Clinically Relevant Outcomes Based on Analysis of Pooled Data from 2 Trials of Duloxetine in Patients with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To determine response with duloxetine versus placebo in patients with osteoarthritis (OA) of the knee using the Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index and other clinically relevant outcomes including minimal clinically important improvement (MCII) and patient acceptable symptom state (PASS) for pain and function.

Methods. Data were pooled from two 13-week, randomized, double-blind, placebo-controlled trials comparing duloxetine 60 to 120 mg/day with placebo in patients with symptomatic OA of the knee. Treatment response was determined according to the OMERACT-OARSI responder index, ≥ 30% pain reduction, ≥ 50% pain reduction, and MCII and PASS for pain and function. (ClinicalTrials.gov identifiers NCT00433290 and NCT00408421)

Results. Duloxetine-treated patients were 33% more likely to experience an OMERACT-OARSI response than placebo-treated patients [$p < 0.001$, number needed to treat (NNT) = 6]. A significantly greater percentage of duloxetine-treated patients, compared with placebo-treated patients, reported ≥ 30% improvement in pain from baseline to endpoint ($p < 0.001$, NNT = 5) and ≥ 50% improvement in pain relative to baseline ($p < 0.001$, NNT = 7). The duloxetine-treated patients were also more likely to fulfill MCII criteria for pain ($p < 0.001$, NNT = 6) and function ($p < 0.001$, NNT = 7), and to achieve PASS for pain ($p < 0.001$, NNT = 6) and function ($p = 0.009$, NNT = 9). More duloxetine-treated patients compared with placebo-treated patients experienced ≥ 1 treatment-emergent adverse event ($p = 0.003$, number needed to harm = 8).

Conclusion. Significantly more patients receiving duloxetine than placebo achieved an OMERACT-OARSI response, improvements in pain and function exceeding the level accepted as MCII, and reached PASS. Results support the clinical relevance of outcomes of prior duloxetine studies in symptomatic OA of the knee. (First Release Dec 1 2011; J Rheumatol 2012;39:352–8; doi:10.3899/jrheum.110307)

Key Indexing Terms:
DULOXETINE OSTEOARTHRITIS OUTCOME ASSESSMENT PAIN

Clinical trials have incorporated various outcome measures in the treatment of patients with osteoarthritis (OA) of the knee. Despite some overlap among efficacy measures, the lack of consistency impedes comparison of results across studies and translation of data into clinical practice. The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index is a commonly used, self-administered measure that assesses pain, functional disability, and stiffness in knee and hip OA[1]. The Brief Pain Inventory (BPI)[2] and the 100-mm visual analog scale (VAS)[3] also evaluate pain, whereas the Lequesne Index[4] and the Arthritis Impact Measurement Scales[5] measure both pain and function.

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the Osteoarthritis Research Society International (OARSI) have developed criteria to identify responders to treatment of OA of the knee and hip[6,7]. The OMERACT-OARSI response criteria include a standardized set of measurements for pain, physical function, and patient global assessment[8], offering the advantage of combining several domains to determine responders in clinical trials and to facilitate comparisons across studies. In addition, several emerging concepts may also facilitate presentation and interpretation of clinical trial results, possibly translating into clinically relevant treatment targets. Minimal clinically important improvement (MCII), defined as the smallest change in a measurement that signifies important improvement in a

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patient's symptom, has been used to describe clinically meaningful results in patients with knee and hip OA[9]. Additionally, the patient acceptable symptom state (PASS), defined as the symptom score beyond which patients consider themselves to be well, has been applied in clinical trials[10]. The MCII and PASS measurements provide complementary and meaningful patient-reported data to aid in the interpretation of clinical trial results[11]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recently recommended provisional benchmarks for interpreting the clinical importance of treatment outcomes in studies of patients with chronic pain[12]. "Moderate" or "substantial" improvement was defined, respectively, as ≥ 30% or ≥ 50% reduction in pain intensity.

