Supplementary Online Content

Smith EML, Pang H, Cirrincione C, et al. Effect of Duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A Randomized Controlled Trial. *JAMA*. doi:10.1001/jama.2013.2813.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Missing Data Analysis

Methods

In addition to the primary analysis, two statistical approaches were employed to handle missing values in this study. The first approach is a multiple imputation procedure. Each missing value is imputed by a set of plausible values that represent the uncertainty of the true value. We first utilized the Monte Carlo Markov Chain (MCMC) methodology to obtain a monotone missing data pattern for 100 simulations of imputed original datasets.[1] The data set obtained was then imputed by a regression method for monotone missing-ness. The results are then summarized by standard multiple imputation inference techniques.[2] The second approach is a based on Pattern-Mixture Models (PMMs). PMMs provide a general framework for sensitivity analyses with clinically interpretable assumptions. To be more conservative, we performed a control-based pattern imputation.[3] Specifically, patients from both the experimental treatment and placebo groups who dropped out were assumed to exhibit the same evolution of the pain score as patients on the control treatment. Similar to the first approach, non-monotone missing data was imputed using the MCMC method initially. This was then followed by PMMs-based imputation by regression method using data from time point t to impute time point t+1.

Results

Sensitivity analysis taking missing data into consideration produced the following results: multiple imputation (p=0.002) and PMM control based imputation (p=0.004). These results are consistent with the primary findings of the trial. The primary analysis p-value lies between the slightly more liberal multiple imputation approach and the more conservative control based imputation method.

eTable 1. Results from Multiple Imputation on Mean Change During Initial Treatment Period

Treatment group	LSMean change	95% CI of mean change
Duloxetine (→ placebo)	1.101	0.76, 1.44
Placebo (→ duloxetine)	0.351	0.029, 0.67

	Difference between LSMean change	t statistic	p-value
Multiple imputation	0.750	3.18	0.0015

eTable 2. Results from Pattern Mixture Model Control-Based imputation on Mean Change During Initial Treatment Period

Treatment group	LSMean change	95% CI of mean change
Duloxetine (→ placebo)	1.018	0.69,1.35
Placebo (→ duloxetine)	0.351	0.029, 0.67

	Difference between LSMean change	t statistic	p-value
PMM control based imputation	0.667	2.9	0.0037

Among those who had week 1 pain scores, patients who had at least one of week 2, week 3, week 4, week 5, or week 6 missing were imputed. Percentages of imputation were 7.1%, 10.8%, 13.7%, 14.6%, and 14.6% for week 2, week 3, week 4, week 5, and week 6, respectively. Baseline covariates for patients with missing data versus those had complete data were similar.

Responder Analysis for Initial Treatment Period

To further address the issue of clinical significance, we first defined response as a decrease in pain from week 1 to week 6 of (1) at least 50% and (2) at least 30%.

eTable 3. Observed Response by Group

Response	Duloxetine	Placebo	Relative effect (95% CI)
Number patients	87	94	
50% decrease	20.7%	8.5%	2.43 (1.11,5.30)
30% decrease	33.3%	17.0%	1.96 (1.15, 3.35)

The observed effect of duloxetine relative to placebo was significant.

eTable 4. Multivariate logistic Regression: Observed Group Effect on Response

Outcome:	Comparison	OR	95% CI	p-value
50% decrease	Dulox : Placebo	2.79	1.14, 6.90	0.025
30% decrease	Dulox : Placebo	2.29	1.12, 4.69	0.023

Adjusted for chemotherapy class, risk of CIPN, and baseline pain score

In two separate logistic regressions, we tested a group effect in predicting response of 50% and of 30%, respectively. Models were adjusted for the two study stratifiers of chemo agent (taxane vs. platinum) and high risk of developing CIPN (yes vs. no), and baseline pain score. We found that group was significantly related to moderate (p=0.023) and large (p=0.025) benefit. In both cases, the odds of achieving benefit were more than double for the duloxetine group compared to placebo.

Subgroup Analysis

Although the study was powered to detect differences between treatment groups as main effects only, in exploratory analyses we examined the potential interaction between treatment group and chemotherapy class on response. We therefore present response by group separately for patients who received platinums and taxanes.

eTable 5. Prior Platinums: Observed Unadjusted Response by Group

Response	Duloxetine	Placebo	Relative effect (95% CI)
Total patients	49	57	
50% decrease	26.5%	7.0%	3.78 (1.32, 10.84)
30% decrease	42.9%	14.0%	3.05 (1.49, 6.27)

eTable 6. Prior Taxanes: Observed Unadjusted Response by Group

Response	Duloxetine	Placebo	Relative effect (95% CI)
Total patients	38	37	
50% decrease	13.2%	10.8%	1.22 (0.35, 4.18)
30% decrease	21.1%	21.6%	0.97 (0.41, 2.32)

The subgroup responder analysis in terms of relative effect also shows results consistent with the mean difference in change score analysis presented in the main manuscript.

