What Makes Patients with Fibromyalgia Feel Better? Correlations Between Patient Global Impression of Improvement and Changes in Clinical Symptoms and Function: A Pooled Analysis of 4 Randomized Placebo-controlled Trials of Duloxetine

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ABSTRACT. ***Objective.*** To investigate the relationship between changes in clinical rating scale items and endpoint Patient Global Impression of Improvement (PGI-I).

Methods. Data were pooled from 4 randomized, double-blind, placebo-controlled studies of duloxetine in patients with fibromyalgia (FM). Variables included in the analyses were those that assessed symptoms in FM domains of pain, fatigue, sleep, cognitive difficulties, emotional well-being, physical function, and impact on daily living. The association of endpoint PGI-I with changes from baseline in individual variables was assessed using Pearson product-moment correlations (r). Stepwise linear regression was used to identify those variables for which changes from baseline were statistically significant independent predictors of the endpoint PGI-I ratings.

Results. Changes in pain variables and interference of symptoms with the ability to work were highly correlated ($r \geq 0.5$ or $r \leq -0.5$) with endpoint PGI-I. Moderate correlation with endpoint PGI-I ($0.30 \leq r < 0.5$ or $-0.5 < r \leq -0.30$) included changes in variables that assessed physical functioning, depression, anxiety, fatigue, and several variables related to impact on daily living. Independent predictor variables of endpoint PGI-I identified by stepwise linear regression included assessments for pain, physical function, vitality, anxiety, social function, and tender point thresholds.

Conclusion. In addition to pain reduction, what makes patients with FM feel better may include improvement in fatigue, physical functioning, mood, and impact on daily living. An assessment of these domains may be important in clinical trials of FM and in the management of patients with FM.
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Fibromyalgia (FM) is characterized by chronic widespread pain and tenderness and is often associated with fatigue, nonrestorative sleep, depressed mood, cognitive difficulties, and other symptoms[1,2]. The multidimensional features of FM affect social and physical functioning, interfere with daily activities, and negatively affect emotional well-being[3,4]. Improvement in pain symptoms has been the primary efficacy goal in FM clinical trials; however, given the multidimensionality of this disorder, evaluating potential treatment effectiveness on other FM symptoms may provide greater understanding of what contributes to a patient's overall assessment of improvement. Through the ongoing work of the Outcomes Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) fibromyalgia initia-

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tive, the clinical domains of FM that were identified by expert opinion as well as clinician and patient Delphi exercises as being among the most important to assess in clinical trials of FM included pain, fatigue, sleep, cognition, emotional well-being, physical function, and impact on daily living[5].

The most commonly used and validated measure of a patient's response to treatment is the Patient Global Impression of Improvement (PGI-I) scale[6]. This is a categorical scale on which patients provide ratings of their overall impression of how they are feeling since treatment began, with following choices: 1 = very much better, 2 = much better, 3 = better, 4 = no change, 5 = worse, 6 = much worse, 7 = very much worse.

The efficacy of duloxetine in the treatment of FM was investigated in 4 randomized, placebo-controlled trials[7-10]. Several rating scales were used to assess multiple clinical domains of FM. The goal of our study was to analyze data pooled from these studies to identify clinical variables most highly associated with patients' overall perception of improvement. Another purpose of the study was to determine whether the clinical variables identified by the analysis were consistent with the key clinical domains selected by the OMERACT fibromyalgia initiative.

MATERIALS AND METHODS

To date, there have been 4 randomized, double-blind, placebo-controlled, multicenter studies on the efficacy of duloxetine in patients with FM[7-10] as defined by American College of Rheumatology criteria[1]. Specific details of the studies and outcome measures are summarized in Table 1. For this analysis only the 3-month data were included and pooled across studies.

Rating scales used across all 4 studies included the Brief Pain Inventory (BPI)[11], the Fibromyalgia Impact Questionnaire (FIQ)[12], the Medical Outcomes Study Short Form-36 (SF-36)[13], the Sheehan Disability Scale (SDS)[14], and the Patient Global Impression of Improvement (PGI-I)[6]. In addition, all studies assessed tender points using dolorimetry[15]. Three studies also included the Beck Depression Inventory-II (BDI)[16] (Studies I, III, and IV). The Hamilton Depression Rating Scale (HAMD)[17] was used in Studies II-IV. Studies III and IV included the Multidimensional Fatigue Inventory (MFI)[18] and the EuroQol Questionnaire 5 Dimensions (EQ5D)[19].