Selective serotonin and norepinephrine reuptake inhibitors (SNRI) have demonstrated efficacy in patients with chronic pain syndromes[13,14,15]. Duloxetine, an SNRI, has demonstrated efficacy in the management of chronic pain and is approved by the US Food and Drug Administration for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain as established in patients with chronic low back pain and chronic pain due to OA[16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31]. In 2 separate 13-week, randomized, double-blind, placebo-controlled trials in patients with symptomatic knee OA, duloxetine demonstrated significant reductions in weekly mean of the 24-hour average pain scores[30] and BPI 24-hour average pain score, in change from baseline to endpoint[31]. In addition, significant improvements were reported in secondary outcome measures, including the WOMAC physical function subscale[30]. In our post-hoc analysis, the OMERACT-OARSI responder index and other outcome measures were applied to the individual trials as well as data pooled from the 2 studies[30,31] in order to examine clinically meaningful outcomes in this patient population.

MATERIALS AND METHODS

Study design. The design and methods used in the two 13-week, randomized, double-blind, parallel-group, placebo-controlled studies evaluating the efficacy of duloxetine compared to placebo in the treatment of pain associated with OA of the knee have been reported in detail[30,31]. The protocols were registered under the US National Institutes of Health ClinicalTrials.gov identifiers NCT00433290 and NCT00408421.

We pooled data from those 2 studies. Briefly, patients ≥ 40 years of age meeting the American College of Rheumatology clinical and radiographic criteria for OA of the knee, with pain for ≥ 14 days per month over the last 3 months prior to study entry, and a weekly mean of the 24-hour average pain rating of ≥ 4 on a scale of 0 to 10, were eligible for study entry. Both studies were approved by participating sites' institutional review boards and appropriate written informed consent was obtained from all patients prior to initiation of study procedures or administration of any study treatment. Both studies incorporated a 1-week screening period prior to randomization. In Study 1, patients were randomly assigned to receive duloxetine 60 mg (n = 111) or placebo (n = 120) once daily (QD) and were stratified by nonsteroidal antiinflammatory drug (NSAID) use at study entry[30]. The duloxetine group included a 1-week titration period with treatment initiated on duloxetine 30 mg QD followed by 6 weeks of duloxetine 60 mg QD. At Week 7, patients receiving duloxetine were randomly reassigned to either duloxetine 60 mg QD or duloxetine 120 mg QD for an additional 6 weeks of treatment. In Study 2, patients were randomly assigned to receive duloxetine 60 mg QD (n = 128) or placebo (n = 128) and were stratified by NSAID use at study entry[31]. Patients in the duloxetine group were started on duloxetine 30 mg QD for 1 week and titrated to duloxetine 60 mg QD. The dosage of duloxetine was increased to 120 mg QD in all patients reporting < 30% pain reduction at Week 7 while maintaining the double-blind design. In the original studies, BPI was an efficacy measure used for consistency with a number of other studies conducted on chronic painful conditions. Patients were not required to discontinue use of NSAID or acetaminophen in either study. During the studies, patients who met pain severity (≥ 4) criteria at randomization were allowed to continuously use the drug(s) but were not allowed to increase their dose.

