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ORIGINAL RESEARCH

Relationship Between Pain Reduction and Improvement in Health-Related Quality of Life in Patients with Knee Pain Due to Osteoarthritis Receiving Duloxetine: Exploratory Post Hoc Analysis of a Japanese Phase 3 Randomized Study

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Purpose: This post hoc analysis of a Japanese phase 3 randomized study (ClinicalTrials.gov identifier: NCT02248480) investigated relationships between changes in pain severity and changes in health-related quality of life (HRQoL) in duloxetine-treated patients with knee osteoarthritis (OA).

Patients and Methods: Patients with knee OA and Brief Pain Inventory (BPI) average pain score ≥4 received duloxetine 60 mg/day or placebo for 14 weeks. Spearman rank correlation coefficients were calculated for change in pain severity, as assessed by the BPI, and change in HRQoL, as assessed by the items of the (i) 36-item Short-Form Health Survey (SF-36; a generic measure of HRQoL) and (ii) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; an OA-specific measure of HRQoL).

Results: After 14 weeks of treatment, there was a significantly greater improvement ($p<0.001$) for duloxetine (n=177) vs placebo (n=176) in BPI average pain severity score and significantly greater improvements ($p<0.01$) for duloxetine vs placebo for 5 of the 8 SF-36 domains (including the Role-Physical, Bodily Pain, and Physical Functioning domains) and all 24 individual WOMAC items. The correlation between BPI change from baseline and SF-36 item change from baseline was statistically significant ($p<0.05$) for 2 of the 8 SF-36 items (Bodily Pain, Physical Functioning) in duloxetine-treated patients. The correlation between BPI change from baseline and WOMAC item change from baseline was statistically significant for 22 of the 24 WOMAC items in duloxetine-treated patients.

Conclusion: This post hoc analysis suggested that the pain reduction observed in duloxetine-treated patients with knee OA was associated with improvements in OA-specific aspects of HRQoL, ie, pain and physical functioning.

Keywords: 36-item Short-form Health Survey, Brief Pain Inventory, placebo effect, Western Ontario and McMaster Universities Osteoarthritis Index

Plain Language Summary

- This study looked at people in Japan with pain from knee osteoarthritis (OA). They took duloxetine or a dummy drug (placebo). Overall, people taking duloxetine had bigger improvements in knee pain than people taking placebo.

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- The researchers looked at whether people's pain affected their quality of life (QoL) during the study. Everyone rated their pain on a scale of 1 to 10 and completed two QoL questionnaires:
  - One with general QoL questions.
  - One with questions specifically designed for people with OA.
- Based on answers to the general QoL questions:
  - For the 177 people taking duloxetine, improved pain was related to better QoL for 2 out of 8 question groups. These 2 question groups asked about pain and movement.
  - For the 176 people taking placebo, improved pain was related to better QoL for 7 out of 8 question groups.
- Based on answers to the QoL questions specific to OA:
  - For people taking duloxetine, improved pain was related to better QoL for 22 out of 24 questions.
  - For people taking placebo, improved pain was related to better QoL for all 24 questions.
- These results suggest that for people taking duloxetine, improvements in their pain helped to improve aspects of their QoL related to OA. However, for people taking placebo, improvements in their pain were related to improvements in a broad range of QoL aspects. This could be because they expected the study treatment to be effective and did not know they were taking a placebo (a so-called "placebo effect").

Introduction

Osteoarthritis (OA) of the knee is a disabling chronic condition,[1,2] which is highly prevalent in Japan. In the large-scale Research on Osteoarthritis Against Disability (ROAD) study conducted in Japan, the prevalence of knee OA in male and female participants aged ≥60 years was 47.0% and 70.2%, respectively.[3] The primary symptoms of knee OA are joint pain, stiffness, and loss of function, which lead to reduced health-related quality of life (HRQoL).[1,4] Recent publications have also shown an association between painful OA and the risk of cardiovascular disease,[5,6] which implies that OA pain has wider effects on a person's health and underlines the importance of OA pain management. OA treatment includes surgical and nonsurgical interventions. Nonsurgical interventions comprise nonpharmaceutical and pharmaceutical treatments, with analgesics being one of the key pillars for treating patients with OA. Current pharmaceutical treatments include acetaminophen, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and intra-articular corticosteroids.[2,7–9] However, these drugs have limited efficacy, provide benefit for only a proportion of patients, and/or their use is restricted by adverse events such as gastrointestinal bleeding and impairment of renal function.[2,7,9,10] In particular, opioids are associated with the risk of abuse and addiction, while not showing an advantage over non-opioid medications with respect to improving pain-related function in patients with knee OA.[11] In light of the opioid epidemic, other, non-opioid, strategies for pain management in the treatment of knee OA are needed, with the treatment goals of improving HRQoL and physical function as well as reducing pain.