The clinical domains of FM identified in this analysis were based on domains identified from Delphi exercises with clinicians and patients with FM[5]. The domains included pain, fatigue, sleep, cognition, emotional well-being, physical function, and impact on daily living. For this analysis, individual scales, subscales, or scale items were selected based on the clinical domains they measured.

Statistical methods. All randomized patients with both baseline and post-baseline data were included. All analyses were performed separately for each treatment group [duloxetine (all doses combined into 1 group) or placebo] and for both groups combined. The associations of endpoint PGI-I with changes from baseline to endpoint in individual variables were assessed using Pearson product-moment correlation (r). The levels of correlation were categorized based upon r values within the following ranges: high ($r \geq 0.5$ or $r \leq -0.5$), moderate ($0.30 \leq r < 0.5$ or $-0.5 < r \leq -0.30$), and low ($-0.30 < r < 0.30$)[20]. Stepwise linear regression was used to identify those variables in the assessments that were included in all studies (BPI, FIQ, SF-36, SDS, tender point dolorimetry) for which the changes from baseline to endpoint were most highly associated with the patients' ratings on the PGI-I at endpoint. Regression analyses were also performed separately for each treatment group (duloxetine or placebo) and for both groups combined. The entry and stay criteria for the stepwise regression were $p = 0.15$ and $p = 0.05$, respectively. Each regression analysis contained an intercept variable.

RESULTS

Responses from 7 patient-rated scales assessing domains of pain, health-related quality of life, the impact of FM, disability, fatigue, and depression, and 1 clinician-rated scale assessing depression were included in the analyses. Rating scales, subscales, or scale items were assigned to symptom domains of pain, fatigue, sleep, cognition, emotional well-being, physical function, and impact on daily living.

The level of correlation with the PGI-I for each of the rating scores within the domains ranged from $r = 0.56$ to $r = 0.02$ (absolute values). Most of the scores (77%, n = 37 out of 48) were correlated with the endpoint PGI-I within the same categorical level for patients in both treatment groups.

Table 2 summarizes results of the correlations among the PGI-I and measures of the pain and physical function domains. Within the pain domain, the PGI-I for patients in both treatment groups was highly correlated with changes in

Table 1. Duloxetine clinical trials in fibromyalgia and clinical measures utilized.

Study	Acute Duration, wks	Dose	Duloxetine (n)	Placebo (n)	Clinical Measures
I[7]	12	60 mg	104	103	BDI, BPI, FIQ, PGI-I, SDS, SF-36, TP
II[8]	12	60 mg	118	120	BPI, HAMD, FIQ, PGI-I, SDS, SF-36, TP
		60 mg	116		
III[9]	15	20 mg	79	144	BDI, BPI, HAMD,
		60 mg	150		EQ5D, FIQ, MFI, PGI-I,
		120 mg	147		SDS, SF-36, TP
IV[10]	28	60/120 mg	162	168	BDI, BPI, HAMD, EQ5D, FIQ, MFI, PGI-I, SDS, SF-36, TP

BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; EQ5D: EuroQol Questionnaire 5 Dimensions; FIQ: Fibromyalgia Impact Questionnaire; MFI: Multidimensional Fatigue Inventory; PGI-I: Patient Global Impression of Improvement; SDS: Sheehan Disability Scale; SF-36: Medical Outcomes Study Short-Form 36; TP: tender point dolorimetry; HAMD: Hamilton Depression Rating Scale.

Table 2. Correlation (r) of endpoint patient global impression of improvement with changes in pain and physical function.

Domain	Variable	Duloxetine		Placebo		Combined	
		n	r	n	r	n	r
Pain	BPI average pain	838	0.54	515	0.53	1353	0.55
	SF-36 bodily pain	794	–0.53	489	–0.56	1283	–0.55
	FIQ pain	820	0.50	506	0.51	1326	0.51
	FIQ stiffness	822	0.45	506	0.50	1328	0.48
	EQ5D pain discomfort	484	0.24	283	0.36	767	0.27
	Tender point threshold	809	0.26	496	0.23	1305	0.26
Physical function	BPI interference with walking	839	0.43	515	0.45	1354	0.45
	FIQ physical function	824	0.39	505	0.33	1329	0.38
	SF-36 physical function	794	–0.37	489	–0.33	1283	–0.36
	EQ5D mobility	484	0.25	283	0.22	767	0.24

BPI: Brief Pain Inventory; EQ5D: EuroQol Questionnaire 5 Dimensions; FIQ: Fibromyalgia Impact Questionnaire; MFI: Multidimensional Fatigue Inventory; SF-36: Medical Outcomes Study Short-Form 36.

