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# BMJ Open

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

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3 1 **Effect of pre-operative duloxetine treatment on postoperative chronic residual pain after**  
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5 2 **total hip or knee arthroplasty: A Randomised Controlled Trial**  
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3 21 **Abstract**  
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6 22 **Objectives** A key predictor for developing chronic residual pain after Total Knee- or Hip  
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8 23 Arthroplasty (TKA/THA) is sensitization. Aim of this study is to investigate the effects of pre-  
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10 24 operative treatment of sensitized knee/hip osteoarthritis patients with duloxetine on  
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12 25 postoperative chronic residual pain up to one year after TKA/THA.  
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15 26 **Setting** A multi-centre, pragmatic, prospective, randomized clinical trial was conducted in 3  
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17 27 secondary care hospitals in the Netherlands.  
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20 28 **Participants** Patients with primary knee/hip osteoarthritis with signs of sensitization who were  
21  
22 29 planned for TKA/THA were eligible for participation. 111 participants were included and  
23  
24 30 randomly assigned 1:1 intervention or usual care. Complete follow-up of all post-operative time  
25  
26 31 points up to 1 year after surgery was retrieved in 92 cases (82.9%).  
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30 32 **Interventions** Pre-operative oral treatment of seven weeks with 60 mg of Duloxetine daily was  
31  
32 33 compared to usual care.  
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35 34 **Primary and secondary outcome measures** The primary outcome measure was pain, assessed  
36  
37 35 with the Pain Subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip  
38  
39 36 disability and Osteoarthritis Outcome Score (HOOS) with a 0-100 scale. Secondary outcome  
40  
41 37 measures were Visual Analogue Scales, and neuropathic-like pain measured using the modified  
42  
43 38 PainDETECT-Questionnaire. These outcome measures were conforming the original research  
44  
45 39 protocol. Longitudinal data collection included time points up to one year post-operatively.  
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49 40 **Results** The mean improvement in KOOS/HOOS pain subscale was 37 (SD 28.1) in the  
50  
51 41 intervention group and 43 (SD 26.5) in the control group. No statistically significant difference  
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53 42 was found in change-score six months after TKA/THA between both groups ( $p=0.280$ ). Within the  
54  
55 43 intervention group, 12 patients discontinued duloxetine due to Adverse Events, constituting 21%  
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57 44 of the intervention group.  
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3 45 **Conclusions** Pre-operative targeted treatment with duloxetine in end-stage knee and hip OA  
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5 46 patients with sensitization does not influence postoperative chronic residual pain after TKA/THA.  
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8 47 **Trial Registration** Netherlands national Trial Register on August-15-2014 (trial ID NTR4744).  
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14 49 **Keywords:** Pain Management, Sensitization, Orthopaedic Hip and Knee surgery, Clinical  
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16 50 Pharmacology  
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22 52 **Strengths and limitations of this study**  
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24  
25 53 - Broad screening of all patients who were planned for Total Knee or Hip Arthroplasty creating  
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27 54 a representative study population  
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29  
30 55 - Using patient-reported outcome measures relevant for clinical practice  
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33 56 - Comparing to usual-care which varied among clinicians and participating centres thereby  
34  
35 57 increasing generalizability  
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38 58 - Long term follow-up focusing on clinical relevance of the efficacy of duloxetine treatment prior  
39  
40 59 to arthroplasty to post-operative outcome  
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43 60 - The substantial difference in treatment effect of duloxetine between hip and knee OA patients  
44  
45 61 was not anticipated and somewhat lessens the interpretability of our results for the total study  
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47 62 group.  
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## 63 Introduction

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

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

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

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3 89 surgery) of sensitized knee OA patients has positive effects on pain up to 12 weeks postoperatively  
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5 90 <sup>38</sup>. To our knowledge, it is unknown whether this beneficial effect is also present in long term  
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7 91 follow-up. By specifically selecting OA patients with signs of sensitization, rather than the general  
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9 92 knee and hip OA population, it will be possible to make a better assessment of the effectiveness of  
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11 93 desensitization prior to THA/TKA on the development of chronic residual pain. Until now, the  
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13 94 effect of duloxetine on pain in OA patients has solely been investigated in comparison to placebo.  
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15 95 It is of clinically relevant value to assess the added effect of duloxetine in OA patients compared  
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17 96 to usual care.  
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21 97 Therefore, aim of this study is to investigate the effect of preoperative treatment of  
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23 98 sensitized hip and knee OA patients with duloxetine on postoperative chronic residual pain up to  
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25 99 one year after TJA.  
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## 100 **Methods**

### 101 *Design*

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

109 This work was supported by the Dutch Arthritis Foundation (Reumafonds; grant number  
110 BP 12-357 3-401), [www.reumafonds.nl](http://www.reumafonds.nl). The funders had no role in study design, data collection  
111 and analysis, decision to publish, or preparation of the manuscript. The study was approved by  
112 the Medical Ethics Committee of the University Medical Center Groningen (2014/087). The  
113 procedures followed were in accordance with the ethical standards of the responsible committee  
114 on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Patients  
115 or the public were not involved in the design, or conduct, or reporting, or dissemination plans of  
116 our research.

