van den Driest Jacoline J. (Orcid ID: 0000-0001-9206-5431)

No added value of duloxetine for patients with chronic pain due to hip or knee osteoarthritis: a cluster randomised trial

Jacoline J. van den Driest MD[1], Dieuwke Schiphof PhD[1], Aafke R. Koffeman MD PhD[2], Marc A. Koopmanschap PhD[3], Patrick J.E. Bindels MD PhD[1], Sita M.A. Bierma-Zeinstra PhD[1,4]

Author affiliations

[1]Department of General Practice, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[2]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

[3] Department of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

[4] Department of Orthopedics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Disclosures of interest: SMAB-Z reports grants from The Netherlands Organisation for Health Research and Development, during the conduct of the study; grants from European union, Foreum, The Netherlands Organisation for Health Research and Development, Dutch Arthritis Association, CZ, personal fees from OARSI, personal fees from Pfizer, outside the submitted work.The other authors declare no conflicts of interest.

Funding: This work was supported by the Netherlands Organisation for Health Research and Development (ZonMW) (80-83600-98-3141).

Contributorship: JJvdD, DS, ARK, MAK, PJEB, SMAB-Z participated in the design of the study and the research protocol. JJvdD and DS coordinated the study, were responsible for data acquisition, and conducted statistical analysis. MAK provided economic statistical consultation. JJvdD, DS, ARK, MAK, PJEB and SMAB-Z were involved in the writing, editing and approval of the final manuscript.

Acknowledgements: None

Ethical approval: The local Medical Ethics Committee of Erasmus Medical Center has approved the trial (MEC-2015-293). The trial is registered in the Dutch Trial registry (NTR4798) and EudractCT database (2015-001669-16).

Data sharing statement: Relevant anonymised patient level data are available on reasonable request.

Corresponding author:

J.J. van den Driest

Department of General Practice, Erasmus MC

Wytemaweg 80

P.O. Box 2040, 3000 CA Rotterdam

The Netherlands

Telephone: +31-10-7033033. Fax: +31-10-7044766

Email: j.vandendriest@erasmusmc.nl

ABSTRACT

Objectives To assess the effectiveness of duloxetine added to usual care for patients with chronic osteoarthritis (OA) pain. Secondary objectives were to assess cost-effectiveness and to assess whether the presence of symptoms of centralized pain alters the response to duloxetine.

Methods An open label, cluster randomised trial was conducted. Patients with chronic OA pain of hip or knee in which paracetamol and NSAIDs had insufficient response were included. GP practices were randomised to duloxetine 60mg/day added to usual care or to usual care alone. The presence of centralized pain was defined as a modified painDETECT score >12. The primary outcome was WOMAC pain (0-20) at 3 months. We aimed to detect a difference between the groups of a clinical relevant effect of 1.9 points (effect size 0.4). A linear mixed model with repeated measurements was used to analyse the data.

Results In total, 133 patients were included and 132 were randomised. 66 patients (31 practices) were randomised to duloxetine added to usual care and 66 patients (34 practices) to usual care alone. No differences were found for WOMAC pain at 3 months (adjusted difference -0.58 95% confidence interval [-1.80 to 0.63]) or at 12 months (adjusted difference -0.26 95% CI[-1.86 to 1.34]). For the subgroup of patients with symptoms of centralized pain no effect of duloxetine was found either (-0.32 95% CI[-2.32 to 1.67]).

Conclusions No effect was found of duloxetine added to usual care compared to usual care alone in patients with chronic OA pain. For patients with symptoms of centralized pain our results need to be confirmed in another trial.

Trial registration Dutch trial registry NTR4798

Keywords osteoarthritis, duloxetine, cluster randomised trial, effectiveness

INTRODUCTION

Osteoarthritis is one of the major chronic pain conditions of the musculoskeletal system and approximately 15% of the population suffers from OA (1, 2). Persistent pain and loss of function are two important complaints of patients with OA. Treatment is symptomatic and consists of education, exercise, physiotherapy, and analgesics.

Analgesics are prescribed in a stepwise approach to patients with OA. The first step is paracetamol, which has a small therapeutic effect, but is often well tolerated and has few contra-indications (3). Next to paracetamol topical non-steroidal anti-inflammatory drugs (NSAIDs) can be prescribed. The next step are oral NSAIDs, which have a moderate effect on OA pain (4). Especially, oral NSAIDs are often contra-indicated and are associated with side-effects. As a third step, opioids can be considered, but effectiveness is often lacking for OA pain and serious side-effects are common (5, 6). Finally, corticosteroid injections can be given when signs of inflammation are present (7), but the debate about whether the injections may accelerate the progression of OA is still ongoing (8, 9). Other treatment options are therefore needed.

An option may be duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI). Duloxetine is hypothesized to reduce chronic pain by central inhibition of pain and acts by modulation of descending (inhibitory) pain pathways in the central nervous system (10). Pain in OA can be caused by nociceptive pain of the joint, peripheral sensitized pain 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 around 23% of the patients with chronic pain due to OA (14).

Several placebo-controlled trials have examined the efficacy of duloxetine for patients with OA and found 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 for patients with knee OA with depression and/or widespread pain (7) and the American College of Rheumatology (ACR) conditionally recommends duloxetine for OA (21).

The trials investigated the short-term use of duloxetine in placebo-controlled trials in highly controlled secondary care settings (15-20). The effectiveness of duloxetine added to usual care compared to usual care alone in a primary care setting is unknown, while most OA patients are treated in this setting for many years. Neither is it known whether the presence of symptoms of centrally sensitized pain alters the response to duloxetine.