BPI average pain severity, FIQ pain, and SF-36 bodily pain. Change in FIQ stiffness for placebo patients was highly correlated with the PGI-I, but was moderately correlated with PGI-I ratings in duloxetine-treated patients. The associations between the EQ5D pain item and PGI-I were moderate in placebo patients and low in duloxetine-treated patients. There were low correlations between changes in tender point threshold and the PGI-I in both treatment groups. Changes in all measures of physical function, with the exception of EQ5D mobility, were moderately correlated with the PGI-I in both treatment groups. There was a low correlation between change in EQ5D mobility and PGI-I ratings in both treatment groups.

None of the variables included in the emotional well-being domain (Table 3) were highly correlated with the PGI-I. Those that were moderately correlated with the PGI-I ratings included MFI motivation, FIQ depression, and SF-36 mental health for patients in both treatment groups, as well as the FIQ anxiety and HAMD Maier items (emotional symptoms of depression)[21] for duloxetine-treated patients, and BDI sadness for placebo-treated patients. Table 4 shows the associations between PGI-I ratings and changes in the cognition, sleep, and fatigue variables. None of the variables in these domains was highly correlated with the PGI-I. Using the MFI mental fatigue subscale as a marker for cognitive difficulties[22], a moderate correlation was noted in

Table 3. Correlation (r) of endpoint patient global impression of improvement with changes in variables assessing the emotional well-being domain.

Domain	Duloxetine		Placebo		Combined	
	n	r	n	r	n	r
FIQ anxiety	821	0.36	506	0.29	1327	0.35
HAMD anxiety subscale*	693	0.18	391	0.12	1084	0.17
MFI motivation	498	0.39	295	0.40	93	0.40
HAMD Maier subscale	693	0.32	391	0.23	1084	0.30
FIQ depression	820	0.32	505	0.32	1325	0.34
SF-36 mental health	794	–0.31	489	–0.30	1283	–0.32
BDI loss of pleasure	615	0.29	403	0.23	1018	0.28
BDI pessimism	615	0.20	402	0.24	1017	0.22
EQ5D anxiety/depression	484	0.19	283	0.23	767	0.21
BDI past failure	615	0.18	403	0.09	1018	0.15
BDI sadness	614	0.17	402	0.31	1016	0.24
BDI self-criticalness	615	0.15	403	0.11	1018	0.13
BDI self-dislike	615	0.12	403	0.15	1018	0.14
BDI suicidality	615	0.07	403	0.02	1018	0.06

BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; EQ5D: EuroQol Questionnaire 5 Dimensions; FIQ: Fibromyalgia Impact Questionnaire; HAMD: Hamilton Depression Rating Scale; MFI: Multidimensional Fatigue Inventory; SDS: Sheehan Disability Scale; SF-36: Medical Outcomes Study Short-Form 36. * HAMD items 10–13, 15, 17.

Table 4. Correlation (r) of endpoint patient global impression of improvement with changes in variables assessing cognition, sleep, and fatigue.

Domain	Variable	Duloxetine		Placebo		Combined	
		n	r	n	r	n	r
Cognition	MFI mental fatigue	500	0.32	294	0.24	794	0.30
	BDI concentration	615	0.26	403	0.14	1018	0.23
Sleep	FIQ morning restedness	821	0.41	506	0.40	1327	0.41
	HAMD sleep subscale	693	0.23	391	0.24	1084	0.24
	BDI changes in sleep	612	0.18	401	0.12	1013	0.14
Fatigue	SF-36 vitality	794	–0.45	489	–0.42	1283	–0.45
	FIQ fatigue	821	0.45	506	0.42	1327	0.44
	BDI loss of energy	614	0.42	402	0.23	1016	0.36
	MFI general fatigue	499	0.40	295	0.39	794	0.39
	BDI tiredness	615	0.34	403	0.25	1018	0.30
	MFI physical fatigue	499	0.39	295	0.35	794	0.38

BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; HAMD: Hamilton Depression Rating Scale; MFI: Multidimensional Fatigue Inventory; SF-36: Medical Outcomes Study Short-Form 36.

patients treated with duloxetine; all other associations between the cognition variables and PGI-I were low. Among the variables assessing sleep, only the change in FIQ morning restedness for patients in both treatment groups was moderately correlated with the PGI-I. In the fatigue domain, measures that were moderately correlated with the PGI-I included the SF-36 vitality, FIQ fatigue, MFI general fatigue, and MFI physical fatigue for patients in both treatment groups, as well as the BDI loss of energy and BDI tiredness items for duloxetine-treated patients. Among those treated with placebo, there were low correlations between changes in the BDI loss of energy and tiredness items and PGI-I ratings.

Table 5 displays the associations between the PGI-I and changes in measures of the impact on daily living domain. This domain comprises 3 subcategories: activity, family/social function, and work. Across all treatment groups, changes in all of the variables relating to activity were moderately correlated with the PGI-I, with the exception of EQ5D self-care, which had very low ($r < 0.10$) correlation. Changes in all the variables relating to family/social function had moderate correlations with the PGI-I. For the variables pertaining to work, change in FIQ ability to work was highly correlated with the PGI-I for duloxetine-treated patients; all other variables were moderately associated with the PGI-I, except HAMD work/activities for placebo patients, which had a low correlation with PGI-I ratings.

Variables common to all 4 studies that were identified by stepwise regression as independent variables associated with patients' PGI-I ratings are presented in Table 6. In patients treated with duloxetine, statistically significant predictors of endpoint PGI-I included changes in pain,

Table 5. Correlation (r) of endpoint patient global impression of improvement with changes in the impact on daily living domain.

Subcategory	Variable	Duloxetine		Placebo		Combined	
		n	r	n	r	n	r
Activity	BPI pain interference	839	0.46	515	0.45	1354	0.47
	EQ5D usual activity	484	0.36	283	0.31	767	0.35
	MFI reduced activity	496	0.36	294	0.34	790	0.36
	SF-36 role-physical	792	–0.36	489	–0.34	1281	–0.36
	EQ5D self-care	484	0.05	283	0.07	767	0.06
Family/ social functioning	SF-36 social functioning	793	–0.41	489	–0.38	1282	-0.41
	BPI pain interference	836	0.38	515	0.39	1351	0.40
	SDS social life	795	0.38	489	0.39	1284	0.39
	SDS family life	796	0.37	489	0.42	1285	0.40
Work	FIQ ability to work	819	0.51	506	0.48	1325	0.51
	BPI pain interference	839	0.47	515	0.47	1354	0.48
	SDS work/school	689	0.38	417	0.42	1106	0.40
	HAMD work/activities	693	0.31	391	0.22	1084	0.28

BPI: Brief Pain Inventory; FIQ: Fibromyalgia Impact Questionnaire; EQ5D: EuroQol Questionnaire 5 Dimensions; MFI: Multidimensional Fatigue Inventory; HAMD: Hamilton Depression Rating Scale; SF-36: Medical Outcomes Study Short-Form 36; SDS: Sheehan Disability Scale.

Table 6. Variables common to all 4 studies, the changes of which were identified by step-wise regression analysis to be statistically significant ($p \leq 0.05$) predictors of endpoint patient global impression of improvement.

Duloxetine		Placebo		Combined	
Variable	ß	Variable	ß	Variable	ß
BPI average pain	0.26	BPI average pain	0.20	BPI average pain	0.24
SF-36 bodily pain	–0.19	SF-36 bodily pain	–0.30	SF-36 bodily pain	–0.21
FIQ physical function	0.14	BPI interference with walking	0.12	FIQ physical function	0.09
SF-36 vitality	–0.12	FIQ stiffness	0.12	SF-36 vitality	–0.10
FIQ anxiety	0.10	SF-36 mental health	–0.15	BPI interference with walking	0.06
Mean tender point threshold	0.07			Mean tender point threshold	0.05
				FIQ anxiety	0.07
				SF-36 social functioning	–0.08

ß: standardized estimate of the regression coefficient; BPI: Brief Pain Inventory; SF-36: Medical Outcomes Study Short-Form 36; FIQ: Fibromyalgia Impact Questionnaire.

physical function, vitality, anxiety, and tender point threshold. In patients treated with placebo, changes in pain, mental health measures, pain interference with walking, and stiffness were identified as statistically significant predictors of endpoint PGI-I. When all patients were included in the stepwise regression analysis, the resulting variables identified were the same as those in the individual treatment groups except that mental health and stiffness dropped out of the model and one new variable, social functioning, was identified.

