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Complete List of Authors:	Rienstra, Wietske; University of Groningen, Department of Rehabilitation Medicine Blikman, Tim; University of Groningen, Department of Rehabilitation Medicine Dijkstra, Baukje; Medical Centre Leeuwarden, Department of Orthopaedic Surgery Stewart, Roy; Rijksuniversiteit Groningen, Department of Health Sciences, Community and Occupational Medicine, University Medical Center Groningen; University of Groningen/UMCG Zijlstra, Wierd; Medical Centre Leeuwarden, Department of Orthopaedic Surgery van Raaij, Tom; Martini Hospital Groningen, Department of Orthopaedic Surgery ten Hagen, Anita; Martini Hospital Groningen, Department of Anaesthesiology Bulstra, Sjoerd ; University of Groningen, Department of Orthopaedic Surgery van den Akker-Scheek, Inge; University Medical Center Groningen, Department of Orthopaedic Surgery Stevens, Martin; University of Groningen, Groningen, The Netherlands, Department of Orthopaedic Surgery
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Effect of pre-operative duloxetine treatment on postoperative chronic residual pain after total hip or knee arthroplasty: A Randomised Controlled Trial

Wietske Rienstra[1,2], Tim Blikman[1,2], Baukje Dijkstra[4], Roy Stewart[3], Wierd P. Zijlstra[4,] Tom M. van Raaij[5], Anita J. ten Hagen[6], Sjoerd K. Bulstra[1], Inge van den Akker-Scheek[1], Martin Stevens[1]

[1] Department of Orthopaedics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2] Department of Rehabilitation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[3] Department of Community and Occupational Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4] Department of Orthopaedics, Medical Center Leeuwarden, Leeuwarden, The Netherlands

[5] Department of Orthopaedics, Martini Hospital Groningen, Groningen, The Netherlands

[6] Department of Anaesthesiology, Martini Hospital Groningen, Groningen, The Netherlands

Correspondence to Wietske Rienstra, MD; w.rienstra@umcg.nl

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Abstract

Objectives A key predictor for developing chronic residual pain after Total Knee- or Hip Arthroplasty (TKA/THA) is sensitization. Aim of this study is to investigate the effects of pre-operative treatment of sensitized knee/hip osteoarthritis patients with duloxetine on postoperative chronic residual pain up to one year after TKA/THA.

Setting A multi-centre, pragmatic, prospective, randomized clinical trial was conducted in 3 secondary care hospitals in the Netherlands.

Participants Patients with primary knee/hip osteoarthritis with signs of sensitization who were planned for TKA/THA were eligible for participation. 111 participants were included and randomly assigned 1:1 intervention or usual care. Complete follow-up of all post-operative time points up to 1 year after surgery was retrieved in 92 cases (82.9%).

Interventions Pre-operative oral treatment of seven weeks with 60 mg of Duloxetine daily was compared to usual care.

Primary and secondary outcome measures The primary outcome measure was pain, assessed with the Pain Subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip disability and Osteoarthritis Outcome Score (HOOS) with a 0-100 scale. Secondary outcome measures were Visual Analogue Scales, and neuropathic-like pain measured using the modified PainDETECT-Questionnaire. These outcome measures were conforming the original research protocol. Longitudinal data collection included time points up to one year post-operatively.

Results The mean improvement in KOOS/HOOS pain subscale was 37 (SD 28.1) in the intervention group and 43 (SD 26.5) in the control group. No statistically significant difference was found in change-score six months after TKA/THA between both groups (p=0.280). Within the intervention group, 12 patients discontinued duloxetine due to Adverse Events, constituting 21% of the intervention group.

Conclusions Pre-operative targeted treatment with duloxetine in end-stage knee and hip OA patients with sensitization does not influence postoperative chronic residual pain after TKA/THA.

Trial Registration Netherlands national Trial Register on August-15-2014 (trial ID NTR4744).

Keywords: Pain Management, Sensitization, Orthopaedic Hip and Knee surgery, Clinical Pharmacology

Strengths and limitations of this study

- Broad screening of all patients who were planned for Total Knee or Hip Artrohroplasty creating a representative study population

- Using patient-reported outcome measures relevant for clinical practice

- Comparing to usual-care which varied among clinicians and participating centres thereby increasing generalizability

- Long term follow-up focusing on clinical relevance of the efficacy of duloxetine treatment prior to arthroplasty to post-operative outcome

- The substantial difference in treatment effect of duloxetine between hip and knee OA patients was not anticipated and somewhat lessens the interpretability of our results for the total study group.

Introduction

Total Hip and Knee Arthroplasty (THA/TKA) are among the most performed surgical procedures in Orthopaedic Surgery for the treatment of patients with severe Osteoarthritis (OA) [1,2]. Projections show that the number of performed procedures will dramatically rise in the future [3–6]. In light of this, the high prevalence of residual pain after total Hip and Knee Arthroplasty must be considered a highly relevant problem. Up to 23% of patients after THA and up to 34% after TKA experience chronic residual pain [7] which leads to declining patient satisfaction, functioning, and quality of life [8–11].

Numerous studies have demonstrated that pain in OA is a highly complex phenomenon in which both intra-articular and extra-articular mechanisms seem to be involved [12,13]. Among these mechanisms is the modification of pain transmission in both the peripheral and central nervous system, leading to sensitization of the pain pathways. A number of mechanisms have been described leading to sensitization, among which modulation of the inhibitory descending control pathways of the central nervous system seems to play an important role [14,15]. Sensitization in OA expresses itself through neuropathic-like symptoms such as allodynia, hyperalgesia, and spreading of the pain. Signs of sensitization seem to be one of the key predictors for poorer outcome after Total Joint Arthroplasty (TJA), especially for chronic residual pain [16–20]. Up to 19% of patients with hip OA and 19-37% of patients with knee OA experience signs of sensitization and are therefore at higher risk of developing chronic residual pain after TJA [14,15,21–32].

As sensitization in OA is an important risk factor for development of chronic residual pain after THA/TKA it is plausible that targeted treatment, for example with neuromodulating medication, aimed at desensitization prior to surgery will reduce chronic residual pain. Duloxetine, a selective serotonin and norepinephrine re-uptake inhibitor, influences the descending inhibitory control pathways of the central nervous system. Recent meta-analysis show that duloxetine has a positive effect on pain in OA patients [33–40]. Moreover, a recent study shows that the use of duloxetine during the peri-operative period (1 day before up to 6 weeks after

surgery) of sensitized knee OA patients has positive effects on pain up to 12 weeks postoperatively [38]. To our knowledge, it is unknown whether this beneficial effect is also present in long term follow-up. By specifically selecting OA patients with signs of sensitization, rather than the general knee and hip OA population, it will be possible to make a better assessment of the effectiveness of desensitization prior to THA/TKA on the development of chronic residual pain. Until now, the effect of duloxetine on pain in OA patients has solely been investigated in comparison to placebo. It is of clinically relevant value to assess the added effect of duloxetine in OA patients compared to usual care.

Therefore, aim of this study is to investigate the effect of preoperative treatment of sensitized hip and knee OA patients with duloxetine on postoperative chronic residual pain up to one year after TJA.

Methods

Design

A multi-centre, pragmatic, prospective, open-label, randomized clinical trial registered in the Netherlands national Trial Register on August-15-2014 (trial ID NTR4744). Participating hospitals were University Medical Center Groningen (UMCG), Martini Hospital Groningen, and Medical Center Leeuwarden. A detailed description of the study design was published earlier [41]. After commencement of the trial, no important changes were made to the methods, and no changes were made to trial outcomes. T.B and W.R generated the random allocation sequence, enrolled participants, and assigned participants to interventions.

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Participants

Patients were recruited between December 2014 and June 2018, follow up was completed in 2019. The recruitment period ended as soon as the aimed sample size was achieved. During the study period, all patients with primary hip or knee OA who were planned for THA or TKA were screened using a self-report questionnaire for neuropathic-like pain symptoms in hip and knee OA , the modified PainDETECT Questionnaire (m-PDQ) [42–45]. If patients reported a neuropathic or at least a mixed neuropathic/nociceptive pain phenotype (m-PDQ scores >12.0), and were eligible

considering the in- and exclusion criteria, they were invited for participation. Patients received oral and written information, and 2 weeks of consideration time. Patients willing to participate were invited for a visit to the outpatient clinic of their Orthopaedic Department where the last safety-related exclusion criteria were ruled out based on laboratory testing and physical examination. A complete list of exclusion criteria can be found in the design paper, and also in supplementary file 1 [41]. Patients who complied to the in- and exclusion criteria and still willing to participate, provided written informed consent and their visit to the outpatient clinic extended into the baseline visit.

Randomization

Randomization took place with an allocation ratio 1:1. The ALEA online randomisation program (ALEA, FormsVision, Abcoude, the Netherlands) localised on the secured servers of the local Trial Coordination Centre of UMCG was used. Participants were stratified on location (hip or knee) of arthroplasty to be performed.

Procedure

Demographic information, patient characteristics and medical history were collected using patient records, and all patients received their first set of questionnaires at baseline. During the pre-operative period, follow-up time points took place two weeks and eight weeks after baseline. At these time points, patients in the intervention group visited the outpatient clinic. During these visits, adverse effects (AEs) were assessed. Additionally, patients received a set of questionnaires during these follow-up visits. Patients in the care as usual group received identical sets of questionnaires by mail at the same time points.

One day prior to surgery all participants from both study groups were visited in the hospital and received a set of questionnaires. Participants from the intervention group were assessed for any discontinuation symptoms. Surgery and the postoperative recovery process were performed following the local protocol. No study related measures were needed. Postoperative,

all participants of both study groups received identical sets of questionnaires by mail at 48 hours, 6 weeks, 6 months and 12 months after surgery in order to assess the effect of the duloxetine treatment on the endpoints in different follow-up stages.

Intervention

Patients randomized for the intervention group received duloxetine added to their usual care during a pre-operative period of 10 weeks. The recommended dosage for chronic musculoskeletal pain is 60 mg per day when considering maximal effectiveness and minimal side-effects [46]. Based on previous studies a 7 week treatment period with 60 mg per day was considered sufficient to establish a relevant effect on pain [47,48]. The total intervention period was 10 weeks, including one week of build-up and two weeks of tapering of the medication dose. For safety reasons regarding possible influence of duloxetine on platelet function, there was a window of 5-8 days between ending of the duloxetine treatment period and surgery.

Usual Care

Patients in the usual care group received regular preoperative care following local protocol, without imposed procedures. No restrictions were imposed on the usage of escape pain medication in either study group, with one exception, the usage of agents specifically targeted on neuropathic pain, like gabapentinoids.

Measurement instruments

The primary endpoint is the difference in hip- or knee specific postoperative pain, 6 months after surgery, assessed with the Pain Subscale of the *Knee injury and Osteoarthritis Outcome Score* (KOOS) or the *Hip disability and Osteoarthritis Outcome Score* (HOOS). The KOOS and HOOS comprise of a 0-100 scale, 0 represents extreme symptoms and 100 represents no symptoms. Missing items in the KOOS/HOOS were imputed according to the KOOS/HOOS manual [51,52].

Secondary study endpoints included:

1. the effect of treatment on general pain relief measured using a Visual Analogue Scale (VAS) (100-mm horizontal line that represents the pain from 0-100);
2. relief of neuropathic-like pain measured using the modified PainDETECT-Questionnaire (m-PDQ) (Total score -1 to 38 pointsa score of ≤12 indicates a nociceptive pain profile, a score of 13-18 a possible neuropathic pain profile, and a score ≥19 a likely neuropathic pain profile [43,53]);
3. relief of the abovementioned pain scores at different time-points up to 1 year post-operatively.

Detailed descriptions of all measurement instruments that were used can be found in the design paper, and also in supplementary file 2 [41].

Sample Size Calculation

Sample size calculation was based on the primary endpoint: change in the KOOS/HOOS pain subscale. According to literature, the pre-operative mean (SD) Pain Subscale scores for the KOOS and HOOS are 35.9 (17.2) and 32.7 (17.7) resp. and the minimally clinical important difference is 10 points [55]. To detect a difference with 80% power (significance level, two-sided, of 0.05), a total sample size of 47 participants per group was needed. A 20% rate of protocol violators/dropouts was taken into account leading to an aimed sample size of 118 participants.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0, Armonk, NY: IBM Corp.). Descriptive statistics were used to report patient characteristics, using mean and standard deviation or median and percentiles in case of continues variables, based on normality assessment by histogram. For normally distributed data, differences between treatment groups was assessed using an independent samples student T-test. For non-normally distributed data a Mann-Whitney U test was performed. For discrete data proportions and percentages were

described and differences between treatment groups were assessed using a Chi-Square test. In case of a participants' discontinuation of the study, all data obtained up to discontinuation was analysed according to the intention to treat-principle. All participants with at least one measurement after baseline were included in the study analyses. In addition, a mixed model for repeated measures was constructed to determine whether duloxetine influences the development of pain over time. A detailed description of this model can be found in supplementary file 3.