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

PATIENTS AND METHODS

Study design

A pragmatic open-label cluster randomised trial with two parallel arms was conducted in general practice. A cluster design was chosen, because this type of design is particularly useful for effectiveness and implementation studies, because the cluster design has the advantage of prevention of treatment group contamination and it reflects 'real-life' most closely(22). The study was approved by the medical ethics committee of the Erasmus MC (MEC 2015-293). Detailed information of the study design is published elsewhere (23).

Setting and participants

GP practices in the South-West of the Netherlands were asked to participate in the study. Participating GPs identified all possible eligible patients in their patient registries and sent

these patients an invitation. If patients were interested, patients were screened for eligibility by the research team and gave written informed consent.

Patients were eligible if they were ≥ 18 years, had hip and/or knee OA based on the clinical ACR criteria(24), had chronic pain, defined as pain on most days of the last three months, and had insufficient benefit of NSAIDs, contra-indications for NSAIDs or previous adverse reactions to NSAIDs (e.g. be 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 using antidepressants or neuropathic pain medication (gabapentin, pregabalin, carbamazepine, capsaicin crème and lidocaine crème), had rheumatoid arthritis, were unable to sign informed consent or had contra-indications for the use of duloxetine (current use of monoamine oxidase inhibitors, uncontrolled narrow-angle glaucoma, the combination with other central nervous acting drugs (e.g. benzodiazepines), hypersensitivity to duloxetine, liver disease resulting in hepatic impairment, severe renal impairment (creatinine clearance <30ml/min), current use of CYP1A2 inhibitors, current use of CYP2D6 inhibitors and substrates, uncontrolled hypertension, pregnancy or lactation).

Intervention

GP practices were randomised to treat patients with duloxetine and usual care or usual care alone. In the intervention group, patients were prescribed duloxetine 60mg/day. Patients started with duloxetine 30mg/day in the first week to minimize potential adverse events. When the dose was tolerated well, this was increased to 60mg/day in the second week. The therapeutic effect was assessed regularly by the treating GP (2 weeks and 1,3,6,9 and 12 months). Duloxetine was gradually discontinued after three months when patients experienced no effect and/or when patients had intolerable side-effects.

Usual care was provided according to the Dutch GP guidelines (25) and consists of education, life style advice, diet, physiotherapy and analgesics. Intra-articular injection of glucocorticoids and referral to secondary care were also allowed.

Randomisation

Randomisation was performed at practice level (cluster design). An independent data-manager of the department provided a computer list (allocation ratio 1:1). Block randomisation was used with blocks varying between 2, 4 and 6. Since care provided by the GP can differ based on practice characteristics randomisation was stratified on 1) socio-economic status of the practice location based on the registration by the Netherlands Institute of Social Research (low vs normal and high) (26), 2) the number of GPs working in the practice (≤1fte vs >1 fte), and the mean age of the GPs (<50 years vs ≥50 years) (27, 28). The randomisation procedure was concealed to the researchers. The research team performed randomisation after all eligible patients were identified and the first patient had signed informed consent. Patients were informed about the outcome of randomisation after filling in the baseline questionnaire. The study was open label; patients, GPs and the research team were not blinded for the treatment.

Outcomes

Patients received questionnaires at baseline, at 6 weeks and at 3, 6, 9 and 12 months. Primary outcome was pain at 3 months measured with the Western Ontario Mc Master Universities (WOMAC) Osteoarthritis Index (29). The WOMAC consists of three domains; pain (0-20), stiffness (0-8) and function (0-68), with higher scores indicating more complaints.

Secondary outcomes were pain and function (WOMAC) at one year. At baseline the modified painDETECT was administered to assess the presence of centralized pain (30, 31). The EQ-

5D-5L was administered to assess the cost-effectiveness of the intervention (32). Co-interventions (medication use, visits to health care professionals, THR or TKR) and patient reported adverse events were recorded. Also patients satisfaction with the treatment of pain measured on a 11-numeric rating scale (0= completely dissatisfied to 10=completely satisfied) and patient improvement (presence of symptoms) measured on a 7-point Likert scale (from 'totally improved' to 'worse than ever') were assessed. Patients were asked what they regarded as their most painful activity, the nominated activity VAS (33), and scored this on a 11-numeric rating scale. Patients could choose this activity from the WOMAC function items and had the possibility to mention another activity.

The percentage of responders was also evaluated by the OMERACT-OARSI response criteria (34). Response is defined as 1) a high improvement in pain or function (≥50%) and an absolute change of ≥20 (scale 0–100) or 2) improvement in at least two of the three following: pain ≥20% and absolute change ≥10; function ≥20% and absolute change ≥10; patients' global assessment ≥20% and absolute change ≥10.

Sample size

To detect a clinically relevant difference in WOMAC pain of 1.9 points (pooled SD 4.8) (15) between the two groups with an effect size of 0.4 (power 80%; alpha 0.05), taking into account the cluster randomisation with the assumption of equal cluster sizes with three patients per practice and an intra-cluster correlation coefficient (ICC) of 0.01, 102 patients per treatment group were required. Around 10% loss to follow-up was expected (35) and we therefore needed to include 224 patients (2x112). In order to detect a larger effect in patients with symptoms of centrally sensitized pain we needed 44 patients per group (effect size 0.6, a difference in WOMAC pain of 2.9 points (pooled SD 4.8), same power and cluster assumptions). In advance we estimated that 37% of the included patients would have

symptoms of centrally sensitized pain (30) and 47% of the 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 intention to treat principle. Descriptive statistics were used to describe baseline characteristics of GP practices and patients.

