imputed missing data on Day 10 with the score from Day 0. In addition, to adjust the pain intensity before treatment (Day 0), the changes in pain intensity from Day 0 to Day 10 between the groups were compared using the one-sided *t*-test.

For responder analysis, comparisons of the percentages of patients with clinically meaningful pain reduction (30% and 50%) were conducted using a chi-squared test.[14] We had adopted 30% pain reduction as the minimal clinically important difference, as 30% or two-point changes were generally regarded as minimal clinically important difference in this population.[32] Group comparisons of each item of the EORTC QLQ-C15-PAL were conducted using a two-sided *t*-test at a significance level of 5% without adjustment for multiple testing. Medians and interquartile ranges were calculated for opioid rescue use. Subgroup analyses were performed in patients nonresponsive vs. intolerant to pregabalin, as well as the patients who eventually received 1) pregabalin and duloxetine, 2) duloxetine only, 3) pregabalin only, and 4) placebo only. The distributions of grades of AEs and the incidence of AEs ≥ Grade 3 were determined. Analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 70 eligible patients were enrolled from July 2015 to November 2017. All 70 patients were randomized, and 65 participants completed the study period. Among the 70 patients, 67 were evaluable: 34 in Group D and 33 in Group P; there were no primary endpoint data for one patient in each group (Fig. 1). Of the 67 evaluable subjects, 94.1% (32/34) of patients in Group D and 87.9% (29/33) of those in Group P completed the protocol treatment on Day 10; 63% of patients in Group D and 66% of those in Group P increased the dose to 40 mg. Baseline characteristics are presented in Table 1. The mean age was 62.9 ± 10.6 years, and 61.4% (43/70) of subjects were male. Groups D and P were comparable in terms of age, sex, performance status, primary tumor sites, and intensity of average pain (5.6 in Group D and 5.7 in Group P).

Primary Outcome Analysis

The primary endpoints (i.e., the BPI-Item 5) were obtained in 33 patients in Group D and 32 patients in Group P. In the CC analysis, mean average pain scores on Day 10 were 4.03 (90% CI, 3.33 to 4.74) for Group D and 4.88 (4.37 to 5.38) for Group P ($P = 0.053$) (Table 2). In the sensitivity analysis using BOCF, average pain scores on Day 10 were 4.06 (90% CI, 3.37 to 4.74) for Group D and 4.91 (90% CI, 4.41 to 5.41) for Group P ($P = 0.048$). Point estimates of the differences in average values between the two groups were −0.84 (90% CI, −1.71 to 0.02) for the CC analysis and −0.85 (90% CI, −1.69 to −0.01) for the BOCF analysis. In addition, the changes in the pain intensity from Day 0 to Day 10 were −1.30 (90% CI, −1.98 to −0.63) for Group D vs. −0.80 (90% CI, −1.36 to −0.33) for Group P ($P = 0.18$). Pain intensity at Day 0 were 5.3 (SD: 1.4) and 5.7 (SD: 1.4) for Group D and Group P, respectively.

Responder Analysis

Figure 2 presents the percentages of patients achieving various levels of pain reduction. At Day 10, 44.1% (15/34) of patients in Group D and 18.2% (6/33) of patients in Group P reported pain improvement ≥ 30% ($p = .02$); 32.4% (11/34) of patients in Group D and 3.0% (1/33) of patients in Group P reported pain improvement ≥ 50% ($P = 0.002$).

