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No Added Value of Duloxetine in Patients With Chronic Pain due to Hip or Knee Osteoarthritis: A Cluster-Randomized Trial

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Objective. To assess the effectiveness of duloxetine in addition to usual care in patients with chronic osteoarthritis (OA) pain. The cost-effectiveness and whether the presence of symptoms of centralized pain alters the response to duloxetine were secondary objectives.

Methods. We conducted an open-label, cluster-randomized trial. Patients with chronic hip or knee OA pain who had an insufficient response to acetaminophen and nonsteroidal antiinflammatory drugs were included. Randomization took place at the general practice level, and patients received duloxetine (60 mg/day) in addition to usual care or usual care alone. The presence of centralized pain was defined as a modified PainDETECT Questionnaire score >12. The primary outcome measure was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (scale 0–20) at 3 months after the initiation of treatment. Our aim was to detect a difference between the groups of a clinically relevant effect of 1.9 points (effect size 0.4). We used a linear mixed model with repeated measurements to analyze the data.

Results. In total, 133 patients were included, and 132 patients were randomized into treatment groups. A total of 66 patients (at 31 practices) were randomized to receive duloxetine in addition to usual care, and 66 patients (at 35 practices) were randomized to receive usual care alone. We found no differences in WOMAC pain scores between the groups at 3 months (adjusted difference –0.58 [95% confidence interval (95% CI) –1.80, 0.63]) or at 12 months (adjusted difference –0.26 [95% CI –1.86, 1.34]). In the subgroup of patients with centralized pain symptoms, we also found no effect of duloxetine compared to usual care alone (adjusted difference –0.32 [95% CI –2.32, 1.67]).

Conclusion. We found no effect of duloxetine added to usual care compared to usual care alone in patients with chronic knee or hip OA pain. Another trial including patients with centralized pain symptoms should be conducted to validate our results.

INTRODUCTION

Osteoarthritis (OA) is one of the major chronic pain conditions involving the musculoskeletal system, and it affects ~15% of the population (1,2). Persistent pain and loss of function are 2 important problems for patients with OA. Treatment is symptomatic and consists of education, exercise, physiotherapy, and analgesics.

In OA, analgesics are prescribed in a stepwise approach. The first step is acetaminophen, which has a small therapeutic effect, but is often well tolerated and has few contraindications (3). Besides acetaminophen, topical nonsteroidal antiinflammatory drugs (NSAIDs) can be prescribed. The next step is the prescription of oral NSAIDs, which have a moderate effect on OA pain (4). Oral NSAIDs especially are often contraindicated and are associated with side effects. As a third step, opioids can be considered, but they often lack effectiveness for OA pain, and serious side effects are common (5,6). Finally, glucocorticoid injections can be administered when signs of inflammation are present (7), but there is ongoing debate regarding whether the injections may accelerate the progression of OA (8,9). Therefore, other treatment options are needed.

One option may be duloxetine, a serotonin and norepinephrine reuptake inhibitor. It is hypothesized that duloxetine reduces

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chronic pain through the central inhibition of pain and acts by modulating descending (inhibitory) pain pathways in the central nervous system (10). In OA, pain can refer to nociceptive pain in the joint, peripheral sensitized pain resulting from inflammatory factors, and centrally sensitized pain (11,12). This centrally sensitized pain can occur after intense, repeated, or prolonged nociceptive input (11,13) and is present in ~23% of patients with chronic pain due to OA (14).

Several placebo-controlled trials have examined the efficacy of duloxetine in patients with OA and demonstrated effect sizes of 0.4–0.5 for pain and 0.6 for disability (15–20). Based on these trials, the Osteoarthritis Research Society International (OARSI) recommends duloxetine in patients with knee OA who have depression and/or widespread pain (7) and the American College of Rheumatology (ACR) conditionally recommends duloxetine for OA (21).

The placebo-controlled trials mentioned above investigated the short-term use of duloxetine in highly controlled secondary care settings (15–20). In a primary care setting, the effectiveness of duloxetine in addition to usual care compared to usual care alone is not known; however, most OA patients receive treatment in this setting for many years. It is also not known whether the presence of symptoms of centrally sensitized pain alters the response to duloxetine.

Therefore, we conducted a cluster-randomized controlled trial with a 12-month follow-up period to examine the effectiveness and cost-effectiveness of duloxetine in a primary care setting in patients with OA and to assess whether a beneficial effect of duloxetine is seen predominantly in patients with symptoms of centrally sensitized pain.

PATIENTS AND METHODS

Study design. A pragmatic open-label cluster-randomized trial with 2 parallel arms was conducted in general practices. A cluster design was chosen because this type of design is particularly useful in effectiveness and implementation studies, since the cluster design has the advantage of preventing treatment group contamination and reflects general practice more closely (22). The study was approved by the Local Medical Ethics Committee at the Erasmus Medical Center (approval no. MEC 2015-293). The trial is registered in the Dutch Trial Registry (identifier: NTR4798) and EudractCT (database no. 2015-001669-16). Detailed information regarding the study design is published elsewhere (23).

Data availability. Relevant anonymized patient-level data are available upon reasonable request.

Setting and participants. General practices in the southwestern region of The Netherlands were asked to participate in the study. Participating general practices identified all possible eligible patients in their patient registries and sent these patients an invitation. If they were interested, patients provided written informed consent and were screened for eligibility by the research team.

Patients were eligible if they were age ≥18 years, had hip and/or knee OA according to the ACR clinical criteria (24), had chronic pain, defined as pain on most days of the last 3 months, and had shown an insufficient response to treatment with NSAIDs, had contraindications for NSAIDs, or had previous adverse reactions to NSAIDs (e.g., were eligible for third choice pain medication).