Duloxetine, a selective serotonin-norepinephrine reuptake inhibitor, has shown efficacy in the treatment of knee OA, accompanied by an acceptable safety profile, in several randomized, placebo-controlled studies conducted in the US, Europe, China, and Japan.[12–16] According to the Osteoarthritis Research Society International (OARSI) treatment guidelines, duloxetine is classified as appropriate for individuals with knee OA without comorbidities and individuals with multiple-joint OA and relevant comorbidities, with uncertain appropriateness for individuals with knee-only OA and comorbidities.[9] In the randomized, placebo-controlled, phase 3 study conducted in 354 Japanese patients with knee OA,[16] duloxetine significantly reduced pain, as assessed by the Brief Pain Inventory (BPI). In addition, duloxetine improved knee function as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; an OA-specific measure of pain relief, stiffness, and functional improvement) and improved several aspects of HRQoL as assessed by the 36-item Short-Form Health Survey (SF-36; a generic measure of HRQoL).[16] Reducing pain intensity and improving HRQoL are the main treatment goals for knee OA. However, there are limited data on the correlation between improvement in pain severity and improvement in HRQoL in patients with knee OA. Information on which aspects of HRQoL may be improved with pharmaceutical interventions for pain would be useful for physicians in making treatment decisions and informing patients of likely treatment outcomes. In addition, placebo effects have been recognized in clinical trials, especially in the case of analgesics.[17] However, correlations between placebo analgesic effects and improvements in HRQoL are not well known.

The aim of the current post hoc analysis was to investigate correlations in duloxetine-treated patients between change in pain severity, as assessed by the BPI, and

change in HRQoL, as assessed by the items of the SF-36 and the WOMAC in the previously conducted phase 3 study of duloxetine vs placebo in Japanese patients with knee OA.[16] In addition, correlations between change in pain severity and change in HRQoL were investigated in placebo-treated patients and compared with the correlations observed in duloxetine-treated patients.

Materials and Methods

Study Design

Full details of the study design have been published elsewhere.[16] This was a multicenter, randomized, placebo-controlled, double-blind, phase 3 study conducted at 47 medical institutions in Japan from October 2014 to June 2015. The study protocol was approved by the Institutional Review Board of each medical institution (Supplementary Table 1) and the study was conducted in accordance with Good Clinical Practice guidelines. All patients provided written informed consent before participating in the study. The study was registered at www.clinicaltrials.gov (NCT02248480).

Study Population

Male and female patients with knee OA were eligible for the study. Additional inclusion criteria were: age 40 to 79 years; pain for ≥14 days of each month for 3 months before study entry; BPI average pain score of ≥4; and satisfying the American College of Rheumatology criteria[18] for idiopathic knee OA (knee pain, bone spurs detected on plain X-ray images, and at least one of age >50 years, morning stiffness resolving within 30 mins, or crepitus). The main exclusion criteria were: previous administration of duloxetine; inflammatory arthritis (eg, rheumatoid arthritis) or autoimmune diseases (except Hashimoto's disease and type 1 diabetes); invasive treatment (eg, joint lavage or intra-articular hyaluronic acid or steroid injections) in either knee within 1 month before Visit 1; arthroscopic surgery of the affected joint within 1 year before Visit 1 or a history of joint replacement or osteotomy; end-stage OA (eg, patients with loss of joint space or loss of articular cartilage) or patients scheduled to undergo surgery of the affected joint during the study; major depressive disorders based on the Mini International Neuropsychiatric Interview.[19]

Treatment Protocol

The study period comprised a 1- to 2-week pretreatment period, a 14-week treatment period, a 1-week taper period, and a 1-week follow-up period. Patients were randomized to receive duloxetine 60 mg once daily (a 20-mg capsule for 1 week, two 20-mg capsules for 1 week, and three 20-mg capsules for 12 weeks) or matching placebo tablets. Drugs with analgesic effect (eg, NSAIDs) were permitted as rescue medication for up to 3 consecutive days and for a cumulative total of 20 days.

Assessments

Pain intensity was assessed using the BPI 24-hr average pain severity score (the primary outcome measure of the study[16]), which measures average pain during the past 24 hrs.[20] The BPI average pain severity score was rated on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"). Generic quality of life was assessed using the SF-36, which comprises 36 questions divided into 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[21] Each of the 8 domains was rated on a scale ranging from 0 to 100, with higher scores indicating better health and well-being. Osteoarthritis-specific quality of life was assessed using the WOMAC, which comprises 24 questions divided into three subscales: pain, stiffness, and physical function.[22] Each of the WOMAC items was rated on a scale of 0 to 4, with lower scores indicating lower levels of symptoms or physical disability.

