

Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy

A Randomized Clinical Trial

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APPROXIMATELY 20% TO 40% OF patients with cancer who receive neurotoxic chemotherapy (eg, taxanes, platinum, vinca alkaloids, bortezomib) will develop painful chemotherapy-induced peripheral neuropathy.¹⁻³ Painful chemotherapy-induced neuropathy can persist from months to years beyond chemotherapy completion, causing significant challenges for cancer survivors due to its negative influence on function and quality of life (QOL).⁴⁻⁸ Chemotherapy-induced peripheral neuropathy is difficult to manage, and most randomized controlled trials

 **CME available online at www.jamanetworkcme.com and questions on p 1412.**

Author Video Interview available at www.jama.com.

Importance There are no known effective treatments for painful chemotherapy-induced peripheral neuropathy.

Objective To determine the effect of duloxetine, 60 mg daily, on average pain severity.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled crossover trial at 8 National Cancer Institute (NCI)-funded cooperative research networks that enrolled 231 patients who were 25 years or older being treated at community and academic settings between April 2008 and March 2011. Study follow-up was completed July 2012. Stratified by chemotherapeutic drug and comorbid pain risk, patients were randomized to receive either duloxetine followed by placebo or placebo followed by duloxetine. Eligibility required that patients have grade 1 or higher sensory neuropathy according to the NCI Common Terminology Criteria for Adverse Events and at least 4 on a scale of 0 to 10, representing average chemotherapy-induced pain, after paclitaxel, other taxane, or oxaliplatin treatment.

Interventions The initial treatment consisted of taking 1 capsule daily of either 30 mg of duloxetine or placebo for the first week and 2 capsules of either 30 mg of duloxetine or placebo daily for 4 additional weeks.

Main Outcome Measures The primary hypothesis was that duloxetine would be more effective than placebo in decreasing chemotherapy-induced peripheral neuropathic pain. Pain severity was assessed using the Brief Pain Inventory-Short Form "average pain" item with 0 representing no pain and 10 representing as bad as can be imagined.

Results Individuals receiving duloxetine as their initial 5-week treatment reported a mean decrease in average pain of 1.06 (95% CI, 0.72-1.40) vs 0.34 (95% CI, 0.01-0.66) among those who received placebo ($P=.003$; effect size, 0.513). The observed mean difference in the average pain score between duloxetine and placebo was 0.73 (95% CI, 0.26-1.20). Fifty-nine percent of those initially receiving duloxetine vs 38% of those initially receiving placebo reported decreased pain of any amount.

Conclusion and Relevance Among patients with painful chemotherapy-induced peripheral neuropathy, the use of duloxetine compared with placebo for 5 weeks resulted in a greater reduction in pain.

Trial Registration clinicaltrials.gov Identifier: NCT00489411

JAMA. 2013;309(13):1359-1367

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testing a variety of drugs with diverse mechanisms of action revealed no effective treatment.⁹

There is mounting evidence that serotonin and norepinephrine dual reuptake inhibitors are effective in treating neuropathy-related pain.¹⁰ Both

serotonin and norepinephrine are key neurotransmitters that suppress transmission of painful peripheral stimuli by

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inhibiting input to the spinal dorsal horn neurons.¹¹ Several phase 3 studies show that duloxetine is an effective treatment for painful diabetic neuropathy.¹²⁻¹⁵ Based on these trials, our hypothesis was that duloxetine would ameliorate chemotherapy-induced peripheral neuropathic pain as well. A randomized phase 3 trial was conducted to test this hypothesis.

METHODS

STUDY DESIGN

The Cancer and Leukemia Group B (CALGB/Alliance) conducted a randomized phase 3 double-blind, placebo-controlled crossover trial to assess whether 60 mg of duloxetine taken orally once daily decreases the severity of chemotherapy-induced peripheral neuropathy (CALGB-170601, NCT00489411). The primary hypothesis was that duloxetine would be more effective than placebo in decreasing the average pain score after a 5-week treatment period. Secondary aims were to assess duloxetine's effect on QOL and function and on adverse events. The study was approved by each site's institutional review board, and participants provided signed informed consent. Enrollment occurred between April 2008 and March 2011. Study follow-up was completed July 2012.

Patients

Using the National Cancer Institute's (NCI's) Clinical Trials Support Unit mechanism to facilitate accrual, participants were recruited from 8 multisite NCI-funded cooperative research networks, resulting in a geographically diverse population of patients distributed throughout the United States. The diagnosis of chemotherapy-induced peripheral neuropathy was determined based on symptom history, loss of deep tendon reflexes, or the presence of symmetrical stocking-glove numbness or paresthesias beginning after neurotoxic chemotherapy. Eligible patients were 25 years or older, had at least grade 1 sensory pain based on the NCI Common Terminology Criteria for Adverse Events version 3.0 grading

scale, and reported 4 on a 10-point scale, average neuropathic pain, for 3 or more months after completing chemotherapy. Patients with any cancer diagnosis or stage were potentially eligible. To diminish the likelihood that symptoms would spontaneously resolve over the course of the study, efficacy data were obtained over 5 weeks.

Initially, patients who had received paclitaxel or oxaliplatin could participate, but eligibility was later expanded to allow prior treatment with single-agent docetaxel, nanoparticle albumin-bound paclitaxel, or cisplatin. Prior or ongoing treatment with other neurotoxic chemotherapeutic agents was not allowed. Participants with a documented medical history of neuropathy from any type of nerve compression (eg, carpal or tarsal tunnel syndrome, radiculopathy, spinal stenosis, brachial plexopathy), leptomeningeal carcinomatosis, severe depression, suicidal ideation, bipolar disease, alcohol abuse, a major eating disorder, and markedly abnormal renal or liver function tests were ineligible.