A linear mixed model with repeated measurements was used to assess the differences between the two groups. The GP practices were included as a random effect to account for clustering. The change of WOMAC scores over time was non-linear and therefore a natural spline was added at 26 weeks.

Generalised estimating equations (GEE) analysis with an autoregressive correlation structure were performed for dichotomous outcomes. Analyses were adjusted for prognostic factors at baseline when they differed ≥10% between the two groups.

Additional per protocol analyses were carried out. Patients were included in this analysis when using duloxetine for ≥4 weeks or when not using neuropathic pain medication in the usual care group. Furthermore, predefined subgroup analysis for patients with symptoms of centrally sensitized pain was performed. Patients were included in this subgroup analysis when scoring >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 when the intervention was found effective. The mixed model analyses and GEE analyses were performed with R (version 3.6.3). All other analyses were performed with SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Participants

Recruitment of patients took place between January 2016 and February 2019 and follow-up was completed in February 2020. 231 GPs in 110 GP practices participated in the study. In total, 4748 patients were registered with knee or hip OA in GP records and 3258 patients could be excluded based on the presence of exclusion criteria in their medical record (Figure 1). 1490 patients were potentially eligible and were invited to participate. 768 patients responded no to the invitation letter, 295 patients were interested but not eligible and 73 patients were interested and eligible, but declined to participate. Most mentioned reason for declining by the eligible patients was fear of side-effects. Finally, 133 patients were included in the study and one patient got lost to follow-up before randomisation; 66 patients (31 GP practices) were randomised to duloxetine and usual care, and 66 patients (35 GP practices) to usual care alone. The 12-month follow-up was completed by 53 patients in each arm (80.3%).

The baseline characteristics of the GP practices and patients are shown in Table 1 (Supplemental data Table S1 for Baseline characteristics of patients with symptoms of centrally sensitized pain). Characteristics of the GP practices were similar in both groups. Some characteristics of the patients differed between the two groups. The duloxetine group consisted of fewer women (59.1% vs 75.8%), patients were slightly younger (63.2 years vs 65.4 years) and had fewer comorbidities (15.2% vs 33.2% had ≥ 2 comorbidities). Most patients included had knee OA (77.3% in duloxetine group and 86.4% in the usual care group) and 40% of the patients had symptoms of centralized pain. Patients with symptoms of centralized pain were on average two years younger and had higher scores on WOMAC pain.

Primary outcome

The primary outcome was WOMAC pain at three months. Patients in the duloxetine group had slightly less pain than patients in the usual care group (adjusted difference -0.49 [95%CI -1.65 to 0.65]), which was not clinically relevant nor statistically significant. The 95% confidence interval even ruled out a clinical relevant effect of 1.9 points. The analyses were adjusted for age, sex, modified painDETECT score, HADS depression score and the presence of two or more comorbidities. The intra-cluster correlation coefficient for the adjusted analysis for WOMAC pain was 0.18 (Figure 2 and Table 2).

Secondary outcomes

The WOMAC pain at 12 months also showed a small difference in favour of the duloxetine group (adjusted difference -0.26 [95% CI -1.86 to 1.34]). The WOMAC function scores also showed a small difference at three months (-1.42 [95% CI -5.31 to 2.47]) and at 12 months (-1.79 [95% CI -7.22 to 3.64]). The other secondary outcomes quality of life, patient satisfaction and the OMERACT-OARSI responder criteria also showed small differences. None of the differences between the two groups were clinically relevant or statistically significant. Patient improvement was significantly different between the two groups (OR 17.40 95% CI [2.85 to 106.18]), but numbers were small and confidence intervals were broad. Additional per protocol analysis showed similar results (Supplemental Table S2). In the subgroup analysis for patients with symptoms of central sensitization a small non-significant difference in WOMAC pain was found at 3 and 12 months (adjusted differences -0.32 95% CI [-2.32 to 1.67] and 1.02 95% CI [-1.22 to 3.27] respectively, Supplemental Table S3). Based on the 95% CI a larger effect of duloxetine could be ruled out (difference of 2.9 point in WOMAC pain scale, effect size 0.6), but a smaller effect cannot be excluded based on the 95% CI (1.9 points, effect size 0.4).

Duloxetine use

Of the 66 patients in the duloxetine group 56 patients (85%) started using duloxetine (Figure 3). The most mentioned reason for not starting with duloxetine was fear of side-effects of duloxetine (7 patients). After three months 61% of the patients and at 1 year 35% of the patients were still using duloxetine. In total, 33 patients (59%) discontinued duloxetine. Patient reported reasons for stopping were no effect (24%), side-effects (49%) and no effect+ side-effects (18%).

Adverse events

At 3 months 89.3% of the patients in the duloxetine group reported at least one side-effect compared to 72.5% in the usual care group (Supplemental Figure S1). Nausea, weight loss, constipation, yawning and hyperhidrosis were reported significantly more frequently by patients in the duloxetine group. These are well known side-effects of duloxetine.

Co-interventions

Patients in the duloxetine group contacted their GP more frequently (51.8% vs 30.8% at 3 months, Table 3) and were more often referred to an orthopaedic surgeon (10.7% vs 3.8% at 3 months). In the total follow-up time, 5 patients in the duloxetine group had a THR or TKR while none of the patients receiving usual care had a THR or TKR. Patients treated according to usual care used more NSAIDs (48.1% vs 28.1% at 3 months) and opioids (11.5% vs 3.6% at 3 months), and were more likely to receive a corticosteroid injection (6.0 vs 1.8% at 3 months).

