Arthritis Care & Research
Vol. 63, No. 6, June 2011, pp 821–826
DOI 10.1002/acr.20449

ORIGINAL ARTICLE

Estimation of Minimum Clinically Important Difference for Pain in Fibromyalgia

PHILIP J. MEASE,[1] MICHAEL SPAETH,[2] DANIEL J. CLAUW,[3] LESLEY M. ARNOLD,[4] LAURENCE A. BRADLEY,[5] I. JON RUSSELL,[6] DANIEL K. KAJDASZ,[7] DANIEL J. WALKER,[8] AND AMY S. CHAPPELL[9]

Objective. **To estimate the minimum clinically important difference (MCID) for several pain measures obtained from the Brief Pain Inventory (BPI) for patients with fibromyalgia.**

Methods. **Data were pooled across 12-week treatment periods from 4 randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of duloxetine for the treatment of fibromyalgia. Each study enrolled subjects with American College of Rheumatology–defined fibromyalgia who presented with moderate to severe pain. The MCIDs for the BPI average pain item score and the BPI severity score (the mean of the BPI pain scale values: right now, average, least, and worst) were estimated by anchoring against the Patient's Global Impressions of Improvement scale.**

Results. **The anchor-based MCIDs for the BPI average pain item and severity scores were 2.1 and 2.2 points, respectively. These MCIDs correspond to 32.3% and 34.2% reductions from baseline in scores.**

Conclusion. **In these analyses, the MCIDs for several pain measures obtained from the BPI were similar (~2 points) and corresponded to a 30–35% improvement from baseline to end point. These findings may be beneficial for use in designing clinical trials in which the BPI is used to evaluate improvements in pain severity.**

INTRODUCTION

Pain throughout the body is generally considered the most debilitating of the symptoms experienced by patients with fibromyalgia. Fibromyalgia experts and patients with fibromyalgia rate pain as the most important symptom domain to evaluate in clinical trials (1). The scales used to measure and monitor pain levels vary and include visual analog scales (VAS) for pain (2), the McGill Pain Questionnaire (3), the Fibromyalgia Impact Questionnaire (FIQ) pain item (4), various numerical rating scales (often recorded in diaries), and the Brief Pain Inventory (BPI) (5).

To date, 3 drugs (duloxetine, pregabalin, and milnacipran) have been approved by the Food and Drug Administration for the management of fibromyalgia. In clinical trials of duloxetine, a serotonin and norepinephrine re-

ClinicalTrials.gov identifiers: NCT00190866, NCT00233025, and NCT00233025.

Supported by Eli Lilly and Boehringer Ingelheim GmbH.

[1]Philip J. Mease, MD: Swedish Medical Center and University of Washington School of Medicine, Seattle; [2]Michael Spaeth, MD: Practice for Internal Medicine, Graefelfing, Munich, Germany; [3]Daniel J. Clauw, MD, PhD: University of Michigan Medical Center, Ann Arbor; [4]Lesley M. Arnold, MD: University of Cincinnati College of Medicine, Cincinnati, Ohio; [5]Laurence A. Bradley, PhD: University of Alabama at Birmingham; [6]I. Jon Russell, MD, PhD: University of Texas Health Science Center, San Antonio; [7]Daniel K. Kajdasz, PhD: Trovis Pharmaceuticals LLC, New Haven, Connecticut; [8]Daniel J. Walker, PhD: Lilly Research Laboratories, Indianapolis, Indiana; [9]Amy S. Chappell, MD: Lilly Research Laboratories and Indiana University School of Medicine, Indianapolis.