Patients were excluded if they were scheduled for total hip replacement (THR) or total knee replacement (TKR), were currently receiving antidepressants or neuropathic pain medication (gabapentin, pregabalin, carbamazepine, capsaicin cream, or lidocaine cream), had rheumatoid arthritis, were unable to sign the informed consent, or had contraindications for the use of duloxetine (current use of monoamine oxidase inhibitors, uncontrolled narrow-angle glaucoma, receiving a combination treatment with other central nervous system–acting drugs [e.g., benzodiazepines], hypersensitivity to duloxetine, liver disease resulting in hepatic impairment, severe renal impairment [creatinine clearance <30 ml/minute], current use of *CYP1A2* inhibitors, current use of *CYP2D6* inhibitors and substrates, uncontrolled hypertension, pregnancy, or lactation).

Intervention. The participating general practices were randomized to prescibe duloxetine in addition to usual care (intervention group) or provide usual care alone to the patients (control group). In the intervention group, patients were prescribed duloxetine at 60 mg/day. In the first week of treatment, patients were prescribed a duloxetine dose of 30 mg/day to minimize potential adverse events. If the dose was well tolerated, it was increased to 60 mg/day in the second week. The therapeutic effect was regularly assessed by the treating general practitioner (at week 2 and months 1, 3, 6, 9, and 12). Duloxetine was gradually discontinued after 3 months when patients experienced no effect and/or when patients had intolerable side effects.

Usual care was provided according to the Dutch general practice guidelines (25) and consists of education, lifestyle advice, diet, physiotherapy, and analgesics. Intraarticular injection of glucocorticoids and referral to secondary care were also allowed.

Randomization. Randomization of patients to a treatment group was performed at the practice level (cluster-randomized design). An independent data manager of the department provided a computer-generated, blinded randomization list (allocation ratio 1:1). Block randomization was used with blocks varying between 2, 4, and 6 numbers. Since care provided by the general practitioner can differ based on practice characteristics, randomization at the practice level was stratified according to 1) socioeconomic status of the practice location based on the registration of The Netherlands Institute for Social Research (low

versus normal and high socioeconomic status) (26), 2) the number of general practitioners working at the practice (≤1 full-time employee versus >1 full-time employee), and the mean age of the general practitioners (<50 years versus ≥50 years) (27,28).

Researchers were blinded with regard to the randomization procedure. The research team performed the randomization after all eligible patients were identified and the first patient had provided signed informed consent. Patients were informed about the outcome of randomization after filling in the baseline questionnaire. The study was open label; patients, general practitioners, and the research team were not blinded with regard to the treatment.

Outcome measures. Patients received questionnaires at baseline, at week 6, and at months 3, 6, 9, and 12. The primary outcome measure was the pain score at month 3, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (29). The WOMAC consists of 3 domains: pain (scale 0–20), stiffness (scale 0–8), and function (scale 0–68), with higher scores indicating more problems.

The secondary outcome measures were the WOMAC scores for pain and function at 1 year. At baseline, the modified PainDETECT Questionnaire was administered to assess the presence of centralized pain (30,31). The 5-level EuroQol 5-domain questionnaire was administered to assess the cost-effectiveness of the intervention (32). Cointerventions (medication use, visits to health care professionals, THR or TKR) and patient-reported adverse events were recorded. Also, patient satisfaction with the treatment of pain was measured using an 11-point numerical rating scale (with a score of 0 indicating completely dissatisfied with treatment to a score of 10 indicating completely satisfied), and patient improvement (presence of symptoms) was measured using a 7-point Likert scale (with a score of 0 indicating total improvement of symptoms to a score of 7 indicating "worse than ever"). Patients were asked what they regarded as their most painful activity, with each designated activity rated on an 11-point numerical visual analog scale (33). Patients could choose this activity from the WOMAC function items and were able to mention another activity.

The percentage of responders was also evaluated using the Outcome Measures in Rheumatology (OMERACT)–Osteoarthritis Research Society International (OARSI) response criteria (34). Response was defined as 1) high improvement in pain or function (≥50%) and an absolute change in the pain or function score of ≥20 points (scale 0–100) or 2) improvement in at least 2 of the following 3 criteria: change in pain score ≥20% and absolute change ≥10 points; change in function score ≥20% and absolute change ≥10 points; and change in patient's global assessment of disease activity ≥20% and absolute change ≥10 points.

Sample size. A total of 102 patients per treatment group was required to detect a clinically relevant difference in WOMAC pain score of 1.9 points (pooled SD 4.8) (15) between the 2 groups with an effect size of 0.4 (80% power to detect a significant difference at a significance threshold of $P \leq 0.05$). This is taking into account the cluster randomization with the assumption of equal cluster sizes with 3 patients per practice and an intracluster correlation coefficient of 0.01. We expected ~10% loss to follow-up (35) and we therefore needed to include 224 patients (2×112). In order to detect a larger effect in patients with symptoms of centrally sensitized pain, we needed to include 44 patients per group (effect size 0.6, a difference in WOMAC pain score of 2.9 points [pooled SD 4.8] with the same power and cluster assumptions). In advance, we estimated that 37% of included patients would have symptoms of centrally sensitized pain (30), and 47% of patients in the trial had symptoms of centrally sensitized pain. Therefore, no sample size adjustments had to be made for this subgroup analysis.

Statistical analysis. Analyses were performed according to the intent-to-treat principle. Descriptive statistics were used to describe baseline characteristics of the general practices and patients.