DISCUSSION

In this study the effectiveness of duloxetine added to usual care compared to usual care alone was examined for patients with chronic OA pain. Furthermore, it was assessed

whether the effect of duloxetine was predominantly found in patients with symptoms of centrally sensitized pain. We did not find a clinically relevant or statistically significant effect of duloxetine for WOMAC pain at 3 months, nor for the other outcomes or at other time points and can rule out the presence of a clinically relevant effect for the total group (1.9 points difference in WOMAC pain). Finally, no effect was found for the subgroup of patients with symptoms of centrally sensitized pain.

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

Finally, we had a follow-up period of one year and found that 35% of the patients were still using duloxetine at one year. The majority of the patients stopped using duloxetine around 3 months because of lack of effect or the presence of side effects. The percentage of patients discontinuing duloxetine is higher in our study than in the two other studies that evaluated the long-term use of duloxetine in OA in an open-label extension phase of the trial. In one

study around 80% of the patients continued to use duloxetine up to 26 weeks (36). In the second study around 85% continued the use of duloxetine up to one year (37). However, only a quarter of the patients entered the extension phase and reasons for not continuing in the extension phase of the study were not mentioned, which could have led to a selection of patients who benefit and tolerate duloxetine well. In our trial GPs were instructed to discontinue duloxetine after three months when patients did not experience an effect or had intolerable side effects. This may also have contributed to the higher percentage of patients that discontinued duloxetine in our trial.

Interestingly, a THR or TKR was performed more often in patients in the duloxetine group than in patients in the usual care group during the follow-up time. At 3 months, patients were referred to an orthopaedic surgeon more frequently and afterwards more THR and TKR were performed. We believe this is caused by the fact that patients in the duloxetine group visited their GP more often and when treatment with duloxetine failed, this was the next step. To our knowledge this has not been reported in other pragmatic trials.

Furthermore, patients in the duloxetine group reported improvement of complaints significantly more often compared to patients in the usual care group while none of the other outcome measurements differed between the two groups. This may have been caused by the open-label character of the trial. The absolute number of patients reporting improvement was low, which lead to wide 95% CI.

For patients with symptoms of central sensitization also no effect was found. Overall, these patients had more pain at baseline and were slightly younger (but had a similar duration of complaints) compared to the complete group. Higher pain scores are known to be associated with the presence of central sensitization (38). Since the prognostic differences between the two groups were slightly different a sensitivity analysis was performed with

adjustment for these variables (age, sex, joint and comorbidities). Results of this analysis were similar to the original analysis (data not shown). We also carried out a post hoc analysis with a higher threshold for the modified painDETECT score (>18), which is indicative for neuropathic pain. No effect of duloxetine was found either with similar estimates, but with very large confidence intervals because of low numbers (data not shown).

We defined the presence of central sensitization as a score of >12 on the modified painDETECT questionnaire (30, 31). The gold standard to examine whether signs of central sensitization are present is quantitative sensory testing (QST) (39). These tests are time-consuming and expensive and therefore not feasible in daily practice. When using a cut-off score of 12, the modified painDETECT questionnaire has sensitivity of 50% and a specificity of 74% to detect symptoms of central sensitization (30). Small to moderate correlations (r= -0.35 to r=-0.23) have been found between painDETECT scores and pain pressure thresholds (40, 41). It might therefore be we did not perfectly selected the patients for the subgroup analyses.

A strength of the current trial is the pragmatic cluster design, which is suitable for evaluating an intervention in 'real-life' and provides information on the effectiveness of the intervention (22). A cluster RCT can be prone to recruitment bias (42, 43), but this was minimised by identifying all eligible patients before randomisation of the GP practice. However, one GP practice in the duloxetine group recruited four patients after randomisation. Sensitivity analysis without those four 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 as calculated in the sample size. However, even with this sample size we can rule out a clinically relevant effect for the complete group since the predefined clinically relevant difference of

1.9 points was not in the 95% confidence interval and makes the presence of an effect highly unlikely (44, 45). For the subgroup analysis of patients with symptoms of centralized pain, we cannot rule out that there may be a clinically relevant effect. We hypothesized that in this subgroup the effect of duloxetine would be larger (difference of 2.9 points on WOMAC pain scale) and this larger effect can be ruled out, but the presence of a smaller difference of 1.9 points on WOMAC pain scale cannot be completely ruled out, though the point estimates of this subgroup analysis were similar to the complete group.

We had a low number of both GPs and patients participating in the trial and decided to stop recruiting after three years, because of these low numbers. We know from previous trials of our department that recruitment of GPs is difficult, because of lack of time of GPs and our rate of participating GPs is similar to other studies from our department (46, 47). Furthermore, we held interviews with GPs about their attitude towards duloxetine for patients with OA pain. GPs were relatively unfamiliar with duloxetine, since duloxetine is not often prescribed (48, 49) and were concerned about the occurrence of side-effects. Some GPs stated that duloxetine may be an option for patients in which other therapies have failed. These factors may have contributed as well to the participation rate of the GPs. The number of patients participating per GP was lower than expected beforehand. Patients could frequently be excluded based on the presence of exclusion criteria in their GP record, or pain was bearable/not present (when using paracetamol or NSAIDs).

To conclude, there was no clinically relevant effect of duloxetine added to usual care compared to usual care alone for chronic OA pain and it should not be implemented. For patients with symptoms of centralized pain an effect cannot be ruled out and future research in this subgroup is needed to confirm our results.