Despite scant evidence supporting the association between certain comorbid illnesses and the risk of developing severe pain,^{9,16} patients with diabetes mellitus and peripheral vascular disease, whose pain was thought to be from chemotherapy-induced peripheral neuropathy, were eligible but were defined as *high risk*. We controlled for comorbid illness as a potential confounder by assigning equal numbers of high-risk patients to each treatment group. Concurrent use of other drugs known to influence serotonin levels was not allowed. Concomitant use of selected analgesics was allowed (eg, opioids, acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs), but only patients receiving stable doses in the 2 weeks before randomization could participate: (1) no new analgesics were added, (2) no analgesics were discontinued, and (3) the weekly 24-hour total analgesic dose did not fluctuate up or down by more than 10% in the 2 weeks before study registration.

Intervention

Eligible patients were randomized using a 1:1 allocation ratio to either group A or group B. In this crossover design, group A received 60 mg of duloxetine daily during the initial treatment period and placebo at crossover period. Group B received placebo as initial treatment and duloxetine as the crossover treatment. Randomization, provided by the CALGB/Alliance Statistical Center, was stratified by neurotoxic drug class (taxanes vs platinum) and by pain risk (high risk vs no risk). A computer-generated kit number was used to order the blinded study drug from a distribution center. Drug labels were applied to the capsule bottles at the distribution center before being mailed to study sites; thus, all patients and personnel were blinded to the treatment assignment.

The initial (weeks 1-5) and crossover (weeks 8-12) treatment periods each consisted of receiving 1 capsule of either placebo or 30 mg of duloxetine for the first week and 2 capsules of either placebo or 30 mg of duloxetine for 4 weeks. The initial 5-week period was followed by a 2-week washout period for a total study duration of 14 weeks (FIGURE 1).

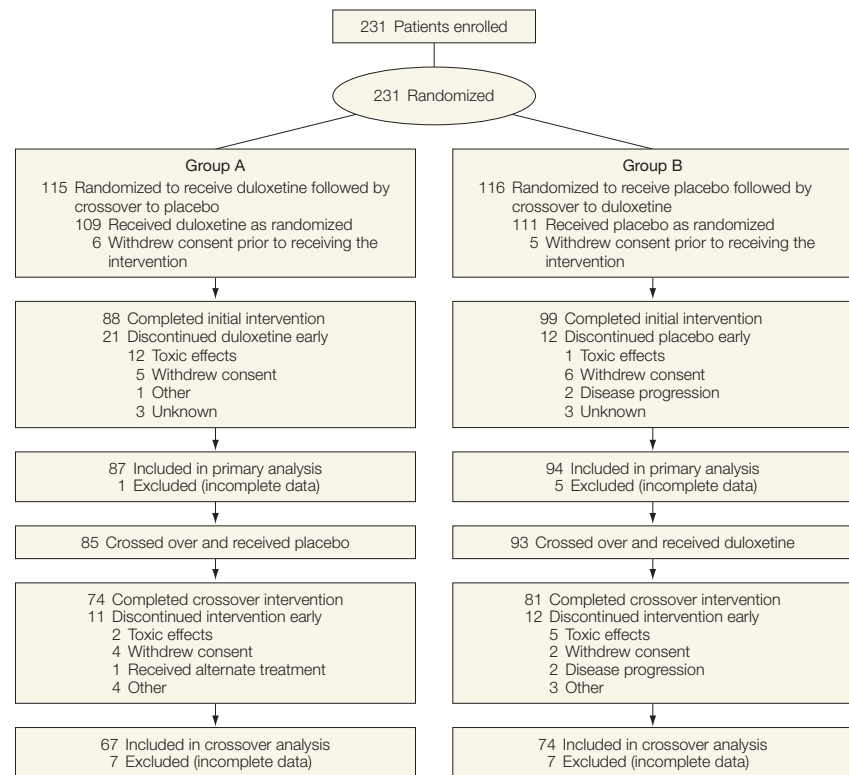
Data Collection and Instruments

Patient-reported pain severity and functional interference was assessed weekly using the well-validated Brief Pain Inventory Short Form (BPI-SF).¹⁷⁻¹⁹ The BPI-SF contains 4 items assessing average, worst, least, and immediate pain severity in the last 24 hours. Pain severity items are scored using an 11-point numeric rating scale (0, no pain; 10, pain as bad as you can imagine). The BPI-SF worst pain severity item has been shown to be reliable and valid for use as a single item.²⁰ However, we chose average pain severity as our primary outcome measure based on recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).²¹ In addition, *average pain* has been defined as the primary out-

come measure in numerous duloxetine phase 3 studies involving patients with peripheral and central neuropathic pain conditions due to diabetic- and oxaliplatin-induced neuropathy, fibromyalgia, and osteoarthritis^{13-15,22-30} and thereby was chosen to facilitate comparison of our findings across similar studies. The *minimal clinically important difference in pain severity* was defined for the current study as a 0.98 difference in mean average pain severity between the duloxetine and placebo groups. Using an accepted method for assessing the influence of pain on function,^{13-15,26-29} 7 BPI-SF items were used to quantify the degree to which pain interfered with daily activities or function (0, does not interfere; 10, completely interferes). The 7 items were summed to obtain a total interference score. Patient-reported QOL was assessed using the Functional Assessment of Cancer Treatment, Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) subscale on day 1 of weeks 1, 6, 8, and 13. The assessment's strong psychometric properties have been previously demonstrated.³¹⁻³³ The instrument contains 11 questions assessing numbness, tingling, and discomfort in the hands or feet; difficulty hearing; tinnitus; joint pain or muscle cramps; weakness; or trouble walking, buttoning buttons, or feeling small shapes when placed in the hand. Items are scored from 0 to 4 (0, not at all; 4, very much) and summed (total score range, 0-44).³³ Because there are no published data defining a cut point for determining a clinically important change in the score, we defined a 2- to 3-point change as a clinically meaningful improvement in QOL per published recommendations specific to similar measures.³⁴⁻³⁷

Using the NCI CTCAE version 3.0, adverse events were reported weekly and graded on a 0 to 4 scale (0, normal; 4, life-threatening)³⁸ as was baseline sensory chemotherapy-induced peripheral neuropathy (0, normal; 1, asymptomatic, weakness on physical examination, loss of reflexes, or paresthesias not interfering with function; 2,

Figure 1. Patient Flow Chart of Initial and Crossover Periods^a



^aThe number screened and the number offered participation but declined was not captured, nor were the reasons captured for why patients did not participate in the crossover treatment period.

weakness and sensory alterations interfering with function; 3, weakness and sensory alterations interfering with activities of daily living or requiring bracing or assistive devices; and 4, life threatening, paralysis, or disabling).