A linear mixed-effects model with repeated measurements was used to assess the differences between the 2 groups. The general practices were included as a random effect to account for clustering. The change in all WOMAC scores over time was nonlinear and therefore a natural spline was added at week 26.

Generalized estimating equation (GEE) analyses with an autoregressive correlation structure were performed for analyses of dichotomous outcomes. Analyses were adjusted for prognostic factors at baseline when they differed ≥10% between the 2 groups.

Additional per-protocol analyses were conducted. Patients were included if they received duloxetine for ≥4 weeks or if they did not receive neuropathic pain medication in the usual care group. Furthermore, a predefined subgroup analysis was performed in which the analysis was limited to patients who had symptoms of centrally sensitized pain. Patients were included in this subgroup analysis if they scored >12 on the modified PainDETECT questionnaire. Scores >12 on this questionnaire are associated with the presence of symptoms of centralized pain in OA (30).

According to the protocol, a cost-utility analysis would only be performed if the intervention was found effective. Mixed-effects model analyses and GEE analyses were performed using R package version 3.6.3. All other analyses were performed using SPSS version 25 (IBM).

RESULTS

Participants. Patient recruitment took place between January 2016 and February 2019, and the follow-up period was completed in February 2020. A total of 231 general practitioners

at 110 general practices participated in the study. In total, 4,748 patients were classified as having knee or hip OA in general practice records, and 3,258 patients were excluded based on the presence of exclusion criteria in their medical records (Figure 1). A total of 1,490 patients were potentially eligible for inclusion and were invited to participate; 768 patients declined the study invitation, 295 patients were interested but not eligible, and 72 patients were interested and eligible but declined to participate. The most frequently mentioned reason for eligible patients declining was fear of side effects. Finally, 133 patients were included in the study, but 1 patient was lost to follow-up before randomization occurred. Therefore, 66 patients (at 31 general practices) were randomized to receive duloxetine and usual care, and 66 patients (at 35 general practices) were randomized to receive usual care alone. A total of 53 patients in each treatment arm completed the 12-month follow-up period (80.3%).

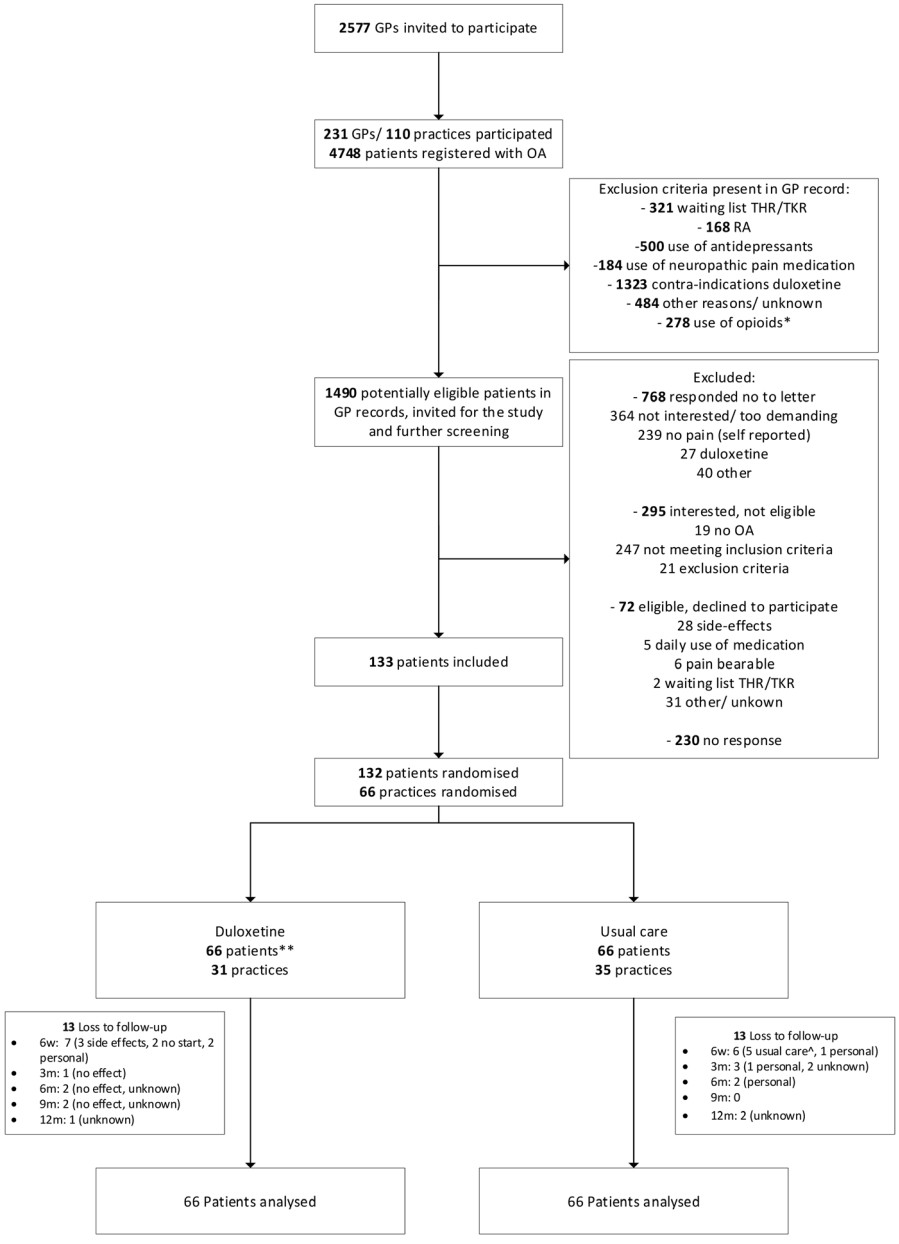

Figure 1. Flow chart of the study design showing that general practitioners were invited to participate and either declined or accepted. General practice records of patients with knee or hip OA were reviewed for exclusion criteria, and included patients were randomized to receive either duloxetine in addition to usual care or usual care alone.