### 118 *Participants*

119 Patients were recruited between December 2014 and June 2018, follow up was completed in  
120 2019. The recruitment period ended as soon as the aimed sample size was achieved. During the  
121 study period, all patients with primary hip or knee OA who were planned for THA or TKA were  
122 screened using a self-report questionnaire for neuropathic-like pain symptoms in hip and knee  
123 OA, the modified PainDETECT Questionnaire (m-PDQ) <sup>42-45</sup>. If patients reported a neuropathic or  
124 at least a mixed neuropathic/nociceptive pain phenotype (m-PDQ scores >12.0), and were eligible

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3 125 considering the in- and exclusion criteria, they were invited for participation. Patients received  
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5 126 oral and written information, and 2 weeks of consideration time. Patients willing to participate  
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7 127 were invited for a visit to the outpatient clinic of their Orthopaedic Department where the last  
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9 128 safety-related exclusion criteria were ruled out based on laboratory testing and physical  
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11 129 examination. A complete list of exclusion criteria can be found in the design paper, and also in  
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13 130 supplementary file 1<sup>41</sup>. Patients who complied to the in- and exclusion criteria and still willing to  
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15 131 participate, provided written informed consent and their visit to the outpatient clinic extended  
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17 132 into the baseline visit.  
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### 21 133 Randomization

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24 134 Randomization took place with an allocation ratio 1:1. The ALEA online randomisation program  
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26 135 (ALEA, FormsVision, Abcoude, the Netherlands) localised on the secured servers of the local Trial  
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28 136 Coordination Centre of UMCG was used. Participants were stratified on location (hip or knee) of  
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30 137 arthroplasty to be performed.  
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### 33 138 Procedure

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36 139 Demographic information, patient characteristics and medical history were collected using  
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38 140 patient records, and all patients received their first set of questionnaires at baseline. During the  
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40 141 pre-operative period, follow-up time points took place two weeks and eight weeks after baseline.  
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43 142 At these time points, patients in the intervention group visited the outpatient clinic. During these  
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45 143 visits, adverse effects (AEs) were assessed. Additionally, patients received a set of questionnaires  
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47 144 during these follow-up visits. Patients in the care as usual group received identical sets of  
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49 145 questionnaires by mail at the same time points.  
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52 146 One day prior to surgery all participants from both study groups were visited in the  
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54 147 hospital and received a set of questionnaires. Participants from the intervention group were  
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56 148 assessed for any discontinuation symptoms. Surgery and the postoperative recovery process were  
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58 149 performed following the local protocol. No study related measures were needed. Postoperative,  
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3 150 all participants of both study groups received identical sets of questionnaires by mail at 48 hours,  
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5 151 6 weeks, 6 months and 12 months after surgery in order to assess the effect of the duloxetine  
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7 152 treatment on the endpoints in different follow-up stages.  
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### 10 153 *Intervention*

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13 154 Patients randomized for the intervention group received duloxetine added to their usual care  
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15 155 during a pre-operative period of 10 weeks. The recommended dosage for chronic musculoskeletal  
16  
17 156 pain is 60 mg per day when considering maximal effectiveness and minimal side-effects<sup>46</sup>. Based  
18  
19 157 on previous studies a 7 week treatment period with 60 mg per day was considered sufficient to  
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21 158 establish a relevant effect on pain<sup>47,48</sup>. The total intervention period was 10 weeks, including one  
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23 159 week of build-up and two weeks of tapering of the medication dose. For safety reasons regarding  
24  
25 160 possible influence of duloxetine on platelet function, there was a window of 5-8 days between  
26  
27 161 ending of the duloxetine treatment period and surgery.  
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### 30 162 *Usual Care*

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34 163 Patients in the usual care group received regular preoperative care following local protocol,  
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36 164 without imposed procedures. No restrictions were imposed on the usage of escape pain  
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38 165 medication in either study group, with one exception, the usage of agents specifically targeted on  
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40 166 neuropathic pain, like gabapentinoids.  
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### 43 167 *Measurement instruments*