Statistical Analyses

Statistical analyses were performed by CALGB/Alliance statisticians. The primary study end point was the change from start to end of the initial treatment period (week 1 to week 5, measured on day 1 of weeks 1 and 6) in average pain based on the BPI-SF average pain severity item. The comparison of interest was the difference between the 2 treatment groups in pain change. With 232 patients (assuming 20% attrition), the study had 90% power (2-sided α of .05) to detect a 0.98-point change between the 2 groups assuming a standard error of 0.31. The target difference of 0.98 is consistent with

diabetic research.³⁰ We calculated the proportion of patients experiencing any decrease in pain. Also, using another accepted approach for assessing clinical significance,^{13-15,22-24,26,39-41} we conducted an exploratory responder analysis based on the proportion of patients in both groups who experienced a 30% (or 50%) decrease in pain severity. Relative risk-benefit was the proportion of patients with 30% (or 50%) pain reduction in the duloxetine group relative to that in the placebo group. It was calculated from contingency tables. We also conducted an exploratory subgroup analyses based on chemotherapy class.

Secondary end points were change in chemotherapy-induced peripheral neuropathy-related QOL, measured by the total score of the FACT/GOG-Ntx, and degree of pain-related functional interference based on the BPI-SF interference score. Changes attributable to ini-

Table. Patient Demographics and Baseline Features

Characteristics	No. (%) of Participants			P Value
	Group A (n = 109)	Group B (n = 111)	Total (n = 220)	
Demographics				
Age, y				
30-39	2 (2)	1 (1)	3 (1)	.70 ^a
40-49	16 (15)	23 (21)	39 (18)	
50-59	43 (39)	39 (35)	82 (37)	
60-69	30 (28)	29 (26)	59 (27)	
≥70	18 (17)	19 (17)	37 (17)	
Mean (SD)	60 (10.4)	59 (10.6)	59 (10.5)	
Sex				
Men	38 (35)	44 (40)	82 (37)	.46
Women	71 (65)	67 (60)	138 (63)	
Race				
White	91 (83)	87 (78)	178 (81)	.50
Black	14 (13)	17 (15)	31 (14)	
Other	4 (4)	5 (5)	9 (4)	
Not reported	0 (0)	2 (2)	2 (1)	
Stratification factors				
Neurotoxic agent				
Paclitaxel	44 (40)	43 (39)	87 (40)	N/A
Oxaliplatin	63 (58)	66 (59)	129 (59)	
Other taxane	2 (2)	2 (2)	4 (2)	
Other platinum	0 (0)	0 (0)	0 (0)	
High risk of CIPN				
No	46 (42)	51 (46)	97 (44)	N/A
Yes	63 (58)	60 (54)	123 (56)	
Disease-related features				
Primary disease				
Breast	41 (38)	42 (38)	83 (38)	.99 ^b
GI	62 (57)	62 (56)	124 (56)	
Both breast & GI tract	0 (0)	1 (1)	1 (0)	
Genitourinary	4 (4)	4 (4)	8 (3)	
Other	2 (2)	1 (1)	3 (1)	
Missing	0 (0)	1 (1)	1 (0)	

(continued)

tial treatment were defined as the difference between the week 1 and week 5 scores (measured on day 1 of weeks 1 and 6). Changes for crossover treatment used week 8 and week 12 scores (measured on day 1 of weeks 8 and 13).

To test for a group effect during the initial treatment period on the primary and secondary end points, we used 3 separate models of analysis of covariance, each stratified by neurotoxic agent and risk of painful chemotherapy-induced peripheral neuropathy, and including the baseline measure of the corresponding end point. Least square means and their 95% confidence intervals were taken from analysis of covariance models. Additionally, for the primary end point, generalized estimating

equations were used to determine whether there was a treatment effect when combining data from both the initial and crossover periods. Multiple imputation and pattern-mixture model were used to evaluate the pattern and potential influence of missing values for the primary end point (eAppendix available at [www.http://www.jama.com](http://www.jama.com)). To univariately compare treatment groups, the Wilcoxon rank test was used for continuous variables and the χ^2 test for proportions. The 95% confidence intervals for proportions used exact binomial methods. Analyses included only patients who began protocol therapy. Statistical analyses with 2-sided significance threshold of $P < .05$ were performed using SAS ver-

sion 9.2 (SAS Institute Inc). Data quality was ensured by review of data by the CALGB/Alliance Statistical Center and by the study chairperson. The study underwent standard biannual monitoring by the CALGB/Alliance data and safety monitoring board with 1 formal interim efficacy analysis resulting in study continuation.

RESULTS

Patients

Patient disposition for the initial treatment period is illustrated in Figure 1. Of the 231 patients recruited to the study, 115 were allocated to group A (duloxetine first, placebo second), and 116 to group B (placebo first, duloxetine second). Eleven patients never received treatment, leaving 220 treated patients. The dropout rate due to adverse events in the duloxetine-first group was 11% vs 1% in the placebo-first group ($P < .001$). Despite using an intent-to-treat analysis approach, 6 patients (1 in group A; 5 in group B) during the initial treatment period were excluded from the primary analysis because they provided no data at all. This resulted in a 19% dropout rate.