Table 1. Baseline characteristics of the general practices and the OA patients in each practice randomized to receive treatment with either duloxetine in addition to usual care or usual care alone*

	Randomization to duloxetine	Randomization to usual care alone
General practices		
No. of general practices	31	35
No. of general practitioners, median	2	2
No. of days general practitioners worked in the practice, mean ± SD	1.7 ± 1.1	1.9 ± 1.0
High SES vs. low SES	23 (74.2)	27 (77.1)
Age of general practitioners, mean ± SD years	48.7 ± 8.2	48.3 ± 8.8
No. of patients included, median (range)	2 (1–6)	2 (1–4)
Patients		
No. of patients randomized	66	66
Sex, female	39 (59.1)	50 (75.8)
Age, mean ± SD years	63.2 ± 10.5	65.4 ± 11.2
BMI, mean ± SD kg/mg^2	30.6 ± 6.6	30.9 ± 6.2
Self-reported comorbidities		
CVDs	4 (6.1)	9 (13.6)
Lung diseases	4 (6.1)	15 (22.7)
Diabetes mellitus	10 (15.2)	8 (12.1)
Neurologic disorders	4 (6.1)	1 (1.5)
Lower back pain	41 (62.5)	34 (51.5)
Other musculoskeletal disorders	32 (48.5)	38 (57.5)
≥2 comorbidities	10 (15.2)	22 (33.3)
Employed at baseline	31 (47.0)	23 (34.8)
Duration of symptoms, mean ± SD years	7.8 ± 6.5	9.2 ± 8.2
Affected joints†		
Hip	15 (22.7)	9 (13.6)
Also knee OA	9 (60.0)	5 (55.6)
OA in both hips	4 (26.7)	5 (55.6)
Knee	51 (77.3)	57 (86.4)
Also hip OA	8 (15.7)	19 (33.3)
OA in both knees	35 (68.8)	34 (59.6)
WOMAC score, mean ± SD		
Pain (scale 0–20)	9.8 ± 4.2	10.5 ± 3.6
Stiffness (scale 0–8)	4.5 ± 1.8	5.0 ± 1.5
Function (scale 0–68)	34.8 ± 13.3	36.2 ± 11.1
Modified PainDETECT score (scale 0–35)		
Mean ± SD	11.4 ± 6.8	13.5 ± 7.0
No. (%)		
≤12	39 (59.1)	32 (48.5)
13–18	14 (21.2)	13 (19.7)
>18	13 (19.7)	19 (28.8)
Most painful activity score, mean ± SD (scale 0–10)‡	7.0 ± 1.3	7.4 ± 1.4
HADS score, mean ± SD		
Depression (scale 0–21)	4.2 ± 3.5	3.6 ± 3.1
Anxiety (scale 0–21)	4.5 ± 3.8	4.0 ± 3.3
EQ-5D-5L score, mean ± SD (scale –0.446, 1)	0.628 ± 0.168	0.613 ± 0.161
Treatment		
None	18 (27.3)	20 (30.3)
Acetaminophen	28 (42.4)	25 (37.9)
Topical NSAIDs	1 (1.5)	0 (0.0)
NSAIDs	30 (45.5)	28 (42.4)
Opioids	6 (9.1)	10 (15.2)

* Except where indicated otherwise, values are the number (%). OA = osteoarthritis; SES = socioeconomic status; BMI = body mass index; CVDs = cardiovascular diseases; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5L = 5-level EuroQol 5-domain questionnaire; NSAIDs = nonsteroidal antiinflammatory drugs.
† When patients reported pain in both hips and both knees, questions were asked about the most painful joint. The denominator for the subgroups is the total number of patients in whom the knee or hip was affected.
‡ Patients were asked what they regarded as their most painful activity; activities are listed in Supplementary Table 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.42040/abstract).

Table 1 shows the baseline clinical and demographic characteristics of the patients at the general practices (for baseline clinical and demographic characteristics of the patients with symptoms of centrally sensitized pain, see Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42040/abstract). In

Table 2. Results for primary and secondary outcomes in patients receiving duloxetine in addition to usual care compared to those receiving usual care alone*