As a sub analysis, another mixed model for repeated measures was constructed comparing the influence of duloxetine on the development of pain over time for knee- and hip OA patients. Further information, as well as the results of this sub analysis can be found in supplementary file 4.

Results

Screening took place over a total number of 3402 patients of which 34.1% had a possible or likely neuropathic pain profile, indicating sensitization. Of this population, 725 patients were eligible and therefore invited to participate. See figure 1 for the flow-chart of the screening and inclusion process. Eventually, 112 patients consented to participate. These patients did not differ from non-participants in mean m-PDQ-score (p=0.999) and the ratio of hip and knee patients (p=0.184). On average, participants were older than non-participants (mean difference: 5.2 year; p<0.0001) and more often male (38% males among participants vs 28% males among non-participants; p=0.031).

Non-eligibility and disinclination to participation

The main reason for declining to participate was the time investment and practical/logistical burden that participation in the study required. Also, disinclination to taking duloxetine and having to relinquish the option of another TJA within the 1-year follow-up period were major reasons not to participate in the study.

One patient failed to pass the baseline screening due to a low sodium level. Therefore, 111 patients were included. Baseline characteristics are shown in table 1. Slightly more females (62.2%) participated and the average participant was 62.7 (SD 8.5) years old. The median duration of symptoms was 42 months (IQR 18-72). After randomization, 57 patients were placed in the intervention group and 54 in the control group. Despite randomization, there were significant differences in baseline HOOS/KOOS pain subscales (38.0 ± 14.0 vs 30.6 ± 12.7; P=0.004) and mean VAS at rest (46.6 ± 24.8 vs 58.7 ± 18.2; p=0.004). Concurrent back pain was reported by 11.9% of participants (7.3% vs 16.7% for the intervention vs control group resp., p=0.151). The incidence of other pain conditions (migraine, irritable bowel syndrome, fibromyalgia, and chronic neck pain) was below 10%, with no significant differences between the groups. Detailed information regarding loss to follow-up, protocol violations, adverse events, and missing data can be found in supplementary file 5. Complete follow-up of all post-operative time points up to 1 year after surgery was retrieved in 92 cases (82.9%).

Please insert figure 1 here

Table 1. Demographics and baseline characteristics

Characteristics	Total (111)	Intervention (57)	Control (54)	P-value
Age	62.7 (8.5)	61.5 (8.1)	64.0 (8.7)	0.114
Gender (female)	69 (62.2)	38 (66.7)	31 (57.4)	0.334
Cohabitation (n=110)	84 (76.4)	43 (76.8)	41 (75.9)	0.999
Education				0.768
Higher	44 (39.6)	23 (40.4)	21 (38.9)	
Secondary	59 (53.2)	29 (50.9)	30 (55.6)	
No or Lower	8 (7.2)	5 (8.8)	3 (5.6)	
BMI	28.9 (4.5)	28.8 (5.0)	29.0 (3.9)	0.874
Smoking	21 (18.9)	15 (26.3)	6 (11.1)	0.053
Knee	61 (54.9)	31 (54.4)	30 (55.6)	0.999
Duration of pain symptoms (months)	42.0 (18; 7)	48 (22.5; 90)	36 (16; 66.8)	0.312
Past Surgery in Index Joint	59 (53.2)	30 (52.6)	29 (53.7)	0.999
ASA score (n=110)				0.169
I	34 (30.9)	19 (33.9)	15 (27.8)	
II	67 (60.9)	31 (54.4)	37 (68.5)	
III	9 (8.2)	7 (12.5)	2 (3.7)	
KL grade				0.167
II	23 (20.7)	8 (14.0)	15 (27.8)	
III	82 (73.9)	45 (78.9)	37 (68.5)	
IV	6 (5.4)	4 (7.0)	2 (3.7)	
KOOS/HOOS (0-100)				
Pain	34.4 (13.8)	38.1 (14.0)	30.6 (12.7)	0.004
Symptoms	42.3 (16.8)	43.4 (18.7)	41.1 (14.6)	0.471
ADL	40.2 (14.9)	41.7 (15.2)	38.6 (14.6)	0.270
QOL	23.5 (13.4)	25.4 (13.8)	21.4 (12.8)	0.114
mPDQ (-1-38)	15.8 (4.6)	15.6 (4.7)	16.0 (4.6)	0.659
VAS-R (110)	52.6 (22.6)	46.6 (24.8)	58.7 (18.2)	0.004
VAS-M (111)	69.5 (16.4)	68.1 (15.6)	71.1 (17.2)	0.337

Dichotomous/categorical N(%), ChiSquare test. Continues, normally distributed mean (SD), student T test (Normality tested by histogram). Continues, not normally distributed median (Q1; Q3), Mann-Whitney U test.

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Postoperative Pain

Table 2 presents the mean scores and standard deviations of the pain outcome scores on different postoperative time points. Baseline scores and scores after 7 weeks of targeted preoperative treatment are also included in the table.

Table 2. Mean scores and standard deviations of the pain outcome scores

		Preoperative	Postoperative			
		Baseline	After 7 wks targeted Tx	6 wks after arthroplasty	6 mos after arthroplasty	12 mos after arthroplasty
KOOS/HOOS	Intervention	38 (14.0)	46.3 (17.1)	65.8 (20.3)	77.3 (24.2	82.3 (19.4)
Pain subscale	Control	30.6 (12.7)	33.6 (12.0)	65.5 (23.7)	73.7 (24.1)	79.2 (23.1)
mPDQ	Intervention	15.6 (4.7)	11.7 (5.9)	10.2 (6.9)	6.8 (7.1)	4.5 (6.4)
	Control	16.0 (4.6)	15.5 (4.8)	9.5 (7.4)	7.5 (7.0)	5.3 (6.5)
VAS-R	Intervention	46.6 (24.8)	39.8 (23.7)	18.8 (17.6)	18.4 (21.8)	10.3 (13.4)
	Control	58.7 (18.2)	57.5 (17.4)	24.1 (26.1)	17.9 (21.7)	18.1 (24.7)
VAS-M	Intervention	68.1 (15.7)	53.6 (24.0)	29.7 (22.0)	22.8 (24.7)	17.0 (21.0)
	Control	71.1 (17.2)	70.7 (13.9)	27.7 (26.6)	23.2 (24.9)	20.7 (26.3)

Mean (SD) scores of the KOOS/HOOS Pain subscale, mPDQ, and VAS at rest and during movement for the treatment groups separately. Intervention group N=57, control group n=54.
Ranges: KOOS/HOOS pain subscale 0-100; mPDQ -1 – 38; VAS-R 0-100; VAS-M 0-100. Tx=treatment, mos=months, wks=weeks

The KOOS and HOOS pain subscales showed a skewed distribution 6 months after surgery. The median scorewas 86.3 (IQR 64.6-95) in the intervention group and 80.6 (IQR 57.5 – 92.5) in the control group. Due to the significant difference in KOOS/HOOS pain subscales at baseline, the change in scores between six months postoperatively and baseline was assessed. The mean change was 37.0 (SD 28.1) in the intervention group and 43.3 (SD 26.5) in the control group. No statistically significant difference was found in change-score 6 months after TJA between both groups, p=0.280.

Based on the mixed model for repeated measures as described above, table 3 presents the estimated means and differences in pain on different time points between treatment groups, and Figure 2 shows the course of the KOOS/HOOS pain subscale over different time points for both groups.

Table 3. Estimated means (95% CI) and Estimated Difference (95% CI) based on the mixed model for repeated measures using a piece-wise design. Ranges

		Intervention (57)	Control (54)	Estm. Difference	Sign.
		Preoperative			
After 7 wks targeted Tx	KOOS/HOOS-p	44.0 (18.3-69.7)	35.7(10.1-61.4)	8.3 (1.3-15.3)	0.021
	mPDQ	12.1 (3.1-21.0)	15.1 (6.2-24.0)	3.0 (0.5-5.6)	0.018
	VAS-R	42.1 (12.1-72.1)	55.2 (25.2-85.1)	13.0 (4.8-21.2)	0.002
	VAS-M	55.5 (24.5-86.5)	68.8 (37.9-99-8)	13.3 (4.9-21.8)	0.002
		Postoperative			
6 wks after arthroplasty	KOOS/HOOS-p	63.4 (37.7-89.1)	67.6 (41.9-93.4)	4.3 (-3.0-11.5)	0.248
	mPDQ	10.7 (1.7-19.6)	9.1 (0.2-18.1)	1.5 (-1.1-4.2)	0.251
	VAS-R	21.3 (-8.7-51.4)	21.8 (-8.2-51.8)	0.5 (-8.0-8.9)	0.914
	VAS-M	31.7 (0.7-62.7)	25.9 (-5.1-56.8)	5.8 (-2.8-14.5)	0.187
6 mos after arthroplasty	KOOS/HOOS-p	74.5 (48.8-100.2)	76.0 (50.3-101.7)	1.5 (-5.8-8.8)	0.690
	mPDQ	7.2 (-1.7-16.1)	7.1 (-1.8-16.02)	0.1 (-2.5-2.6)	0.952
	VAS-R	21.4 (-8.6-51.4)	15.5 (-14.5-45.5)	5.9 (-2.6-14.4	0.173
	VAS-M	25.3 (-5.7-56.3)	21.3 (-9.7-52.2)	4.0 (-4.8-12.8)	0.370
12 mos after arthroplasty	KOOS/HOOS-p	79.8 (54.1-105.5)	81.6 (55.9-107.3)	1.8 (-5.5-9.1)	0.623
	mPDQ	4.9 (-4.0-13.9)	4.9 (-4.0-13.8)	0.1 (-2.5-2.6)	0.967
	VAS-R	12.9 (-17.1-43.0)	15.7 (-14.3-45.7)	2.8 (-5.7-11.3)	0.518
	VAS-M	19.1 (-11.9-50.2)	18.7 (-12.2-49.7)	0.4 (-8.3-9.1)	0.929

Abbreviations: KOOS/HOOS-p: KOOS/HOOS Pain subscale

Ranges: KOOS/HOOS pain subscale 0-100; mPDQ -1 – 38; VAS-R 0-100; VAS-M 0-100. Tx=treatment, mos=months, wks=weeks

Please insert figure 2 here

Chronic residual pain

When looking at proportions of patients with moderate chronic residual pain, at 6 months after surgery, 32.6% of the intervention group and 31.9% of the control group scored a KOOS/HOOS pain scale < 70 points. This percentages decreased to 27.3% and 31.3% at 12 months after surgery for the intervention group and control group resp. When looking at hip and knee patients separately, 14.3% of the hip patients and 47.1% of the knee patients had a KOOS/HOOS pain scale <70 points 6 months after arthroplasty. Twelve months after arthoplasty this was 19% for hip patients and 38% for knee patients.

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Discussion

In this study, a 7-week pre-operative targeted treatment with duloxetine in a study population of end-stage hip/knee OA patients suffering from sensitization did not show an effect on postoperative chronic residual pain after THA/TKA. Extensive literature describes the association between signs of sensitization in OA and chronic residual pain after TJA [1,2,7,16–20,22–24,29]. Forthcoming was the hypothesis that targeted treatment aimed at desensitization prior to surgery would reduce chronic residual pain. However, the present randomised clinical trial does not support this hypothesis.

Several factors could play a role in our findings. Firstly, if we were not successful in identifying the sensitized subpopulation of OA patients it is possible that the study population was not as 'enriched' as we anticipated and the treatment effect would be diluted accordingly. However, we used a screening questionnaire specifically modified for measuring sensitization in knee- and hip OA patients. Previous studies showed a sensitivity and specificity of 50% and 74% resp. for the cut-off point of >12 points (possible sensitization), whereas a cut-off point of >18 points (likely sensitization) showed substantially higher sensitivity and specificity (both 80%) [43,53]. However, it should be noted that these figures are based only on a small study considering knee OA patients and a study performed in a heterogenous group of patients with low back-pain. We deliberately chose the cut-off point for possible sensitization because in OA, it is most likely that patients will experience a mixed pain phenotype with nociceptive and neuropathic-like symptoms due to the multifactorial pathophysiology of OA pain [13]. A solely neuropathic-like pain experience in OA is less likely. Moreover, we found 34.1% of the screened OA patients had a possible or likely neuropathic pain profile, which is in line with literature and thereby increasing the likelihood that we identified the target subpopulation [14,15,21–32].