REFERENCES

1. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol. 2014;28(1):5-15.
2. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-30.
3. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev. 2019;2:CD013273.
4. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390(10090):e21-e33.
5. da Costa BR, Nuesch E, Kasteler R, Husni E, Welch V, Rutjes AW, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014(9):CD003115.
6. Toupin April K, Bisaillon J, Welch V, Maxwell LJ, Juni P, Rutjes AW, et al. Tramadol for osteoarthritis. Cochrane Database Syst Rev. 2019;5:CD005522.
7. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019.
8. Zeng C, Lane NE, Hunter DJ, Wei J, Choi HK, McAlindon TE, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2019;27(6):855-62.
9. Conaghan PG. Corticosteroids and osteoarthritis progression: a confounded issue. Osteoarthritis Cartilage. 2019;27(6):e5-e6.
10. Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. J Rheumatol. 2011;38(8):1546-51.
11. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: the genesis of pain. Rheumatology (Oxford). 2018;57(suppl_4):iv43-iv50.
12. Clauw DJ, Hassett AL. The role of centralised pain in osteoarthritis. Clin Exp Rheumatol. 2017;35 Suppl 107(5):79-84.
13. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(7):1043-56.
14. French HP, Smart KM, Doyle F. Prevalence of neuropathic pain in knee or hip osteoarthritis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2017;47(1):1-8.
15. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. Age Ageing. 2012;41(5):646-52.
16. Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract. 2011;11(1):33-41.

17. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011;27(12):2361-72.
18. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain. 2009;146(3):253-60.
19. Wang G, Bi L, Li X, Li Z, Zhao D, Chen J, et al. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage. 2017;25(6):832-8.
20. Uchio Y, Enomoto H, Alev L, Kato Y, Ishihara H, Tsuji T, et al. A randomized, double-blind, placebo-controlled Phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis. J Pain Res. 2018;11:809-21.
21. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020;72(2):149-62.
22. Allen KD, Bierma-Zeinstra SM, Foster NE, Golightly YM, Hawker G. OARSI Clinical Trials Recommendations: Design and conduct of implementation trials of interventions for osteoarthritis. Osteoarthritis Cartilage. 2015;23(5):826-38.
23. van den Driest JJ, Schiphof D, Luijsterburg PAJ, Koffeman AR, Koopmanschap MA, Bindels PJE, et al. Effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip or knee osteoarthritis: protocol of a pragmatic open-label cluster randomised trial (the DUO trial). BMJ Open. 2017;7(9):e018661.
24. Altman RD. Classification of disease: osteoarthritis. Semin Arthritis Rheum. 1991;20(6 Suppl 2):40-7.
25. Dutch College of General Practitioners (NHG). NHG Standaard Niet-traumatische knieklachten. 2016 [cited 01-12-2019]; Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-niet-traumatische-knieklachten#Richtlijnendiagnostiek
26. The Netherlands Institute for Social Science https://www.scp.nl/Onderzoek/Lopend_onderzoek/A_Z_alle_lopende_onderzoeken/Statusscores. Accessed 04 July 2017
27. Smink AJ, Bierma-Zeinstra SM, Dekker J, Vliet Vlieland TP, Bijlsma JW, Swierstra BA, et al. Agreement of general practitioners with the guideline-based stepped-care strategy for patients with osteoarthritis of the hip or knee: a cross-sectional study. BMC Fam Pract. 2013;14:33.
28. Landon BE, Reschovsky J, Reed M, Blumenthal D. Personal, organizational, and market level influences on physicians' practice patterns: results of a national survey of primary care physicians. Med Care. 2001;39(8):889-905.
29. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. 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):1833-40.
30. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1236-42.

31. Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage. 2011;19(6):647-54.
32. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.
33. Parkes MJ, Callaghan MJ, O'Neill TW, Forsythe LM, Lunt M, Felson DT. Sensitivity to Change of Patient-Preference Measures for Pain in Patients With Knee Osteoarthritis: Data From Two Trials. Arthritis Care Res (Hoboken). 2016;68(9):1224-31.
34. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12(5):389-99.
35. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med. 2008;148(4):268-77.
36. Wang G, Bi L, Li X, Li Z, Zhao D, Chen J, et al. Maintenance of effect of duloxetine in Chinese patients with pain due to osteoarthritis: 13-week open-label extension data. BMC Musculoskelet Disord. 2019;20(1):174.
37. Uchio Y, Enomoto H, Ishida M, Tsuji T, Ochiai T, Konno S. Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, Phase III extension study. J Pain Res. 2018;11:1391-403.
38. Lluch E, Nijs J, Courtney CA, Rebbeck T, Wylde V, Baert I, et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. Disabil Rehabil. 2018;40(23):2836-45.
39. Uddin Z, MacDermid JC. Quantitative Sensory Testing in Chronic Musculoskeletal Pain. Pain Med. 2016;17(9):1694-703.
40. Moore RL, Clifford AM, Moloney N, Doody C, Smart KM, O'Leary H. The Relationship Between Clinical and Quantitative Measures of Pain Sensitization in Knee Osteoarthritis. Clin J Pain. 2020;36(5):336-43.
41. Moreton BJ, Tew V, das Nair R, Wheeler M, Walsh DA, Lincoln NB. Pain phenotype in patients with knee osteoarthritis: classification and measurement properties of painDETECT and self-report Leeds assessment of neuropathic symptoms and signs scale in a cross-sectional study. Arthritis Care Res (Hoboken). 2015;67(4):519-28.
42. Brierley G, Brabyn S, Torgerson D, Watson J. Bias in recruitment to cluster randomized trials: a review of recent publications. J Eval Clin Pract. 2012;18(4):878-86.
43. Eldridge S, Kerry S, Torgerson DJ. Bias in identifying and recruiting participants in cluster randomised trials: what can be done? Bmj. 2009;339:b4006.
44. Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. Ann Intern Med. 1994;121(3):200-6.
45. Ranstam J. Why the P-value culture is bad and confidence intervals a better alternative. Osteoarthritis Cartilage. 2012;20(8):805-8.
46. Schreijenberg M, Luijsterburg PAJ, Van Trier YDM, Rizopoulos D, Koopmanschap MA, Voogt L, et al. Discontinuation of the PACE Plus trial: problems in patient recruitment in general practice. BMC Musculoskelet Disord. 2018;19(1):146.
47. Wartna JB, Bohnen AM, Elshout G, Pijnenburg MW, Pols DH, Gerth van Wijk RR, et al. Symptomatic treatment of pollen-related allergic rhinoconjunctivitis in children: randomized controlled trial. Allergy. 2017;72(4):636-44.

