

## Early Improvement in Pain Predicts Pain Response at Endpoint in Patients With Fibromyalgia

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**Abstract:** An unanswered, but clinically important question is whether there are early indicators that a patient might respond to duloxetine treatment for fibromyalgia pain. To address this question, pooled data from 4 double-blind, placebo-controlled trials in duloxetine-treated patients (N = 797) with primary fibromyalgia as defined by the American College for Rheumatology were analyzed. Classification and Regression Tree (CART) analysis was used to determine what level of early pain improvement as measured by the 24-hour average pain severity question on the Brief Pain Inventory (BPI) best predicted later response. The predictor variables tested were 10, 15, 20, 25, and 30% decrease in BPI 24-hour average pain from baseline to Week 1 and Week 2. The results of the CART analysis showed that for patients with  $\geq 15\%$  improvement in pain at Week 1 and  $\geq 30\%$  improvement at Week 2, the probability of response at 3 months was 75%. For patients with  $< 15\%$  improvement at both Week 1 and Week 2, the probability of not responding at 3 months was 86%. Quantifiable early improvement in pain during the first 2 weeks of treatment with duloxetine was highly predictive of response or nonresponse after 3 months of treatment.

**Perspective:** This article presents early indicators that can highly predict later pain response or non-response in fibromyalgia patients treated with duloxetine. The results may aid clinicians to predict the likelihood of response at 3 months within the first 2 weeks of treatment.

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**Key words:** Fibromyalgia, duloxetine, prediction, response, pain.

An estimated 5 million individuals in the United States have fibromyalgia,<sup>13</sup> and prevalence is higher in women than in men.<sup>7</sup> Fibromyalgia has been defined as a hyperalgesic state associated with augmented pain processing.<sup>1</sup> Descending pain pathways, involving the neurotransmitters serotonin, norepinephrine, and dopamine, may be selectively attenuated.<sup>1</sup>

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has shown efficacy in double-blind, placebo-controlled trials in patients with fibromyalgia<sup>4,14</sup> and has been approved by the US Food and Drug Administration (FDA) for the management of fibromyalgia.<sup>9</sup> However, not all patients with fibromyalgia respond to treatment with duloxetine,<sup>2</sup> as defined

by at least a 30% reduction in pain after 3 months of treatment.<sup>10</sup>

A statistical approach to identify early indicators for later response from clinical data sets is classification and regression tree (CART) analysis.<sup>5</sup> Recently, CART analysis was used to successfully develop an early predictor ( $\geq 20\%$  improvement on the positive and negative syndrome scale) for longer-term response to olanzapine treatment in patients with schizophrenia.<sup>12</sup>

Here, we examined if early improvement in pain predicted later response using CART analysis of data collected in placebo-controlled clinical studies in patients with fibromyalgia. These analyses were designed to help clinicians and patients to determine the likelihood of response after initiating treatment with duloxetine.

## Methods

This is a post hoc analysis of data from 4 clinical trials that examined the efficacy and safety of duloxetine

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treatment in adult patients with fibromyalgia. The results of the primary study objectives have been previously published.<sup>3,4,6,14</sup> The study protocols were reviewed and approved by individual participating sites' institutional review boards prior to enrolling patients. All participants provided written informed consent before receiving any study therapy or undergoing any study procedure.<sup>3,4,6,14</sup> The data included in the current analyses were de-identified before use.

## Patients and Study Designs

All patients met criteria for primary fibromyalgia as defined by the American College for Rheumatology<sup>17</sup> and were assessed for the presence of major depressive disorder (MDD) with the Mini International Neuropsychiatric Interview (MINI).<sup>15</sup> All 4 clinical trials were double-blind and placebo-controlled, and included adult patients  $\geq 18$  years of age of either sex (except Study 2, which included only female patients). In Study 1, patients had to also have a score of  $\geq 4$  on the pain severity item of the Fibromyalgia Impact Questionnaire (FIQ) at randomization. In Studies 2 through 4, patients had to have a score of  $\geq 4$  on the 24-hour average pain item on the Brief Pain Inventory (BPI) at randomization. Studies 1 through 3 were 12 weeks long, while Study 4 lasted 6 months (only the first 3 months of data were included in this analysis). The following duloxetine doses and titration schedules were used in the individual studies.