DISCUSSION

We performed an exploratory investigation of the association between the patients' perception of improvement at the end of a 3-month treatment regimen and changes in clinical rating scale items assessing pain and other domains in FM. Changes in variables that were moderately to highly correlated with PGI-I outcomes for all patients included those for assessments in the domains of pain, physical functioning, fatigue, and impact on daily living. These domains are among those identified in the OMERACT fibromyalgia initiative as being important and perceived to have the greatest impact on quality of life[23]. Several variables that assessed emotional well-being had correlation values that were in the middle to lower range of moderate. While an evaluation of mood may also be important in FM, mood symptoms, including depression and anxiety, may not be weighted as heavily as other more highly correlated domains in the assessment of the impact of FM. The finding that, irrespective of treatment group, most of the correlations with the PGI-I were within the same category (high, moderate, or low) provides justification for pooling of results across the treatment groups to obtain a summary measure.

The set of independent statistical predictors of endpoint PGI-I, identified by stepwise linear regression, varied somewhat between the analyses for the duloxetine group, the placebo group, and the combined group. All analyses included pain variables, but among the non-pain variables, vitality, physical function, anxiety, and tenderness were identified for the duloxetine group; mental health, pain interference with walking, and stiffness were identified for the placebo group; and physical function, vitality, anxiety, social functioning, and tenderness were identified for the combined group. The consistent finding that all analyses included domains in addition to pain provides evidence for the multidimensionality of FM, and suggests that improvement in pain is not the only symptom that may contribute to the overall impression of feeling better. The differences between analyses in the set of non-pain variables identified might possibly reflect differences between duloxetine and placebo treatment in the mechanisms responsible for improvement. However, the variables selected by stepwise regression procedures for one model and not another do not necessarily differ much in their strength of association with the outcome variable, and we observed very similar correlations between change in individual variables and endpoint PGI-I across treatment groups. Therefore, we cannot draw any conclusions regarding the potential importance of differences between the duloxetine and placebo groups in the set of independent predictor variables that were identified.

It is important to note that the causal pathways responsible for the correlations of domains with PGI-I and the sets of statistically independent predictor variables identified by stepwise multivariate linear regression cannot be determined from these data. For example, change in a given variable that is highly correlated with endpoint PGI-I, or that is identified as an independent predictor of endpoint PGI-I, may not necessarily influence the PGI-I. Rather, it is possible that the PGI-I influences patients' reports of change in this variable, or that this variable and the PGI-I are influenced by another variable common to both. Further, in the multivariate analysis, a variable could have an important causal influence on the PGI-I but is not identified by the model as an independent predictor because it is strongly correlated with another variable that is selected by the analytic procedure. Nevertheless, this study does provide the first data regarding correlates of PGI-I ratings of patients with FM and thus provides an empirical foundation for efforts to

identify the causal factors contributing to global improvement ratings among these individuals.

There are several limitations to our study that should be considered. First, the data were obtained from clinical trial patients carefully selected for study entry, so the results may not be generalizable to all individuals with FM. Further, even though most of the variable changes correlated with the PGI-I within the same categorical level of high, moderate, or low irrespective of treatment group, this study examined only the effect of duloxetine; other treatments, especially those with a different mode of action, may show different results. Second, most of the rating scales, with the exception of the FIQ, have not been validated for use in FM, and none of the individual items, or subscales, has been validated for assessing individual symptoms or symptom domains. Third, none of the studies included a validated instrument for assessing cognitive impairment or sleep quality/disturbance. Although the results point to the need for the development of instruments that better measure conceptual domains for use in FM studies, a number of instruments have been identified that appear to be sensitive to change for assessing each key OMERACT domain, with the exception of health-related quality of life[24].

In this pooled analysis of studies of duloxetine treatment in patients with FM, the global impression of improvement was correlated with changes in clinical rating scale items or subscales assessing multiple symptom domains that were consistent with key OMERACT domains. In addition to pain reduction, the factors that may contribute to perceptions of improvement among patients with FM may include positive changes in fatigue, physical functioning, mood, and impact on daily living. These domains may be important for outcome assessments in clinical trials of FM and in the management of patients with FM.

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