Outcome Measures

The efficacy outcome measures in this post hoc analysis were the change from baseline to Week 14 in BPI 24-hr average pain severity score, individual SF-36 item scores, and WOMAC total, pain, stiffness, and physical function subscale, and individual item scores.

Statistical Analysis

This post hoc analysis was performed on the full analysis set, which consisted of all randomized patients who received at least 1 dose of study drug and had a baseline and postbaseline BPI average pain severity score. Analysis of covariance was used to compare the change from baseline to Week 14 for duloxetine vs placebo in BPI average pain severity score, SF-36 item scores, and WOMAC total, subscale, and item scores. Spearman rank correlation coefficients were calculated for (i) change in pain severity (as assessed by the BPI) at Week 14 and change in generic HRQoL (as assessed by the SF-36 items) at Week 14 and (ii) change in pain severity (as assessed by the BPI) at

Week 14 and change in OA-specific HRQoL (as assessed by the WOMAC items) at Week 14. The correlation coefficients were calculated separately for duloxetine- and placebo-treated patients. When the value at Week 14 was missing, the last observation carried forward method was used for the imputation. Data were missing for 17/177 patients (9.6%) in the duloxetine group and 15/176 patients (8.5%) in the placebo group for the BPI and each of the items of the SF-36 and WOMAC scales. Statistical tests were performed at a two-sided significance level of 0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographic and Baseline Clinical Characteristics

In total, 354 patients were randomized, with 353 patients analyzed for efficacy: 177 patients received duloxetine and 176 patients received placebo. The mean (standard deviation [SD]) baseline BPI average score was 5.0 (1.0) and 5.1 (1.0) in the duloxetine and placebo groups, respectively (Table 1). The mean baseline SF-36 item scores were similar between the duloxetine and placebo groups (Table 1). The 2 worst-rated individual SF-36 items (lower score = worse status) at baseline in both the duloxetine and placebo groups were SF363 (Bodily Pain; mean [SD]: duloxetine: 45.9 [12.9]; placebo: 45.1 [12.9]) and SF361 (Physical Functioning; mean [SD]: duloxetine: 57.6 [19.1]; placebo: 55.9 [18.2]) (Table 1). The mean baseline WOMAC total scores were similar between the duloxetine and placebo groups, as were the mean baseline WOMAC pain, stiffness, and physical function subscale scores (Table 1). The 2 worst-rated individual WOMAC items (higher score = worse status) at baseline in both the duloxetine and placebo groups were: PAIN2W ("How much pain have you had when going up or down stairs?"; mean [SD]: duloxetine: 2.28 [0.71]; placebo: 2.28 [0.79]) and PFTN8W ("How much difficulty have you had when going down stairs?"; mean [SD]: duloxetine: 2.11 [0.89]; placebo: 2.09 [0.85]) (Table 1).

Effect of Duloxetine Treatment on BPI Average Pain Severity

After 14 weeks of treatment, there was a significantly greater improvement ($p<0.001$) in the duloxetine group compared with the placebo group in BPI average pain severity score (least squares [LS] mean difference [95% CI]: −0.78 [−1.12, −0.44]).

Effect of Duloxetine Treatment on SF-36 and WOMAC

As reported previously,[16] after 14 weeks of treatment, there were significantly greater improvements ($p<0.01$) in the duloxetine group compared with the placebo group for 5 of the 8 SF-36 domains (SF361, SF362, SF363, SF364, and SF367; Table 2). The 3 individual SF-36 items with the greatest improvement for duloxetine vs placebo were SF362 (Role-Physical; LS mean difference [95% CI]: 7.78 [4.18, 11.39]), SF363 (Bodily Pain; LS mean difference [95% CI]: 6.69 [3.30, 10.08]), and SF361 (Physical Functioning; LS mean difference [95% CI]: 6.39 [2.85, 9.94]) (Table 2). Two of these 3 items, SF363 and SF361, were the 2 worst-rated SF-36 items at baseline.

As reported previously,[16] after 14 weeks of treatment, there were significantly greater improvements ($p<0.05$) in the duloxetine group compared with the placebo group in the WOMAC total score and pain, stiffness, and physical subscale scores (Table 2). In addition, there were significantly greater improvements for duloxetine vs placebo in all of the 24 individual WOMAC items (Table 2). The 3 individual WOMAC items with the greatest improvement for duloxetine vs placebo were PAIN4W ("How much pain have you had while sitting or lying down?"; LS mean difference [95% CI]: −0.40 [−0.57, −0.24]), PFTN12W ("How much difficulty have you had when bending to the floor?"; LS mean difference [95% CI]: −0.38 [−0.53, −0.23]), and STIFF6W ("How severe has your stiffness been after you first woke up in the morning?"; LS mean difference [95% CI]: −0.36 [−0.51, −0.20]) (Table 2). The 2 worst-rated WOMAC items at baseline, PAIN2W and PFTN8W, were also significantly improved from baseline.