Secondly, if we were not successful at adequately desensitising patients prior to surgery this could explain the lack of effect on chronic residual pain after TJA. A statistically significant treatment effect of 8.3 points (CI 1.3-15.3) was found in the pre-operative treatment

phase. However, this difference does not seem clinically relevant compared to literature although reports regarding the clinically important differences in hip and knee OA patients specifically following conservative treatment is scarce [50,56,57]. If the effect of desensitization is too small to make a clinically relevant difference immediately following the treatment phase, this could explain the lack of effect on chronic residual pain after TJA. A detailed analysis of the treatment effect in the pre-operative study period was published earlier [58]. As more extensively described in this previous publication, effects of duloxetine found in previous literature are similar to the effect in the present study regarding knee OA, although comparison is only possible to a limited extent due to the more controlled-nature of previous studies and only knee OA study populations [33–36,38–40]. There is a lack of studies concerning hip OA patients. Moreover, due to the enriched nature of the present study, a greater effect of duloxetine could have been expected when comparing to previous studies. The applied duloxetine regiment was in accordance with the recommended treatment-dose based on previous literature although the applied treatment time can be considered relatively short compared to literature [33,34,47,48]. Future studies could investigate whether a longer pre-operative treatment duration would show more effect on chronic residual pain after TJA. As described in the subanalysis in supplementary file 4, the found effect of duloxetine treatment can be principally attributed to the knee OA group of the study population. No effect of duloxetine treatment was found in the hip OA study population. The cause of the lack of effect in the hip OA subgroup of patients can only be speculated [58]. Also, for hip OA patients, despite having screened for signs of sensitization, we found a relatively low percentage of chronic residual pain, 14.3% after 6 months and 19% after 12 months, whereas literature reports up to 23% [19,20]. Consequently, the association between sensitization in hip OA and development of chronic residual pain after THA is less prominent in the present study. The proportion of patients with chronic residual pain is relatively high in the knee OA patients after TKA, 47.1% after 6 months and 38% after 12 months, compared to up to 34% in literature [16–20,23]. This was expected due to the enriched nature of our study population. However, the numbers of the subgroups of knee and hip OA patients are low, rendering generalizability of these findings limited.

Thirdly, it is possible that the effect of duloxetine treatment diminishes after tapering of the treatment dose and that the desensitization is becoming undone in the (short) interval period between tapering and surgery. This interval period was imposed due to safety reasons (see methods section). In the previous publication focusing on the pre-operative study period, a decrease in the treatment effect could be observed after the tapering phase [58]. This could be a possible explanation for the lack of treatment effect on chronic residual pain. In a recent study by Koh et al. a 30 mg duloxetine regimen was administered 1 day prior up to 6 weeks after TKA in knee OA patients with signs of sensitization. In this study, perioperative duloxetine treatment significantly reduced pain up to 12 weeks postoperatively [38]. Maybe the timing of duloxetine treatment would be more prudent in the perioperative period. However, Koh et al. do not report any information regarding more than 12 weeks postoperatively. Future studies are needed to determine whether a different timing of pre-operative duloxetine treatment continued up to (or shortly after) TJA has a different effect on chronic residual pain compared to the present study.

Fourthly, the present study is formed around the hypothesis that treatment of sensitization in OA patients leads to less development of chronic residual pain after THA/TKA. Although signs of sensitization are a known predictor in literature for developing chronic residual pain after TJA, that does not necessarily imply that treatment of the first prevents the development of the latter. Our present findings could therefore be in line with a theory by Neogi et al [12,13]. Rather than being induced by nociceptive input from the OA pathology, sensitization should possibly be seen as a 'trait' related to a person's genetic/systemic predisposition to increased pain perception which is being unmasked once nociceptive input is supplied by structural OA pathology. Maybe sensitization in OA and chronic residual pain after TJA are both traits of an underlying proneness/vulnerability to enhanced pain experience which explains why people who develop sensitization in OA are at risk to also develop chronic residual pain, but that treatment of the first does not influence the underlying vulnerability and therefore does not lessen the development of chronic residual pain. As this is the first study known to us to investigate the direct effect of treatment of sensitization in OA on chronic residual pain, future research is needed to re-assess

the present findings and to further investigate the complex causal pathways in the development of chronic residual pain.

Strengths and limitations

This study contributes important pragmatic insights to the existing literature. There is an increasing demand for pragmatic studies in the field of OA research [59–61]. Pragmatic trials try to demonstrate whether an intervention works in the reality of daily practice rather than under highly controlled circumstances. Pragmatic dimensions of the DOA study are specified in detail in our design study [41].

There are also limitations to this study. Firstly, the substantial difference in treatment effect of duloxetine in the two different joint-groups was not anticipated and somewhat lessens the interpretability of our results for the total study group because the study population was underpowered to analyse the hip and knee OA patients separately. However, by designing a mixed model for repeated measures including joint as a fixed variable (see subanalysis in supplement 3), we were able to assess the effect of joint-group in the study population as a whole. Secondly, by comparing duloxetine treatment with usual care, we can only assess the combination of the pharmacological effect together with the accompanying placebo and nocebo effects. However, to some extent these factors would also play a role in daily application of this treatment and therefore are relevant for assessing the effectiveness of the total intervention.

Applicability

Considering applicability of duloxetine in the targeted treatment population, the percentage of AEs was high in the intervention group. 21.1% of intervention participants discontinued the study treatment due to AEs. In a previous study, the incidence and nature of the AEs in the treatment period are described in more detail [58]. Also, due to the risk of side effects a substantial proportion of patients had a disinclination to participating in the study. This, in combination with the

substantial number of contra-indications for duloxetine on medical reasons lessens the practical applicability of duloxetine in general practice of OA patients with accompanying co-morbidity.

In conclusion, based on the results of the present study, pre-operative targeted treatment with duloxetine in end-stage hip and knee OA patients with sensitization does not influence postoperative chronic residual pain after arthroplasty. Duloxetine does seem to have a treatment effect on pain in end-stage knee OA patients suffering from sensitization, but clinically relevant thresholds were not met and applicability seems limited. No treatment effect was found in end stage hip OA patients with sensitization. The percentage of patients with chronic residual pain in this sensitized study population was relatively high for knee patients (38%, 12 months after TKA), but relatively low for hip patients (19%, 12 months after THA). Future studies are necessary especially regarding the timing and duration of duloxetine treatment. Other treatment options for OA patients with sensitization as well as for chronic residual pain should be explored. Separate studies specifically addressing these issues in hip OA patients are indicated considering the apparent differences between hip- and knee OA patients found in the present study.

Figure Legends:

Figure 1. Flow chart of screening and inclusion process.

Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

Competing Interests

There are no competing interests for any authors

Author Contributions

Conception and design of the study: Wietske Rienstra, Tim Blikman, Roy Stewart, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

Acquisition, analysis and interpretation of data: Wietske Rienstra, Tim Blikman, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

Drafting and revising of the manuscript: Wietske Rienstra, Tim Blikman, Baukje Dijkstra, Roy Stewart, Wierd P. Zijlstra, Tom M. van Raaij, Anita J. ten Hagen, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

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Patient and Public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Licence Statement

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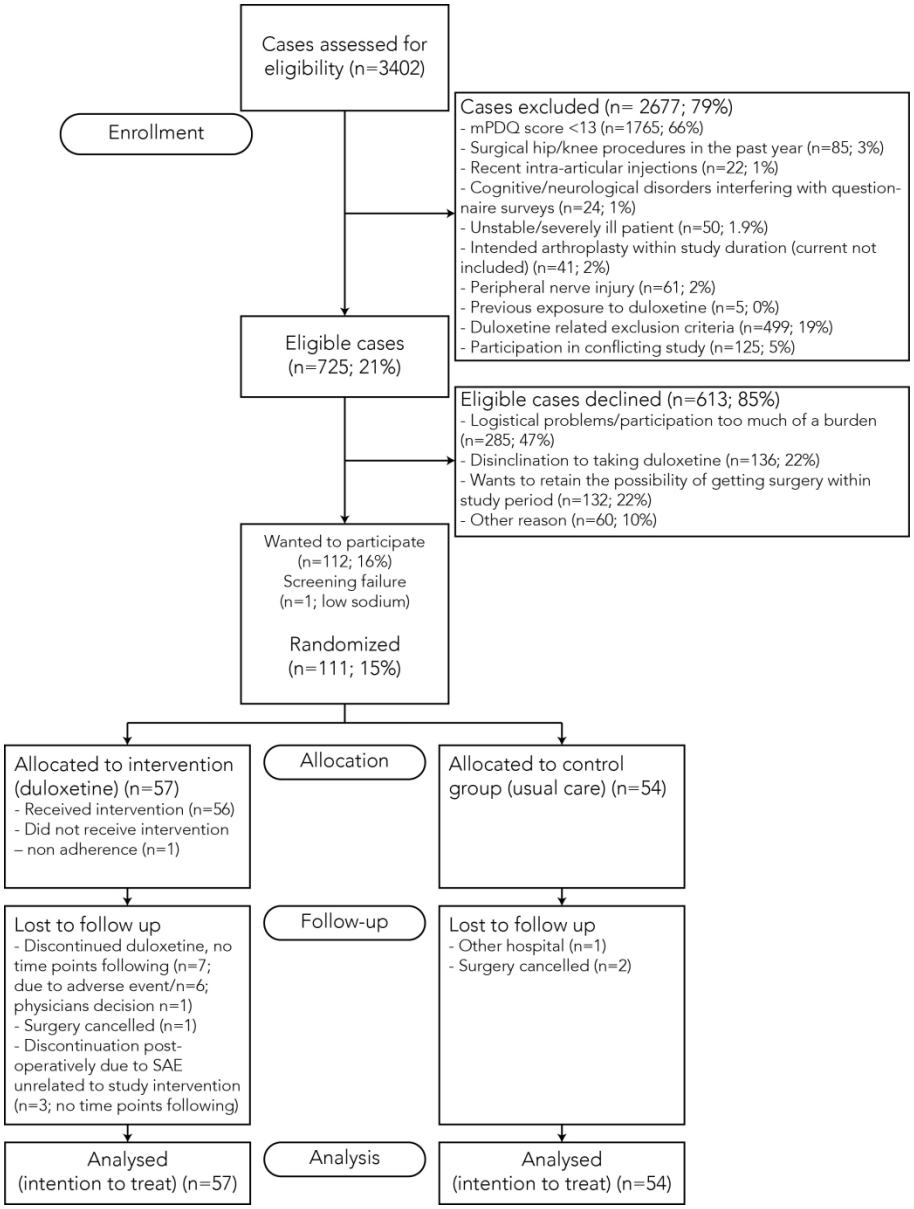

Figure 1. Flow chart of screening and inclusion process.

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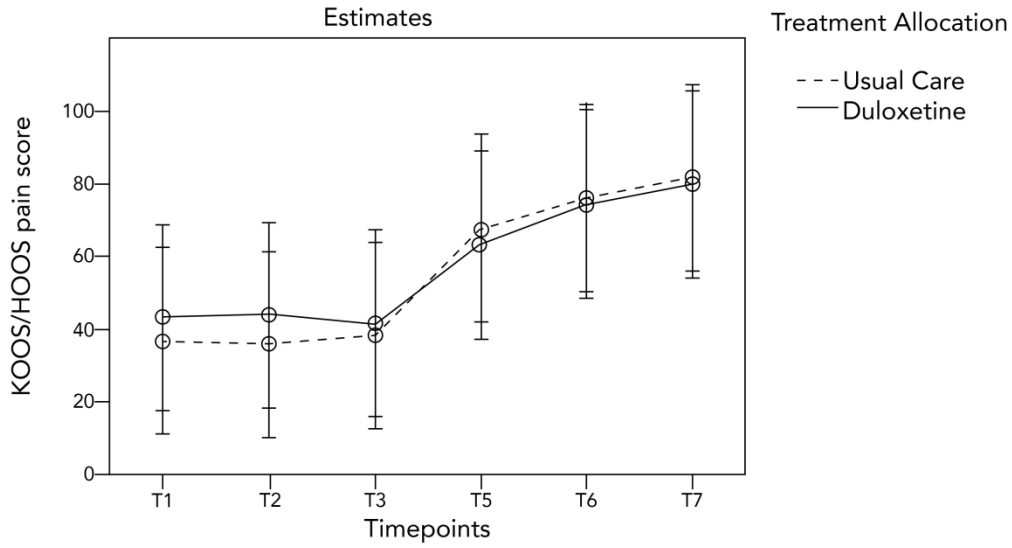

Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

250x136mm (300 x 300 DPI)

Supplementary 1/5: exclusion criteria

- surgical hip or knee joint procedures in the past year;

- intra articular hip/knee injection/arthroscopy in the past 3 months;

- cognitive or neurological disorders that could strongly interfere with questionnaire surveys;

- a history of significant peripheral nerve injury;

- serious or unstable (mental) medical conditions that could possibly interfere with study participation; -intended THA/TKA to another joint within the study period;

- previous exposure to duloxetine or a medical contra-indication for the usage of duloxetine.