48. Aarts N, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly. Eur Psychiatry. 2014;29(6):365-70.
49. van den Driest JJ, Schiphof D, de Wilde M, Bindels PJE, van der Lei J, Bierma-Zeinstra SMA. Antidepressant and anticonvulsant prescription rates in patients with osteoarthritis: a population-based cohort study. Rheumatology (Oxford). 2021;60(5):2206-16.

FIGURE LEGENDS

Figure 1. Flowchart of the study

Figure 2. Course of WOMAC pain and function

Figure 3. Patients using duloxetine

TABLES

Table 1 Baseline characteristics

	Duloxetine (n=66)	Usual care (n=66)
GP Practice		
Number of practices	31	35
Number of GPs, median	2	2
Number of GPs fte	1.7 (1.1)	1.9 (1.0)
High SES (vs low SES)	23 (74.2)	27 (77.1)
Age (years) of GP, mean (SD)	48.7 (8.2)	48.3 (8.8)
Patients included, median (range)	2 (1-6)	2 (1-4)
Patients		
Female, n (%)	39 (59.1)	50 (75.8)
Age, mean (SD)	63.2 (10.5)	65.4 (11.2)
BMI, mean (SD)	30.6 (6.6)	30.9 (6.2)
Comorbidities (self-reported), n (%)		
Cardiovascular diseases	4 (6.1)	9 (13.8)
Lung diseases	4 (6.1)	15 (23.1)
Diabetes mellitus	10 (15.2)	8 (12.3)
Neurological disorders	4 (6.1)	1 (1.5)
Low back pain	41 (62.5)	34 (52.3)
Other musculoskeletal disorders	32(48.5)	38 (58.5)
≥ 2 comorbidities	10 (15.2)	22 (33.8)
Employment, n (%)	31 (47.0)	23 (34.8)
Duration of symptoms (years), mean (SD)	7.8 (6.5)	9.2 (8.2)
Joint affected*, n (%)		
Hip	15 (22.7)	9 (13.6)
Both hips	4 (26.7)	5 (55.6)
Knee	9 (60.0)	5 (55.6)
Knee	51 (77.3)	57 (86.4)
Both knees	35 (68.8)	34 (59.6)
Hip	8 (15.7)	19 (33.3)
WOMAC, mean (SD)		
Pain (0-20)	9.8 (4.2)	10.5 (3.6)
Stiffness (0-8)	4.5 (1.8)	5.0 (1.5)
Function (0-68)	34.8 (13.3)	36.2 (11.1)
Modified painDETECT (0-35), mean (SD)	11.4 (6.8)	13.5 (7.0)
≤12, n (%)	39 (59.1)	32 (48.5)
13-18, n (%)	14 (21.2)	13 (21.2)
> 18, n (%)	13 (19.7)	19 (28.8)
Most painful activity** (0-10), mean (SD)	7.0 (1.3)	7.4 (1.4)
HADS		
Depression, (0-21), mean (SD)	4.2 (3.5)	3.6 (3.1)
Anxiety, (0-21), mean (SD)	4.5 (3.8)	4.0 (3.3)
EQ5D (-0.446;1), mean (SD)	0.628 (0.168)	0.613 (0.161)
Treatment, n (%)		
None	18 (27.3)	20 (30.3)
Paracetamol	28 (42.4)	25 (37.9)
Topical NSAIDs	1 (1.5)	0

NSAIDs	30 (45.5)	28 (42.4)
Opioids	6 (9.1)	10 (15.2)

*When patients had complaints in both hips and knees; questions were asked about the most painful joint **Most painful activity as mentioned by the patient, activities are mentioned in Supplemental Table S4.
GP=general practitioner, SES=socio-economic status, SD=standard deviation, BMI=body mass index, WOMAC=Western Ontario and McMaster University Index, HADS=hospital anxiety and depression scale, EQ5D=Euroqol, NSAIDs=non-steroidal anti-inflammatory drugs
The range mentioned for WOMAC, modified painDETECT, most painful activity, HADS and EQ5D are the *possible* ranges of these scores.