Correlations Between BPI Change from Baseline and SF-36 Item Change from Baseline

In duloxetine-treated patients, the correlation between BPI change from baseline and SF-36 item change from baseline was statistically significant ($p<0.05$) for 2 of the 8 SF-36 items (25%; Table 3). The correlation coefficient was negative for all SF-36 items, meaning that a decrease in BPI score (ie, improvement in pain severity) was associated with an increase in SF-36 item score (ie, improvement in HRQoL). The two strongest correlations between BPI change from baseline and SF-36 item change from baseline were SF363 (Bodily Pain; Spearman correlation:

Table 1 Patient Demographics and Baseline Characteristics

Parameter[a]	Duloxetine n=177	Placebo n=176	Total n=353
Age, years	65.5 (8.0)	66.4 (8.4)	65.9 (8.2)
Male, n (%)	35 (19.8)	44 (25.0)	79 (22.4)
Duration of OA, years	4.0 (4.2)	4.5 (4.3)	4.2 (4.2)
BPI average pain score	5.0 (1.0)	5.1 (1.0)	5.0 (1.0)
SF-36 score			
SF361: Physical Functioning	57.6 (19.1)	55.9 (18.2)	56.8 (18.7)
SF362: Role-Physical[b]	71.2 (23.7)	73.5 (20.0)	72.3 (21.9)
SF363: Bodily Pain	45.9 (12.9)	45.1 (12.9)	45.5 (12.9)
SF364: General Health	62.7 (16.0)	64.0 (16.3)	63.4 (16.1)
SF365: Vitality	66.3 (18.1)	65.4 (16.8)	65.9 (17.4)
SF366: Social Functioning	84.7 (19.3)	85.8 (18.9)	85.2 (19.1)
SF367: Role-Emotional[c]	80.8 (23.5)	85.8 (17.4)	83.3 (20.8)
SF368: Mental Health	79.0 (17.0)	78.4 (14.8)	78.7 (15.9)
WOMAC[d] total score	32.67 (13.18)	32.70 (13.71)	32.68 (13.43)
WOMAC pain subscale score	7.46 (2.66)	7.55 (2.74)	7.50 (2.70)
PAIN1W: Walking on a flat surface	1.41 (0.74)	1.45 (0.70)	1.43 (0.72)
PAIN2W: Going up or down stairs	2.28 (0.71)	2.28 (0.79)	2.28 (0.75)
PAIN3W: At night while in bed (pain that disturbs your sleep)	0.98 (0.85)	0.97 (0.80)	0.98 (0.83)
PAIN4W: While sitting or lying down	1.62 (0.83)	1.72 (0.89)	1.67 (0.86)
PAIN5W: While standing	1.16 (0.74)	1.12 (0.86)	1.14 (0.80)
WOMAC stiffness subscale score	3.01 (1.49)	3.02 (1.55)	3.01 (1.52)
STIFF6W: On first waking up in the morning	1.39 (0.91)	1.41 (0.90)	1.40 (0.91)
STIFF7W: After sitting or lying down or while resting later in the day	1.62 (0.80)	1.60 (0.87)	1.61 (0.84)
WOMAC physical function subscale score	22.20 (10.21)	22.14 (10.51)	22.17 (10.35)
PFTN8W: Difficulty going down stairs	2.11 (0.89)	2.09 (0.85)	2.10 (0.87)
PFTN9W: Difficulty going up stairs	1.73 (0.82)	1.68 (0.86)	1.71 (0.83)
PFTN10W: Difficulty getting up from a sitting position	1.90 (0.94)	1.92 (0.94)	1.91 (0.94)
PFTN11W: Difficulty while standing	1.03 (0.77)	1.05 (0.82)	1.04 (0.79)
PFTN12W: Difficulty bending to the floor	1.53 (0.85)	1.52 (0.89)	1.52 (0.87)
PFTN13W: Difficulty walking on a flat surface	1.18 (0.81)	1.11 (0.77)	1.14 (0.79)
PFTN14W: Difficulty getting in or out of a car, or getting on or off a bus	1.35 (0.84)	1.38 (0.89)	1.36 (0.87)
PFTN15W: Difficulty while going shopping	1.17 (0.83)	1.19 (0.78)	1.18 (0.80)
PFTN16W: Difficulty putting on socks or panty hose or stockings	1.11 (0.84)	1.16 (0.85)	1.14 (0.84)
PFTN17W: Difficulty getting out of bed	1.14 (0.88)	1.17 (0.84)	1.16 (0.86)
PFTN18W: Difficulty taking off socks or panty hose or stockings	1.11 (0.85)	1.09 (0.85)	1.10 (0.85)
PFTN19W: Difficulty while lying in bed	0.66 (0.74)	0.72 (0.74)	0.69 (0.74)
PFTN20W: Difficulty getting in or out of the bathtub	1.06 (0.86)	0.98 (0.81)	1.02 (0.84)
PFTN21W: Difficulty while sitting	1.64 (1.09)	1.63 (1.04)	1.63 (1.07)
PFTN22W: Difficulty getting on or off the toilet	0.91 (0.84)	0.88 (0.89)	0.89 (0.86)
PFTN23W: Difficulty doing heavy household chores	1.80 (0.87)	1.81 (0.93)	1.80 (0.90)
PFTN24W: Difficulty doing light household chores	0.79 (0.68)	0.77 (0.73)	0.78 (0.71)