Supplementary 2/5. Detailed Description of Questionnaires used

HOOS/KOOS

The KOOS and the HOOS are self-administered, disease-specific questionnaires designed to assess patients' opinion about their knee or hip symptoms and associated problems. Both scores consist of five subscales: Pain, other Symptoms, Activities of Daily Living (ADL), Sport and Recreational function, and hip/knee related Quality of Life (QOL). Answers are given on a 0-4 Likert scale. For each subscale a normalized 0-100 score is calculated. These 0-100 scores were transformed so that 0 represents extreme symptoms and 100 represents no symptoms. To our knowledge, there is no validated cut-off score on the KOOS/HOOS pain subscale indicating categories of light, moderate, or severe pain. We considered a KOOS/HOOS pain subscale score of <70 points as moderate to severe pain. The validity and reliability of the Dutch version of the KOOS and HOOS has been assessed quite extensively in previous literature 13,49,50. Missing items in the KOOS/HOOS were imputed according to the KOOS/HOOS manual 51,52.

Dutch Modified PainDETECT Questionnaire (m-PDQ)

The m-PDQ is a self-administered questionnaire consisting of 12 items on neuropathic pain symptoms in the left/right knee or hip during the past week. The first item concerns the presence of pain radiation using a body map. The second item concerns pain patterns, where patients have to choose between four figures representing distinctly described (and visually illustrated) pain patterns. Seven items concern pain quality on a 0-5 Likert scale, 0 representing 'never' and 5 representing 'very strongly'. These items concern burning sensation, tingling or prickling sensation, pain at light touch, sudden pain attacks, pain at cold or warm stimulus, numbness and pain at light pressure, respectively. The total score ranges from -1 to 38 points. Analogously to the original PainDETECT Questionnaire, a score of ≤12

indicates a nociceptive pain profile, a score of 13-18 a possible neuropathic pain profile, and a score ≥19 a likely neuropathic pain profile 43,53. m-PDQ scores >12.0 were associated with greater odds of having signs of sensitization. Correcting for age, knee OA patients with m-PDQ scores >12.0 were almost six time more likely to have signs of sensitization (on Quantitative Sensory Testing) than those with scores ≤12 43. Furthermore, Gwillym et al. found significant positive correlations between PainDETECT scores and functional-MRI activity indicating central sensitization within hip OA patients 14. The Dutch version of the m-PDQ is considered to be a reliable and valid self-report instrument in patients with hip and knee OA 44,45.

Visual Analogue Scale Pain (VAS pain)

Visual Analogue Scales (VAS) are widely used to measure pain. Patients place a marking on a 100-mm horizontal line that represents their pain. The left ending of the line represents 'no pain at all' and the right ending 'worst pain imaginable'. The distance between the marking and the left ending of the line is measured in whole millimetres and represents the pain score. Patients were asked to note their present pain status and their mean pain status over the last week; at rest (VAS-R: defined as pain in rest while sitting, standing or lying down) and during movement (VAS-M defined as pain during regular walking). VAS have been reported as valid and reliable measures for the intensity of pain 54.

Supplementary 3/5: mixed model description

In addition, a more sophisticated analysis was performed to the longitudinal data to determine whether there is a difference in the development of pain over time between both groups. A mixed model for repeated measures was constructed including, time, treatment-allocation, and baseline KOOS/HOOS pain scale. A variable was added differentiating between preoperative and postoperative time points (coded 0 or 1 for pre- and postoperative time points resp.) thereby creating a piece-wise analysis. This way the post-operative effect of duloxetine treatment could be distinguished whilst including the data from all time points. Apart from baseline KOOS/HOOS pain subscale, interaction terms between this piece-wise variable and all other separate variables were added as well as a three-way interaction term between time, treatment and the 'piece-wise' variable. A random intercept was added for individual subjects. The model was designed based on the best fit, Schwartz's Bayesian Information Criterion was 4976.818 and Akaike Corrected Information Criterion was 4968.141. Once the model was constructed for the HOOS/KOOS pain scale, it was also be applied to the other pain outcome measures (VAS-R, VAS-M, m-PDQ).

Supplementary 4/5: sub-analysis knee vs hip

As a sub analysis, another mixed model for repeated measures was constructed adding a fixed variable for joint to the abovementioned model. In this way, the difference explained by whether the hip or knee was the affected joint could be taken in consideration. In addition to the variable 'joint' interaction terms were added between the variables joint, time, the piece-wise variable, and treatment allocation. Also, a three-way interaction term between time, treatment allocation and joint were added. Considering the fit of this model, the Akaike Corrected Information Criterion improved to 4839.136, and the Bayesian Information Criterion improved to 4847.770.

Results of sub analysis:

Sub analysis mixed model for repeated measures including joint as a fixed variable.

The study group consisted of 61 knee OA patients and 50 hip OA patients. Table 4. Presents Estimated means and Difference based on the mixed model for repeated measures using a piece-wise design including joint as a fixed variable. Figure 3. shows the course of the KOOS/HOOS pain subscale for the different treatment groups based on the mixed model for repeated measures including joint groups.

Table 4. Estimated means (95% CI) and Estimated Difference (95% CI) on the mixed model for repeated measures using a piece-wise design with joint as a fixed variable.

KOOS/HOOS -p		Intervention (57)	Control (54)	Estm. Difference	Sign.
After 7 wks targeted Tx	Hip	39.9 (14.0-65.7)	38.0 (12.3-63.7)	1.8 (-8.0-11.7)	0.714
	Knee	47.2 (21.6-72.8)	33.9 (8.3-59.5)	13.3 (4.4-22.3)	0.004
6 wks after arthroplasty	Hip	70.8 (45.1-96.6)	78.0 (52.2-103.9)	7.2 (-3.0-17.4)	0.165
	Knee	56.5 (30.7-82.2)	60.0 (34.4-85.6)	3.6 (-5.8-12.9)	0.455
6 mos after arthroplasty	Hip	82.9 (57.1-108.8)	87.0 (61.2-112.9)	4.1 (-6.1-14.3)	0.432
	Knee	66.7 (40.9-92.4)	67.1 (41.5-92.8)	0.5 (-9.1-10.0)	0.924
12 mos after arthroplasty	Hip	84.6 (58.8-110.4)	88.8 (63.0-114.7)	4.2 (-6.0-14.4)	0.418
	Knee	75.5 (49.8-101.2)	75.9 (50.3-101.5)	0.4 (-9.0-9.8)	0.936

Abbreviations: KOOS/HOOS-p: KOOS/HOOS Pain subscale

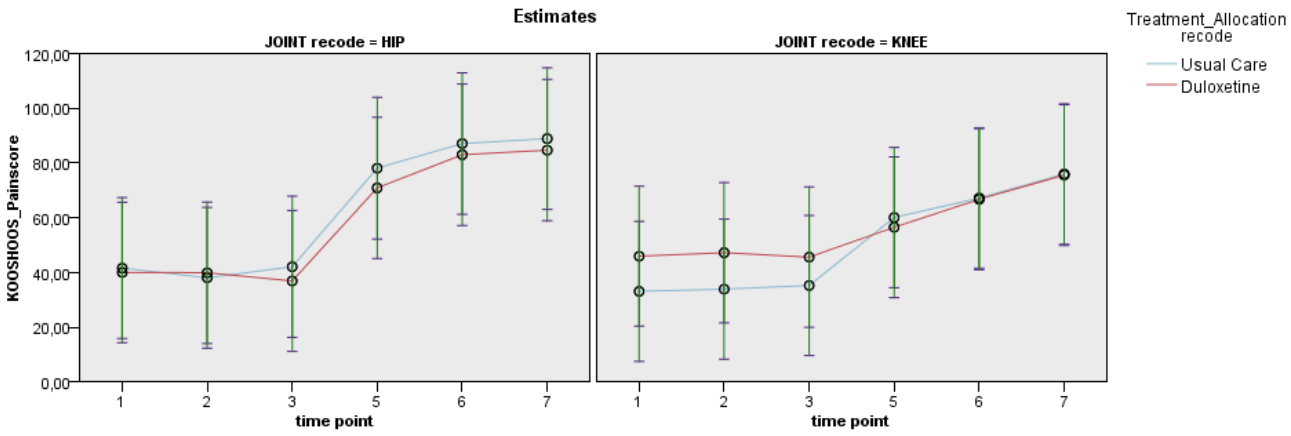

Figure 3. Course of KOOS/HOOS pain subscale per treatment group for hip- and knee patients.

Supplementary 5/5: Loss to Follow-up, Protocol violations, Adverse Events, and Missing Data

Within the intervention group, 12 patients discontinued duloxetine due to Adverse Events (AE), constituting 21.1% of the intervention group. In 6 of these cases no following time points were retrieved after discontinuation and these patients were consequently lost to follow-up. There were some other losses to follow-up, as shown in figure 1 of the manuscript, which constitute approximately 5% of participants. There were 10 registered protocol violations, 9 of which constituted of another TJA within the year of follow-up (2 in the intervention group vs 7 in the care as usual group). These patients all remained in the study up to 1-year follow-up. Three patients discontinued the study during the postoperative follow-up period due to Serious Adverse Events not related to the intervention, all three patients were included in the intervention group. Additionally, one patient suffered from postoperative infection after TKA and underwent extensive additional treatment involving surgery and antibiotic treatment. However, this patient remained in the follow-up process up to the end of the study. Another patient suffered from aseptic loosening of the tibial component after TKA. This patient also remained in the study up to the last follow-up time point. Later on, this patient received revision surgery. Both these patients were part of the intervention group. Apart from the abovementioned discontinuations, some patients did not return their questionnaires on all follow-up time points (despite a reminder by telephone and/or mail). Complete follow-up of all post-operative time points up to 1 year after surgery was retrieved in 92 cases (82.9%).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6 and 7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6 and 7 + suppl 1
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7 and 8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8 and 9 + suppl 2
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9 and 10 + suppl 3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10 and Suppl 4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10 and 11 + figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	11 and suppl 5
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	13 and 14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13 and 14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Suppl 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11 and suppl 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19 and 20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19 and 20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16 to 19
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Effect of preoperative duloxetine treatment on postoperative chronic residual pain after total hip or knee arthroplasty: A Randomised Controlled Trial

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Effect of preoperative duloxetine treatment on postoperative chronic residual pain after total hip or knee arthroplasty: A Randomised Controlled Trial

Wietske Rienstra[1,2], Tim Blikman[1,2], Baukje Dijkstra[4], Roy Stewart[3], Wierd P. Zijlstra[4,] Tom M. van Raaij[5], Anita J. ten Hagen[6], Sjoerd K. Bulstra[1], Martin Stevens[1], Inge van den Akker-Scheek[1]

[1] Department of Orthopaedics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2] Department of Rehabilitation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[3] Department of Community and Occupational Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4] Department of Orthopaedics, Medical Center Leeuwarden, Leeuwarden, The Netherlands

[5] Department of Orthopaedics, Martini Hospital Groningen, Groningen, The Netherlands

[6] Department of Anaesthesiology, Martini Hospital Groningen, Groningen, The Netherlands

Corresponding author: Inge van den Akker-Scheek, PhD; i.scheek@umcg.nl

Abstract

Objectives A key predictor for developing chronic residual pain after total knee or hip arthroplasty (TKA/THA) is sensitisation. Sensitisation can be defined as an "increased responsiveness of nociceptive neurons in the nervous system". Aim of this study is to investigate the effects of preoperative treatment with duloxetine in sensitised knee and hip osteoarthritis patients on postoperative chronic residual pain up to one year after arthroplasty.

Setting A multi-centre, pragmatic, prospective, randomised clinical trial was conducted in three secondary care hospitals in the Netherlands.

Participants Patients with primary knee/hip osteoarthritis who were planned for TKA/THA were screened using the modified painDETECT Questionnaire. Patients whose painDETECT score indicated that sensitisation may be present were eligible for participation. 111 participants were included and randomly assigned 1:1 to an intervention or control group. The intervention group received additional duloxetine treatment, the control group did not receive any additional treatment but was allowed to continue with any pain medication they were already taking.

Interventions Preoperative oral treatment for seven weeks with 60 mg/day of duloxetine was compared to usual care.