Table 1
Baseline Characteristics, by Group

Item	Duloxetine Group ($n = 35$)	Placebo Group ($n = 35$)
Age (yrs), mean (SD)	64.7 (9.3)	61.2 (11.6)
Sex, *n* (%)		
Males	22 (62.9)	21 (60.0)
Females	13 (37.1)	14 (40.0)
Performance status, *n* (%)		
0	4 (11.4)	3 (8.6)
1	12 (34.3)	13 (37.1)
2	14 (40.0)	11 (31.4)
3	5 (14.3)	7 (20.0)
4	0 (0.0)	1 (2.9)
Primary tumor sites, *n* (%)		
Esophagus, stomach, colon	10 (28.6)	4 (11.4)
Hepatobiliary tract and pancreas	2 (5.7)	4 (11.4)
Lung	11 (31.4)	9 (25.7)
Breast	0 (0.0)	4 (11.4)
Head and neck	1 (2.9)	1 (2.9)
Uterus and ovary	1 (2.9)	1 (2.9)
Prostate, kidney, bladder	5 (14.3)	3 (8.6)
Bloods, lymph nodes	0 (0.0)	2 (5.7)
Unknown	1 (2.9)	2 (5.7)
Bone, soft tissue	1 (2.9)	3 (8.6)
Others	3 (8.6)	2 (5.7)
BPI-Item 5, mean (SD)	5.6 (1.4)	5.7 (1.4)
BPI-Item 5 ≥ 8, *n* (%)	5 (14.3)	5 (14.3)
HADS ≥ 11, *n* (%)	18 (51.4)	21 (60.0)
Outpatients, *n* (%)	17 (48.6)	18 (51.4)
Spinal cord infiltration, *n* (%)	9 (25.7)	10 (28.6)
Nonresponsive to pregabalin, *n* (%)	12 (34.3)	8 (22.9)
Background pregabalin dose (mg)		
Median	300	300
Interquartile range	300–300	300–375
Intolerant to pregabalin, *n* (%)	23 (65.7)	27 (77.1)
Background pregabalin dose (mg)		
Median	125	150
Interquartile range	50–150	75–150
Discontinuation of pregabalin, *n* (%)	10 (28.6)	7 (20.0)
Discontinuation of pregabalin because of intolerance, *n* (%)	7 (70.0)	7 (87.5)
Discontinuation of pregabalin because of other reasons, *n* (%)	3 (30.0)	1 (12.5)
Background oral morphine equivalent daily doses (mg)		
Median	60	60
Interquartile range	30–90	30–120
Concomitant medications, *n* (%)		
Nonsteroidal anti-inflammatory drugs	17 (48.6)	24 (68.6)
Acetaminophen	12 (34.3)	13 (37.1)
Anticonvulsants (pregabalin, all)	25 (71.4)	28 (80.0)
Antiarrhythmic drugs	1 (2.9)	0 (0.0)
NMDA receptor antagonists	3 (8.6)	1 (2.9)
Steroids	11 (31.4)	10 (28.6)
Anxiolytics	2 (5.7)	5 (14.3)

BPI = Brief Pain Inventory; HADS = Hospital Anxiety and Depression Scale; NMDA = *N*-methyl-D-aspartate; SD = standard deviation.

EORTC QLQ-C15-PAL

There was no difference in overall quality of life, physical function, or emotional function between the groups on Day 10 (Table 3). Compared with Group P, Group D demonstrated significantly better scores for pain ($P = 0.04$) and worse scores for appetite loss ($P = 0.001$) on Day 10. In a comparison of Day 0 and Day 10 values in Group D,

Table 2
Analysis of Pain During the Treatment Period: BPI-Item 5 and Sensitivity Analysis

	Duloxetine Group ($n = 34$)	Placebo Group ($n = 33$)	Difference in Means Between Two Groups	
Analysis	Mean (90% CI), *n*	Mean (90% CI), *n*	Mean (90% CI)	*t*-Test (One-Sided)
CC analysis	4.03 (3.33 to 4.74), $n = 33$	4.88 (4.37 to 5.38), $n = 32$	−0.84 (−1.71 to 0.02)	0.053
BOCF analysis	4.06 (3.37 to 4.74), $n = 34$	4.91 (4.41 to 5.41), $n = 33$	−0.85 (−1.69 to 0.01)	0.048

BPI = Brief Pain Inventory; CC = complete case; BOCF = baseline observation carried forward; CI = confidence interval.
Duloxetine and placebo group data reported as BPI-Item 5 over the previous 24 hours (main study outcome).