Notes: [a]Except where otherwise indicated, data are mean (standard deviation). [b]Role limitations because of physical problems. [c]Role limitations because of emotional problems. [d]WOMAC scale items from Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833–1840. Copyright © 1996 Nicholas Bellamy. All Rights Reserved.[28]

Abbreviations: BPI, Brief Pain Inventory; OA, osteoarthritis; SF-36, 36-item Short Form Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 Least Squares Mean Change from Baseline to Week 14 in SF-36 Subscale Scores and WOMAC Total and Subscale Scores in Duloxetine- and Placebo-Treated Patients

Scale Item[a]	Duloxetine n=177 LS Mean (SE)	Placebo n=176 LS Mean (SE)	LS Mean Difference (95% CI)	P-value
SF-36 score				
SF361	12.62 (1.27)	6.23 (1.27)	6.39 (2.85, 9.94)	<0.001
SF362	11.44 (1.29)	3.66 (1.30)	7.78 (4.18, 11.39)	<0.001
SF363	16.32 (1.22)	9.63 (1.22)	6.69 (3.30, 10.08)	<0.001
SF364	5.58 (0.93)	1.82 (0.94)	3.77 (1.16, 6.37)	0.005
SF365	3.99 (1.04)	3.16 (1.04)	0.83 (−2.05, 3.72)	0.570
SF366	5.66 (1.14)	2.54 (1.15)	3.12 (−0.07, 6.31)	0.055
SF367	6.32 (1.27)	0.70 (1.28)	5.62 (2.06, 9.17)	0.002
SF368	3.02 (0.99)	1.48 (0.99)	1.55 (−1.21, 4.30)	0.270
WOMAC total score	−16.94 (0.90)	−9.99 (0.90)	−6.95 (−9.47, −4.44)	<0.001
WOMAC pain subscale score	−3.90 (0.21)	−2.31 (0.21)	−1.59 (−2.17, −1.01)	<0.001
PAIN1W	−0.81 (0.05)	−0.48 (0.05)	−0.33 (−0.47, −0.19)	<0.001
PAIN2W	−1.01 (0.06)	−0.71 (0.06)	−0.30 (−0.46, −0.13)	<0.001
PAIN3W	−0.63 (0.05)	−0.34 (0.05)	−0.29 (−0.42, −0.16)	<0.001
PAIN4W	−0.79 (0.06)	−0.39 (0.06)	−0.40 (−0.57, −0.24)	<0.001
PAIN5W	−0.62 (0.05)	−0.34 (0.05)	−0.28 (−0.41, −0.15)	<0.001
WOMAC stiffness subscale score	−1.61 (0.09)	−0.91 (0.09)	−0.70 (−0.96, −0.44)	<0.001
STIFF6W	−0.74 (0.05)	−0.38 (0.06)	−0.36 (−0.51, −0.20)	<0.001
STIFF7W	−0.83 (0.05)	−0.53 (0.05)	−0.30 (−0.44, −0.16)	<0.001
WOMAC physical function subscale score	−11.44 (0.65)	−6.76 (0.66)	−4.67 (−6.50, −2.85)	<0.001
PFTN8W	−0.84 (0.06)	−0.58 (0.06)	−0.26 (−0.44, −0.09)	0.004
PFTN9W	−0.74 (0.06)	−0.45 (0.06)	−0.29 (−0.45, −0.13)	<0.001
PFTN10W	−0.93 (0.06)	−0.60 (0.06)	−0.33 (−0.50, −0.16)	<0.001
PFTN11W	−0.62 (0.05)	−0.33 (0.05)	−0.28 (−0.41, −0.15)	<0.001
PFTN12W	−0.83 (0.05)	−0.45 (0.05)	−0.38 (−0.53, −0.23)	<0.001
PFTN13W	−0.65 (0.05)	−0.41 (0.05)	−0.24 (−0.37, −0.11)	<0.001
PFTN14W	−0.70 (0.05)	−0.36 (0.05)	−0.34 (−0.48, −0.20)	<0.001
PFTN15W	−0.62 (0.05)	−0.41 (0.05)	−0.21 (−0.34, −0.07)	0.003
PFTN16W	−0.60 (0.05)	−0.35 (0.05)	−0.25 (−0.39, −0.11)	<0.001
PFTN17W	−0.73 (0.04)	−0.42 (0.04)	−0.32 (−0.44, −0.19)	<0.001
PFTN18W	−0.56 (0.05)	−0.32 (0.05)	−0.25 (-0.39, −0.11)	<0.001
PFTN19W	−0.44 (0.04)	−0.30 (0.04)	−0.14 (−0.25, −0.03)	0.014
PFTN20W	−0.53 (0.05)	−0.26 (0.05)	−0.27 (−0.39, −0.14)	<0.001
PFTN21W	−0.72 (0.06)	−0.49 (0.06)	−0.23 (−0.41, −0.05)	0.012
PFTN22W	−0.56 (0.04)	−0.35 (0.04)	−0.21 (−0.33, −0.09)	<0.001
PFTN23W	−0.72 (0.06)	−0.47 (0.06)	−0.25 (−0.42, −0.08)	0.005
PFTN24W	−0.47 (0.04)	−0.22 (0.04)	−0.25 (−0.37, −0.13)	<0.001