Table 2 Results for primary and secondary outcomes

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=66)	*Usual care(n=66)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
WOMAC pain	6w	8.5 (4.9)	9.2 (4.1)	-0.87 (-2.17; 0.42)	0.22	-0.49 (-1.62; 0.65)	0.14
(0-20)	3m	8.0 (4.3)	9.3 (3.7)	-0.84 (-2.18; 0.49)	0.21	-0.58 (-1.80; 0.63)	0.16
	6m	8.4 (3.9)	9.1 (3.8)	-0.80 (-2.32; 0.70)	0.18	-0.66 (-2.09; 0.78)	0.15
	9m	8.5 (4.6)	8.9 (3.8)	-0.79 (-2.28; 0.71)	0.18	-0.52 (-1.93; 0.89)	0.12
	12m	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	6w	29.4 (15.6)	34.4 (12.6)	-3.95 (-8.03; 0.13)	0.32	-1.42 (-5.31; 2.47)	0.12
(0-68)	3m	28.2 (15.1)	33.3 (13.4)	-4.19 (-8.61; 0.23)	0.32	-2.10 (-6.39; 2.20)	0.16
	6m	30.1 (16.1)	31.9 (13.2)	-4.49 (-9.70; 0.71)	0.29	-2.84 (-8.00; 2.33)	0.18
	9m	29.2 (14.8)	32.3 (13.8)	-4.52 (-9.57; 0.53)	0.30	-2.61 (-7.52; 2.31)	0.18
	12m	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	6w	4.1 (2.0)	4.5 (1.7)	-0.56 (-1.07; -0.05)	0.37	-0.58 (-1.10; -0.06)	0.37
(0-8)	3m	4.0 (1.8)	4.7 (1.7)	-0.54 (-1.06; -0.01)	0.34	-0.57 (-1.11; -0.03)	0.35
	6m	4.2 (1.6)	4.5 (1.7)	-0.48 (-1.07; 0.11)	0.27	-0.51 (-1.13; 0.11)	0.27
	9m	4.0 (1.6)	4.4 (1.6)	-0.38 (-0.93; 0.17)	0.23	-0.37 (-0.94; 0.20)	0.22
	12m	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	3m	6.1 (2.3)	6.8 (1.8)	-0.45 (-0.98; 0.06)	0.29	-0.52 (-1.05; 0.02)	0.32
(0-10)	12m	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	3m	0.678 (0.157)	0.641 (0.144)	0.01 (-0.01; 0.03)	0.17	0.02 (-0.04; 0.07)	0.12
(-0,446;1)	6m	0.642 (0.171)	0.623 (0.180)	0.01 (-0.02; 0.05)	0.10	0.02 (-0.04; 0.09)	0.10
	9m	0.656 (0.172)	0.617 (0.187)	0.01 (-0.03; 0.05)	0.08	0.02 (-0.04; 0.08)	0.11
	12m	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	3m	6.0 (2.8)	5.6 (2.7)	0.56 (-0.66; 1.78)	0.15	0.62 (-0.67; 1.91)	0.16
(0-10)	6m	5.9 (2.7)	5.6 (2.3)	0.56 (-0.66; 1.78)	0.33	0.63 (-0.66; 1.93)	0.16
	9m	5.9 (2.8)	5.7 (2.3)	0.56 (-0.66; 1.77)	0.15	0.63 (-0.66; 1.92)	0.16
	12m	5.8 (2.7)	5.5 (2.5)	0.55 (-0.65; 1.75)	0.15	0.61 (-0.66; 1.88)	0.16
		n(%)	*n (%)*	*OR (95% CI)*		*OR (95% CI)*	
Perceived improvement	3m	16 (28.6)	3 (6.0)	6.38 (1.68-24.21)		17.40 (2.85-106.18)	
(yes/no)	12m	15 (29.4)	4 (7.8)	4.65 (1.39-15.45)		5.33 (1.57-19.29)	
Responder according to OARSI omeract criteria	3m	21 (37.5)	13 (25.0)	1.74 (0.75-4.01)		1.95 (0.78-4.84)	
(yes/no)	12m	17 (32.1)	13 (24.5)	1.69 (0.70-4.04)		1.33 (0.51-3.50)	

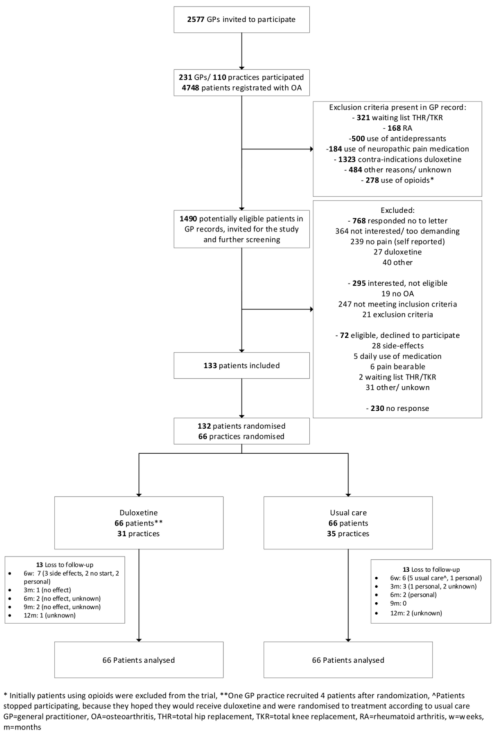
*Adjusted for age, gender, modified painDETECT score, HADS depression scale score and the presence of 2 or more comorbidities, WOMAC=Western Ontario and McMaster University Index, SD=standard deviation, CI=confidence interval, OR=odds ratio, w=weeks, m=months