- Study 1.<sup>3</sup> Duloxetine 20 mg once daily (QD) for 5 days, followed by duloxetine 20 mg twice daily (BID) for at least 3 days, followed by duloxetine 40 mg BID for at least 2 days, followed by duloxetine 60 mg BID for the remainder of the study.
- Study 2.<sup>4</sup> Duloxetine patients were randomized to either 60 mg QD or 60 mg BID. Patients randomized to duloxetine 60 mg QD received this dose without titration throughout the study. Patients randomized to duloxetine 60 mg BID received duloxetine 60 mg QD for 3 days, followed by duloxetine 60 mg BID for the remainder of the study.
- Study 3.<sup>14</sup> Duloxetine patients were randomized to 20 mg QD, 60 mg QD, or 120 mg QD. Patients randomized to duloxetine 20 mg QD received this dose without titration throughout the acute study phase. Patients randomized to duloxetine 60 mg QD received duloxetine 30 mg QD for 1 week followed by duloxetine 60 mg QD for the remainder of the acute study phase. Patients randomized to duloxetine 120 mg QD received duloxetine 30 mg QD for the first week, duloxetine 60 mg QD for the second week, followed by duloxetine 120 mg QD for the remainder of the acute study phase. Patients who received duloxetine 20 mg QD were not included in the analysis as this dose is deemed to be nonefficacious.<sup>14</sup>
- Study 4.<sup>6</sup> Duloxetine patients received duloxetine 30 mg QD for 1 week followed by duloxetine 60 mg QD for the remainder of the acute study phase.

In the 4 different trials from which data were pooled a total of 797 patients received treatment with duloxe-

tine, of which 774 patients had pain measurements at both baseline and postbaseline and were included in the current analyses. A total of 464 of the 774 patients completed the 3-month period, and 310 of the 774 patients dropped out early but had postbaseline measurements.

## Pain Assessment and Response to Treatment

The 24-hour average pain item on the patient-rated BPI short form<sup>8</sup> (11-point Likert Scale) was used to assess pain in all 4 studies. Response to treatment was defined as a  $\geq 30\%$  decrease of the 24-hour average pain item on the BPI at the 3 month endpoint compared to baseline.<sup>4,10</sup>

## Statistical Analyses

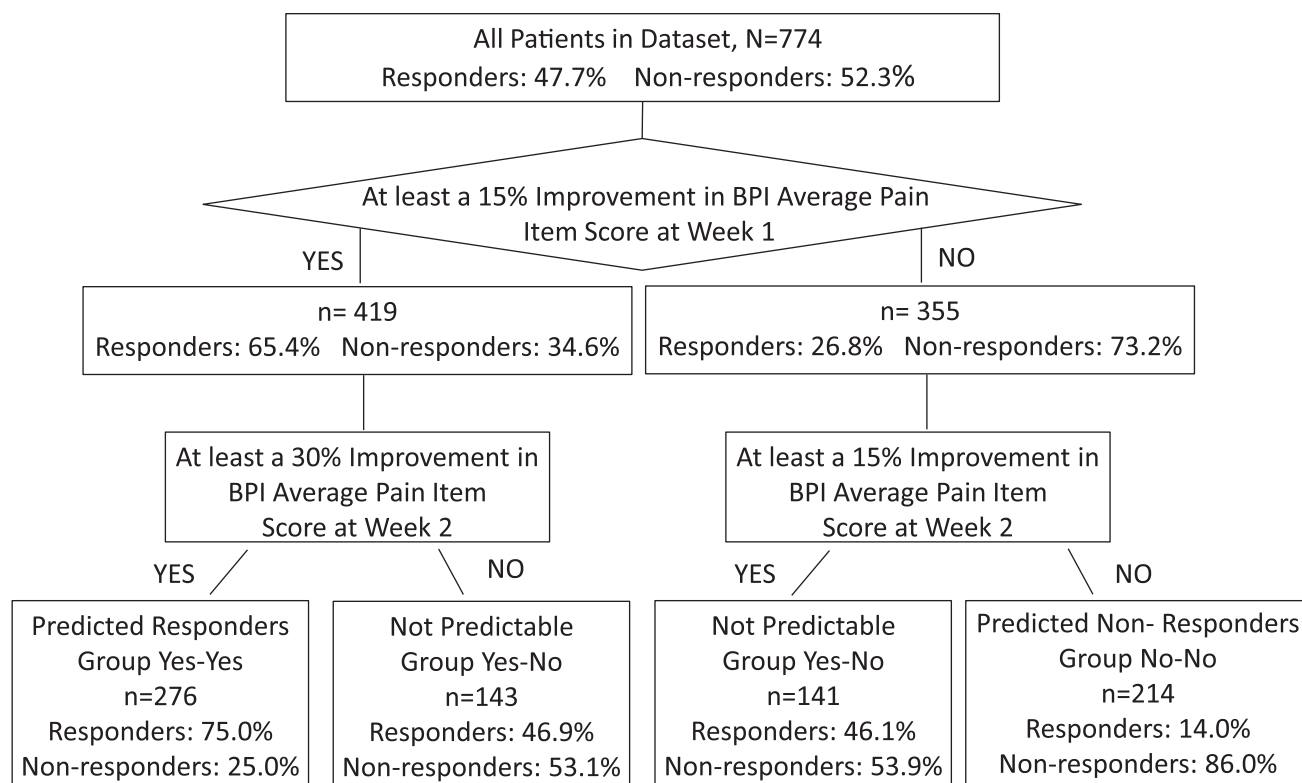
CART analyses<sup>5</sup> were used to determine which percentage decrease of the BPI 24-hour average pain item score observed after 1, 2, or 4 weeks of treatment with duloxetine would best predict patient response after approximately 3 months of treatment. CART analysis is a commonly used method to identify the best possible predictors.<sup>5</sup> It is an easy and intuitive method to understand and can generate results that are more useful and applicable for clinicians and researchers (since they are based on dichotomous decision rules) than the linear or logistic regressions, which rely on more complex functional equations. In this study, we selected CART analysis to find the best predictor of response among all the potential candidates. The poor predictors were not reported here because they do not answer the research question.