In our post-hoc analysis, responders were classified according to OMERACT-OARSI responder index using Scenario D[6,7]. Scenario D is defined as (1) large improvement in either pain or physical function (≥ 50% relative improvement from baseline with an absolute change ≥ 20 mm on a 100-mm VAS); or (2) moderate improvement (≥ 20% relative improvement from baseline with an absolute change ≥ 10 mm on a 100-mm VAS) in at least 2 of 3 domains (i.e., pain, physical function, and patient's global assessment). In the pooled data, the Patient Global Impressions of Improvement (PGI-I)[32] was used for the patient global assessment domain rather than an assessment similar to VAS; moderate improvement in the patient global assessment component was defined as a PGI-I score of "better" or "very much better." In addition, MCII and PASS outcomes for pain and function were derived for comparison with the OMERACT-OARSI responder index. MCII for pain requires a change of 40.8% from baseline and an absolute change of 19.9 points based on a 0 to 100 VAS or normalized unit scale (implemented as a change of ≥ 2 points on the BPI average pain item, which is identified on a 0 to 10 scale)[9]. MCII for function requires 26.0% improvement relative to baseline and an absolute change of 9.1 points based on a 0–100 scale (implemented as a change of ≥ 7 points on the WOMAC physical function subscale, which has a range of 0–68). PASS for pain requires an endpoint pain score ≤ 32.3 based on a 0–100 VAS or normalized unit scale (implemented as a BPI average pain score ≤ 3)[10]. PASS for function requires an endpoint function score of ≤ 31.0 on a 0–100 VAS or normalized unit scale (implemented as a WOMAC physical function subscale score ≤ 21). Improvement with respect to baseline (≥ 30% or ≥ 50% reduction in pain intensity), as recommended by the IMMPACT group in studies of chronic pain, was predefined in both protocols and is included in this analysis.

Statistical analyses. All analyses were conducted on a modified intent-to-treat basis. Patients with nonmissing baseline data and at least 1 postbaseline assessment of a measure were included in the analysis of that measure. Outcomes involving multiple measures included only patients with no missing data in any of the individual measures. Our analysis was based on pooled data from 2 primary studies of change from baseline to endpoints over 13 weeks. Results of comparisons are considered significant when $p < 0.05$. No adjustments were made for multiple comparisons.

Demographic and illness characteristics at baseline were compared between pooled treatment groups using the Cochran-Mantel-Haenszel (CMH) test, with strata defined by study for binary characteristics, and using ANOVA for continuous variables incorporating terms for treatment, study, and interaction. Last-observation-carried-forward (LOCF) imputation was used to structure the response outcomes consistent with the OMERACT-OARSI outcome recommendations. Use of the LOCF imputation allows data from patients who discontinue study treatment early to be included in analytical results wherein a patient's score or condition at endpoint is based on score or condition from the assessment(s) made at the last available timepoint prior to discontinuation. For each of the outcomes pooled across studies, the proportion of patients in each treatment group meeting the criteria was compared using the CMH test with strata defined by study; the Breslow-Day test was used to examine consistency of treatment advantage between the 2 study strata. Outcomes were compared using Fisher's exact test for individual studies. The relative risk (RR) of response comparing duloxetine treatment to placebo with 95% CI was calculated based on the logit estimator. The number

needed to treat (NNT), a measure of clinical benefit, was computed for each outcome comparing duloxetine treatment to placebo, with 95% CI[33]. For the OMERACT-OARSI response outcome, an analysis of the duloxetine treatment effect comparing NSAID-use subgroups was performed using a logistic regression model with terms for treatment, study, the NSAID subgrouping, and the interaction between treatment and NSAID subgrouping.

Rates are provided of treatment-emergent adverse events (TEAE) with ≥ 5% incidence for duloxetine-treated patients or $p \leq 0.05$ comparing duloxetine-treated and placebo-treated patients, and rates of discontinuations due to adverse events for each treatment. The number needed to harm (NNH) was computed for each TEAE, comparing duloxetine treatment to placebo with 95% CI constructed as described[33]. Following convention[34,35], NNT and NNH estimates and confidence limits were rounded up to the next whole number. Statistical analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition. In the pooled study population, 487 patients were stratified based on NSAID use. An NSAID user was defined as a patient who took an NSAID at a therapeutic dose for > 14 days per month for 3 months before study entry. Following stratification, patients were randomly assigned to either the duloxetine group (n = 239) or the placebo group (n = 248) for 13 weeks. The baseline demographic and clinical characteristics of the patients were consistent between the 2 treatment groups with one exception — significantly more women were randomly assigned to the placebo group than to the duloxetine group ($p = 0.02$; Table 1). Overall, the majority of patients were white (91%) and women (71%), with a mean age of about 62 years. There were no significant differences between the duloxetine and placebo groups with regard to history of OA, baseline pain measures, and use of NSAID.