Primary and secondary outcome measures Primary outcome measure was pain at six months after arthroplasty, assessed with the Pain Subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip disability and Osteoarthritis Outcome Score (HOOS) with a 0-100 scale. Secondary outcome measures were Visual Analogue Scales, and neuropathic-like pain measured using the modified PainDETECT Questionnaire. Longitudinal data collection included timepoints directly after duloxetine treatment, one day preoperatively, and six weeks, six months and twelve months postoperatively.

Results Mean improvement in the KOOS/HOOS pain subscale at six months postoperatively was 37 (SD 28.1) in the intervention group and 43 (SD 26.5) in the control group. No statistically

significant difference was found in change score six months postoperatively between the two groups (p=0.280). 12 patients from the intervention group (21%) discontinued duloxetine due to adverse effects.

Conclusions Preoperative targeted treatment with duloxetine in end-stage knee and hip OA patients with sensitisation does not influence postoperative chronic residual pain after TKA/THA.

Trial Registration Netherlands Trial Register on 15-August-2014 (trial ID NTR4744).

Keywords: Pain Management, Sensitization, Orthopaedic Hip and Knee surgery, Clinical Pharmacology

Strengths and limitations of this study

- Broad screening of all patients who were planned for total knee or hip arthroplasty, creating a representative study population.
- Using patient-reported outcome measures relevant for clinical practice.
- Comparing to usual care, which varied among clinicians and participating centres, thereby increasing generalizability.
- Long-term follow-up focusing on clinical relevance of the efficacy of duloxetine treatment from prior to arthroplasty to postoperative outcome.
- The substantial difference in treatment effect of duloxetine between hip and knee OA patients was not anticipated and somewhat lessens the interpretability of our results for the total study group.

Introduction

Total hip and knee arthroplasties are among the most performed procedures in orthopaedic surgery for the treatment of patients with severe osteoarthritis (OA).[1,2] Projections show that the number of performed procedures will dramatically rise in the future.[3–5] In light of this, the high prevalence of residual pain after these procedures must be considered a highly relevant problem. Chronic residual pain is pain that persists after the postoperative recovery process is over. Up to 23% of patients after total hip arthroplasty (THA) and up to 34% after total hip arthroplasty (TKA) experience chronic residual pain,[6–10] which leads to declining patient satisfaction, functioning, and quality of life.[11–14]

Numerous studies have demonstrated that pain in OA is a highly complex phenomenon that seems to involve both intra-articular and extra-articular mechanisms[1,7,13–16] like modification of pain transmission in both the peripheral and the central nervous system, leading to sensitisation of the pain pathways. Several mechanisms have been described leading to sensitisation, among which modulation of the inhibitory descending control pathways of the central nervous system seems to play an important role.[7,17] Sensitisation in OA expresses itself through neuropathic-like symptoms such as allodynia, hyperalgesia, and spreading of the pain. Signs of sensitisation seem to be among the key predictors for poorer outcome after total joint arthroplasty (TJA), especially for chronic residual pain.[18–22] Up to 19% of patients with hip OA and 19-37% of patients with knee OA experience signs of sensitisation and are therefore at a higher risk of developing chronic residual pain after TJA.[7,10–14,16,23]

As sensitisation in OA is an important risk factor for developing chronic residual pain after THA/TKA, it is plausible that targeted treatment aimed at preoperative desensitisation, for example with neuromodulating medication, will reduce chronic residual pain. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, influences the descending inhibitory control pathways of the central nervous system. A recent meta-analysis shows that duloxetine has a positive effect on pain in OA patients.[24–27] A recent study shows that use of duloxetine

perioperatively (1 day before up to 6 weeks after surgery) in sensitised knee OA patients has positive effects on pain up to 12 weeks postoperatively.[27] To our knowledge, it is unknown whether this beneficial effect remains in long-term follow-up. Specifically selecting OA patients with signs of sensitisation rather than the general knee and hip OA population will enable a better assessment of the effectiveness of pre-THA/TKA desensitisation on the development of chronic residual pain. Until now, the effect of duloxetine on pain in OA patients has solely been investigated compared to placebo. It is of clinically relevant value to assess the added effect of duloxetine in OA patients compared to usual care.

Aim of this study is therefore to investigate whether preoperative treatment with duloxetine of hip and knee OA patients with signs of sensitisation reduces postoperative chronic residual pain up to one year post-TJA.

Methods

Design

This article describes the outcome of a multi-centre, pragmatic, prospective, open-label, randomised clinical trial registered in the Netherlands Trial Register on 15 August 2014 (trial ID NTR4744). Participating hospitals were University Medical Center Groningen (UMCG), Martini Hospital Groningen and Medical Center Leeuwarden. A detailed description of the study design was published earlier.[28] No important changes were made to the methods and no changes were made to trial outcomes after commencement of the trial. Authors T.B. and W.R. generated the random allocation sequence, enrolled participants, and assigned participants to interventions.

This work is supported by the Dutch Arthritis Foundation *Reumafonds* (grant number BP 12-357 3-401), www.reumafonds.nl. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The study was approved by the Medical Ethics Committee of University Medical Center Groningen (2014/087). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of our research.

Participants and screening

Patients were recruited between December 2014 and June 2018; follow-up was completed in 2019. During the study period, all patients with primary hip or knee OA planned for THA or TKA were screened using a self-report tool for neuropathic-like pain symptoms in hip and knee OA, the modified PainDETECT Questionnaire (m-PDQ). The m-PDQ is a self-administered questionnaire consisting of 12 items on neuropathic pain symptoms in the left/right knee or hip during the past week. The questions ask about presence of pain radiation; pattern of pain over time; pain quality,

including burning, tingling or prickling sensation; pain at light touch; sudden pain attacks; pain at cold or warm stimulus; numbness; and pain at light pressure. The total score ranges from -1 to 38 points. Analogously to the original PainDETECT Questionnaire, scoring ≤12 indicates a nociceptive pain profile, 13-18 a possible neuropathic pain profile, and ≥19 a likely neuropathic pain profile. Apart from nociceptive discrimination from neuropathic pain, m-PDQ scores >12.0 are associated with greater odds of having signs of sensitisation.[8,29–32] The supplementary file includes more detailed information on the m-PDQ. Patients who reported m-PDQ scores >12.0 and were eligible based on the inclusion and exclusion criteria were invited to participate.

Exclusion criteria were: surgical hip or knee joint procedures in the past year; intra-articular hip/knee injection/arthroscopy in the past 3 months; cognitive or neurological disorders that could strongly interfere with questionnaire surveys; a history of significant peripheral nerve injury; serious or unstable physical or mental medical conditions that could interfere with study participation; intended THA/TKA to another joint within the study period; previous exposure to duloxetine or a medical contraindication for usage of duloxetine. A complete list of inclusion and exclusion criteria can be found in the design paper.[28]

Patients received oral and written information plus two weeks' consideration time. Patients willing to participate were invited to visit the outpatient clinic of their orthopaedic department, where the last safety-related exclusion criteria were ruled out based on laboratory testing and physical examination. Patients who complied with the inclusion and exclusion criteria and were still willing to participate, provided written informed consent and their visit to the outpatient clinic extended into a baseline visit.

Randomisation

Randomisation took place with a 1:1 allocation ratio. The ALEA online randomisation program (ALEA, FormsVision, Abcoude, The Netherlands) localised on the secured servers of the local Trial Coordination Centre of UMCG was used. Participants were stratified by type of arthroplasty to be performed (hip or knee), with block sizes of 4 and 6.

Procedure

Demographic information, patient characteristics and medical history were collected using patient records (see Table 1), and all patients received their first set of questionnaires at baseline. The preoperative treatment period was divided into three timepoints. As the risk of side effects was highest at initiation of treatment, the dosage of duloxetine was built up from 30 mg/day in week 1 to 60 mg/day in week 2. The first timepoint, two weeks after baseline, was therefore primarily instated for safety reasons and to assess side effects. The second timepoint was eight weeks after baseline, right after the 7-week treatment period with 60 mg/day duloxetine. This timepoint aimed to measure the effect of duloxetine on pain directly after treatment. Before surgery the dosage of duloxetine was tapered for two weeks to 30 mg/day, to reduce discontinuation symptoms. For safety reasons related to possible influence of duloxetine on platelet function, there was a window of 5-8 days between ending the duloxetine treatment period and surgery. The third and last preoperative timepoint took place one day prior to surgery. Patients in the care-as-usual group were mailed identical sets of questionnaires at the same timepoints.

Surgery and the postoperative recovery process followed local protocols. No study-related measures were needed. All participants of the two study groups were mailed identical sets of questionnaires at 48 hours, 6 weeks, 6 months and 12 months postoperatively, to assess the effect of the duloxetine treatment on the endpoints at different follow-up stages. A detailed description of all measurement instruments used and the timepoints at which they were administered can be found in the design paper and in the supplementary file.[28]

Intervention

Patients randomised for the intervention group received duloxetine added to their usual care for 10 weeks preoperatively. The recommended dosage for chronic musculoskeletal pain is 60 mg/day when considering maximal effectiveness and minimal side effects.[33] Based on previous studies a 7-week treatment period with 60 mg/day was considered sufficient to establish a

relevant effect on pain.[34,35] The total intervention period was 10 weeks, including one week of build-up and two weeks of tapering off the medication dose as described above. See the supplementary file for a visual illustration of the intervention phase.

Usual Care

Patients in the usual-care group remained on the waiting list for arthroplasty. They were allowed to continue with any pain medication they were already taking as well as any other ongoing treatment (like physiotherapy). Since the use of neuropathic pain medication is not registered for OA pain in the Netherlands, none of the participants had a prescription for such medication in the preoperative stage. Usual-care patients received regular preoperative care following local protocols, without imposed procedures. No restrictions were imposed on usage of escape pain medication in either study group – with one exception, that of agents specifically targeted for neuropathic pain, like gabapentinoids perioperatively.

Measurement instruments

Primary endpoint is the mean difference between the intervention and control groups in hip- or knee-specific pain six months postoperatively, assessed with the pain subscale of the *Knee injury and Osteoarthritis Outcome Score* (KOOS) or the *Hip disability and Osteoarthritis Outcome Score* (HOOS). Both KOOS and HOOS use a 0-100 scale, where 0 represents extreme symptoms and 100 no symptoms. In literature a score <70 points on the KOOS or HOOS pain subscale is considered a moderate amount of joint-specific pain.[36,37] Missing items in the KOOS/HOOS were handled according to the KOOS/HOOS manual.[36,37]. This primary outcome measure was chosen at 6 months, as in practice this was considered the first possible timepoint to evaluate chronic residual pain after arthroplasty. Because it is known from practice that the amount of chronic residual pain is not likely to change after one year postop, we aimed to follow up to one year postop in order to be as thorough as possible.

Secondary study endpoints included:

1. the effect of treatment on change in general pain six months postoperatively, measured using a Visual Analogue Scale (VAS) (100-mm horizontal line representing pain from 0 (no pain) to 100 (worst pain imaginable));
2. amount of neuropathic-like pain measured using the modified PainDETECT-Questionnaire (m-PDQ) six months postoperatively;
3. course of the above-mentioned pain scores at different timepoints. A detailed description of all timepoints and the measurements performed during those timepoints is provided in the design paper.[28] Timepoints 1, 2 and 3 cover the preoperative intervention phase, timepoints 4, 5, 6 and 7 cover the postoperative period, ranging from 48 hours (the primary outcome measure was not assessed at this timepoint) to six weeks, six months and twelve months, respectively. See also figure 1 of the supplementary file for a visual overview of the study timepoints. As timepoints 1, 3 and 4 were appointed primarily for the evaluation of side effects, discontinuation effects, or peri-operative complications and not for the evaluation of the primary outcome measures, these timepoints were omitted from analyses in the present paper.

Sample Size Calculation

Sample size calculation was based on the primary endpoint: difference in the KOOS/HOOS pain subscale at six months after arthroplasty between the intervention and control group. According to literature, the preoperative mean (SD) pain subscale scores for the KOOS and HOOS are 35.9 (17.2) and 32.7 (17.7), respectively, and the minimally clinical important difference is 10 points.[38] To detect a difference with 80% power (0.05 two-sided significance level), a total sample size of 47 participants per group was needed (94 participants in total). To account for an estimated 20% rate of protocol violators/dropouts we aimed to include 118 participants.