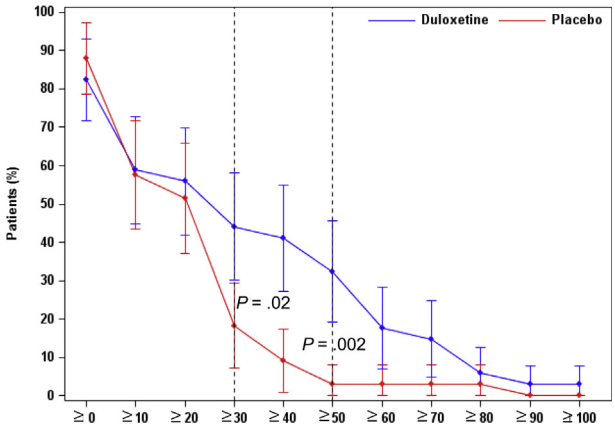

Fig. 2. Degree of pain reduction from baseline to Day 10. The plot and the error bar show the proportion and 90% CIs of patients achieving various levels of pain reduction at the completion of the initial treatment period. We analyzed 65 subjects using the BPI-Item 5 over the previous 24 hours. BPI = Brief Pain Inventory.

there were tendencies toward improvement of pain ($P = 0.09$) and worsening of anorexia ($P = 0.07$).

Frequency of Rescue Use

The average numbers of breakthrough opioid uses were 2.5 times (1.0 to 5.5 times) per day in Group D and 3.0 times (2.0 to 5.0 times) per day in Group P. The amount of opioid breakthrough doses was morphine 7.5 mg (interquartile range, 2.5 to 16.9 mg) equivalent dose per time in Group D and morphine 8.8 mg (5.0 to 15.0 mg) equivalent dose per time in Group P.

Subgroup Analyses

Among patients nonresponsive to pregabalin, mean average pain scores on Day 10 were 4.36 (90% CI, 2.93 to 5.79) for Group D ($n = 11$) and 5.57 (90% CI, 3.94 to 7.21) for Group P ($n = 7$) ($P = 0.16$). Among patients intolerant to pregabalin, mean average pain scores were 3.86 (90% CI, 3.01 to 4.71) for Group D ($n = 23$) and 4.68 (90% CI, 4.16 to 5.20) for Group P ($n = 26$) ($P = 0.08$). The proportions of the patients who achieved 30% or more pain reduction were 37.5% (90% CI, 18.80 to 59.41) in the patients eventually receiving pregabalin and duloxetine ($n = 24$), 60.0% (90% CI, 26.24 to 87.84) in those receiving duloxetine only ($n = 10$), 23.1% (90% CI, 8.97 to 43.65) in those receiving pregabalin only ($n = 26$), and 0.00% (90% CI, 00.00 to 40.96) in those receiving placebo only ($n = 7$).

Adverse Events

Nausea and malaise (grade ≥ 1) were reported in 41.2% and 20.5% of patients, respectively, in Group D, and in 9.1% and 0.0% of patients, respectively, in Group P (Table 4). In addition, 52.9% and 45.4% of patients in Groups D and P, respectively, exhibited somnolence ≥ grade 1. One case of discontinuation of treatment due to Grade 3 AEs was due to deterioration of the primary disease and had no relation to the treatment.

Discussion

To the best of our knowledge, this is the first randomized, double-blinded, placebo-controlled trial to

Table 3
Analysis of Quality of Life During the Treatment Period: EORTC QLQ-C15-PAL Scores

		Duloxetine	Placebo	Difference Between Two Groups
Item	Time	Mean (SD)	Mean (SD)	*t*-Test (Two-Sided)
Overall quality of life	Day 10	47.5 (21.7)	44.6 (20.4)	0.59
	Change from baseline	3.5 (21.14)	4.3 (19.2)	0.88
Physical functioning	Day 10	39.6 (26.6)	44.7 (27.56)	0.45
	Change from baseline	−8.3 (23.0)	−3.0 (19.3)	0.33
Emotional functioning	Day 10	70.7 (23.2)	73.1 (15.8)	0.63
	Change from baseline	−2.5 (20.9)	1.3 (22.9)	0.48
Fatigue	Day 10	57.9 (24.3)	57.7 (22.84)	0.97
	Change from baseline	5.7 (25.3)	−0.7 (25.3)	0.31
Nausea/vomiting	Day 10	10.1 (15.0)	5.9 (11.0)	0.21
	Change from baseline	−3.5 (19.9)	−1.1 (10.5)	0.54
Pain	Day 10	53.5 (23.84)	66.1 (24.5)	0.04
	Change from baseline	−17.7 (34.3)	−4.8 (24.8)	0.09
Dyspnea	Day 10	27.3 (25.6)	21.5 (20.3)	0.32
	Change from baseline	2.0 (27.6)	2.2 (14.74)	0.98
Insomnia	Day 10	28.3 (26.5)	34.4 (31.6)	0.40
	Change from baseline	−8.1 (31.2)	−11.8 (31.7)	0.64
Appetite loss	Day 10	64.6 (28.8)	38.7 (32.3)	0.001
	Change from baseline	16.2 (36.4)	0.0 (33.3)	0.07
Constipation	Day 10	37.4 (37.0)	25.8 (25.4)	0.15
	Change from baseline	−5.1 (37.4)	−9.7 (31.3)	0.59

EORTC = European Organization for Research and Treatment of Cancer; SD = standard deviation.