			Unadjusted model		Adjusted model†	
	Duloxetine (n = 66)	Usual care alone (n = 66)	Difference (95% CI)	Effect size	Difference (95% CI)	Effect size
WOMAC pain score (scale 0–20)						
Week 6	8.5 ± 4.9	9.2 ± 4.1	−0.87 (−2.17, 0.42)	0.22	−0.49 (−1.62, 0.65)	0.14
Month 3	8.0 ± 4.3	9.3 ± 3.7	−0.84 (−2.18, 0.49)	0.21	−0.58 (−1.80, 0.63)	0.16
Month 6	8.4 ± 3.9	9.1 ± 3.8	−0.80 (−2.32, 0.70)	0.18	−0.66 (−2.09, 0.78)	0.15
Month 9	8.5 ± 4.6	8.9 ± 3.8	−0.79 (−2.28, 0.71)	0.18	−0.52 (−1.93, 0.89)	0.12
Month 12	8.5 ± 4.8	9.6 ± 4.2	−0.78 (−2.46, 0.91)	0.15	−0.26 (−1.86, 1.34)	0.05
WOMAC function score (scale 0–68)						
Week 6	29.4 ± 15.6	34.4 ± 12.6	−3.95 (−8.03, 0.13)	0.32	−1.42 (−5.31, 2.47)	0.12
Month 3	28.2 ± 15.1	33.3 ± 13.4	−4.19 (−8.61, 0.23)	0.32	−2.10 (−6.39, 2.20)	0.16
Month 6	30.1 ± 16.1	31.9 ± 13.2	−4.49 (−9.70, 0.71)	0.29	−2.84 (−8.00, 2.33)	0.18
Month 9	29.2 ± 14.8	32.3 ± 13.8	−4.52 (−9.57, 0.53)	0.30	−2.61 (−7.52, 2.31)	0.18
Month 12	29.8 ± 16.2	34.1 ± 13.8	−4.38 (−9.84, 1.09)	0.27	−1.79 (−7.22, 3.64)	0.11
WOMAC stiffness score (scale 0–8)						
Week 6	4.1 ± 2.0	4.5 ± 1.7	−0.56 (−1.07, −0.05)	0.37	−0.58 (−1.10, −0.06)	0.37
Month 3	4.0 ± 1.8	4.7 ± 1.7	−0.54 (−1.06, −0.01)	0.34	−0.57 (−1.11, −0.03)	0.35
Month 6	4.2 ± 1.6	4.5 ± 1.7	−0.48 (−1.07, 0.11)	0.27	−0.51 (−1.13, 0.11)	0.27
Month 9	4.0 ± 1.6	4.4 ± 1.6	−0.38 (−0.93, 0.17)	0.23	−0.37 (−0.94, 0.20)	0.22
Month 12	4.0 ± 1.8	4.3 ± 1.7	−0.26 (−0.92, 0.41)	0.13	−0.18 (−0.87, 0.50)	0.09
Most painful activity score (scale 0–10)						
Month 3	6.1 ± 2.3	6.8 ± 1.8	−0.45 (−0.98, 0.06)	0.29	−0.52 (−1.05, 0.02)	0.32
Month 12	6.2 ± 2.6	6.8 ± 1.8	−0.46 (−0.98, 0.05)	0.30	−0.52 (−1.05, 0.01)	0.33
Quality of Life score (scale −0.446, 1)						
Month 3	0.678 ± 0.157	0.641 ± 0.144	0.01 (−0.01, 0.03)	0.17	0.02 (−0.04, 0.07)	0.12
Month 6	0.642 ± 0.171	0.623 ± 0.180	0.01 (−0.02, 0.05)	0.10	0.02 (−0.04, 0.09)	0.10
Month 9	0.656 ± 0.172	0.617 ± 0.187	0.01 (−0.03, 0.05)	0.08	0.02 (−0.04, 0.08)	0.11
Month 12	0.652 ± 0.221	0.638 ± 0.177	0.00 (−0.05, 0.05)	0.00	0.01 (−0.06, 0.08)	0.05
Patient satisfaction score (scale 0–10)						
Month 3	6.0 ± 2.8	5.6 ± 2.7	0.56 (−0.66, 1.78)	0.15	0.62 (−0.67, 1.91)	0.16
Month 6	5.9 ± 2.7	5.6 ± 2.3	0.56 (−0.66, 1.78)	0.33	0.63 (−0.66, 1.93)	0.16
Month 9	5.9 ± 2.8	5.7 ± 2.3	0.56 (−0.66, 1.77)	0.15	0.63 (−0.66, 1.92)	0.16
Month 12	5.8 ± 2.7	5.5 ± 2.5	0.55 (−0.65, 1.75)	0.15	0.61 (−0.66, 1.88)	0.16
Perceived improvement, no. (%)						
Month 3	16 (28.6)	3 (6.0)	6.38 (1.68, 24.21)‡	–	17.40 (2.85, 106.18)‡	–
Month 12	15 (29.4)	4 (7.8)	4.65 (1.39, 15.45)‡	–	5.33 (1.57, 19.29)‡	–
OMERACT–OARSI criteria responder, no. (%)§						
Month 3	21 (37.5)	13 (25.0)	1.74 (0.75, 4.01)‡	–	1.95 (0.78, 4.84)‡	–
Month 12	17 (32.1)	13 (24.5)	1.69 (0.70, 4.04)‡	–	1.33 (0.51, 3.50)‡	–

* Except where indicated otherwise, values are the mean ± SD. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 95% CI = 95% confidence interval; OMERACT–OARSI = Outcome Measures in Rheumatology–Osteoarthritis Research Society International.
† Adjusted for age, sex, modified PainDETECT score, Hospital Anxiety and Depression Scale score, and the presence of ≥2 comorbidities.
‡ Values are the odds ratio (95% confidence interval [95% CI]).
§ At month 3, 56 patients in the duloxetine group and 52 patients in the usual care group filled out the questionnaire. At month 12, 53 patients filled out the questionnaire in each group.

both groups, baseline characteristics of the general practices were similar. Some clinical characteristics of the patients differed between the 2 groups. The duloxetine group consisted of fewer women (59.1% versus 75.8%) and patients were slightly younger (mean 63.2 years versus 65.4 years) and had fewer comorbidities (15.2% versus 33.3% had ≥2 comorbidities). Most of the patients who were included had knee OA (77.3% in the duloxetine group and 86.4% in the usual care group) and 40% of patients had symptoms of centralized pain. On average, patients with symptoms of centralized pain were 2 years younger and had higher WOMAC pain scores.