Patient characteristics are described in the TABLE. Both groups were similar at baseline, except for the mean (SD) pain score of 6.1 (1.7) in group A, duloxetine first, and 5.6 (1.6) in group B, placebo first ($P = .02$).

Pain (Primary Outcome)

At the end of the initial treatment period, patients in the duloxetine-first group reported a larger decrease in average pain (mean change score, 1.06; 95% CI, 0.72-1.40) than those in the placebo-first group (mean change score, 0.34; 95% CI, 0.01-0.66; $P = .003$; FIGURE 2). The effect size attributed to duloxetine was moderately large at 0.513.⁴² The observed mean difference in the average pain score between the duloxetine-first and placebo-first groups was 0.73 (95% CI, 0.26-1.20). Results of the sensitivity analysis taking missing data into consideration are consistent with the primary findings of the trial (eTables 1 and 2 available at

http://www.jama.com): multiple imputation ($P = .002$) and pattern-mixture model control-based imputation ($P = .004$). The primary analysis P value lies between the slightly more liberal multiple imputation approach and the more conservative pattern-mixture model. A post hoc power calculation is provided in the eAppendix.

Of the patients treated with duloxetine first, 59% reported any decrease in pain vs 38% of patients treated with placebo first. Thirty percent of duloxetine-treated patients reported no change in pain and 10% reported increased pain. Based on the exploratory responder analysis, the proportion of patients achieving various levels of pain reduction is illustrated in FIGURE 3. Compared with placebo, the relative risk of experiencing a 30% pain reduction with duloxetine was 1.96 (95% CI, 1.15-3.35) and experiencing a 50% pain reduction was 2.43 (95% CI, 1.11-5.30; eTable 3).

Although the study was powered to detect differences between treatments as main effects only, in exploratory analyses, we examined the potential interaction between treatment group and chemotherapy class. Results suggested that patients who received platinum (oxaliplatin) experienced more benefit from duloxetine than those who received taxanes ($P = .13$). The ob-

Table. Patient Demographics and Baseline Features (continued)

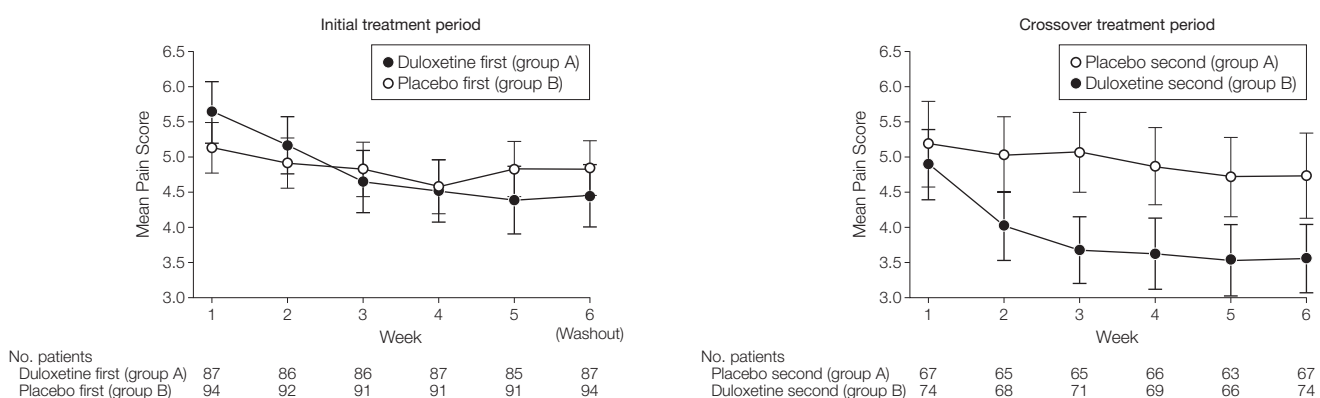
Characteristics	No. (%) of Participants			P Value
	Group A (n = 109)	Group B (n = 111)	Total (n = 220)	
Disease-related features				
Disease stage				.69
Early, I-II	38 (44)	38 (41)	76 (35)	
III	34 (39)	42 (45)	76 (35)	
Metastatic	14 (16)	12 (13)	26 (12)	
Missing	1 (1)	2 (2)	3 (1)	
Concurrent medications use				
No	68 (62)	58 (52)	126 (57)	.10
Yes	31 (28)	43 (39)	74 (34)	
Missing	10 (9)	10 (9)	20 (9)	
Performance status				
0	60 (55)	60 (54)	120 (55)	.78
1	44 (40)	47 (42)	91 (41)	
2	4 (4)	2 (2)	6 (3)	
3	1 (1)	1 (1)	2 (1)	
Missing	0 (0)	1 (1)	1 (0)	
Pretreatment sensory neuropathy grade				
1, Asymptomatic	1 (1)	2 (2)	3 (1)	.47
2, Moderate	77 (71)	84 (76)	161 (73)	
3, Severe	31 (28)	24 (22)	55 (25)	
4, Life-threatening	0 (0)	0 (0)	0 (0)	
Missing	0 (0)	1 (1)	1 (0)	
Pretreatment pain score				
<4	2 (2)	2 (2)	4 (2)	.02 ^a
4-5	44 (40)	58 (52)	102 (46)	
6-7	39 (36)	35 (32)	74 (34)	
8-10	24 (22)	15 (14)	39 (18)	
Missing	0 (0)	1 (1)	1 (0)	
Mean (SD)	6.1 (1.7)	5.6 (1.6)	5.8 (1.7)	

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; GI, gastrointestinal; N/A, not applicable (comparative testing is not applicable because these are stratification variables).