Notes: [a]See Table 1 for a description of each item. WOMAC scale items from Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833–1840. Copyright © 1996 Nicholas Bellamy. All Rights Reserved.[28]

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error; SF-36, 36-item Short Form Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

−0.452) and SF361 (Physical Functioning; Spearman correlation: −0.289) (Table 3).

In contrast to duloxetine-treated patients, the correlation between BPI change from baseline and SF-36 item change from baseline in placebo-treated patients was statistically significant ($p<0.05$) for 7 of the 8 SF-36 items (87.5%; Table 3). As observed for duloxetine-treated patients, the two strongest correlations between BPI change from baseline

Table 3 Correlation Between BPI Change from Baseline and SF-36 Change from Baseline in Duloxetine-Treated and Placebo-Treated Patients

Scale Item[a]	Duloxetine n=177		Placebo n=176	
	Spearman Correlation	P-value	Spearman Correlation	P-value
SF363: Bodily Pain	−0.452	<0.001	−0.502	<0.001
SF361: Physical Functioning	−0.289	<0.001	−0.326	<0.001
SF365: Vitality	−0.135	0.073	−0.261	<0.001
SF368: Mental Health	−0.130	0.084	−0.225	0.003
SF362: Role-Physical[b]	−0.089	0.241	−0.285	<0.001
SF366: Social Functioning	−0.079	0.298	−0.136	0.072
SF364: General Health	−0.055	0.470	−0.244	0.001
SF367: Role-Emotional[c]	−0.011	0.884	−0.164	0.030

Notes: [a]Individual SF-36 items arranged in descending order of the size of Spearman correlation coefficient in duloxetine-treated patients. [b]Role limitations because of physical problems. [c]Role limitations because of emotional problems.
Abbreviations: BPI, Brief Pain Inventory; SF-36, 36-item Short-Form Survey.

and SF-36 item change from baseline for placebo-treated patients were SF363 (Bodily Pain; Spearman correlation: −0.502) and SF361 (Physical Functioning: −0.289; placebo: −0.326) (Table 3). For each of the SF-36 items, the size of the correlation coefficient was larger in placebo-treated patients than duloxetine-treated patients.

Correlations Between BPI Change from Baseline and WOMAC Item Change from Baseline

In duloxetine-treated patients, the correlation between BPI change from baseline and WOMAC item change from baseline was statistically significant ($p<0.05$) for the total score, the pain, physical function, and stiffness subscale scores, and 22 of the 24 WOMAC items (91.7%; Table 4). The strongest correlations between BPI change from baseline and WOMAC item change from baseline were PFTN23W ("How much difficulty have you had while doing heavy household chores?"; Spearman correlation: 0.428), PAIN2W ("How much pain have you had when going up or down stairs?"; Spearman correlation: 0.421), and PFTN24W ("How much difficulty have you had while doing light household chores?"; Spearman correlation: 0.401) (Table 4).

In placebo-treated patients, the correlation between BPI change from baseline and WOMAC item change from baseline was statistically significant ($p<0.001$) for the total score, the pain, physical function, and stiffness subscale scores, and all 24 WOMAC items (100%; Table 4). The strongest correlations between BPI change from baseline and WOMAC item change from baseline were PAIN2W ("How much pain have you had when going up or down stairs?"; Spearman correlation: 0.591), PFTN8W ("How much difficulty have you had when going down stairs?"; Spearman correlation: 0.555), and PAIN1W ("How much pain have you had when walking on a flat surface?"; Spearman correlation: 0.539) (Table 4). For most of the WOMAC items, the size of the correlation coefficient was larger in placebo-treated patients than in duloxetine-treated patients.