Responders. The OMERACT-OARSI response rates were significantly greater in the duloxetine group than in the placebo group in the individual studies, as well as in the pooled analysis (Table 2). The proportion of OMERACT-OARSI responders was 69.7% in the pooled duloxetine group and 52.1% in the pooled placebo group (RR 1.33, 95% CI 1.15, 1.55; $p < 0.001$). About 64.9% of patients in the duloxetine group, compared with 44.9% in the placebo group, reported ≥ 30% improvement in pain from baseline to endpoint (RR 1.45, 95% CI 1.22, 1.71; $p < 0.001$). The proportion of patients treated with duloxetine experiencing ≥ 50% improvement in pain relative to baseline was 47.4% compared with 30.9% among the patients treated with placebo (RR 1.53, 95% CI 1.21, 1.94; $p < 0.001$). Similar results were seen in the proportion of patients fulfilling criteria for MCII and for achieving PASS for pain and function. A significantly greater proportion of duloxetine-treated patients fulfilled criteria for MCII for pain (51.8%, RR 1.55, 95% CI 1.25, 1.93; $p < 0.001$) and for function (65.3%, RR 1.32, 95% CI 1.13, 1.55; $p < 0.001$) compared with patients in the placebo group (33.3% and 49.4%, respectively). Among patients treated with duloxetine, 53.1% achieved PASS for pain (RR 1.54, 95% CI 1.24, 1.90; $p < 0.001$) and 48.6% achieved PASS for function (RR 1.33, 95% CI 1.07, 1.65; $p = 0.009$) compared with 34.6% and 36.5%, respectively, in patients treated with placebo. Pooled estimates of OMERACT-OARSI response and MCII pain in patients receiving duloxetine resulted in an estimated NNT of 6 patients for each (95% CI 4, 12, and 95% CI 4, 11, respectively). Similarly, the estimated NNT for MCII function was 7

Table 1. Summary of patient characteristics for the pooled population.

Characteristics	Duloxetine, n = 239	Placebo, n = 248
Age, yrs, mean (SD)	62.7 (9.17)	62.2 (9.23)
Sex, female, n (%)	159 (66.5)	188 (75.8)
Origin, n (%)		
White	220 (92.1)	224 (90.3)
Hispanic	11 (4.6)	10 (4.0)
African American	6 (2.5)	9 (3.6)
East Asian	0 (0)	4 (1.6)
Native American	2 (0.8)	1 (0.4)
NSAID use, n (%)	105 (43.9)	112 (45.2)
Duration of OA since diagnosis, yrs, mean (SD)	6.52 (7.15)	6.33 (6.73)
Duration of OA pain since onset, yrs, mean (SD)	8.56 (8.16)	7.98 (7.54)
WOMAC physical function subscale, mean (SD) [range]		
Total score (normalized to 0–100)	52.6 (16.0)[8–100]	54.4 (13.7) [4–84]
Pain score* (normalized to 0-100)	52.7 (14.7) [15–100]	53.0 (14.3) [10–85]
Stiffness score (normalized to 0–100)	55.8 (18.6) [0–100]	57.9 (18.9) [0–100]
Physical Function score** (normalized to 0–100)	54.0 (15.5) [4–100]	55.2 (13.5) [4–85]
BPI average pain score, mean (SD) [range]	6.11 (1.48) [3–10]	6.18 (1.40) [2–10]
CGI-Severity, mean (SD)† [range]	3.04 (1.41) [1–6]	2.98 (1.44) [1–6]

* Duloxetine group, n = 239; placebo group, n = 247. ** Duloxetine group, n = 231; placebo group, n = 245. † Duloxetine group, n = 235; placebo group, n = 248. BPI: Brief pain Inventory; CGI: clinical global impression; NSAID: nonsteroidal antiinflammatory drug; OA: osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index.

Table 2. Summary of the osteoarthritis outcomes.