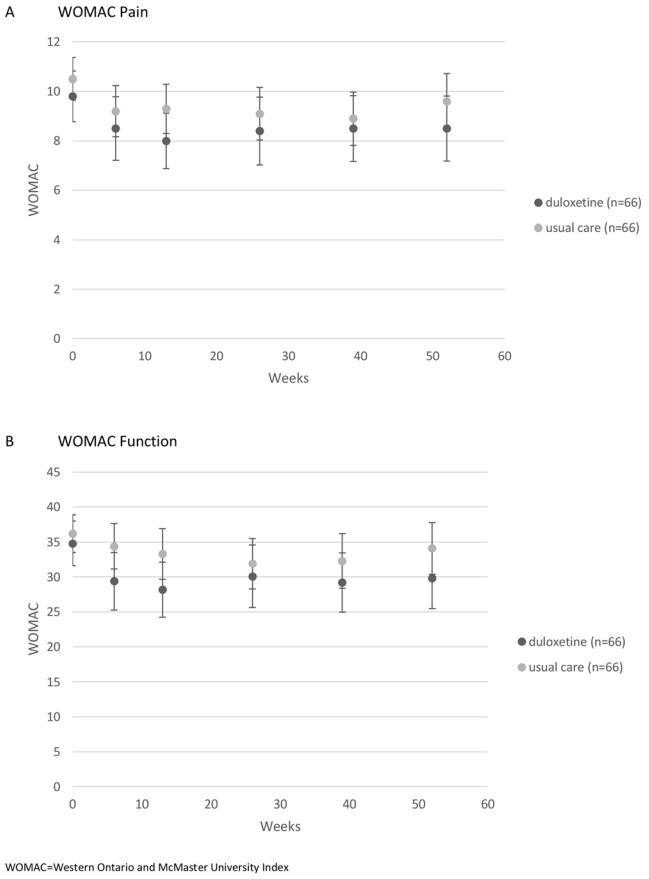

Figure 2. Course of WOMAC scores for for pain (**A**) and function (**B**) over time in OA patients receiving duloxetine in addition to usual care compared to those receiving usual care alone. Results are the mean ± SD, in which circles represent the mean for the indicated group and bars represent the SD.

Primary outcome measure. The primary outcome measure was the WOMAC pain score at month 3. Patients in the duloxetine group reported slightly less pain than patients in the usual care group (adjusted difference –0.58 [95% confidence interval (95% CI) –1.80, 0.63]), which was not clinically relevant or statistically significant. The 95% CI ruled out a clinically relevant effect size of 1.9 points. Our analyses were adjusted for age, sex, modified PainDETECT Questionnaire score, Hospital Anxiety and Depression Scale score, and the presence of ≥2 comorbidities. The intraclass correlation coefficient for the adjusted analysis for WOMAC pain scores was 0.18 (Table 2 and Figure 2).

Secondary outcome measures. The WOMAC pain scores at month 12 also showed a small difference in favor of the duloxetine group compared to the usual care group (adjusted difference –0.26 [95% CI –1.86, 1.34]). There was also a small between-group difference in WOMAC function scores at month 3 (adjusted difference –2.10 [95% CI –6.39, 2.20]) and at month 12 (adjusted difference –1.79 [95% CI –7.22, 3.64]). There were small differences in the other secondary outcome measures: quality of life, patient satisfaction, and the OMERACT–OARSI responder criteria. None of the differences between the 2 groups were clinically relevant or statistically significant. Patient improvement scores (based on patients' ratings of symptom improvement versus worsening) were significantly different between the 2 groups, with an increased likelihood of greater improvement in the duloxetine group relative to the usual care group (odds ratio 17.40 [95% CI 2.85, 106.18]); however, the numbers of patients assessed were small, and the CIs were broad. An additional per-protocol analysis yielded similar results (Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42040/abstract). In the subgroup analysis of patients with symptoms of central sensitization of pain, there was a small, but not statistically significant, difference in WOMAC pain scores at months 3 and 12 (adjusted difference –0.32 [95% CI –2.32, 1.67] at month 3; adjusted difference 1.02 [95% CI –1.22, 3.27] at month 12) (Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.42040/abstract). Based on the 95% CI, we ruled out a larger effect of duloxetine (difference of 2.9 points in WOMAC pain scale scores, effect size 0.6), but based on the 95% CI, the possibility that duloxetine had a smaller effect size (difference in WOMAC pain score 1.9 points, effect size 0.4) cannot be excluded.

Duloxetine use. Of the 66 patients in the duloxetine group, 56 patients (85%) initiated treatment with duloxetine (Figure 3). The most frequently mentioned reason for not initiating treatment with duloxetine was fear of side effects (7 patients). After 3 months, 61% of patients were still receiving duloxetine, and at 1 year, 35% of patients were still receiving duloxetine. In total, 33 patients (59%) discontinued treatment with duloxetine. Patient-reported reasons for stopping were a lack of effect (24%), side effects (49%), and a lack of effect in addition to side effects (18%) (data were missing for 10% of patients).

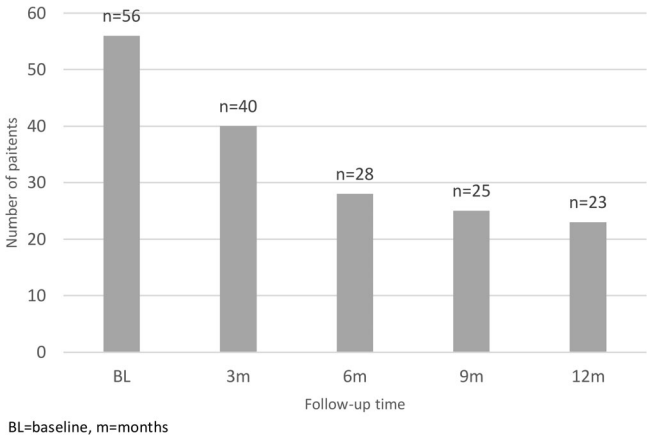

Figure 3. Number of patients with chronic hip or knee osteoarthritis pain who were receiving treatment with duloxetine at baseline (BL) and at months 3, 6, 9, and 12 of follow-up.