Discussion

Treatment goals for patients with knee OA include improving HRQoL as well as reducing pain intensity. Few studies have demonstrated correlations between pain reduction attributed to analgesics with the amelioration of HRQoL. The primary report from this study[16] showed that duloxetine treatment both reduced pain (as assessed by the BPI) and improved HRQoL (as assessed by the SF-36 and WOMAC) in Japanese patients with knee OA. This post hoc analysis extends these findings by showing that there were correlations between pain reduction in duloxetine-treated patients and improvements in the SF-36 items related to pain and physical functioning and improvements in nearly all items of the OA-specific WOMAC. These results suggest that the pain reduction resulting from duloxetine treatment is associated with improvements in the disease-specific aspects of HRQoL that are compromised in patients with knee OA.

In duloxetine-treated patients, the correlation between pain reduction and SF-36 item change from baseline was statistically significant for 2 of the 8 SF-36 items, namely, SF363 (Bodily Pain) and SF361 (Physical Functioning). In contrast, in placebo-treated patients, the correlation between pain reduction and SF-36 item change from baseline was statistically significant for all SF-36 items except SF366

Table 4 Correlation Between BPI Change from Baseline and WOMAC Change from Baseline in Duloxetine-Treated and Placebo-Treated Patients

Scale Item[a]	Duloxetine n=177		Placebo n=176	
	Spearman Correlation	P-value	Spearman Correlation	P-value
WOMAC total score	0.420	<0.001	0.577	<0.001
WOMAC pain subscale score	0.446	<0.001	0.596	<0.001
WOMAC physical function subscale score	0.389	<0.001	0.543	<0.001
WOMAC stiffness subscale score	0.230	0.002	0.325	<0.001
WOMAC items[b]				
PFTN23W	0.428	<0.001	0.391	<0.001
PAIN2W	0.421	<0.001	0.591	<0.001
PFTN24W	0.401	<0.001	0.308	<0.001
PAIN1W	0.386	<0.001	0.539	<0.001
PFTN14W	0.366	<0.001	0.352	<0.001
PFTN8W	0.333	<0.001	0.555	<0.001
PFTN15W	0.312	<0.001	0.438	<0.001
PFTN16W	0.309	<0.001	0.348	<0.001
PFTN12W	0.306	<0.001	0.416	<0.001
PAIN5W	0.294	<0.001	0.350	<0.001
PFTN22W	0.278	<0.001	0.292	<0.001
PFTN9W	0.278	<0.001	0.462	<0.001
PAIN3W	0.260	<0.001	0.360	<0.001
PFTN13W	0.252	<0.001	0.415	<0.001
PAIN4W	0.239	0.001	0.375	<0.001
PFTN18W	0.237	0.001	0.330	<0.001
PFTN17W	0.234	0.002	0.340	<0.001
PFTN11W	0.212	0.005	0.381	<0.001
STIFF6W	0.194	0.010	0.350	<0.001
PFTN10W	0.177	0.018	0.391	<0.001
STIFF7W	0.172	0.022	0.256	<0.001
PFTN20W	0.171	0.023	0.363	<0.001
PFTN21W	0.134	0.076	0.350	<0.001
PFTN19W	0.119	0.115	0.342	<0.001

Notes: [a]See Table 1 for a description of each item. WOMAC scale items from Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833–1840. Copyright © 1996 Nicholas Bellamy. All Rights Reserved.[28] [b]Individual WOMAC items arranged in descending order of the size of Spearman correlation coefficient in duloxetine-treated patients.

Abbreviations: BPI, Brief Pain Inventory; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

(Social Functioning). These results suggest that pain reduction in response to duloxetine treatment was associated with improvements in specific aspects of HRQoL related to OA (ie, pain and physical functioning, which were the 2 worst-rated SF-36 items at baseline), while the pain reduction in response to placebo treatment appeared to be associated with broader effects on HRQoL, with improvements in general aspects of HRQoL as well as pain and physical functioning. Intriguingly, the correlation coefficient values were higher in placebo-treated patients than in duloxetine-treated patients. However, it should be noted that the magnitude of improvement in the SF-36 items was smaller in placebo-treated patients than in duloxetine-treated patients, which may be suggestive of a placebo effect. It has been reported that expectation of benefit is one of the mechanisms contributing to placebo analgesia, which activates the reward system of the brain to reduce pain.[23–25] It might be possible that different mechanisms of action between duloxetine and placebo in reducing pain are responsible for the different patterns of correlations between pain reduction and improvement in HRQoL, as assessed by the generic HRQoL measure SF-36, in the two treatment groups.