Measure	Duloxetine Study	Duloxetine N	Duloxetine n (%)	Placebo N	Placebo n (%)	NNT Estimate (95% CI)	Relative Risk Estimate (95% CI)	p Treatment Comparison**	p Breslow-Day†
OMERACT-OARSI*	Pooled	218	152 (69.7)	236	123 (52.1)	6 (4, 12)	1.33 (1.15, 1.55)	< 0.001	0.441
	1	102	72 (70.6)	110	54 (49.1)			0.002	
	2	116	80 (69.0)	126	69 (54.8)			0.025	
MCII pain	Pooled	228	118 (51.8)	243	81 (33.3)	6 (4, 11)	1.55 (1.25, 1.93)	< 0.001	0.423
	1	107	59 (55.1)	116	38 (32.8)			0.001	
	2	121	59 (48.8)	127	43 (33.9)			0.020	
MCII function	Pooled	222	145 (65.3)	241	119 (49.4)	7 (5, 15)	1.32 (1.13, 1.55)	< 0.001	0.771
	1	104	67 (64.4)	115	54 (47.0)			0.010	
	2	118	78 (66.1)	126	65 (51.6)			0.027	
PASS pain	Pooled	228	121 (53.1)	243	84 (34.6)	6 (4, 11)	1.54 (1.24, 1.90)	< 0.001	0.814
	1	107	60 (56.1)	116	42 (36.2)			0.003	
	2	121	61 (50.4)	127	42 (33.1)			0.007	
PASS function	Pooled	222	108 (48.6)	241	88 (36.5)	9 (5, 32)	1.33 (1.07, 1.65)	0.009	0.904
	1	104	46 (44.2)	115	38 (33.0)			0.097	
	2	118	62 (52.5)	126	50 (39.7)			0.054	
≥ 30% pain reduction	Pooled	228	148 (64.9)	243	109 (44.9)	5 (4, 9)	1.45 (1.22, 1.71)	< 0.001	0.793
	1	107	69 (64.5)	116	53 (45.7)			0.007	
	2	121	79 (65.3)	127	56 (44.1)			< 0.001	
≥ 50% pain reduction	Pooled	228	108 (47.4)	243	75 (30.9)	7 (4, 13)	1.53 (1.21, 1.94)	< 0.001	0.248
	1	107	55 (51.4)	116	34 (29.3)			0.001	
	2	121	53 (43.8)	127	41 (32.3)			0.068	

* Scenario D, defined as (1) large improvement in either pain or physical function (≥ 50% relative improvement from baseline with absolute change ≥ 20 mm on 100-mm VAS); or (2) moderate improvement (≥ 20% relative improvement from baseline with absolute change ≥ 10 mm on 100-mm VAS) in at least 2 of 3 domains (i.e., pain, physical function, and patient global assessment). ** Frequencies for the individual studies analyzed using Fisher's exact test. Frequencies for pooled data analyzed using Cochran-Mantel-Haenszel test. † Breslow-Day test reflects the probability of differential treatment effects comparing studies. NNT: number needed to treat; OMERACT-OARSI: Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International; MCII: minimal clinically important improvement; PASS: patient acceptable symptom state.

patients (95% CI 5, 15). The estimated NNT based on achieving PASS for pain was 6 patients (95% CI 4, 11) and achieving PASS for function was 9 patients (95% CI 5, 32). Homogeneity of the treatment effects between studies is supported by the nonsignificant results of the Breslow-Day test, where p values range from about 0.25 to 0.90 across the various outcome measures.

The treatment effect was not significantly different with concomitant NSAID use. In the group that used NSAID, the OMERACT-OARSI response incidence was 61.0% for duloxetine and 49.1% for placebo; in the group that did not use NSAID, the response incidence was 70.1% and 51.5%, respectively. The advantage of duloxetine over placebo was 11.9 percentage points for NSAID users compared to 18.6 for NSAID nonusers; the result of the test of interaction ($p = 0.557$) was not significant, indicating that there was no significant differential treatment response between groups based on NSAID use.