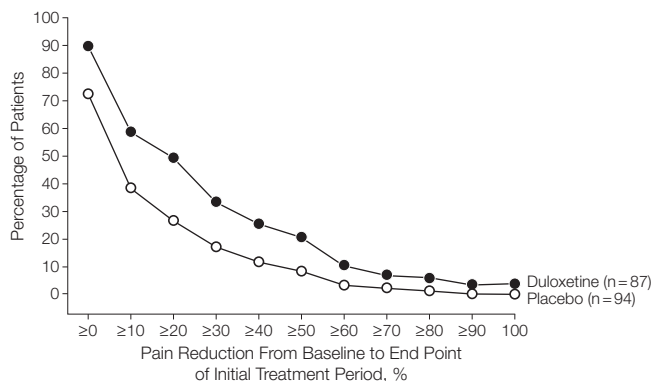
^aTested as a continuous variable.

^bWhen testing for differences between groups based on primary disease, the groups were collapsed into 3 categories (breast, gastrointestinal, or other).

Figure 2. Duloxetine and Placebo Effects on Average Pain Severity During the Initial and Crossover Treatment Periods



The mean average pain score was measured on the first day of each week in the initial and crossover treatments periods. Day 1 of the first week begins the initial treatment period. Day 1 of week 6 begins the washout period when patients received 1 capsule of duloxetine or placebo. Patients took no drug during week 7. Error bars represent 95% CIs.

Figure 3. Percent Decrease in Pain Score Due to Duloxetine vs Placebo

The plot shows the proportion of patients achieving various levels of pain reduction at the completion of the initial treatment period.

served mean difference in platinum-related average pain score between the duloxetine and placebo treatment was 1.06 (95% CI, 0.48 to 1.63) vs 0.19 (95% CI, -0.61 to 0.98) for patients treated with taxane. Results of the exploratory responder analysis revealed that compared with placebo, the relative risk of experiencing a reduction in pain by 30% with duloxetine among patients treated with platinum was 3.05 (95% CI, 1.49-6.27) and a reduction by 50% was 3.78 (95% CI, 1.32-10.84; eTables 4-6 available at <http://www.jama.com>). However, compared with placebo, the relative risk of experiencing a 30% pain reduction with duloxetine among patients treated with taxane was 0.97 (95% CI, 0.41-2.32) and a 50% pain reduction was 1.22 (95% CI, 0.35-4.18), neither of which was statistically significant. There was no difference in duloxetine efficacy based on risk of developing painful chemotherapy-induced peripheral neuropathy.

We also concurrently evaluated changes in pain severity during the crossover treatment period. After adjusting for the study stratifiers (chemotherapy class and pain risk), there was a statistically significant treatment effect on change in pain score ($P < .001$), but an order effect was not significant ($P = .43$). An additional generalized estimating equation model with carryover effect was performed.

The treatment remained significant ($P = .002$), whereas the period ($P = .55$) and carryover ($P = .95$) effects were not. The change in mean pain score during the crossover treatment period for group A (placebo second) was 0.41 (95% CI, 0.06-0.89) and for group B (duloxetine second) was 1.42 (95% CI, 0.97-1.87). The mean difference between the 2 groups in mean change score during the crossover period was 1.01 (95% CI, 0.36-1.65).

Secondary Outcome

Pain Interference With Daily Function. At the end of the initial treatment period, when compared with placebo, patients treated with duloxetine first reported a greater decrease in the amount that pain had interfered with daily functioning ($P = .01$; eFigure 1). The change in mean interference score for patients treated with duloxetine first was 7.9 (95% CI, 5.4-10.5) vs 3.5 (95% CI, 1.1-5.9) for patients treated with placebo first. The mean difference between the 2 groups in mean change score was 4.40 (95% CI, 0.93-7.88).

Quality of Life. Pain-related QOL improved to a greater degree for those treated with duloxetine during the initial treatment than for those treated with placebo. The mean change in the FACT/GOG-Ntx total score was 2.44 (95% CI, 0.43-4.45) for patients treated with duloxetine first vs 0.87 (95% CI, 1.09-

2.82) for patients treated with placebo first ($P = .03$). The mean difference between the 2 groups in mean change score was 1.58 (95% CI, 0.15-3.00; $P = .03$).

Adverse Effects. No hematologic or grade 4 (moderately severe) or 5 (severe) adverse events were reported. In the initial treatment period, 16% treated with duloxetine and 27% treated with placebo reported grade 2 (mild) and 7% treated with duloxetine and 3% treated with placebo reported grade 3 (moderate) nonhematologic adverse events. Fatigue (7%), insomnia (5%), and nausea (5%) were the most common adverse effects reported by patients treated by duloxetine, whereas somnolence (8%), insomnia (7%), and fatigue (5%) were the most common adverse effects reported by patients treated with placebo (eTable 7 available at <http://www.jama.com>).

Other Findings

Nonpainful Symptoms. After the initial treatment period, 41% of patients treated with duloxetine reported a decrease in numbness and tingling in the feet (95% CI, 31%-52%) vs 23% of patients treated with placebo (95% CI, 15%-33%). The trend held through the crossover period with 41% of patients treated with duloxetine (95% CI, 31%-53%) vs 21% of patients treated with placebo (95% CI, 13%-32%). The proportion of patients with improved hand numbness and tingling at the end of the initial treatment period was similar among those treated with duloxetine (36%) and those treated with placebo (34%).