Statistical Analysis and handling of data

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY). Descriptive statistics were used to report patient characteristics, using mean

and standard deviation or median and percentiles in case of continuous variables, based on normality assessment by histogram. For normally distributed data, differences between treatment groups were assessed using an independent samples student T-test. For non-normally distributed data a Mann-Whitney U-test was performed. Our planned analysis was the inferential test between difference in KOOS/HOOS pain subscale between the intervention and the control group at six months after surgery. Proportions and percentages were described for discrete data, In case of discontinued participation in the study, all data obtained up to the participant's discontinuation was analysed according to the intention-to-treat principle. All participants with at least one measurement after baseline were included in the study analyses. The data was not imputed. We decided to use a Full Information Maximum Likelyhood technique using multilevel mixed model analysis for repeated measures. Multilevel models have the ability to handle models by using all available data, which is an advance over traditional repeated-measures analysis, where the usual treatment is to remove the entire patient if one of the outcomes is missing. With the multilevel model, we use as estimated strategy Full information maximum likelihood, where we get parameter estimates even in the presence of missing data. Missing items in the primary outcome scores, the pain subscales of the KOOS/HOOS questionnaires, were handled according to the KOOS/HOOS manual.[36,37]

A multilevel mixed model analysis for repeated measures was performed on the longitudinal data to determine whether there is a difference in the modification of pain over time between the two groups. A mixed model was constructed that included time, treatment allocation and baseline KOOS/HOOS pain subscale (in order to correct for the differences between groups at baseline). A variable was added differentiating between preoperative and postoperative timepoints (coded 0 or 1, respectively), thereby creating a piece-wise analysis. This way the postoperative effect of duloxetine treatment could be distinguished while including the data from all timepoints. Apart from the baseline KOOS/HOOS pain subscale, interaction terms between this piece-wise variable and all other separate variables were added, as well as a three-way interaction term between time, treatment and the piece-wise variable. A random intercept was added for

individual subjects. The model was designed based on the best fit, Schwartz's Bayesian Information Criterion was 4976.818, and Akaike Corrected Information Criterion was 4968.141. Once the model was constructed for the HOOS/KOOS pain subscale, it was also applied to the other pain outcome measures (VAS-R, VAS-M, m-PDQ).

As a sub-analysis, another mixed model for repeated measures was constructed comparing the influence of duloxetine on the development of pain over time for knee and hip OA patients. In this model a fixed variable for joint was added to the above-mentioned model. This way, the difference explained by whether the hip or the knee was the affected joint could be taken into consideration. Further information, as well as the results of this sub-analysis, can be found in the supplementary file.

Results

Screening took place over a total number of 3402 patients, 34.1% of whom had a possible or likely neuropathic pain profile, indicating sensitisation. Of this population, 725 patients were eligible and therefore invited to participate (see Figure 1 for the flowchart of the screening and inclusion process). The 112 patients who consented to participate did not differ from non-participants in mean m-PDQ-score (p=0.999) or hip-versus-knee ratio (p=0.184). On average, participants were older than non-participants (mean difference: 5.2 years; p<0.0001) and more often male (38% males among participants vs 28% males among non-participants; p=0.031).

Non-eligibility and disinclination to participate

The main reason for declining to participate was the time investment and practical/logistical burden that participation in the study required. Also, disinclination to take duloxetine and having to relinquish the option of another TJA within the one-year follow-up period were major reasons not to participate in the study.

One patient failed to pass the baseline screening due to a low sodium level, so ultimately 111 patients were included. Baseline characteristics are shown in Table 1. Slightly more females

(62.2%) participated and the average participant was 62.7 (SD 8.5) years old. Median duration of symptoms was 42 months (IQR 18-72). After randomisation, 57 patients were placed in the intervention group and 54 in the control group. Despite randomisation, there were significant differences in baseline HOOS/KOOS pain subscales (38.0±14.0 in the duloxetine group vs 30.6±12.7 in the control group; P=0.004) and mean VAS at rest (46.6±24.8 in the duloxetine group vs 58.7±18.2 in the control group; p=0.004). Concurrent back pain was reported by 11.9% of participants (7.3% vs 16.7% for the intervention vs control group, respectively; p=0.151). The incidence of other pain conditions (migraine, irritable bowel syndrome, fibromyalgia, chronic neck pain) was below 10%, with no significant differences between the groups.

Please insert figure 1 here

Table 1. Demographics and baseline characteristics

Characteristics	Total (111)	Duloxetine (57)	Care as usual (54)	P-value
Age	62.7 (8.5)	61.5 (8.1)	64.0 (8.7)	0.114
Gender (female)	69 (62.2)	38 (66.7)	31 (57.4)	0.334
Cohabitation (n=110)	84 (76.4)	43 (76.8)	41 (75.9)	0.999
Education				0.768
Higher	44 (39.6)	23 (40.4)	21 (38.9)	
Secondary	59 (53.2)	29 (50.9)	30 (55.6)	
None or Lower	8 (7.2)	5 (8.8)	3 (5.6)	
BMI	28.9 (4.5)	28.8 (5.0)	29.0 (3.9)	0.874
Smoking	21 (18.9)	15 (26.3)	6 (11.1)	0.053
Knee	61 (54.9)	31 (54.4)	30 (55.6)	0.999
Duration of pain (months)	42.0 (18; 7)	48 (22.5; 90)	36 (16; 66.8)	0.312
Past surgery in index joint	59 (53.2)	30 (52.6)	29 (53.7)	0.999
ASA score (n=110)				0.169
I	34 (30.9)	19 (33.9)	15 (27.8)	
II	67 (60.9)	31 (54.4)	37 (68.5)	
III	9 (8.2)	7 (12.5)	2 (3.7)	
KL grade				0.167
II	23 (20.7)	8 (14.0)	15 (27.8)	
III	82 (73.9)	45 (78.9)	37 (68.5)	
IV	6 (5.4)	4 (7.0)	2 (3.7)	
KOOS/HOOS (0-100)				
Pain	34.4 (13.8)	38.1 (14.0)	30.6 (12.7)	0.004
Symptoms	42.3 (16.8)	43.4 (18.7)	41.1 (14.6)	0.471
ADL	40.2 (14.9)	41.7 (15.2)	38.6 (14.6)	0.270
QOL	23.5 (13.4)	25.4 (13.8)	21.4 (12.8)	0.114
mPDQ (-1-38)	15.8 (4.6)	15.6 (4.7)	16.0 (4.6)	0.659
VAS-R (110)	52.6 (22.6)	46.6 (24.8)	58.7 (18.2)	0.004
VAS-M (111)	69.5 (16.4)	68.1 (15.6)	71.1 (17.2)	0.337

Dichotomous/categorical N(%), Chi-square test. Continuous, normally distributed mean (SD), Student T-test (normality tested by histogram). Continuous, not normally distributed median (Q1; Q3), Mann-Whitney U-test. BMI= body mass index; ASA score= American Society of Anesthesiologists score; KL grade= Kelgren and Lawrence grade; KOOS/HOOS= Knee injury and Osteoarthritis Outcome Score (KOOS) / *Hip disability and Osteoarthritis Outcome Score* (HOOS)*; ADL= activities of daily living; QOL= quality of life; mPDQ= modified painDETECT Questionnaire; VAS-R= Visual Analogue Scale for pain in Rest; VAS-M= Visual Analogue Scale for pain during Movement*

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Postoperative Pain

Figure 2 presents visual report of the course of the KOOS/HOOS pain subscale over different timepoints for both groups. The KOOS and HOOS pain subscales showed a skewed distribution six months postoperatively. Median score was 86.3 (IQR 64.6-95) in the intervention group and 80.6 (IQR 57.5 – 92.5) in the control group. Due to the significant difference in KOOS/HOOS pain subscales and VAS pain scales at baseline, the mean change in scores between six months postoperatively and baseline was assessed for these measurement outcomes. The mean change in KOOS/HOOS pain subscales was 37.0 (SD 28.1) in the intervention group and 43.3 (SD 26.5) in the control group. At p=0.280, no statistically significant difference was found in change score six months post-TJA between the groups (non-parametrically tested).

Please insert figure 2 here

Based on the multilevel mixed model for repeated measures as described above, Table 2 presents the estimated means and differences in pain at different timepoints between treatment groups.

Table 2. Estimated means (95% CI) and estimated difference (95% CI) based on the mixed model for repeated measures using a piece-wise design.

		Intervention (57)	Control (54)	Difference	Significance
Preoperatively					
After 7 weeks targeted treatment	KOOS/HOOS-p	44.0 (18.3-69.7)	35.7(10.1-61.4)	8.3 (1.3-15.3)	0.021
	mPDQ	12.1 (3.1-21.0)	15.1 (6.2-24.0)	3.0 (0.5-5.6)	0.018
	VAS-R	42.1 (12.1-72.1)	55.2 (25.2-85.1)	13.0 (4.8-21.2)	0.002
	VAS-M	55.5 (24.5-86.5)	68.8 (37.9-99-8)	13.3 (4.9-21.8)	0.002
Postoperatively					
6 weeks post-arthroplasty	KOOS/HOOS-p	63.4 (37.7-89.1)	67.6 (41.9-93.4)	4.3 (-3.0-11.5)	0.248
	mPDQ	10.7 (1.7-19.6)	9.1 (0.2-18.1)	1.5 (-1.1-4.2)	0.251
	VAS-R	21.3 (-8.7-51.4)	21.8 (-8.2-51.8)	0.5 (-8.0-8.9)	0.914
	VAS-M	31.7 (0.7-62.7)	25.9 (-5.1-56.8)	5.8 (-2.8-14.5)	0.187
6 months post-arthroplasty	**KOOS/HOOS-p**	**74.5 (48.8-100.2)**	**76.0 (50.3-101.7)**	**1.5 (-5.8-8.8)**	**0.690**
	mPDQ	**7.2 (-1.7-16.1)**	**7.1 (-1.8-16.02)**	**0.1 (-2.5-2.6)**	**0.952**
	VAS-R	**21.4 (-8.6-51.4)**	**15.5 (-14.5-45.5)**	**5.9 (-2.6-14.4**	**0.173**
	VAS-M	**25.3 (-5.7-56.3)**	**21.3 (-9.7-52.2)**	**4.0 (-4.8-12.8)**	**0.370**
12 months post-	KOOS/HOOS-p	79.8 (54.1-105.5)	81.6 (55.9-107.3)	1.8 (-5.5-9.1)	0.623

arthroplasty	mPDQ	4.9 (-4.0-13.9)	4.9 (-4.0-13.8)	0.1 (-2.5-2.6)	0.967
	VAS-R	12.9 (-17.1-43.0)	15.7 (-14.3-45.7)	2.8 (-5.7-11.3)	0.518
	VAS-M	19.1 (-11.9-50.2)	18.7 (-12.2-49.7)	0.4 (-8.3-9.1)	0.929

Abbreviations: KOOS/HOOS-p: KOOS/HOOS Pain subscale.
Ranges: KOOS/HOOS pain subscale 0-100; mPDQ -1–38; VAS-R 0-100; VAS-M 0-100.
Bold = primary endpoint, 6 months post-arthroplasty.

Results of sub-analysis:

The study group consisted of 61 knee OA patients and 50 hip OA patients. The table in the upplementary file presents the estimated means and difference based on the mixed model for repeated measures using a piece-wise design including joint as a fixed variable. A significant effect was seen in knee OA patients after 7 weeks of targeted treatment with duloxetine compared to usual care, with an estimated mean KOOS pain subscale score of 47.2 (95% CI 21.6-72.8) for duloxetine and 33.9 (95% CI 8.3-59.5) for usual care (estimated difference 13.3, 95% CI 4.4-22.3; p=0.004). As seen in the table in the supplementary file, the duloxetine treatment does not show a similar effect in hip OA patients, with an estimated mean HOOS pain subscale score of 39.9 (95% CI 14.0-65.7) for duloxetine and 38.0 (95% CI 12.3-63.7) for usual care (estimated difference 1.8, 95% CI -8.0-11.7; p=0.714). For both subgroups there was no significant effect of duloxetine treatment on any of the postoperative timepoints (estimated differences of 4.1 (95% CI -6.1-14.3 p=0.432 for hip OA patients and estimated differences of 0.5 (95% CI -9.1-10.0 p=0.924 for knee OA patients at six months postoperatively. Supplementary Figure 3 shows the course of the KOOS/HOOS pain subscale for the different treatment groups based on the mixed model for repeated measures including joint groups.

Chronic residual pain

At six months postoperatively, 32.6% of the intervention group and 31.9% of the control group scored a KOOS/HOOS pain subscale <70 points, representing moderate chronic residual pain. These percentages decreased to 27.3% and 31.3% at 12 months postoperatively for the intervention and control groups, respectively. When looking at hip and knee patients separately,

14.3% of hip patients and 47.1% of knee patients had a KOOS/HOOS pain subscale <70 six months post-arthroplasty. Twelve months post-arthroplasty this was 19% for hip patients and 38% for knee patients.