Duloxetine treatment significantly improved all of the individual WOMAC items in this study population compared

with placebo, suggesting that pain reduction from duloxetine treatment was associated with improvement in OA-specific aspects of HRQoL in patients with knee OA. This is in contrast to the SF-36 results, where 5 of the 8 items were significantly improved following duloxetine treatment. In addition, a higher proportion of WOMAC items (22 of 24) than SF-36 items (2 of 8) showed statistically significant correlations between pain reduction and improvement in HRQoL item in duloxetine-treated patients. These findings are possibly related to the SF-36 being a generic HRQoL measure that evaluates multiple aspects of HRQoL, not just those aspects specifically associated with OA. In particular, patients with knee OA are likely to have comorbid conditions contributing to their overall HRQoL; the aspects of HRQoL related to such conditions may be captured by the SF-36 items not improved by duloxetine treatment.[26,27]

In duloxetine-treated patients, the correlations between pain reduction and WOMAC item change from baseline were statistically significant for all but 2 of the 24 items, indicating that pain reduction from duloxetine treatment was associated with improvement in aspects of HRQoL associated with knee OA. The two WOMAC items for which the correlations were not statistically significant (PFTN21W: How much difficulty have you had while sitting?; PFTN19W: How much difficulty have you had while lying in bed?) might be less sensitive indicators of the pain reduction associated with duloxetine treatment. In placebo-treated patients, the correlations between pain reduction and WOMAC item change from baseline were statistically significant for all 24 WOMAC items. As observed for the SF-36, the magnitude of improvement in the WOMAC items was smaller in placebo-treated patients than duloxetine-treated patients, and the correlation coefficient values were higher in placebo-treated patients than duloxetine-treated patients, which may be suggestive of a placebo effect. However, we note the difficulty of determining a placebo effect based on high correlation coefficient values given that correlation coefficient values can be high even if both pain and HRQoL do not improve. Placebo effects on OA-specific aspects of HRQoL have been documented, with a meta-analysis of 198 trials with 193 placebo groups (16,364 patients) showing that placebo treatment was effective in relieving pain (usually assessed by the WOMAC pain score) and improving stiffness and function in patients with hand, hip, or knee OA.[17] It may be noted that the three WOMAC items for which the correlation between pain reduction and improvement in HRQoL was stronger in duloxetine-treated patients than placebo-treated patients were related to physical function, in particular, doing heavy (PFTN23W) and light (PFTN24W) household chores and getting in or out of a car (PFTN14W).

Strengths of this analysis include the study being a randomized, placebo-controlled, double-blind, phase 3 study and the use of individual item scores in the HRQoL analyses. The use of two HRQoL measures allowed assessment of the effect of duloxetine treatment on different aspects of HRQoL. The SF-36, being a generic measure, assesses the effect of treatment on a patient's general health, including assessment of side effects of treatment that may be unrelated to the condition. In contrast, the WOMAC is an OA-specific measure, which assesses the effect of treatment on the domains of HRQoL directly affected by the condition itself. In addition to its post hoc nature, limitations of this analysis include the study being conducted in Japanese patients only and the treatment duration being relatively short and, therefore, the analysis results might not be applicable for other populations or longer treatment durations. Another limitation of the correlation analyses is that it is not possible to determine a causal direction for the correlations, only to state that there was an association between pain reduction and improvement in HRQoL. More complex analyses, for example, mediation models, are required to determine the direction of the relationship between these two parameters. We note that there may be other interactions that influence the associations between pain reduction and improvement in HRQoL. For example, if individual HRQoL items are correlated with each other, then it is difficult to assess whether the correlation between the change in HRQoL item and the change in pain item is a direct or indirect effect. We also note the exploratory nature of these analyses and that the results should be interpreted with caution. Future research into the relationship between pain and HRQoL in patients with knee pain from OA requires studies specifically designed to examine this relationship. Such studies should employ statistical methods capable of interpreting complex interactions between pain and HRQoL, as assessed by the instruments constructed to evaluate these parameters.

In conclusion, this post hoc analysis found different correlation profiles for pain reduction and improvements in HRQoL between duloxetine- and placebo-treated patients with knee OA. The results suggest that the pain reduction observed in this population of duloxetine-treated patients was associated with improvements in OA-specific aspects of HRQoL. In contrast, the pain reduction observed in placebo-treated patients was associated with improvements in a broad spectrum of HRQoL domains, possibly due to a placebo effect.

Data Sharing Statement

Individual participant data have not been made available at this time; however, future requests for de-identified patient-level data may be considered.

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Author Contributions

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript, and all authors agree to be accountable for all aspects of the work. HE was involved in the design of the analyses and SF was involved in the statistical analyses.

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Disclosure

TT is an employee of Shionogi & Co., Ltd. and owns stock in Shionogi & Co., Ltd. and Takeda Pharmaceutical Company Ltd. HE, SF, and KO are employees of Eli Lilly Japan K.K. HE, SF, and KO own stock in Eli Lilly and Company. ST has received research grants from Eli Lilly Japan K.K. The authors report no other conflicts of interest in this work.

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