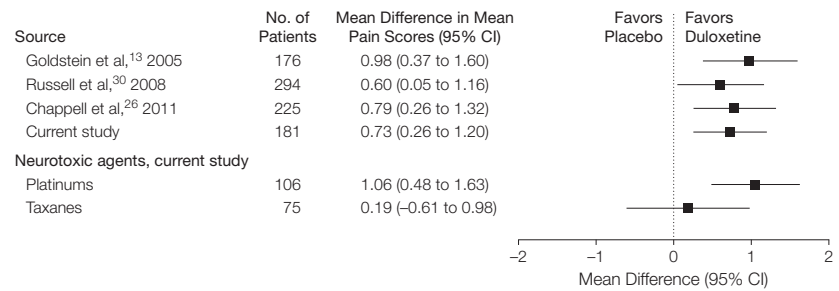
Ancillary Analgesics. Compared with group A (duloxetine first), a higher proportion of those in group B (placebo first) were taking concomitant medications at the start (43% of patients in group B vs 31% in group A) and at the end of the initial treatment period (36% in group B vs 29% in group A). Twenty-seven percent of patients who started out taking concomitant medications in the group A discontinued all medications by the end of the initial treatment period compared with 19% of patients in group B.

COMMENT

Treatment of painful chemotherapy-induced peripheral neuropathy continues to be a challenge because most drugs tested to date have fallen short of providing adequate pain relief.⁴³⁻⁴⁷ To our knowledge, the current study is the first large phase 3 trial to elucidate an effective intervention for painful chemotherapy-induced peripheral neuropathy caused by platinum and taxane agents (mainly paclitaxel or oxaliplatin). During initial treatment, the mean difference between the 2 groups of the change in average pain score was 0.73 ($P = .003$), which compares favorably to mean differences in average pain scores (range, 0.60-0.98) observed in patients receiving duloxetine for US Food and Drug Administration–approved indications for painful diabetic neuropathy, fibromyalgia, and osteoarthritis (eTable 8 available at [www.http://www.jama.com](http://www.jama.com)).^{13,26,30} The observed mean difference in the average pain score between the duloxetine and placebo groups in patients treated with platinum was larger than results reported by Goldstein and colleagues¹³ (FIGURE 4). However, duloxetine-related clinically meaningful improvement in other painful conditions may not be directly comparable with painful chemotherapy-induced peripheral neuropathy.

In addition to the magnitude of the improvement, several other factors should be considered when judging clinical significance, such as the treatment effect size.³⁹ Our results revealed a moderately large treatment effect size (0.513). Based on the IMMPACT recommendations, clinical meaningfulness is also based on the results of a responder analysis, specifically the proportion of patients experiencing a 30% or a 50% improvement in pain severity.^{21,39,48} A 10% to 20% decrease in pain severity is considered to represent a minimal clinically important change, a 30% change represents a moderately important improvement and a 50% change represents a substantially important improvement.^{21,39,48} During initial treatment, the mean change in average pain score reported by patients treated with duloxetine in the current study was 1.06, an improve-

Figure 4. Comparison of the Mean Differences in Average Pain Scores Across Duloxetine Chronic Pain Studies



Duloxetine was compared against placebo in studies involving patients with diabetic neuropathy, Goldstein et al; fibromyalgia, Russell et al; osteoarthritis, Chappell et al; and chemotherapy-induced peripheral neuropathy, the current study, including a breakdown by neurotoxic agent that patients in the current study took.

ment of approximately 10% that is consistent with the IMMPACT definition of a minimal clinically important difference. In addition, results of the exploratory responder analysis suggest that the relative risk of experiencing a 30% and 50% improvement in pain severity statistically favored duloxetine.

Other factors to consider when judging clinical significance include how quickly the drug takes effect, tolerability, and the drug's influence on other efficacy end points such as function and QOL.³⁹ In the current study, pain scores decreased in patients treated with duloxetine relatively quickly, within the first week of therapy (Figure 2). Consistent with our results (eTable 7), several studies show that duloxetine is safe and well-tolerated.^{13,14,26,30,49-51} Furthermore, duloxetine is associated with improved function and QOL. Therefore, after considering the many factors in addition to the magnitude of improvement in pain scores, study results strongly suggest that duloxetine treatment is associated with a clinically meaningful improvement in chemotherapy-induced peripheral neuropathic pain.

Results from our exploratory subgroup analysis lend support to the premise that differences in pathophysiologic mechanisms may help to explain duloxetine response rate variations across neuropathic pain conditions. Just as response rates may vary when duloxetine is used to treat diabetic vs chemotherapy-induced peripheral neuropathy due to differences in

nerve injury mechanisms,^{16,52-55} the mechanisms of taxane- vs platinum-induced peripheral nerve injury are quite different,¹⁶ possibly explaining why patients treated with platinum reported less pain in the current study.

The current trial has several strengths and limitations. The strengths include the prospective, randomized, placebo-controlled trial design and the geographically diverse sample. Regarding limitations, first, there was an imbalance in the dropout rate due to adverse effects in patients treated with duloxetine vs placebo (11% vs 1%, respectively), despite similar adverse effect rates in both groups. One reason for this differential in the dropout rate may be the higher proportion of grade 3 adverse events reported by patients treated with duloxetine. These patients may have been able to guess which drug they were taking, and those experiencing no or minimal pain relief may have dropped out.

Another potential study limitation has to do with how baseline pain was determined. Oncology providers commonly use the NCI CTCAE, or other similar grading scales, to guide a history and physical examination focused on chemotherapy-induced peripheral neuropathy and to grade its severity.^{9,16} Therefore, we relied on standard CTCAE-guided practices for determining severity at baseline. We did not specifically train the examiners regarding CTCAE use because its grading is deeply embedded into oncology practice. Of

note, despite its everyday use in oncology clinical settings, the CTCAE is known for its suboptimal interrater reliability and poor sensitivity to detect subtle changes.^{32,56-60} As such, use of the CTCAE could have resulted in misdiagnosis. Despite its limitations, CTCAE use is consistent with community and academic clinical practice,⁹ and thus the generalizability of our findings is enhanced. Other limitations are that changes in concurrent ancillary analgesic dosage were not assessed, study findings may not be applicable to patients with painful chemotherapy-induced peripheral neuropathy caused by other neurotoxic agents, and the study did not address long-term duloxetine treatment (beyond 5 weeks).