Adverse Events

eTable 7 highlights the maximum grade of adverse effects (AEs) attributed to duloxetine and placebo therapy that were reported during initial treatment by group. Toxicity incidence was low, with the listed AEs occurring in ≥ 3% patients.

eTable 7. Incidence of Grade 2 or 3 Adverse Events (AEs) by Arm (Initial Treatment Period)

	Group A (*n* = 96)		Group B (*n* = 99)	
Adverse event, No. (%)	Grade 2	Grade 3	Grade 2	Grade 3
Dizziness	2 (2)	1 (1)	1 (1)	0 (0)
Anorexia	3 (3)	0 (0)	1 (1)	0 (0)
Pain	4 (4)	0 (0)	3 (3)	0 (0)
Nausea	4 (4)	1 (1)	3 (3)	0 (0)
Somnolence	3 (3)	0 (0)	8 (8)	0 (0)
Fatigue	6 (6)	1 (1)	5 (5)	0 (0)
Insomnia	4 (4)	1 (1)	5 (5)	2 (2)

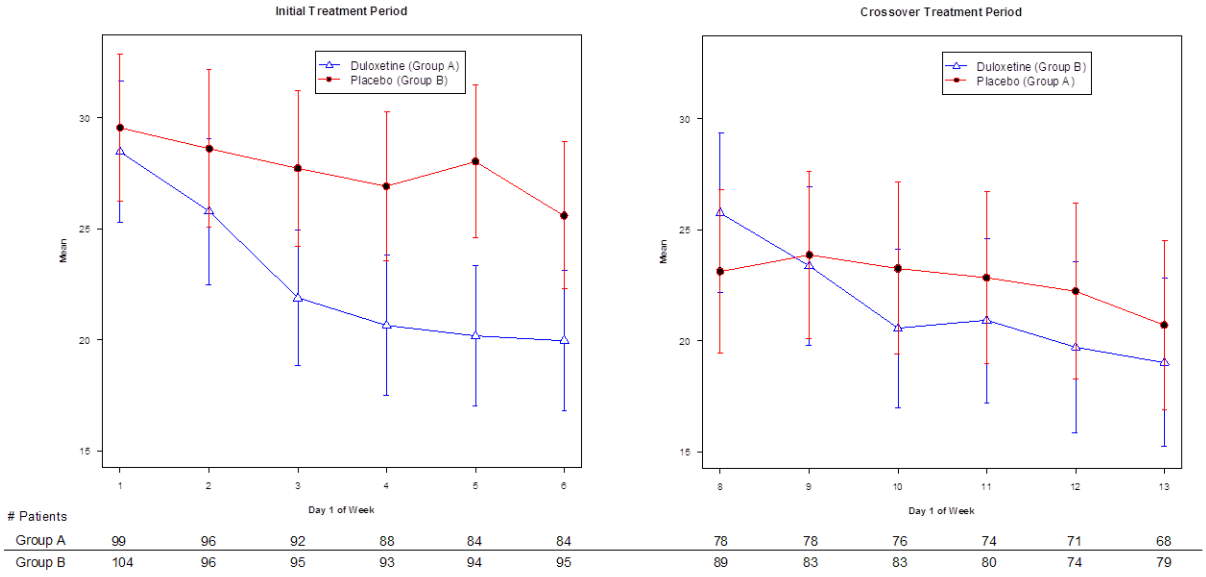
There were no grade 4 or 5 adverse events. Only adverse events occurring in ≥ 3% are reported above.

eTable 8. Duloxetine Effect: Comparison of Published Studies to Current Study

	Duloxetine 60 mg			Placebo			
	Mean change score*	SD	Total	Mean change score*	SD	Total	Mean difference** in change score 95% CI
Goldstein 2005 Diabetic Neuropathy	2.89	2.06	88	1.91	2.06	88	0.98 (0.37, 1.60)
Russell 2008 Fibromyalgia	1.99	2.45	150	1.39	2.40	144	0.60 (0.05, 1.16)
Chappell 2011 Osteoarthritis	2.51	2.04	104	1.72	1.98	121	0.79 (0.26, 1.32)
Smith current study Chemotherapy-Induced PN***	1.06	1.61	87	0.34	1.62	94	0.73 (0.26, 1.20)
Smith - Subgroup analysis							
Platinums ***	1.39	1.49	49	0.65	1.49	57	1.06 (0.48, 1.63)
Taxanes ***	0.34	1.72	38	0.47	1.71	37	0.19 (-0.61, 0.98

Note: SD = Standard deviation.
* Change from baseline to study-specific treatment endpoint.
** Mean difference between Duloxetine and Placebo.
*** Results taken from ANCOVA models.

eFigure. Pain Interference



# Patients												
Group A	99	96	92	88	84	84	78	78	76	74	71	68
Group B	104	96	95	93	94	95	89	83	83	80	74	79

The Y axis is the mean interference score (and 95% CI) by week during initial and crossover periods by group. The number of patients with interference score data at each time point is shown along the x-axis. Data was collected on Day 1 of each week.

Primary Analysis on Initial Treatment Period with Cross-over Design

The major reason for using a crossover design was to allow patients in both treatment groups to receive the study drug. Since the drug was already FDA approved for diabetic neuropathy, we believed that patients might not participate and would seek out duloxetine off-study instead of risking being assigned to the placebo. We believed that the crossover design would promote enrollment by allowing all patients to try the study drug without cost. The reasons for focusing on the initial period as the primary endpoint included: 1) consistency with Goldstein's study primary endpoint, 2) concern about the adequacy of the washout period for this patient population, and 3) uncertainly regarding CIPN maturation and the post-crossover period drop-out rate.

Order and Carryover Effects

In the GEE model, the period effect was taken into account. However, the p-value was not significant at 0.428. An additional GEE model with carryover effect was performed. The treatment remained significant (p=0.0023) while period and carryover effects were not; p=0.546 and p=0.953, respectively.

Post-hoc Power Calculation

With a 0.726 mean change score and an associated standard error of 0.24 (smaller than Goldstein's 0.3), we obtain a relative efficiency ratio of 3.019. The final sample size provides

85% power to detect a difference of 0.726 in mean change score between the duloxetine and placebo groups.

eReferences

1. Schafer, J.L. (1997), Analysis of Incomplete Multivariate Data, New York: Chapman and Hall.

2. Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.

3. Little, R., Yau, L. (1996), Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics, 52, 1324-1333.