Dr. Mease has received consultant fees, speaking fees, and/or honoraria (more than $10,000) from Lilly. Dr. Spaeth has received consultant fees and speaking fees (less than $10,000 each) from AstraZeneca, Bial, Essex, Jazz Pharmaceuticals, Lilly, Pfizer, Pierre Fabre, and UCB. Dr. Clauw has received consultant fees, speaking fees, and/or honoraria (more than $10,000 each) from Pfizer, Lilly, Forest, Cypress Biosciences, Pierre Fabre, Merck, UCB, and Jazz Pharmaceuticals. Dr. Arnold has received consultant fees (less than $10,000 each) from Eli Lilly, Pfizer, Cypress Biosciences, Boehringer Ingelheim, Forest Laboratories, Theravance, Allergan, Takeda, UCB, AstraZeneca, and Sanofi Aventis, and has received research support from Eli Lilly, Pfizer, Cypress Biosciences, Boehringer Ingelheim, Allergan, and Forest Laboratories. Dr. Bradley has received consultant fees, speaking fees, and/or honoraria (less than $10,000) from Eli Lilly. Dr. Russell has received consultant fees, speaking fees, and/or honoraria (more than $10,000) from Eli Lilly. Dr. Kajdasz owns stock and/or holds stock options in Eli Lilly and was employed by Eli Lilly from September 2003 to October 2008. Dr. Walker owns stock and/or holds stock options in Eli Lilly. Dr. Chappell owns stock and/or holds stock options in Eli Lilly.

Address correspondence to Philip J. Mease, MD, Seattle Rheumatology Associates, 1101 Madison Street, Suite 1000, Seattle, WA 98104. E-mail: pmease@philipmease.com.

Submitted for publication June 25, 2009; accepted in revised form January 26, 2011.

uptake inhibitor (SNRI), the BPI average pain item score was used as the primary measure of pain severity in 3 phase III, multicenter, placebo-controlled trials (6–8), while the FIQ pain item score was used in an earlier placebo-controlled, phase II feasibility trial (9). With the SNRI milnacipran, a VAS was used to measure pain levels in 2 clinical trials (10,11). In studies of the anticonvulsant pregabalin, a VAS was used to measure pain in 1 trial (12) and an 11-point numerical rating scale was used in another trial (13).

To appropriately interpret the results from any pain scale, regardless of which specific scale is utilized, the minimum clinically important difference (MCID) (14) must be determined for the respective scale. The MCID is the smallest level of change in a given scale associated with a clinically meaningful improvement in a patient. The MCID value is unique to each pain scale and is a quality that should be determined as part of the scale's validation process. Additionally, MCIDs may differ for a given scale based on the type (e.g., chronic versus acute) or location (e.g., low back versus headache) of the pain (15,16).

There are 2 main types of MCIDs: group and individual (17). Group MCIDs focus on an average minimum response, such as mean change, across patients, and are important for study design and planning. Individual MCIDs provide information about response at the individual level and may be represented, for example, by a cutoff value or percent change. Individual MCIDs, while also potentially useful in study design and planning, provide the clinician with a means of determining clinically significant responses at the patient level.

There are a variety of approaches for determining both group and individual MCIDs (15–18). Copay et al (16) have placed the various methodologies into 2 categories: anchor-based methods and distribution-based methods. Anchor-based methods compare the changes in patient-rated outcomes to an anchor, which is usually a patient-rated outcome such as a global assessment scale; the Patient's Global Impressions of Improvement (PGI-I) (19) is one example. Moreover, there are several variations of anchor-based methodology (16). Distribution-based methods also have a variety of approaches to estimate the MCID, including use of the SEM, SD, and effect sizes. The merits and limitations for both anchor- and distribution-based methods have been reviewed previously (15).

In this analysis, we have pooled data from 4 clinical trials designed to assess the efficacy of duloxetine for the treatment of pain associated with fibromyalgia, and we estimated the group MCID for the BPI average pain item score and the BPI pain severity score using anchor-based methodology. Estimation of the group MCID for these measures will provide useful information for future clinical trial design and interpretation using these pain measures (15).

PATIENTS AND METHODS

Study design. Pain data were pooled from 4 randomized, double-blind, placebo-controlled trials of duloxetine for the treatment of fibromyalgia (6–9). Data were integrated from the entire 12-week treatment phase of 2 studies and from the initial 3-month treatment periods of 2 1-year studies (Table 1). In study 3, patients were randomly assigned to fixed dosages of duloxetine: 20 mg/day (n = 79), 60 mg/day (n = 150), 120 mg/day (n = 147), or placebo (n = 144) for the first 15 weeks. In study 4, patients were randomly assigned to 23 weeks of duloxetine treatment including 8 weeks at 60 mg/day, followed by 15 weeks of duloxetine continuing at 60 mg/day or increasing to 120 mg/day depending on clinical response and tolerability (n = 162) or placebo (n = 168). Although patients in both studies 3 and 4 could be treated for up to 1 year, data were only taken from the first 3 months to ensure that MCID assessments were based on patient outcomes obtained from similar treatment durations.