Loss to follow-up, Protocol violations, Adverse effects, and Missing data

Within the intervention group, 12 patients (21.1%) discontinued duloxetine due to adverse effects (AEs). No subsequent timepoints were retrieved after these patients' discontinuation, so they were lost to follow-up. Other losses to follow-up constituted approximately 5% of participants (see Figure 1). There were 10 registered protocol violations, nine from another TJA within the follow-up year (two in the intervention group vs seven in the usual-care group). These patients all remained in the study up to one-year follow-up. Three patients from the intervention group discontinued participation during the follow-up period due to serious AEs not related to the intervention. One patient (intervention group) developed post-TKA infection and underwent extensive additional treatment involving surgery and antibiotics. This patient did remain in the follow-up process up to the end of the study. Another patient (intervention group) suffered from post-TKA aseptic loosening of the tibial component, also remained in the study up to the last follow-up timepoint, and later on underwent revision surgery. Apart from these discontinuations, some patients did not return their questionnaires for any of the follow-up timepoints despite phone and/or mail reminders. Complete follow-up of all postoperative timepoints up to 1 year postoperatively was retrieved in 92 cases (82.9%).

Discussion

In this study, a 7-week preoperative targeted treatment with duloxetine in a study population of end-stage hip/knee OA patients suffering from sensitisation did not show an effect on postoperative chronic residual pain after THA/TKA. Extensive literature describes the association between signs of sensitisation in OA and chronic residual pain after TJA.[1,6,10,13,14,16,18,20,21] Forthcoming was the hypothesis that targeted treatment aimed at desensitisation prior to surgery would reduce chronic residual pain postoperatively. However, the present randomised clinical trial does not support this hypothesis.

Several factors could be playing a role in our findings. First, if we weren't successful in identifying the sensitised subpopulation of OA patients, the study population may not have been as sensitised as we anticipated and the treatment effect would be diluted accordingly. However, we used a screening questionnaire specifically modified to measure sensitisation in knee and hip OA patients. Previous studies showed sensitivity and specificity of 50% and 74%, respectively, for the >12-point cut-off (possible sensitisation), whereas a >18-point cut-off (likely sensitisation) showed substantially higher sensitivity and specificity (both 80%).[8,32] It should be noted, however, that these figures are based only on a small study involving knee OA patients and a study performed on a heterogenous group of patients with low-back pain.[8,32]. We deliberately chose the cut-off point for possible sensitisation, because OA patients are more likely to experience a mixed-pain phenotype with nociceptive and neuropathic-like symptoms due to the multifactorial pathophysiology of OA pain.[1] A solely neuropathic-like pain experience in OA is less likely. Moreover, in line with literature we found that 34.1% of screened OA patients had a possible or likely neuropathic pain profile, thereby increasing the likelihood that we identified the target subpopulation.[7,10–12,16,23,39]

Second, if we weren't successful in adequately desensitising patients prior to surgery this could explain the lack of effect on chronic residual pain after TJA. A statistically significant treatment effect of 8.3 points (CI 1.3-15.3) was found in the preoperative treatment phase, yet this

difference does not seem clinically relevant compared to reported minimally important changes (MIC) of 10 points in literature.[40–42] It should be noted that these MIC values are mostly reported after operative treatments and therefore cannot automatically be extrapolated to relevant changes following conservative treatment. If the effect of desensitisation is too small to make a clinically relevant difference immediately following the treatment phase, this could explain the lack of effect on chronic residual pain after TJA. A detailed analysis of the treatment effect in the preoperative study period was published earlier,[43] describing more extensively how effects of duloxetine found in previous literature are similar to the effect in the present study for knee OA. Still, comparison is only possible to a limited extent due to the more controlled nature of previous studies and investigating only knee OA populations.[24–27] There is a lack of studies on hip OA patients. Thanks to the enriched nature of the present study a greater effect of duloxetine could have been expected when comparing to previous studies. The administered duloxetine regimen was in accordance with the recommended treatment dose based on previous literature, although the treatment duration can be considered relatively short compared to literature.[24,25,34,35] Future studies could investigate whether a longer preoperative treatment duration would show more effect on chronic residual pain post-TJA. As described in the sub-analysis in the supplementary file, the found effect of duloxetine treatment can be principally attributed to the knee OA group of the study population. No effect of duloxetine treatment was found in the hip OA study population. The cause of the lack of effect in the hip OA subgroup of patients can only be speculated on.[43] Also, for hip OA patients, despite having screened for signs of sensitisation, we found a relatively low percentage of chronic residual pain – 14.3% after 6 months and 19% after 12 months – whereas literature reports up to 23%.[21,22] Consequently, the association between sensitisation in hip OA and development of chronic residual pain after THA is less prominent in the present study. The proportion of patients with chronic residual pain is relatively high in knee OA patients after TKA, 47.1% after 6 months and 38% after 12 months, compared to up to 34% in literature.[10,18,20,21] This was expected due to the enriched nature of our study population. And yet the numbers of the

subgroups of knee and hip OA patients are low, rendering generalisability of these findings limited.

Third, it is possible that the effect of duloxetine treatment diminishes after tapering of the treatment dose and that the desensitisation is becoming undone in the (short) interval period between tapering and surgery. This interval period was imposed for safety reasons (see Methods section). In the previous publication focusing on the preoperative study period, a decrease in treatment effect could be observed after the tapering phase.[43] This could explain the lack of treatment effect on chronic residual pain. In a recent study a 30mg duloxetine regimen was administered one day before up to six weeks after TKA to knee OA patients with signs of sensitisation; the perioperative duloxetine treatment significantly reduced pain up to 12 weeks postoperatively.[27] Maybe the treatment timing should have been more suitability and safety of the perioperative period, but no information is reported beyond 12 weeks postoperatively. Studies are needed to determine whether a different timing of preoperative duloxetine treatment continuing up to (or shortly after) TJA has a different effect on chronic residual pain compared to the present study.

Fourth, this study centres around the hypothesis that treatment of sensitisation in OA patients curbs development of chronic residual pain after THA/TKA. Although in literature signs of sensitisation are a known predictor for developing chronic residual pain post-TJA, that does not necessarily imply that treatment of the first prevents development of the latter. Our present findings could therefore be in line with a theory by Neogi et al.:[1,14] rather than being induced by nociceptive input from the OA pathology, sensitisation should be seen as a trait related to a person's genetic/systemic predisposition to increased pain perception, which is unmasked once nociceptive input is supplied by structural OA pathology. Maybe sensitisation in OA and chronic residual pain post-TJA are both traits of an underlying proneness/vulnerability to enhanced pain experience, which explains why people who develop sensitisation in OA are also at risk of developing chronic residual pain, but treatment of the first does not influence the underlying

vulnerability and therefore does not lessen the development of chronic residual pain. As to our knowledge this is the first study to investigate the direct effect of treatment of sensitisation in OA on chronic residual pain, additional research is needed to reassess the present findings and to further investigate the complex causal pathways in the development of chronic residual pain.

Strengths and limitations

This study contributes important pragmatic insights to the existing literature. There is an increasing demand for pragmatic studies in the field of OA research.[44–46] Pragmatic trials attempt to demonstrate whether an intervention works in the reality of daily practice rather than under highly controlled conditions. Pragmatic dimensions of the DOA study are specified in detail in our design study.

There are also limitations to this study. First, the substantial difference in treatment effect of duloxetine in the two different joint groups was not anticipated and somewhat lessens the interpretability of our results for the total study group, as the study population was underpowered to analyse hip and knee OA patients separately. However, by designing a mixed model for repeated measures including joint as a fixed variable (see sub-analysis in supplementary file) we were able to assess the effect of joint group in the study population as a whole. Second, by comparing duloxetine treatment with usual care we can only assess the combination of the pharmacological effect together with the accompanying placebo and nocebo effects. However, to some extent these factors would also play a role in daily administration of this treatment and are therefore relevant for assessing the effectiveness of the total intervention. Due to lack of blinding and the high percentage of AEs in the duloxetine treatment group, there is a possibility of a nocebo effect, especially during and shortly after the intervention period. Still, due to the extensive time period between the actual study intervention and the surgery that took place in-between, this effect is not very likely to have influenced the primary endpoint of this study at six months post-arthroplasty.

Suitability and safety

Regarding suitability and safety of duloxetine in the targeted treatment population, the percentage of AEs was high in the intervention group, with 21.1% of intervention participants discontinuing the study treatment due to AEs. The incidence and nature of the AEs in the treatment period are described in more detail elsewhere.[43] Also, due to the risk of side effects a substantial proportion of patients was disinclined to participate in the study. This, in combination with the substantial number of contraindications for duloxetine for medical reasons, lessens the practical applicability of duloxetine in general practice for OA patients with accompanying comorbidity.

In conclusion, based on the results of the present study, preoperative targeted treatment with duloxetine in end-stage hip and knee OA patients with sensitisation does not influence postoperative chronic residual pain after arthroplasty. Duloxetine does seem to have a treatment effect on pain in end-stage knee OA patients suffering from sensitisation, but clinically relevant thresholds were not met and applicability seems limited. No treatment effect was found in end-stage hip OA patients with sensitisation. The percentage of patients with chronic residual pain in this sensitised study population was relatively high for knee patients (38%, 12 months post-TKA) but relatively low for hip patients (19%, 12 months post-THA). Additional studies are needed, especially regarding timing and duration of duloxetine treatment. Other treatment options for OA patients with sensitisation as well as for chronic residual pain should be explored. Dedicated studies specifically addressing these issues in hip OA patients are indicated, considering the apparent differences between hip and knee OA patients found in the present study.

Figure Legends:

Figure 1. Flowchart of screening and inclusion process.

Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

Competing Interests

There are no competing interests for any of the authors.

Author Contributions

Conception and design of the study: Wietske Rienstra, Tim Blikman, Roy Stewart, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

Acquisition, analysis and interpretation of data: Wietske Rienstra, Tim Blikman, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

Drafting and revision of the manuscript: Wietske Rienstra, Tim Blikman, Baukje Dijkstra, Roy Stewart, Wierd P. Zijlstra, Tom M. van Raaij, Anita J. ten Hagen, Sjoerd K. Bulstra, Inge van den Akker-Scheek, Martin Stevens.

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Data Sharing

Data are available upon reasonable request.

Licence Statement

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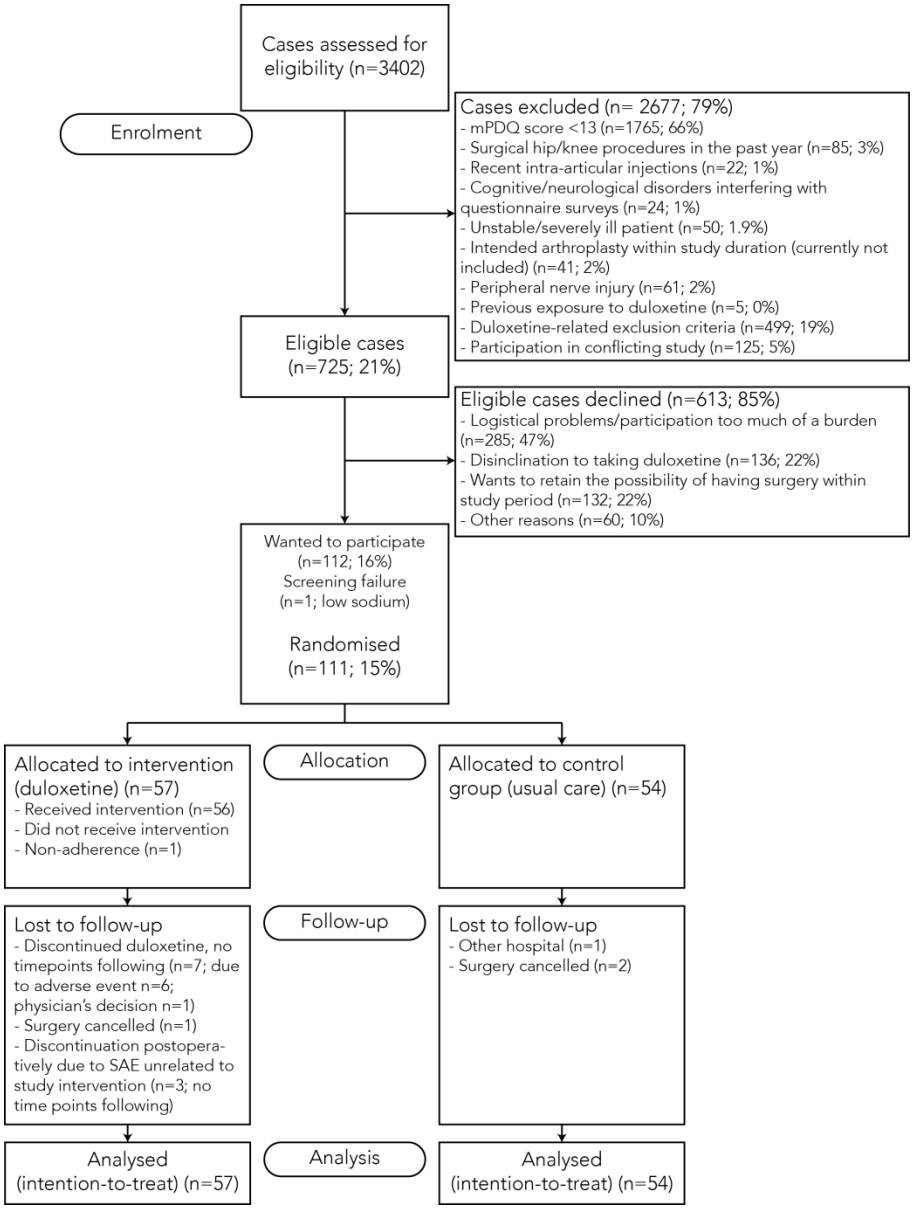

Figure 1. Flowchart of screening and inclusion process.