For patients who discontinued the clinical trials early, data from their last nonmissing visit was used as endpoint value. As predictor variables, 5 levels of pain improvement were tested: 10, 15, 20, 25, and 30% decrease of the BPI 24-hour average pain item score. All levels of pain improvement were assessed compared to baseline. The goal was to maximize the separation between the responders and non-responders at endpoint. Groups of patients (called "nodes") were split into 2 "daughter nodes" defined by the cut-off created by the CART analysis using the above-described predictor variables. The branching of the decision tree was limited to 2 decision steps to help create the simplest tools possible. JMP software (SAS Institute Inc., Cary, NC) was used to perform the CART analysis. Mixed-effect model repeated measure (MMRM) analysis was used to further describe the changes in pain over time for the different predicted groups. The model included study, group (ie, response status at endpoint), week, group  $\times$  week, week  $\times$  week, group  $\times$  week  $\times$  week, and baseline. The unstructured covariance option was used.

## Results

### Demographics

In the 4 different trials from which data were pooled, a total of 797 patients received treatment with duloxetine, of which 774 patients had pain measurements at



**Figure 1.** Prediction of treatment response for 30% BPI average pain reduction in duloxetine-treated patients at weeks 1 and 2.

both baseline and postbaseline and were included in the current analyses. Patients were mostly women (94.6%) with a mean age of 50.6 years.

### Prediction of 30% Response Using Pain Improvement Data at Weeks 1 and 2

Fig 1 shows the classification tree generated by the CART analysis based on Week 1 and Week 2 data of duloxetine-treated patients. Of the patients who showed both at least 15% improvement of BPI 24-hour average pain item score at Week 1 and at least 30% improvement of BPI 24-hour average pain item score at Week 2 ("yes-yes" group), 75% responded to treatment with duloxetine at endpoint of the acute phase (positive predictive value [PPV] = 75.0%). Of the patients with less than 15% improvement of BPI 24-hour average pain item score at Week 1, and less than 15% improvement of BPI 24-hour average pain item score at Week 2 ("no-no" group), 86.0% did not respond to treatment with duloxetine at the end of the acute phase (negative predictive value [NPV] = 86.0%). Of the original 774 patients with pain measurement at both baseline and postbaseline, 36.7% had mixed responses to the 2 criteria described above (responses to criteria were "yes-no" or "no-yes") and their 3-month outcome was classified as unpredictable. The remaining 63.3% could be predicted as responders or non-responders using the criteria above (responses to criteria were "yes-yes" or "no-no"). The pain response rates (46.9 and 46.1%, respectively) in the mixed (unpredictable) groups were similar to the overall pain response rate of 47.7%,<sup>2</sup> indicating that

there is no improvement in the accuracy of prediction for the mixed group. Repeat of this analysis for each study separately using the same prediction parameters yielded similar predictive values across all 4 studies (Table 1).