All patients provided written informed consent, and the institutional review board for each clinical study site approved the protocol, which was developed in accordance with the ethical standards of Good Clinical Practice and the Declaration of Helsinki. Further details about the methods can be found in the published reports for each of the 4 studies (6–9).

Patient population. Patients were ages ≥18 years, male or female outpatients (only women included in study 2), and with or without major depressive disorder (MDD). All patients met the criteria for fibromyalgia as defined by the American College of Rheumatology (20). Patients in all studies were also required to have a score of ≥4 on either the pain intensity item of the FIQ (study 1), or the average pain item of the BPI (studies 2–4). Patients were excluded from each study if they had any current primary psychiatric diagnosis other than MDD: had a positive urine drug screen for any substances of abuse; were taking concomitant medications (such as antidepressants, anticonvulsants, and opioids) that may interfere with pain evaluations; were a serious suicidal risk; or had a serious medical illness. Details of inclusion and exclusion criteria can be found in the published studies (6–9).

MCID assessments. The modified short form of the BPI was used in these analyses to determine the MCID (5). The BPI is a patient self-reported 11-point numerical rating scale that measures the severity of pain and the interference of pain on function. There are 4 questions assessing worst pain, least pain, average pain, and pain right now. The scores range from 0 (no pain) to 10 (pain as severe as you can imagine). The MCID was determined for the BPI average pain item score and for the BPI severity score, which is the mean of the BPI pain severity items, defined as worst pain, least pain, average pain, and pain right now. These 2 BPI scores are most often used as primary measures of average pain severity. The MCIDs (i.e., BPI average pain item score and BPI severity score) were determined by anchoring against the PGI-I scale (19). The PGI-I is a patient-rated 7-category ordinal assessment that measures the patient's general level of improvement and is scored as follows: 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse.

Table 1. Fibromyalgia studies used in the MCID analyses*

Study	Overall treatment duration, weeks	Treatment arm, no.	Primary efficacy measures
Study 1: phase II Proof of concept (9)	12	DLX (120 mg) = 104 PBO = 103	FIQ total† FIQ pain item
Study 2: phase III fixed Dose pivotal (females only) (6)	12	DLX (60 mg) = 118 DLX (120 mg) = 116 PBO = 120	BPI average pain item
Study 3: phase III Fixed dose pivotal (7)	28/ 28-week extension‡	DLX (20 mg) = 79 DLX (60 mg) = 150 DLX (120 mg) = 147 PBO = 144	BPI average pain item PGI-I at 15 weeks
Study 4: phase III Flexible dose supportive (8)	27/ 29-week extension‡	DLX (60–120 mg) = 162 PBO = 168	BPI average pain item PGI-I at 27 weeks

* MCID = minimum clinically important difference; DLX = duloxetine; FIQ = Fibromyalgia Impact Questionnaire; PBO = placebo; BPI = Brief Pain Inventory; PGI-I = Patient's Global Impressions of Improvement.
† BPI also measured in study 1.
‡ Used data from initial 3 months of treatment.

The PGI-I–based group MCID was calculated as the difference in mean change from baseline to end point in the BPI item scores between patients considered "clinically stable" and patients demonstrating "minimal clinically relevant improvement." "Clinically stable" was defined as those patients having an end point PGI-I score of 4 (no change). "Minimal clinically relevant improvement" was defined as those patients having an end point PGI-I score of 2 (much better). Patients reporting a PGI-I score of 3 (a little better) at end point were not considered to have achieved clinically relative improvement (21). All patients with at least 1 postbaseline BPI observation were included in the calculation of the MCID, irrespective of treatment assignment. The MCIDs for both the BPI average pain score and the BPI severity score were also determined for subgroups, including patients with or without MDD (22,23), to determine whether the presence of comorbid depression affected the MCIDs. The definition of MDD was defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. To evaluate whether the presence of an analgesic agent from duloxetine affected the MCIDs, the MCIDs for the same pain scores were also determined for patients taking placebo and duloxetine.