Table 3. Cointerventions at week 6 and months 3, 6, 9, and 12 of follow-up in patients receiving treatment with duloxetine in addition to usual care compared to those receiving usual care alone*

	Week 6	Month 3	Month 6	Month 9	Month 12
Medication					
Acetaminophen					
Duloxetine	24 (43.6)	31 (55.4)	30 (60.0)	28 (59.6)	30 (56.6)
Usual care	29 (50.0)	34 (51.5)	31 (60.8)	27 (56.3)	31 (58.5)
NSAIDs†					
Duloxetine	10 (18.2)	16 (28.6)	25 (50.0)	18 (38.3)	19 (35.8)
Usual care	18 (31.0)	25 (48.1)	28 (54.9)	24 (50.0)	29 (54.7)
Opioids					
Duloxetine	1 (1.8)	2 (3.6)	5 (10.0)	4 (8.5)	5 (9.4)
Usual care	3 (5.2)	6 (11.5)	5 (9.8)	4 (8.3)	6 (11.3)
None					
Duloxetine	25 (45.5)	17 (30.4)	7 (14.0)	11 (23.4)	13 (24.5)
Usual care	17 (29.3)	8 (15.4)	4 (7.8)	9 (18.7)	12 (22.6)
Cumulative visits to a general practitioner					
Duloxetine	NA	29 (51.8)	36 (54.5)	40 (60.6)	42 (63.6)
Usual care	NA	16 (24.2)	18 (35.3)	22 (45.8)	26 (49.1)
Cumulative visits for physiotherapy					
Duloxetine	NA	11 (19.6)	12 (24.0)	14 (29.8)	15 (28.3)
Usual care	NA	9 (17.3)	14 (27.4)	16 (33.3)	16 (30.2)
Cumulative visits to an orthopedic surgeon					
Duloxetine	NA	6 (10.7)	9 (18.0)	10 (21.2)	11 (20.8)
Usual care	NA	2 (3.8)	5 (9.8)	6 (12.5)	7 (13.2)
Cumulative glucocorticoid injections					
Duloxetine	1 (1.8)	1 (1.8)	3 (6.0)	3 (6.4)	3 (5.7)
Usual care	4 (7.0)	6 (11.5)	7 (13.7)	9 (18.9)	9 (17.0)
Cumulative joint replacements					
Duloxetine	1 (1.8)	0 (0)	2 (4.0)	3 (6.3)	5 (9.4)
Usual care	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* Except where indicated otherwise, values are the number (%) of patients. Values were missing for some patients at some time points. Visiting a general practitioner was not considered an applicable cointervention. NA = not applicable.
† Nonsteroidal antiinflammatory drugs (NSAIDs) refers to oral NSAIDs. One patient in the usual care group was receiving treatment with topical NSAIDs at month 9.

Adverse events. At month 3, 89.3% of patients in the duloxetine group reported having at least 1 side effect compared to 72.5% of patients in the usual care group (Supplementary Figure 1). Nausea, weight loss, constipation, yawning, and hyperhidrosis, which are well-known side effects of duloxetine, were significantly more frequently reported by patients in the duloxetine group.

Cointerventions. Patients in the duloxetine group contacted their general practitioner more frequently (51.8% versus 24.2% at month 3) (Table 3) and were more often referred to an orthopedic surgeon (10.7% versus 3.8% at month 3). Over the total follow-up period, 5 patients in the duloxetine group had a THR or TKR, while none of the patients receiving usual care had a THR or TKR. At month 3, more patients in the usual care group compared to the duloxetine group were receiving treatment with NSAIDs (48.1% versus 28.6%) and opioids (11.5% versus 3.6%), and patients in the usual care group were more likely to receive a glucocorticoid injection (11.5% versus 1.8% of patients in the duloxetine group at month 3).

DISCUSSION

In this study of patients with chronic OA pain, we examined the effectiveness of duloxetine when added to usual care compared to usual care alone. Furthermore, we assessed whether a beneficial effect of duloxetine is seen predominantly in patients with symptoms of centrally sensitized pain. We did not find a clinically relevant or statistically significant effect of duloxetine on WOMAC pain scores at month 3 or other time points, nor was there an effect for the other outcomes, and we can therefore rule out a clinically relevant effect in the overall group (1.9-point difference in WOMAC pain scores). Finally, we found no effect in the subgroup of patients with symptoms of centrally sensitized pain.

While other studies have identified a small-to-moderate effect of duloxetine (15–20), we did not find an effect of duloxetine in patients with OA pain. In our trial, patients' baseline pain scores were similar to the pain scores reported by patients in the other trials (15–20). This difference in outcome could be due to the fact that we studied the effectiveness of duloxetine in a primary care setting, while the other studies examined the efficacy in placebo-controlled trials in secondary care. Furthermore, the patients in our trial were older, reported OA pain for a longer time, and had more comorbidities than those in the other studies. It is established that smaller effects are found in these real-life primary care populations and in effectiveness studies rather than in highly controlled efficacy trials (22). We evaluated duloxetine as a third-choice analgesic, i.e., one used when treatment with acetaminophen and NSAIDs is unsuccessful. In most other studies this was not a prerequisite to participate in the study. The study by Frakes et al (17) is the only one in which treatment was first optimized with NSAIDs and patients were included in the trial when still in pain despite receiving optimal treatment with NSAIDs.