Similar CART analysis was performed in placebo-treated patients (N = 526) and the corresponding PPV and NPV in placebo-treated patients were 67.0 and 83.4% respectively, slightly worse than the results from the model using duloxetine-treated patients (data not shown). For the rest of the analyses, we focused on duloxetine-treated patients only.

### Baseline Demographics by Predicted Response Group (Week 1 and Week 2 of Treatment)

Stratification of all patients in the data set by predicted response group revealed no apparent relationship between baseline demographics (age, gender, weight, and ethnicity) and predicted response group (Table 2).

### Changes over Time in BPI Average Pain Scores

Fig 2A illustrates mean changes in BPI 24-hour average pain scores over time stratified by predicted group (based on Week 1 and Week 2 prediction). The predicted responders ("yes-yes") group showed a rapid decrease in BPI 24-hour average pain scores within the first week after initiation of treatment and maintained this magnitude of improvement throughout the study; and the

**Table 1. Summary of Prediction Results**

PATIENT POPULATION	STUDIES	NUMBER OF PATIENTS	PPV	NPV	NOT PREDICTABLE	MIS-CLASSIFIED
Duloxetine-treated	1–4	774	75.0%	86.0%	36.7%	20.2%
Duloxetine-treated	1	100	68.2%	87.2%	39.0%	19.7%
Duloxetine-treated	2	230	80.7%	82.0%	37.8%	18.9%
Duloxetine-treated	3	286	78.4%	84.1%	37.1%	19.4%
Duloxetine-treated	4	158	61.2%	90.0%	37.3%	24.2%
Placebo-treated	1–4	526	67.0%	83.5%	33.8%	21.3%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

NOTE. All prediction results for duloxetine-treated patients are based on the Model presented in Fig 1; results for placebo-treated patients were based on the model presented in Fig 1B.

predicted non-responders (“no-no”) group had a small increase in BPI 24-hour average pain scores within the first 2 weeks after initiation of treatment (Week 1 and Week 2 assessments), followed by a small decrease in scores. The unpredictable group (“no-yes” and “yes-no”) had response profiles that were more indicative of their mixed response. There are modest distinctions in their profiles, but both groups had responses that were intermediate to the predicted responders and the predicted non-responders. The eventual responder (“no-yes”) group had a small decrease in pain score early on, with a moderate decrease in score overall. The eventual non-responder (“yes-no”) group demonstrated a stronger decrease in pain score within the first week after initiation of treatment and maintained this level throughout the study.

Analysis of BPI 24-hour average pain scores over time by prediction group and endpoint responder status produced distinct patterns of score changes for both “yes-yes” and “no-no” groups (Fig 2B). Patients in the predicted responders (“yes-yes”) group who were actually responders at endpoint experienced a strong pain improvement within 1 week after initiation of treatment, followed by a continual, steady decline in pain scores (“rapid responders”). Patients in the predicted responders (“yes-yes”) group who were actually non-responders at endpoint experienced a similar strong

pain improvement within 1 week after initiation of treatment, but exhibited a steady increase in pain scores thereafter (“responders losing efficacy”). In contrast, patients in the predicted non-response (“no-no”) group who were actually responders at endpoint showed a small increase in scores within 1 week after treatment initiation, followed by a steady decline in scores (“slow responders”). Finally, patients in the predicted non-responders (“no-no”) group who were actually non-responders at endpoint showed a small increase in scores after treatment initiation, followed by a minimal decrease through the remainder of the study (“non-responders”).