Table 3 Co-interventions

		Duloxetine	Usual care
Medication			
Paracetamol, n (%)	6w	24 (43.6)	29 (50.0)
	3m	31 (55.4)	34 (51.5)
	6m	30 (60.0)	31 (60.8)
	9m	28 (59.6)	27 (56.3)
	12m	30 (56.6)	31 (58.5)
NSAIDs^, n(%)	6w	10 (18.2)	18 (31.0)
	3m	16 (28.6)	25 (48.1)
	6m	25 (50.0)	28 (54.9)
	9m	18 (38.3)	24 (50.0)
	12m	19 (35.8)	29 (54.7)
Opioids, n (%)	6w	1 (1.8)	3 (5.2)
	3m	2 (3.6)	6 (11.5)
	6m	5 (10.0)	5 (9.8)
	9m	4 (8.5)	4 (8.3)
	12m	5 (9.4)	6 (11.3)
None, n(%)	6w	25 (45.5)	17 (29.3)
	3m	17 (30.4)	8 (15.4)
	6m	7 (14.0)	4 (7.8)
	9m	11 (23.4)	9 (18.7)
	12m	13 (24.5)	12(22.6)
Co-interventions			
Visit GP	6w	NA	NA
Cumulative visits, n(%)	3m	29 (51.8)	16 (24.2)
	6m	36 (54.5)	18 (35.3)
	9m	40 (60.6)	22 (45.8.)
	12m	42(63.6)	26 (49.1)
Physiotherapy	6w	NA	NA
Cumulative visits, n(%)	3m	11 (19.6)	9 (17.3)
	6m	12 (24.0)	14(27.4)
	9m	14 (29.8)	16 (33.3)
	12m	15 (28.3)	16 (30.2)
Visit orthopedic surgeon	6w	NA	NA
Cumulative visits, n(%)	3m	6 (10.7)	2 (3.8)
	6m	9 (18.0)	5 (9.8)
	9m	10 (21.2)	6 (12.5)
	12m	11 (20.8)	7 (13.2

Corticosteroid injections	6w	1 (1.8)	4 (7.0)
Cumulative, n(%)	3m	1 (1.8)	6 (11.5)
	6m	3 (6.0)	7 (13.7)
	9m	3(6.4)	9 (18.9)
	12m	3 (5.7)	9 (17.0)
Joint replacements	6w	1 (1.8)	0
Cumulative, n(%)	3m	0	0
	6m	2 (4.0)	0
	9m	3 (6.3)	0
	12m	5 (9.4)	0

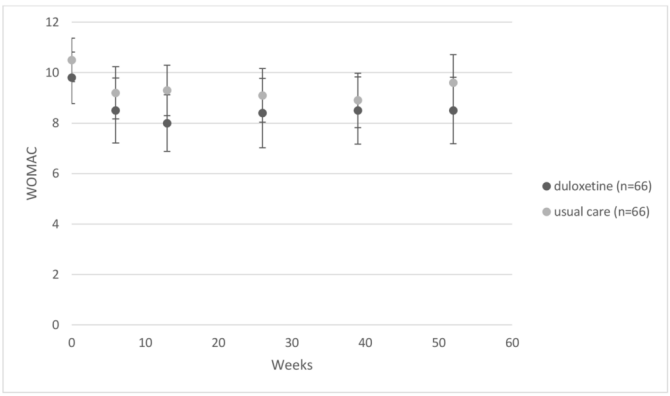
NSAIDS=non-steroidal anti-inflammatory drugs, GP=general practitioner, w=weeks, m=months, NA=not applicable, ^Oral NSAIDs, 1 patient in usual care group was using topical NSAIDs at 9 months



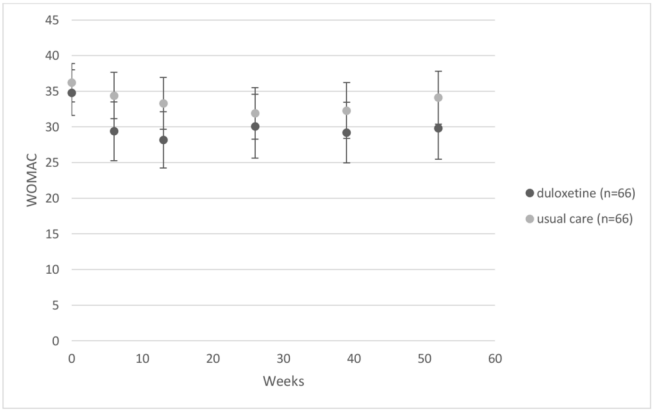
* Initially patients using opioids were excluded from the trial, **One GP practice recruited 4 patients after randomization, ^Patients stopped participating, because they hoped they would receive duloxetine and were randomised to treatment according to usual care GP=general practitioner, OA=osteoarthritis, THR=total hip replacement, TKR=total knee replacement, RA=rheumatoid arthritis, w=weeks, m=months

ART_42040_Figure 1 Flowchart of the study_R1.tiff

A WOMAC Pain

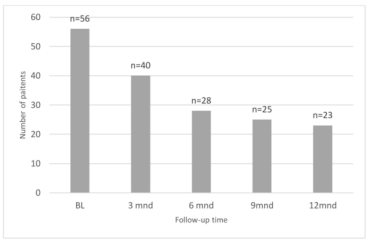


B WOMAC Function



WOMAC=Western Ontario and McMaster University Index

ART_42040_Figure 2 Course of WOMAC pain and function_R1.tiff



BL=baseline, m=months

ART_42040_Figure 3 Patients using duloxetine_R1.tiff