Despite duloxetine's acceptable adverse effect profile, the risk of duloxetine-drug interactions should not be overlooked. Duloxetine should not be used with other drugs that inhibit serotonin reuptake due to the associated increased risk of serotonin syndrome.⁶¹ Also, because duloxetine is a moderate cytochrome (CYP) P450 2D6 enzyme-inhibitor, coadministration with CYP P450 2D6 substrates can lead to increased substrate drug serum concentrations and associated toxicities.⁶²⁻⁶⁵ Concurrent use of duloxetine with warfarin, nonsteroidal anti-inflammatory drugs, or both may also increase bleeding risk.^{61,66} Lastly, if duloxetine and tamoxifen are taken together, duloxetine-induced CYP P450 2D6 enzyme inhibition could inhibit tamoxifen conversion to its active metabolite, endoxifen.^{61,63,67,68}

In conclusion, 5 weeks of duloxetine treatment was associated with a statistically and clinically significant improvement in pain compared with placebo. Exploratory analyses raise the possibility that duloxetine may work better for oxaliplatin-induced rather than taxane-induced painful chemotherapy-induced peripheral neuropathy.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Smith reported receiving support from CALGB/Alliance for travel to meetings. Dr Paskett reported institutional support from CALGB/Alliance for travel to meetings. Dr Ahles reported receiving support from CALGB/Alliance for travel to meetings. Dr Fadul reported pending institutional grants from Genentech. Dr Gilman reported institutional and direct grants pending from the NCI. No other financial disclosures were made.

Funding/Support: This study was supported by grant CA31946 from the NCI Division of Cancer Prevention, the Alliance Statistics and Data Center, and the Alliance Chairman. Drug and placebo were supplied by Eli Lilly. The NCI provided funding for data management and statistical analysis.

Role of the Sponsor: The NCI and Eli Lilly each reviewed and approved the study concept via the usual peer-review process. Minor suggestions were made by each group regarding aspects of the study design. Neither the NCI Division of Cancer Prevention nor Eli Lilly had a role in data collection or management, analysis, interpretation of the data, or with manuscript preparation, review, or approval.

Online-Only Material: The eAppendix, eTables, eFigure, and Author Video Interview are available at <http://www.jama.com>.

Additional Contributions: We thank the study participants and the research staff at all participating sites. Special thanks are extended to the CALGB Oncology Nursing Committee, Richard Schilsky, MD (American Society of Clinical Oncology), Xiaofei Wang, PhD (Duke University), John Taylor, MA (Alliance), Brandelyn Pitcher, MS (Duke University), Sara Jasinski, BA (Duke University), Celia Bridges, BSN, RN (University of Michigan),

and Asa B. Smith, Student (University of Michigan). Dr Wang, Mr Taylor, Ms Pitcher, and Ms Jasinski received salary support from the Alliance Cooperative Group Grant for their contributions to this work. All others provided assistance without receiving financial compensation.

REFERENCES

- Smith EM, Cohen JA, Pett MA, Beck SL. The reliability and validity of a modified total neuropathy score-reduced and neuropathic pain severity items when used to measure chemotherapy-induced peripheral neuropathy in patients receiving taxanes and platinum. *Cancer Nurs*. 2010;33(3):173-183.
- Kautio AL, Haanpää M, Kautiainen H, Kalso E, Saarto T. Burden of chemotherapy-induced neuropathy—a cross-sectional study. *Support Care Cancer*. 2011;19(12):1991-1996.
- Loprinzi CL, Reeves BN, Dakhil SR, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCCT N08C1. *J Clin Oncol*. 2011;29(11):1472-1478.
- Smith EML, Bakitas MA, Homel P, et al. Preliminary assessment of a neuropathic pain treatment and referral algorithm for patients with cancer. *J Pain Symptom Manage*. 2011;42(6):822-838.
- Bakitas MA. Background noise: the experience of chemotherapy-induced peripheral neuropathy. *Nurs Res*. 2007;56(5):323-331.
- Shimozuma K, Ohashi Y, Takeuchi A, et al. Taxane-induced peripheral neuropathy and health-related quality of life in postoperative breast cancer patients undergoing adjuvant chemotherapy: N-SAS BC 02, a randomized clinical trial. *Support Care Cancer*. 2012;20(12):3355-3364.
- Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs*. 2010;14(2):101-110.
- Toftagen C. Surviving chemotherapy for colon cancer and living with the consequences. *J Palliat Med*. 2010;13(11):1389-1391.
- Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN task force report: management of neuropathy in cancer. *J Natl Compr Canc Netw*. 2009;7(suppl 5):S1-S26.
- Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007;(4):CD005454.
- Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol*. 1997;14(1):2-31.
- Bril V, England JD, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy—report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation. *Muscle Nerve*. 2011;43(6):910-917.
- Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116(1-2):109-118.
- Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67(8):1411-1420.
- Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med*. 2005;6(5):346-356.
- Argyriou AA, Bruna J, Marmioli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. *Crit Rev Oncol Hematol*. 2012;82(1):51-77.

17. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 2004;5(2):133-137.
18. Cleeland CS. The brief pain inventory user guide. http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf. Updated 2009. Accessed July 28, 2009.
19. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129-138.
20. Atkinson TM, Mendoza TR, Sit L, et al. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial end point considerations. *Pain Med*. 2010;11(3):337-346.
21. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149(2):177-193.
22. Kaur H, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. *Diabetes Care*. 2011;34(4):818-822.
23. Yang YH, Lin JK, Chen WS, et al. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: an open-label pilot study. *Support Care Cancer*. 2011;20(7):1491-1497.
24. Pritchett YL, McCarberg BH, Watkin JG, Robinson MJ. Duloxetine for the management of diabetic peripheral neuropathic pain: response profile. *Pain Med*. 2007;8(5):397-409.
25. Mease PJ, Spaeth M, Clauw DJ, et al. Estimation of minimum clinically important difference for pain in fibromyalgia. *Arthritis Care Res (Hoboken)*. 2011;63(6):821-826.
26. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract*. 2011;11(1):33-41.
27. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain*. 2009;146(3):253-260.
28. Marangell LB, Clauw DJ, Choy E, et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. *Pain*. 2011;152(1):31-37.
29. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin*. 2011;27(12):2361-2372.
30. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008;136(3):432-444.
31. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003;13(6):741-748.
32. Griffith KA, Merckies JSJ, Hill EE, Cornblath DR. Measures of chemotherapy-induced peripheral neuropathy: a systematic review of psychometric properties. *J Peripher Nerv Syst*. 2010;15(4):314-325.
33. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. *Int J Gynecol Cancer*. 2007;17(2):387-393.
34. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire? results from Eastern Cooperative Oncology Group (ECOG) study 5592. *J Clin Epidemiol*. 2002;55(3):285-295.
35. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582-592.
36. Dubois D, Dhawan R, van de Velde H, et al. Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. *J Clin Oncol*. 2006;24(6):976-982.
37. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage*. 2002;24(6):547-561.
38. Common terminology criteria for adverse events version 4.02 (CTCAE). <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>. Updated 2009. Accessed January 7, 2010.
39. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146(3):238-244.
40. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121.
41. Kajdasz DK, Iyengar S, Desaiah D, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther*. 2007;29(suppl):2536-2546.
42. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
43. Hammack JE, Michalak JC, Loprinzi CL, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain*. 2002;98(1-2):195-203.
44. Kautio AL, Haanpää M, Leminen A, Kalso E, Kautiainen H, Saarto T. Amitriptyline in the prevention of chemotherapy-induced neuropathic symptoms. *Anticancer Res*. 2009;29(7):2601-2606.
45. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011;19(6):833-841.
46. Rao RD, Flynn PJ, Sloan JA, et al. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer*. 2008;112(12):2802-2808.
47. Rao RD, Michalak JC, Sloan JA, et al; North Central Cancer Treatment Group. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer*. 2007;110(9):2110-2118.
48. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158.
49. Hall JA, Wang F, Oakes TM, Utterback BG, Crucitti A, Acharya N. Safety and tolerability of duloxetine in the acute management of diabetic peripheral neuropathic pain: analysis of pooled data from three placebo-controlled clinical trials. *Expert Opin Drug Saf*. 2010;9(4):525-537.
50. Skljarevski V, Desaiah D, Liu-Seifert H, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine (Phila Pa 1976)*. 2010;35(13):E578-E585.
51. Raskin J, Wang F, Pritchett YL, Goldstein DJ. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. *Pain Med*. 2006;7(5):373-385.
52. Spallone V, Lacerenza M, Rossi A, Sicuteri R, Marchettini P. Painful diabetic polyneuropathy: approach to diagnosis and management. *Clin J Pain*. 2012;28(8):726-743.
53. Morales-Vidal S, Morgan C, McCoyd M, Hornik A. Diabetic peripheral neuropathy and the management of diabetic peripheral neuropathic pain. *Postgrad Med*. 2012;124(4):145-153.
54. Smith AG, Singleton JR. Diabetic neuropathy. *Continuum (Minneapolis)*. 2012;18(1):60-84.
55. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol*. 2012;11(6):521-534.
56. Postma TJ, Heijmans JJ, Muller MJ, Ossenkoppele GJ, Vermorken JB, Aaronson NK. Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. *Ann Oncol*. 1998;9(7):739-744.
57. Kuroi K, Shimozuma K, Ohashi Y, et al. Prospective assessment of chemotherapy-induced peripheral neuropathy due to weekly paclitaxel in patients with advanced or metastatic breast cancer (CSP-HOR 02 study). *Support Care Cancer*. 2009;17(8):1071-1080.
58. Cavaletti G, Frigeni B, Lanzani F, et al. Chemotherapy-induced peripheral neurotoxicity assessment: a critical revision of the currently available tools. *Eur J Cancer*. 2010;46(3):479-494.
59. Lavoie Smith EM, Cohen JA, Pett MA, Beck SL. The validity of neuropathy and neuropathic pain measures in patients with cancer receiving taxanes and platinum. *Oncol Nurs Forum*. 2011;38(2):133-142.
60. Frigeni B, Piatti M, Lanzani F, et al. Chemotherapy-induced peripheral neurotoxicity can be misdiagnosed by the National Cancer Institute Common Toxicity scale. *J Peripher Nerv Syst*. 2011;16(3):228-236.
61. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26(1):39-67.
62. Patroneva A, Connolly SM, Fatato P, et al. An assessment of drug-drug interactions: the effect of desvenlafaxine and duloxetine on the pharmacokinetics of the CYP2D6 probe desipramine in healthy subjects. *Drug Metab Dispos*. 2008;36(12):2484-2491.
63. Skinner MH, Kuan HY, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther*. 2003;73(3):170-177.
64. Hua TC, Pan A, Chan C, et al. Effect of duloxetine on tolterodine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol*. 2004;57(5):652-656.
65. Preskorn SH, Greenblatt DJ, Flockhart D, et al. Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. *J Clin Psychopharmacol*. 2007;27(1):28-34.
66. Glueck CJ, Khalil Q, Winiarska M, Wang P. Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA*. 2006;295(13):1517-1518.
67. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*. 2005;97(1):30-39.
68. Caraci F, Crupi R, Drago F, Spina E. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. *Curr Drug Metab*. 2011;12(6):570-577.