The clinically important difference (CID) was also estimated for the BPI average pain score and the BPI severity score. The CID is the level of change in a scale associated with any level of clinically significant improvement in patients (21), and is a value that may be helpful in aspects of clinical trial design (24). In our determination of the group CID based on PGI-I anchoring, patients having an end point PGI-I score of either 1 (very much better) or 2 (much better) were used to identify those patients who had an overall clinically important difference.

Statistical analysis. Patients with a baseline and at least 1 postbaseline measurement were included in the MCID analyses. The baseline score was defined as the last nonmissing observation prior to receiving treatment. The end point observation was defined as the last nonmissing observation within the 3-month treatment period. The MCID was calculated as the difference in the unadjusted mean change in the BPI scores between the "stable" group and the group with "minimal clinically relevant improved" for each measure. The MCID was also expressed as a percentage reduction from the mean baseline scores for the stable and improved groups of each measure. To assess any impact of treatment effect or baseline MDD status on the MCIDs, subgroup analyses were also conducted. Similar to the MCID, the CID was estimated as the difference in the unadjusted mean change in the BPI scores between the "stable" group and the group with "clinically relevant improvement" (PGI-I end point score of 1 or 2).

RESULTS

The majority of the patients included in the analyses were women (94.9%) and white (87.5%), with a mean age of 50.3 years (Table 2). The degree of pain was considered moderately severe as indicated by a score of 6.5 on the BPI average pain item. The number of patients rating them-

Table 2. Baseline demographics and illness characteristics*

Variable	All patients (n = 1,411)†
Age, mean ± SD years	50.3 ± 11.0
Sex, no. (%)	
Females	1,339 (94.9)
Males	72 (5.1)
Race, no. (%)	
White	1,235 (87.5)
Hispanic	127 (9.0)
African descent	33 (2.3)
Other	18 (1.2)
BPI average pain score, mean ± SD	6.5 ± 1.5
CGI-S, mean ± SD	4.2 ± 1.0
PGI-S, mean ± SD‡	3.9 ± 1.4

* BPI = Brief Pain Inventory; CGI-S = Clinical Global Impressions of Severity; PGI-S = Patient's Global Impressions of Severity.
† Numbers may vary slightly due to missing data.
‡ PGI-S at baseline collected only in studies 3 and 4.

Table 3. Estimation of mean changes in BPI average pain and BPI severity scores*

BPI score	Anchor status	No.	Baseline, mean ± SD	End point, mean ± SD	LS mean change, mean ± SEM	MCID†
Average pain	PGI-I improved	249	6.45 ± 1.59	3.70 ± 2.02	−2.75 ± 0.12	−2.09 (32.3)
	PGI-I stable	240	6.50 ± 1.43	5.85 ± 1.97	−0.65 ± 0.12	
Severity	PGI-I improved	249	6.29 ± 1.58	3.60 ± 1.99	−2.70 ± 0.11	−2.16 (34.2)
	PGI-I stable	240	6.35 ± 1.55	5.81 ± 1.90	−0.54 ± 0.11	

* BPI = Brief Pain Inventory; LS = least squares; MCID = minimum clinically important difference; PGI-I = Patient's Global Impressions of Improvement.
† Expressed as score reduction (PGI-I improved − PGI-I stable) and percent reduction from baseline.

selves as "very much better" (PGI-I of 1) was 142, whereas 249 patients rated themselves as "much better" (PGI-I of 2).

Table 3 shows the analyses of MCIDs for the BPI average pain score and BPI severity score. The MCIDs for both scores using the PGI-I as the anchor were an improvement of ~2.1 points. The MCIDs expressed as percentage improvement from baseline were 32.3% for the BPI average pain score and 34.2% for the BPI severity score.

The subgroup results were similar to the main results in that all MCIDs were between 30% and 35% improvement on the BPI pain scores (Figure 1). The MCIDs for both the BPI average pain scores and BPI severity scores were identical for the placebo and duloxetine when the PGI-I was used as the anchor. The patients without MDD had a similar MCID to patients with MDD (~1–3%) using the PGI-I as anchor for both the BPI average pain and BPI severity scores.