489x647mm (118 x 118 DPI)

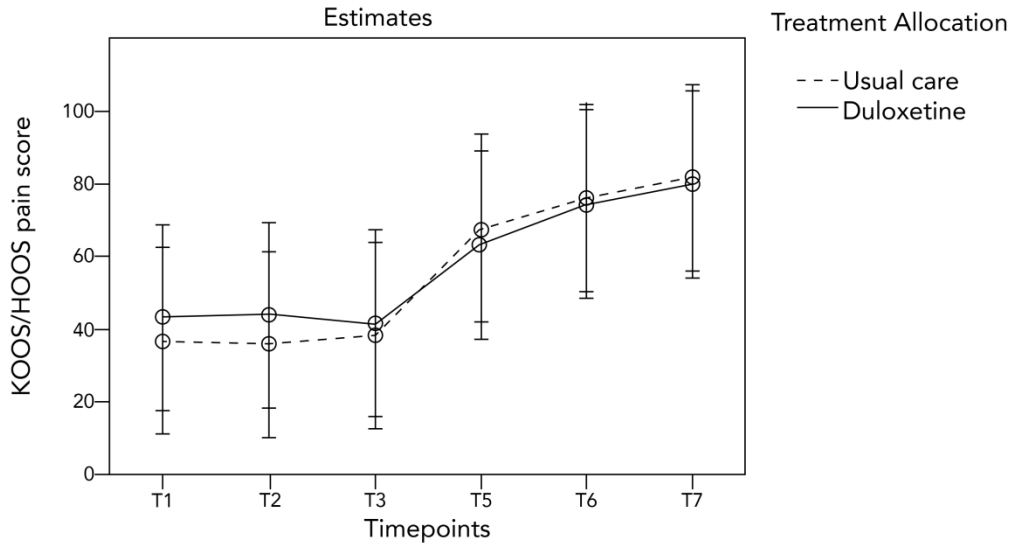

Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

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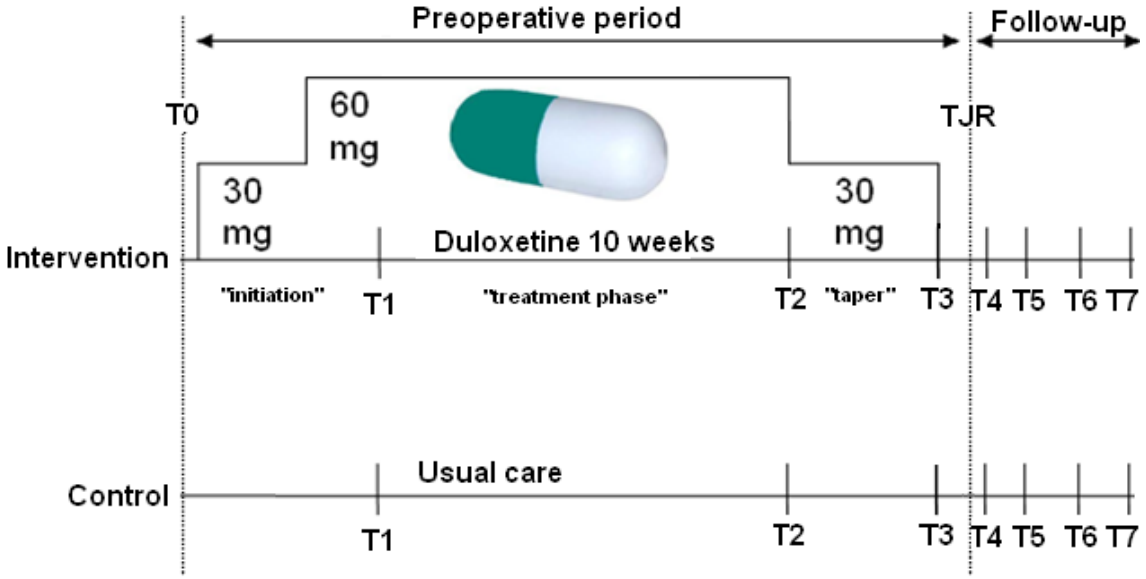
Supplementary 1/3: Scheme of the DOA trial



Supplementary 2/3. Detailed description of questionnaires used

HOOS/KOOS

The KOOS and the HOOS are self-administered, disease-specific questionnaires designed to assess patients' opinion about their knee or hip symptoms and associated problems. Both scores consist of five subscales: pain, other symptoms, activities of daily living (ADL), sport and recreational function, and hip/knee related quality of life (QOL). Answers are given on a 0-4 Likert scale. For each subscale a normalised 0-100 score is calculated. These 0-100 scores were transformed so that 0 represents extreme symptoms and 100 represents no symptoms. To our knowledge, there is no validated cut-off score on the KOOS/HOOS pain subscale indicating categories of light, moderate or severe pain. We considered a KOOS/HOOS pain subscale score <70 points as moderate to severe pain. The validity and reliability of the Dutch version of the KOOS and HOOS have been assessed quite extensively in previous literature.[13,49,50] Missing items in the KOOS/HOOS were imputed according to the KOOS/HOOS manual.[51,52]

Dutch Modified PainDETECT Questionnaire (m-PDQ)

The m-PDQ is a self-administered questionnaire consisting of 12 items on neuropathic pain symptoms in the left/right knee or hip during the past week. The first item concerns the presence of pain radiation using a body map. The second item concerns pain patterns, where patients have to choose between four figures representing distinctly described (and visually illustrated) pain patterns. Seven items concern pain quality on a 0-5 Likert scale, 0 representing 'never' and 5 representing 'very strongly': burning sensation, tingling or prickling sensation, pain at light touch, sudden pain attacks, pain at cold or warm stimulus, numbness, and pain at light pressure. The total score ranges from -1 to 38 points. Analogously to the original PainDETECT Questionnaire, a score ≤12 indicates a nociceptive pain profile, 13-18 a

possible neuropathic pain profile, and ≥19 a likely neuropathic pain profile.[43,53] m-PDQ scores >12.0 were associated with greater odds of having signs of sensitisation. Correcting for age, knee OA patients with m-PDQ scores >12.0 were almost six times more likely to have signs of sensitisation (on Quantitative Sensory Testing) than those with scores ≤12.[43] Gwilym et al. found significant positive correlations between PainDETECT scores and functional MRI activity, indicating central sensitisation among hip OA patients.[14] The Dutch version of the m-PDQ is considered to be a reliable and valid self-report instrument in patients with hip and knee OA.[44,45]

Visual Analogue Scale Pain (VAS pain)

Visual Analogue Scales (VAS) are widely used to measure pain. Patients place a marking on a 100-mm horizontal line that represents their pain. The left ending of the line represents 'no pain at all' and the right ending 'worst pain imaginable'. The distance between the marking and the left ending of the line is measured in whole millimetres and represents the pain score. Patients were asked to note their present pain status and their mean pain status over the last week, at rest (VAS-R: defined as pain at rest while sitting, standing or lying down) and during movement (VAS-M defined as pain during regular walking). VAS have been reported as valid and reliable measures for pain intensity.[54]

Supplementary 3/3: Sub-analysis of knee vs hip patients

As a sub-analysis, another mixed model for repeated measures was constructed adding a fixed variable for joint to the above-mentioned model. In this way, the difference explained by whether the hip or knee was the affected joint could be taken in consideration. In addition to the variable 'joint' interaction, terms were added between the joint, time, piece-wise and treatment allocation variables. Also, a three-way interaction term between time, treatment allocation and joint were added. Considering the fit of this model, the Akaike Corrected Information Criterion improved to 4839.136, and the Bayesian Information Criterion improved to 4847.770.

Results of sub-analysis:

Sub-analysis mixed model for repeated measures including joint as a fixed variable.

The study group consisted of 61 knee OA patients and 50 hip OA patients. Table 4 presents estimated means and differences based on the mixed model for repeated measures using a piece-wise design that includes joint as a fixed variable. Figure 3 shows the course of the KOOS/HOOS pain subscale for the different treatment groups based on the mixed model for repeated measures, including joint groups.

Table 3. Estimated means (95% CI) and Estimated difference (95% CI) on the mixed model for repeated measures using a piece-wise design with joint as a fixed variable.

KOOS/HOOS pain subscale		Intervention (57)	Control (54)	Difference	Significance
After 7 weeks targeted	Hip	39.9 (14.0-65.7)	38.0 (12.3-63.7)	1.8 (-8.0-11.7)	0.714
treatment	Knee	47.2 (21.6-72.8)	33.9 (8.3-59.5)	13.3 (4.4-22.3)	0.004
6 weeks post-arthroplasty	Hip	70.8 (45.1-96.6)	78.0 (52.2-103.9)	7.2 (-3.0-17.4)	0.165
	Knee	56.5 (30.7-82.2)	60.0 (34.4-85.6)	3.6 (-5.8-12.9)	0.455
6 months post-arthroplasty	Hip	82.9 (57.1-108.8)	87.0 (61.2-112.9)	4.1 (-6.1-14.3)	0.432
	Knee	66.7 (40.9-92.4)	67.1 (41.5-92.8)	0.5 (-9.1-10.0)	0.924
12 months post-arthroplasty	Hip	84.6 (58.8-110.4)	88.8 (63.0-114.7)	4.2 (-6.0-14.4)	0.418
	Knee	75.5 (49.8-101.2)	75.9 (50.3-101.5)	0.4 (-9.0-9.8)	0.936

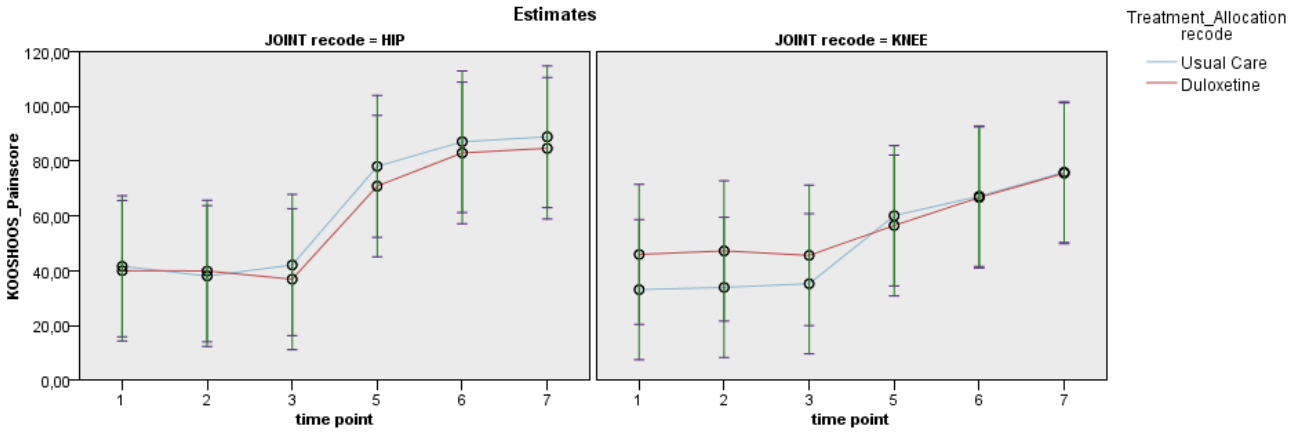


Figure 3. Course of KOOS/HOOS pain subscale per treatment group for hip and knee patients.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6 and 7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6 and 7 + suppl 1
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7 and 8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8 and 9 + suppl 2
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9 and 10 + suppl 3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10 and Suppl 4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10 and 11 + figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	11 and suppl 5
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	13 and 14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13 and 14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Suppl 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11 and suppl 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19 and 20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19 and 20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16 to 19
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.