Finally, we had a follow-up period of 1 year and found that 35% of patients were still receiving treatment with duloxetine at the end of the follow-up period. The majority of the patients discontinued treatment with duloxetine around month 3 because of a lack of effect or the presence of side effects. The percentage of patients discontinuing treatment with duloxetine was higher in our study than in the 2 other studies that evaluated the long-term use of duloxetine in OA in an open-label extension phase of the trial. In one study, ~80% of patients continued to receive treatment with duloxetine until week 26 (36). In the second study, ~85% of patients continued treatment with duloxetine for up to 1 year (37). However, only 25% of patients entered the extension phase, and those who discontinued did not mention reasons for not continuing in the extension phase of the study, which could have resulted in the selection of patients who showed tolerance to treatment with duloxetine and whose condition improved with the treatment. In our trial, general practitioners were instructed to discontinue treatment with duloxetine after 3 months, when either treatment was unsuccessful or the patient had intolerable side effects. This may also have contributed to the higher percentage of patients who discontinued treatment with duloxetine in our trial.

Interestingly, during the follow-up period, patients in the duloxetine group more often underwent a THR or TKR than patients in the usual care group. At month 3, these patients were more frequently referred to an orthopedic surgeon, and afterward, more THR and TKR procedures were performed. We believe this is caused by the fact that patients in the duloxetine group visited their general practitioner more often, and when treatment with duloxetine was unsuccessful, this was the next step. To our knowledge, this has not been demonstrated in other pragmatic trials.

Furthermore, patients in the duloxetine group more often reported significant improvement in OA pain compared to patients in the usual care group, while none of the other outcome measures differed between the 2 groups. This may have been caused by the open-label nature of the trial. The number of patients reporting improvement was low, which resulted in a wide 95% CI.

We also found no effect in patients with symptoms of central sensitization of pain. Overall, these patients reported more pain at baseline and were slightly younger (but reported a similar duration of pain) compared to the overall group. Higher pain scores are associated with the presence of central sensitization of pain (38). Since the prognostic differences between the 2 groups were slightly different, a sensitivity analysis was performed, adjusting for these variables (age, sex, affected joint, and comorbidities). Results of this analysis were similar to those of the original analysis (data not shown). We also conducted a post hoc analysis with a higher threshold for the modified PainDETECT score (>18), which is indicative of neuropathic pain. We found no effect of duloxetine with similar estimates, but there were very large CIs because of low numbers (data not shown).

The presence of central sensitization of pain was defined as a score of >12 on the modified PainDETECT Questionnaire (30,31). The gold standard to identify the presence of central sensitization of pain is quantitative sensory testing (39). These tests are time consuming and expensive and therefore not feasible in daily clinical practice. When using a cutoff score of 12, the modified PainDETECT Questionnaire has a sensitivity of 50% and a specificity of 74% to detect symptoms of central sensitization of pain (30). Small-to-moderate correlations between PainDETECT scores and pressure pain thresholds have been found (40,41). Therefore, we might not have perfectly selected patients for the subgroup analyses.

One strength of the current trial is the pragmatic cluster design, which is suitable for evaluating an intervention in clinical practice and demonstrating the effectiveness of the intervention (22). Cluster randomized controlled trials can be prone to recruitment bias (42,43), but this was minimized by identifying all eligible patients before randomization. However, one general practice in the duloxetine group recruited 4 patients after the randomization period. Conducting a sensitivity analysis without those 4 patients did not alter the results (data not shown).

A limitation of the current trial is that we did not recruit the number of patients calculated in the sample size. However, even with the sample size, we can rule out the presence of a clinically relevant effect in the overall group, since the predefined clinically relevant difference of 1.9 points was not within the 95% CI and makes the presence of an effect highly unlikely (44,45). We cannot rule out the fact that there may be a clinically relevant effect in the subgroup analysis of patients with symptoms of centralized pain. We hypothesized that in this subgroup the effect of duloxetine would be greater (difference of 2.9 points in WOMAC pain scale score), and though this larger effect can be ruled out, the presence of a smaller difference of 1.9 points on the WOMAC pain score scale cannot be completely ruled out, though the point

estimates in this subgroup analysis were similar to the point estimates in the overall group.

We had a low number of both general practitioners and patients participating in the trial and therefore decided to stop recruiting after 3 years. The rate of participation by general practitioners was similar to previous trials in our department, and recruitment is difficult because general practitioners lack time (46,47). Furthermore, we interviewed general practitioners about their attitude toward duloxetine in patients with OA pain. General practitioners were relatively unfamiliar with duloxetine, since duloxetine is not often prescribed (48,49), and were concerned about the occurrence of side effects. Some general practitioners stated that duloxetine may be an option for patients in whom other therapies have proven unsuccessful. These factors may have also contributed to the participation rate of the general practitioners. The number of patients participating per general practice was lower than we expected beforehand. Patients were frequently excluded based on the presence of exclusion criteria in their medical records at the general practice or because pain was bearable or not present (when receiving acetaminophen or NSAIDs).

To conclude, there was no clinically relevant effect of duloxetine added to usual care compared to usual care alone for the treatment of chronic OA pain, and it should not be implemented. In patients with symptoms of centralized pain, a potential effect of duloxetine cannot be ruled out, so future studies in this subgroup including patients with centralized pain symptoms should be conducted to validate our results.

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 published. Dr. van den Driest 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. Van den Driest, Schiphof, Koffeman, Koopmanschap, Bindels, Bierma-Zeinstra.

Acquisition of data. Van den Driest, Schiphof, Bierma-Zeinstra.

Analysis and interpretation of data. Van den Driest, Schiphof, Koopmanschap.

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