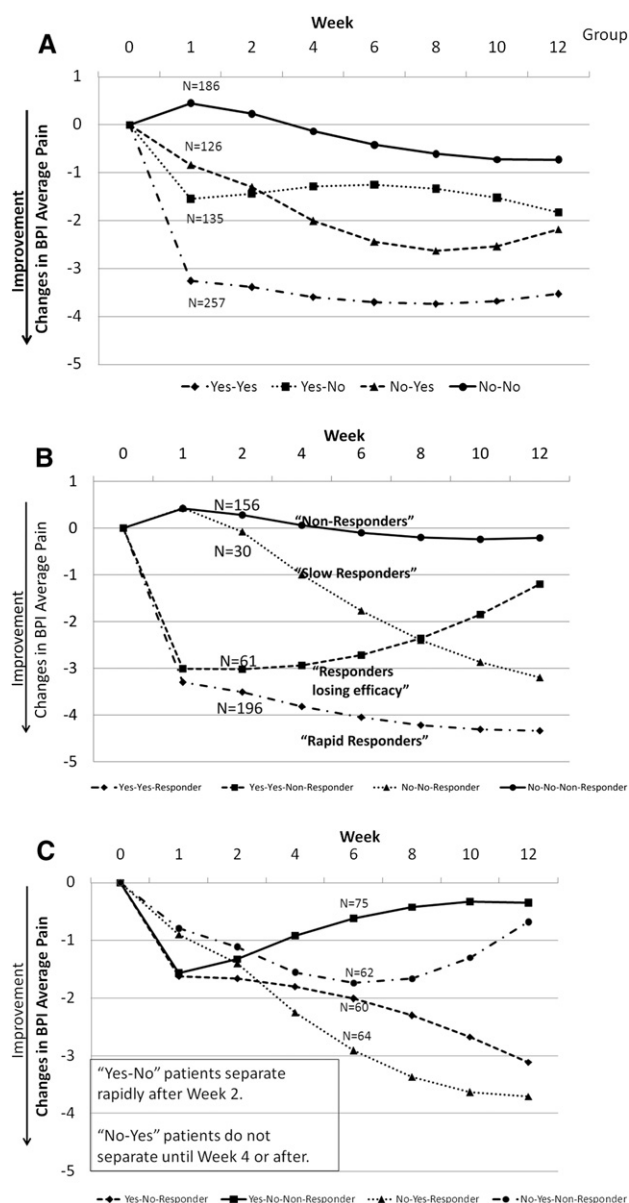
When the unpredictable groups (“yes-no” and “no-yes” groups) were stratified based on endpoint response, the development of BPI 24-hour average pain scores over time followed different patterns compared with the “yes-yes” and “no-no” groups (Fig 2C). “Yes-no” patients showed a modest decrease in scores within 1 week after initiation of treatment. By Week 2, the curves for endpoint responders and non-responders separated within the “yes-no” cohort—patients who responded at endpoint showed a small but steady decrease in scores throughout the study; in contrast, “yes-no” patients who were non-responders at endpoint showed a steady increase in scores starting at Week 2, nearly returning to baseline. Separation of pain score curves by endpoint

**Table 2. Patient Baseline Demographics by Prediction Group Based on Week 1 and Week 2 Improvement**

	LIKELY RESPONDERS YES-YES GROUP	NOT PREDICTABLE YES-NO GROUP	NOT PREDICTABLE NO-YES GROUP	LIKELY NON-RESPONDERS NO-NO GROUP
Age, years; mean (SD)	50.5 (11.1) N = 257	49.2 (10.5) N = 135	50.6 (9.5) N = 126	51.2 (11.2) N = 186
Female gender, %	96.1	91.8	93.6	94.1
Weight, kg; mean (SD)	80.3 (19.7) N = 257	80.5 (19.9) N = 135	80.6 (19.8) N = 125*	78.3 (18.2) N = 184*
Ethnicity, %				
African American	2.7	2.2	.8	2.1
White	89.1	86.7	89.7	87.6
East Asian	0	.7	.8	.5
Hispanic	7.4	8.9	7.9	9.7
Native American	.8	0	0	0
West Asian	0	.7	.8	0
Other	0	.7	0	0

Abbreviations: n, number of patients; SD, standard deviation.

\*Weight data was not available for all patients.



**Figure 2.** (A) Changes in BPI 24-hour average pain over time by predicted group. BPI, Brief Pain Inventory; N, number of patients at Week 1. (B) Changes in BPI 24-hour average pain over time by predicted group and outcome. Abbreviations: BPI, Brief Pain Inventory; N, number of patients at Week 1. (C) Changes in BPI 24-hour average pain over time by prediction group for not-predictable groups. BPI, Brief Pain Inventory; N, number of patients at Week 1.

response occurred later for the “no-yes” patients. The whole “no-yes” group experienced a slow but steady decrease in scores until Week 6—thereafter, endpoint non-responders showed a steady increase in scores, while endpoint responders continued to demonstrate score decreases.