The CID was also analyzed using the PGI-I as the anchor. The CID for the BPI average pain score was 2.82, which corresponds to a 43.4% improvement from baseline. The CID for the BPI severity score was 2.79 (36.9% improvement). The CID on the BPI average pain score was an improvement of 2.56 (40.0%) for the placebo group and 2.67 (41.0%) for the duloxetine group. The CID for the BPI severity score was 2.51 (40.4%) for the placebo group and 2.76 (43.5%) for the duloxetine group. The CID for the BPI average pain score was 2.61 (40.8%) for patients without MDD and 2.89 (42.8%) for patients with MDD. The CID for the BPI severity score was 2.65 (42.7%) for patients without MDD and 2.86 (43.2%) for patients with MDD.

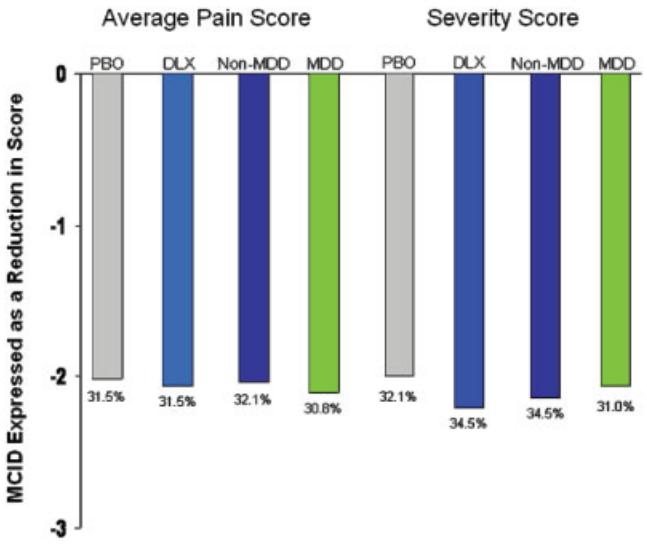

Figure 1. Minimum clinically important differences (MCIDs) by subgroup using the Patient's Global Impressions of Improvement as anchor. Percentages represent the percentage of improvement from baseline in the Brief Pain Inventory scores. Placebo (PBO): n = 124 for stable, n = 71 for improved. Duloxetine (DLX): n = 116 for stable, n = 178 for improved. Non–major depressive disorder (MDD): n = 175 for stable, n = 183 for improved. MDD: n = 65 for stable, n = 66 for improved.

DISCUSSION

In these analyses, the MCID for both the BPI average pain score and BPI severity score averaged somewhat more than a 2-point improvement for all patients with moderate to severe pain that met criteria for the analyses as well as for each of the subgroups. Moreover, the MCIDs, as expressed by the percentage improvement from baseline, were all between 30% and 35%. The CIDs ranged from 40–44%.

The results of these analyses are similar to MCIDs calculated in other pain conditions, i.e., approximately a 2-point improvement on a scale of 0 (no pain) to 10 (most severe pain). A study by Farrar and colleagues analyzed 10 trials of pregabalin for various chronic pain conditions to determine clinical importance of changes on a numerical rating scale similar to the BPI (21). They used the PGI-I as the anchor in these analyses. They found that a PGI-I improvement score of 2 (much better) resulted in an improvement of between 2.2 and 3.2 points on the rating scale, depending on the study. The percentage of improvement varied from 35–55%. These estimates are somewhat greater than what we found in our study; however, one should keep in mind that variables such as different patient and/or study populations, pain types, and study design may influence MCIDs.

Of important note, the MCID estimates present in this study were adjusted for the increased sensitivity to change possessed by the BPI item scores as compared with the PGI-I, which may be attributed to the BPI items' broader response profile. By adjusting the MCID estimates through subtraction of the amount of improvement in the BPI scores associated with "no change" in the PGI-I from that associated with PGI-I indicated as "much better," a more precise estimate of the MCID is obtained. Had this adjustment not been instituted, the MCIDs for the BPI average pain score and severity score would be 2.8 and 2.7 points, respectively. This corresponds to overestimates of the MCIDs of 31.6% and 24.5%, respectively. Such imprecision may have considerable impact on the design of pain

trials, particularly with consideration to sample size and power.