Safety. The TEAE with incidence rates ≥ 5% for patients in the duloxetine group or a p value ≤ 0.05 between duloxetine and placebo groups, as well as NNH, are presented in Table 3. Details of adverse events from the 2 individual studies have been published[30,31]. Adverse events reported most frequently were nausea, constipation, erectile dysfunction, fatigue, hyperhidrosis, upper abdominal pain, asthenia, decreased libido, and anorexia. More duloxetine-treated patients (50.2%) experienced ≥ 1 TEAE compared with patients in the placebo group (36.7%; $p = 0.003$). The NNH was calculated to be 8 (95% CI 5, 21) for patients treated with duloxetine to experience ≥ 1 TEAE. The rate of discontinuation due to adverse events among duloxetine-treated patients was 16.3% compared with 5.6% among placebo-treated patients ($p < 0.001$). The NNH calculated for discontinuation from any adverse events was 10 patients (95% CI 7, 20). No deaths occurred during these studies.

DISCUSSION

The objective of this post-hoc analysis was to determine the clinically relevant outcomes of duloxetine treatment compared to placebo in patients with symptomatic OA of the knee as defined using OMERACT-OARSI responder index and newer outcomes, including IMMPACT recommendations, MCII, and PASS, using data from 2 published 13-week trials. Some published trials have used the OMERACT-OARSI responder index to assess efficacy of treatments for symptomatic OA of the knee[36,37,38,39,40,41,42,43,44]. However, to our knowledge, this analysis is the first to use the OMERACT-OARSI responder index, IMMPACT recommendations, MCII, and PASS in the same dataset.

Our analyses showed that the OMERACT-OARSI

Table 3. Summary of treatment-emergent adverse events (TEAE).*

	Duloxetine, N = 239 n (%)	Placebo, N = 248 n (%)	NNH Estimate (95% CI)	Relative Risk Estimate (95% CI)	p**
Patients with ≥ TEAE	120 (50.2)	91 (36.7)	8 (5, 21)	1.37 (1.11, 1.68)	0.003
Nausea	20 (8.4)	5 (2.0)	16 (10, 42)	4.15 (1.58, 10.88)	0.002
Constipation	14 (5.9)	2 (0.8)	20 (13, 54)	7.26 (1.67, 31.62)	0.002
Erectile dysfunction†	4 (5.0)	0	20 (11, 447)	#	0.107
Fatigue	10 (4.2)	2 (0.8)	30 (17, 166)	5.19 (1.15, 23.43)	0.015
Hyperhidrosis	8 (3.3)	1 (0.4)	34 (19, 189)	8.30 (1.05, 65.87)	0.017
Upper abdominal pain	7 (2.9)	1 (0.4)	40 (21, 405)	7.26 (0.90, 58.59)	0.031
Asthenia	6 (2.5)	0	40 (23, 190)	#	0.013
Decreased libido	5 (2.1)	0	48 (26, 361)	#	0.020
Anorexia	4 (1.7)	0	60 (31, 2115)	#	0.043
Discontinuation from any AE	39 (16.3)	14 (5.6)	10 (7, 20)	2.89 (1.61, 5.18)	< 0.001

* Events with ≥ 5% incidence for duloxetine or p ≤ 0.05. ** Frequencies analyzed using Cochran-Mantel-Haenszel test with study as stratification variable. † Males only; n = 80 for duloxetine and n = 60 for placebo. # The relative risk cannot be estimated when there are no patients with the event in at least 1 treatment group. NNH: number needed to harm; AE: adverse event.

response rates were significantly greater in the duloxetine treatment group than in the placebo treatment group. Patients randomly assigned to duloxetine were 33% more likely to experience an OMERACT-OARSI response compared to placebo. In addition, the proportion of patients fulfilling criteria for MCII and for achieving PASS for pain and function were significantly greater in the duloxetine group compared with the placebo group. The results were consistent across the 2 individual studies. The results from this post-hoc analysis support the efficacy of duloxetine for the treatment of pain in patients with symptomatic OA of the knee.