### Patient Disposition and Treatment-Emergent Adverse Events by Predicted Group

The highest percentage of patients who completed the clinical trials was in the group of patients that was predicted to be likely responders (“yes-yes” answer in

the decision tree) to treatment with duloxetine (Fig 3). Similar percentages of patients out of each group discontinued the clinical trials due to adverse events in all 4 prediction groups (Fig 3), and adverse events were the main reason for discontinuation in all 4 prediction groups. Analysis of all treatment-emergent adverse events (TEAEs) that occurred in >10% of the whole study population revealed that the group of patients who were predicted to be likely responders had higher rates for all of the top TEAEs compared with the groups of patients who were predicted to be likely non-responders (Fig 4).

### Additional Prediction Models for Treatment Outcome

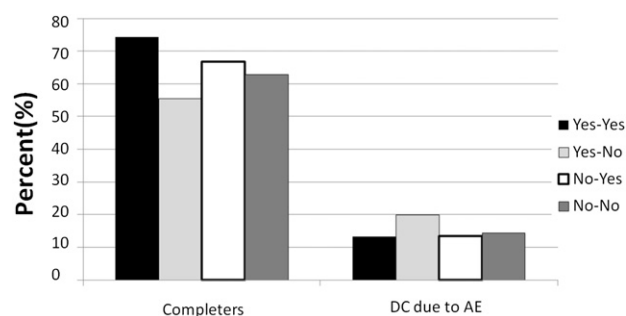
In addition to the prediction model based on Week 1 and Week 2 data, 4 other models were developed. Two models were based on Week 2 and Week 4 data and the others used different response criteria (ie, 50% reduction in pain) or predictor variable (ie, PGI-I). The purpose of these additional models was to examine how well the prediction models based on other conditions or criteria would perform. The results are shown in Table 3.

### Discussion

These post hoc analyses demonstrated that it is possible to quantitate early improvement in pain in order to predict longer term treatment response to duloxetine in patients with fibromyalgia even though the patients’ response level may fluctuate over time. Conversely, these analyses showed that minimal improvement in pain scores at both Week 1 and Week 2 were highly predictive of non-response at Week 12. Baseline characteristics were similar across all prediction and response groups, with the exception that patients in the group of slow responders had milder symptoms (similar pain levels but lower scores on several BPI and FIQ items) of fibromyalgia at baseline compared with the other groups. Prediction models based on Week 2 and Week 4 assessments or only on Week 4 assessments had lower PPVs and NPVs than the model based on Week 1 and Week 2 assessments. Since there was no increase in predictive value by waiting until Week 4 observations are made, the predictions based on Week 1 and Week 2 assessments are preferable. Additional prediction models using Week 1 and Week 2 pain improvement or PGI-I to predict 50% or 30% pain response also show similar or worse results.

To the best of our knowledge, these analyses are the first to identify early indicators for treatment response to duloxetine in patients with fibromyalgia. Based on these analyses, it appears that the observation of some improvement after the first week of treatment followed by more improvement after the second week of treatment may indicate a high probability for response to treatment further on during therapy.

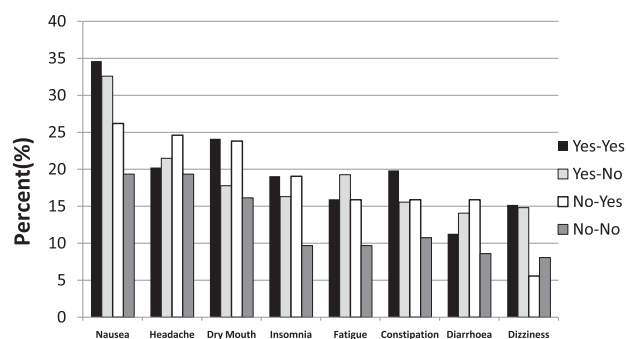
Overall, these results suggest that a successful treatment strategy may be one that monitors responses of patients frequently—ideally weekly—at the beginning of treatment in order to capture early changes (or lack



**Figure 3.** Patient disposition by predicted group. The denominator used to calculate the percentage for each group was the total number of patients who had efficacy data at both Week 1 and Week 2 in that group. AE, adverse event; DC, discontinuation.

thereof) in the patients' pain level and to use these observations when considering ongoing treatment decisions. The importance of early improvements in pain during treatment with duloxetine in patients with fibromyalgia mirrors the results of clinical trials with duloxetine in patients with MDD; there, onset of efficacy for depression at Week 2 was correlated with depression response at Week 8<sup>16</sup> and at 8 months,<sup>11</sup> respectively.