In reviewing MCID estimates for other pain scales and in other pain conditions, findings appear to be consistent with those presented herein. To our knowledge, the BPI has not been used to determine the MCID in fibromyalgia or any other chronic pain state. However, a number of similar numerical rating scales have been used to assess the MCID. In a study of patients with low back pain, a 2-point improvement on a scale of 0–10 was calculated as the MCID (25). Patients with neck pain exhibited an MCID of 1.3 points on a 0–10 numerical rating scale for pain (26). That study used a global rating scale that rated improvement from −7 (a very great deal worse) to 0 (about the same) to 7 (a very great deal better). Overall, and for a variety of pain conditions, the MCID tends to be approximately a 2-point improvement on an 11-point scale.

Where other scales have been used, such as the VAS, the amount of improvement is also quite comparable to our study. For example, in a study of patients who have been treated for chronic low back pain (27), the MCID was found to be an 18-point improvement on a VAS back pain measure (100-point scale). This would translate to a 1.8-point improvement on a scale of 0–10; therefore, the minimal amount of improvement considered to be clinically important is comparable using the BPI or VAS. Similar to our study, the mean score for the "unchanged" group was subtracted from the mean score for those who were "better" to determine the MCID. A variety of methods have been used to determine the MCID in pain conditions. The group MCID was evaluated using both distribution-based and anchor-based methods in patients with neck pain using the Northwick Park Neck Pain Questionnaire (NPQ) (28). The main finding was that the MCID was a 25% reduction in the NPQ score with a global rating having to be at least "better" (0 = much worse, 1 = worse, 2 = no change, 3 = better, and 4 = much better). Jordan et al also used a mix of distribution-based and anchor-based methodology to determine the individual MCID in patients with low back pain (24). In that study, back pain was assessed using the Roland-Morris Disability Questionnaire (RMDQ). As above, the back pain had to be rated as better on a global scale and the RMDQ score had to be improved by 30% from baseline. These MCIDs that use different methods, patient populations, and pain scales are, again, comparable to the 30–35% improvement we observed in our analyses of fibromyalgia pain using group MCID methodology.

Farrar and colleagues have derived both group and individual MCIDs in patients with various pain conditions (21,29). They found approximately a 2.5 point, or 35%, improvement in pain on a 0–10 rating scale in patients with fibromyalgia who had rated themselves as "much improved" on the patient's global impression of change (21). This group-level finding is similar to the group MCID observed in our analyses in patients with fibromyalgia. The group CID of −2.8 points in the present study is similar to the individual CID of −2.5 for BPI average pain in a pooled analysis of patients with diabetic peripheral neuropathic pain (3 studies) and fibromyalgia (2 studies) treated with duloxetine or placebo (29). These results, along with the previously mentioned studies, suggest that MCIDs and/or CIDs will likely have very similar results if assessed using either individual or group measurements.

The MCID estimates derived from subgroup assessments based on MDD status and treatment assignment were virtually identical (expressed as percentage improvement) to the MCID for the overall study populations. Evaluations of these subgroups were important to ensure that estimates of MCIDs were not confounded by the presence of patients with MDD, since a significant percentage of patients with MDD report having painful physical symptoms (22,23), and duloxetine has been shown to improve these symptoms in patients with MDD (30,31). Interestingly, patients without MDD actually had a slightly higher MCID (expressed as a percentage) than did the patients with MDD, although this difference was not clinically meaningful.

Several limitations should be considered when reviewing this study. These were post hoc analyses from 4 duloxetine studies conducted using patient populations that were very similar to one another; therefore, extrapolation of our findings to other studies of patients with fibromyalgia should be made with care. We used only anchor-based methodology to determine the MCID, and it should be noted that there could be subjectivity in how the values of the anchor are mapped to clinical importance. Future work could include determining the MCID using distribution-based methodology and using tools that offer increased sensitivity to patient-rated improvement compared with the PGI-I, such as the Patient Acceptable Symptom State (32), which identifies the symptom state that patients consider as acceptable.