Data from clinical trials may not necessarily reflect clinical practice, making trial results difficult to translate into clinical relevance. One reason for this may be that participants in clinical trials may not accurately reflect the breadth of medical histories and complexities of patients seen in general clinical practice. Many patients are excluded from clinical trials due to the presence of comorbid medical conditions or the use of excluded concomitant therapies. Another reason may be due to the practice of reporting clinical trial results in terms of the group studied (i.e., change in mean scores for pain in the treatment groups and the difference between these scores). Recently, IMMPACT has emphasized the differences between the clinical importance of individual patient improvements and of group differences[12]. Benchmarks recommended by IMMPACT include defining moderately important improvements as decreases in pain intensity ≥ 30% and substantial improvements as decreases in pain intensity ≥ 50%. The OMERACT and OARSI groups advocated a similar approach to justify the development of the OMERACT-OARSI responder criteria[6,7]. In addition, analysis of data from clinical trials evaluating treatment of pain in OA also may benefit from including other measures that may provide complementary information to assist interpretation of trial data by reporting results in terms of proportion of patients with important improvement or in an acceptable state, such as MCII and PASS. A survey of the special interest group at the OMERACT 8 conference confirmed the relevance and usefulness of MCII and PASS in rheumatology, although additional work was felt to be needed to establish a consensus on the specific wording and values for disease-specific criteria[11].

Consideration of the benefits of treatment with potential risks and adverse events is also important when assessing the clinical relevance of data from clinical trials. A high number of patients experienced ≥ 1 TEAE while participating in the current studies, with more duloxetine-treated patients reporting ≥ 1 TEAE (50.2%) compared with placebo-treated patients (36.7%). The NNT, a measure of clinical benefit, should be considered along with the NNH when making decisions in clinical practice, particularly rheumatology[45]. In the pooled analysis, the estimated NNT for duloxetine associated with achieving OMERACT-OARSI response, clinically meaningful improvements in pain and function exceeding the level accepted as MCII, or acceptable levels of pain or function by PASS ranged between 6 and 9 patients. On the other hand, the estimated NNH for discontinuing duloxetine treatment due to an adverse event was 10 patients (Table 3). With these estimates, for example, in 100 patients with OA treated with duloxetine, 11 to 16 additional patients would be expected to achieve a positive outcome than if all patients were treated with placebo. Conversely, 10 additional patients would be expected to discontinue treatment due to adverse event, which results in a net advantage of 1 to 6 additional positive outcomes over negative outcomes in 100 treated patients. In this way, the benefit-to-risk ratio appears to favor treatment.

Certain limitations should be considered when interpreting these results. First, our study was a post-hoc analysis; the limited degree of uncertainty of treatment effect is important to consider in statistical evaluations with the post-hoc approach. Second, the data were pooled from 2 separate 13-week studies. While the studies were not identical in design, they were similar and had only small differences between them. A key

difference relates to dose adjustment at the midpoint of each study. In Study 1, patients in the duloxetine group underwent random reassignment at Week 7 to either continued duloxetine 60 mg QD or to increased duloxetine 120 mg QD for the remaining 6 weeks of treatment[30]. In Study 2, the dosage of duloxetine was increased from 60 mg QD to 120 mg QD at Week 7 in patients with < 30% reduction in pain based on the BPI average pain score[31]. Patients with ≥ 30% reduction in pain continued taking duloxetine 60 mg QD. Despite these study design differences, the outcome measures showed similar treatment differences as evidenced by the Breslow-Day test results shown in Table 2. Third, both studies were relatively short in duration. Studies of longer duration are needed to further validate additional efficacy measures, such as MCII and PASS, and to determine longterm clinical relevance based on persistence of treatment effect and safety. Fourth, the PGI-I was used to measure patients' overall global assessment instead of a 0–100 VAS-like instrument, as recommended when applying the OMERACT-OARSI criteria; it is unclear how this may have affected the results.

The findings of our post-hoc analysis imply that incorporating OMERACT-OARSI response criteria may be beneficial in determining clinical response to therapy and reporting results of trials. This approach warrants further investigation in future clinical trials.

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