In the current analyses, the subgroup of patients who were predicted as likely responders to treatment with duloxetine was also the subgroup of patients who reported more TEAEs compared with the other subgroups. Previous studies have not examined or reported differences in the frequency of TEAEs between responders and non-responders to treatment with duloxetine. This observation may raise a question as to whether responders and non-responders may differ in metabolism of duloxetine, which may affect both the response to treatment and the susceptibility to TEAEs. It is also possible that the distinct response profiles (illustrated with BPI 24-hour average pain score



Reported are treatment-emergent adverse events that were observed in >10% of the study population.

**Figure 4.** Treatment-emergent adverse events by predicted group. Reported are treatment-emergent adverse events that were observed in >10% of the study population.

changes over time in Figs 2A–2C) are due to so far unknown interindividual differences, eg, genetic polymorphisms, which may ultimately influence treatment response. Further research might help to answer these questions.

Several study limitations apply to the interpretation of these results. For one, the results of these analyses are only applicable to treatment with duloxetine; no other therapy options for fibromyalgia pain were evaluated in these studies. Within these analyses, only a limited number of predictors were examined—thus, the possibility that other measurements might produce more accurate predictions of treatment outcome cannot be excluded. Additionally, the majority of patients included in our analyses were women. Thus, the value of predictors for males is unknown. Further, these 4 clinical trials utilized different dosing regimes. In Study 1, patients were titrated from duloxetine 20 mg QD to duloxetine 60 mg BID during the initial 2 weeks of the study. In Studies 1, 3, and 4, patients had reached their study dose before the first assessment of changes in pain occurred at the end of Week 1.

**Table 3.** Additional Prediction Models for Duloxetine-Treated patients

RESPONSE VARIABLE	PREDICTOR VARIABLE	WEEK 1 CRITERIA	WEEK 2 CRITERIA	WEEK 4 CRITERIA	PPV	NPV	NOT PREDICTABLE	MIS-CLASSIFIED
Endpoint 30% pain reduction	BPI average pain at Week 2 and Week 4	NA	≥30% pain reduction	If Week 2–Yes: ≥15% pain reduction If Week 2–No: ≥30% pain reduction	72.1%	77.1%	19.0%	25.5%
Endpoint 30% pain reduction	BPI average pain at Week 4	NA	NA	≥30% pain reduction	66.8%	72.0%	NA	30.6%
Endpoint 50% pain reduction	BPI average pain at Week 1 and Week 2	≥20% pain reduction	If Week 1–Yes: ≥30% pain reduction If week 1–No: ≥15% pain reduction	NA	63.1%	91.7%	38.4%	23.9%
Endpoint 30% pain reduction	PGI-I	PGI-I ≤2	If week 1–Yes: PGI-I ≤3 If week 1–No: PGI-I ≤3	NA	67.7%	65.9%	55.0%	33.6%

Abbreviations: PGI-I, Patient global impression – improvement; NPV, negative predictive value; PPV, positive predictive value.

NOTE. "Pain reduction" means the change from baseline in BPI (Brief Pain Inventory) average pain. The criteria were determined by the CART algorithm.

However, comparison of prediction results across individual studies yielded similar results, indicating that differences in titration schedules might not significantly affect our predictive classification models or clinical outcome.

In conclusion, results presented here showed that early improvement of pain in patients with fibromyalgia during treatment with duloxetine indicates a greater potential for overall treatment success compared with no early improvement in pain. Frequent monitoring of patients with fibromyalgia during the initial weeks after starting treatment with duloxetine might therefore provide useful information in the management of fibromyalgia.

## Disclosures

This work was sponsored by Eli Lilly and Company. Dr Wang is a former employee of, and Dr Ruberg is a full-time employee of, Eli Lilly and Company. Dr Gaynor

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