In general, there have been a number of alternate terms used within the literature when referring to the concept of the MCID for a given measure, and this can be further complicated by similar, yet different, measures such as the minimally clinically detectable difference. It is, therefore, important that readers understand the concept underlying the values discussed within the literature to ensure proper use and application. Importantly, our anchor-based approach to determining the MCID is one of many available methods for estimating this measure, and MCIDs obtained from different methods may be variable. Strengths of this work include the availability of a large patient population for these analyses, as well as improved precision in MCID estimates based on adjustments in sensitivity between the outcomes of interest (the BPI items) and the global anchor (the PGI-I score).

In conclusion, findings from these analyses suggest that a 2-point improvement on the BPI average pain score and BPI severity score, or a 30–35% improvement from baseline to end point in both BPI scores, represents the MCID for these items in fibromyalgia patients presenting with moderate to severe pain.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mease had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mease, Spaeth, Clauw, Arnold, Bradley, Russell, Kajdasz, Chappell.
Acquisition of data. Mease, Spaeth, Russell, Kajdasz, Chappell.
Analysis and interpretation of data. Mease, Spaeth, Bradley, Russell, Kajdasz, Walker, Chappell.

ROLE OF THE STUDY SPONSOR

Eli Lilly and Boehringer Ingelheim GmbH played a role in the study design, collection and analysis of the data, and preparation of the manuscript. Eli Lilly employees were involved in review of the manuscript prior to submission for publication. Publication of this article was not contingent upon approval by the study sponsors.

REFERENCES

1. Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, et al. Fibromyalgia syndrome. J Rheumatol 2005;32:2270–7.
2. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102–6.
3. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7.
4. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728–33.
5. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
6. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005;119:5–15.
7. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, 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;136:432–44.
8. Chappell AS, Bradley LA, Wiltse C, Detke MJ, D'Souza DN, Spaeth M. A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia. Int J Gen Med 2008;1:91–102.
9. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974–84.
10. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther 2008;30:1988–2004.
11. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. J Rheumatol 2009;36:398–409.
12. Crofford LJ, Mease PJ, Simpson SL, Young JP Jr, Martin SA, Haig GM, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain 2008;136:419–31.
13. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP Jr, Sharma U, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008;9:792–805.
14. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–15.
15. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr Opin Rheumatol 2002;14:109–14.
16. Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. Spine J 2007;7:541–6.
17. Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V, et al. Minimal clinically important differences: review of methods. J Rheumatol 2001;28:406–12.
18. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
19. Guy W. ECDEU assessment manual for psychopharmacology, revised. US Department of Health, Education, and Welfare publication (ADM). Rockville (MD): National Institute of Mental Health; 1976. p. 76–338.
20. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
21. 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;94:149–58.
22. Demyttenaere K, Bonnewyn A, Bruffaerts R, Brugha T, de Graaf R, Alonso J. Comorbid painful physical symptoms and depression: prevalence, work loss, and help seeking. J Affect Disord 2006;92:185–93.
23. Garcia-Cebrian A, Gandhi P, Demyttenaere K, Peveler R. The association of depression and painful physical symptoms: a review of the European literature. Eur Psychiatry 2006;21:379–88.
24. Jordan K, Dunn KM, Lewis M, Croft P. A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain. J Clin Epidemiol 2006;59:45–52.
25. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. Spine 2005;30:1331–4.
26. Cleland JA, Childs JD, Whitman JM. Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. Arch Phys Med Rehabil 2008;89:69–74.
27. Hagg O, Fritzell P, Nordwall A, for the Swedish Lumbar Spine Study Group. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J 2003;12:12–20.
28. Sim J, Jordan K, Lewis M, Hill J, Hay EM, Dziedzic K. Sensitivity to change and internal consistency of the Northwick Park Neck Pain Questionnaire and derivation of a minimal clinically important difference. Clin J Pain 2006;22:820–6.
29. Farrar JT, Pritchett YL, Robinson M, Prakash A, Chappell A. The clinical importance of changes in the 0 to 10 numeric rating scale for worst, least, and average pain intensity: analyses of data from clinical trials of duloxetine in pain disorders. J Pain 2010;11:109–18.
30. Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesis or antidepressant effect? Int Clin Psychopharmacol 2006;21:311–7.
31. Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. J Psychiatr Res 2009;43:512–8.
32. Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. J Rheumatol 2007;34:1188–93.