Table 4
Numbers of Patients Reporting Adverse Events, by Group

	Duloxetine Group ($n = 34$)					Placebo Group ($n = 33$)				
Adverse Event	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	≥Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	≥Grade 3, *n* (%)	Grade 4, *n* (%)
Somnolence	15 (44.1)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (24.2)	6 (18.2)	0 (0.0)	1 (3.0)	1 (3.0)
Dizziness	7 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	11 (32.4)	2 (5.9)	1 (2.9)	1 (2.9)	0 (0.0)	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	6 (17.6)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

explore the efficacy of adding duloxetine to treatment regimens for CNP patients nonresponsive or intolerant to opioid-pregabalin combination therapy. The group difference of the mean pain scores was statistically marginal ($P = 0.053$ for CC analysis and $P = 0.048$ for BOCF analysis), although the value was close to the estimate (i.e., 1 point). Responder analysis demonstrated that 44% of Group D responders vs. 18% of Group P responders reported pain reduction ≥ 30% ($P = 0.02$) and that 32% and 3% ($P = 0.002$) of Group D and Group P responders, respectively, reported ≥50% reduction. In addition, the quality of life measure suggested some benefits in pain intensity among patients receiving duloxetine ($P = 0.04$). These findings suggest that adding duloxetine to opioid-pregabalin combination therapy might be effective for CNP, but the marginal statistical significance with the primary endpoint data warrants caution to make a definite conclusion. In another painful situation in patients with breast cancer, that being aromatase inhibitor–induced arthralgia, results of treatment with duloxetine were superior to those of placebo.[33] The average joint pain score was 0.82 points lower in patients who received duloxetine than those who received placebo; the results provide support for the efficacy of duloxetine in certain types of cancer-related pain.

The current trial has several strengths. First, this trial was a multi-institutional, randomized, double-blinded, placebo-controlled trial design. This means that the risk of evaluation bias, which is often problematic in evaluating subjective endpoints such as pain, is minimized. In addition, selection bias was minimized by use of a properly stratified population. Furthermore, there were very low dropout rates for this study. In palliative care clinical trials, very high attrition rates often weaken the statistical power and may even cause discontinuation of a study.[34] Our eligibility criteria selected patients for whom the protocol treatment was feasible, and the treatment was safely conducted. Finally, changes in concurrent analgesics and adjuvant analgesics were not allowed during the protocol treatment period. These factors combined to yield a study carefully designed to detect only the effects of duloxetine.

There are, however, several limitations. First, the dose of duloxetine used in this study (20–40 mg/day) was relatively small compared with the international standard dose (60 mg/day). The rationale for the dose range used in this study was that our preliminary study suggested 20–40 mg/day is enough for analgesia.[15] Use of a higher dose of duloxetine may result in better pain outcomes. The doses of opioids used were also relatively low, considering that all the patients had advanced-stage cancer. Second, the observation periods were relatively short (i.e., 10 days) because we used the previous Phase III study design[11] and longer study periods decrease the feasibility. Thus, long-term efficacy and safety of duloxetine warrant further investigation. Third, primary responsible palliative care specialists made a diagnosis of NP based on the International Association for the Study of Pain algorithm[18] and they did not use NP scales. Fourth, the sample size was rather modest, and marginal statistical significance in the primary endpoints should be a focus of debate. A large-scale long-term study using comprehensive outcome measures could be used to confirm the results. Finally, pretreatment intensity of pain was generally moderate at 5.6, compared with that observed in the previous study (7.0). The findings may not be applicable to patients with severe CNP.

In conclusion, the addition of duloxetine to opioid-pregabalin combination therapy might have benefit in alleviating pain in CNP patients nonresponsive or intolerant to opioid-pregabalin combination therapy. Further clinical trials are needed to conform the results.

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