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47 168 The primary endpoint is the difference in hip- or knee specific postoperative pain, 6 months after  
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49 169 surgery, assessed with the Pain Subscale of the *Knee injury and Osteoarthritis Outcome Score*  
50  
51 170 (KOOS) or the *Hip disability and Osteoarthritis Outcome Score* (HOOS). The KOOS and HOOS  
52  
53 171 comprise of a 0-100 scale, 0 represents extreme symptoms and 100 represents no symptoms.  
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55 172 Missing items in the KOOS/HOOS were imputed according to the KOOS/HOOS manual<sup>51,52</sup>.  
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58 173 Secondary study endpoints included:  
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3 174 1. the effect of treatment on general pain relief measured using a Visual Analogue Scale (VAS)  
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5 175 (100-mm horizontal line that represents the pain from 0-100);  
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7 176 2. relief of neuropathic-like pain measured using the modified PainDETECT-Questionnaire  
8  
9 (m-PDQ) (Total score -1 to 38 points a score of  $\leq 12$  indicates a nociceptive pain profile,  
10 177  
11 a score of 13-18 a possible neuropathic pain profile, and a score  $\geq 19$  a likely neuropathic  
12 178  
13 pain profile <sup>43,53</sup>);  
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16 180 3. relief of the abovementioned pain scores at different time-points up to 1 year post-  
17  
18 operatively.  
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21 182 Detailed descriptions of all measurement instruments that were used can be found in the  
22  
23 183 design paper, and also in supplementary file 2 <sup>41</sup>.  
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### 29 185 *Sample Size Calculation*

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32 186 Sample size calculation was based on the primary endpoint: change in the KOOS/HOOS pain  
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34 187 subscale. According to literature, the pre-operative mean (SD) Pain Subscale scores for the KOOS  
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36 188 and HOOS are 35.9 (17.2) and 32.7 (17.7) resp. and the minimally clinical important difference is  
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38 189 10 points <sup>55</sup>. To detect a difference with 80% power (significance level, two-sided, of 0.05), a total  
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40 190 sample size of 47 participants per group was needed. A 20% rate of protocol violators/dropouts  
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42 191 was taken into account leading to an aimed sample size of 118 participants.  
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### 45 192 *Statistical Analysis*

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48 193 Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0, Armonk,  
49  
50 194 NY: IBM Corp.). Descriptive statistics were used to report patient characteristics, using mean and  
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52 195 standard deviation or median and percentiles in case of continuous variables, based on normality  
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54 196 assessment by histogram. For normally distributed data, differences between treatment groups  
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56 197 was assessed using an independent samples student T-test. For non-normally distributed data a  
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58 198 Mann-Whitney U test was performed. For discrete data proportions and percentages were  
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3 199 described and differences between treatment groups were assessed using a Chi-Square test. In  
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5 200 case of a participants' discontinuation of the study, all data obtained up to discontinuation was  
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7 201 analysed according to the intention to treat-principle. All participants with at least one  
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9 202 measurement after baseline were included in the study analyses. In addition, a mixed model for  
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11 203 repeated measures was constructed to determine whether duloxetine influences the development  
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14 204 of pain over time. A detailed description of this model can be found in supplementary file 3.

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17 205 As a sub analysis, another mixed model for repeated measures was constructed comparing  
18  
19 206 the influence of duloxetine on the development of pain over time for knee- and hip OA patients.  
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21 207 Further information, as well as the results of this sub analysis can be found in supplementary file  
22  
23 208 4.

## 26 209 **Results**

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29 210 Screening took place over a total number of 3402 patients of which 34.1% had a possible or likely  
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31 211 neuropathic pain profile, indicating sensitization. Of this population, 725 patients were eligible  
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33 212 and therefore invited to participate. See figure 1 for the flow-chart of the screening and inclusion  
34  
35 213 process. Eventually, 112 patients consented to participate. These patients did not differ from non-  
36  
37 214 participants in mean m-PDQ-score ( $p=0.999$ ) and the ratio of hip and knee patients ( $p=0.184$ ). On  
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39 215 average, participants were older than non-participants (mean difference: 5.2 year;  $p<0.0001$ ) and  
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41 216 more often male (38% males among participants vs 28% males among non-participants;  
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43 217  $p=0.031$ ).

### 47 218 *Non-eligibility and disinclination to participation*

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49  
50 219 The main reason for declining to participate was the time investment and practical/logistical  
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52 220 burden that participation in the study required. Also, disinclination to taking duloxetine and  
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54 221 having to relinquish the option of another TJA within the 1-year follow-up period were major  
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56 222 reasons not to participate in the study.  
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3 223 One patient failed to pass the baseline screening due to a low sodium level. Therefore, 111 patients  
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5 224 were included. Baseline characteristics are shown in table 1. Slightly more females (62.2%)  
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7 225 participated and the average participant was 62.7 (SD 8.5) years old. The median duration of  
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9 226 symptoms was 42 months (IQR 18-72). After randomization, 57 patients were placed in the  
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11 227 intervention group and 54 in the control group. Despite randomization, there were significant  
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13 228 differences in baseline HOOS/KOOS pain subscales ( $38.0 \pm 14.0$  vs  $30.6 \pm 12.7$ ;  $P=0.004$ ) and mean  
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15 229 VAS at rest ( $46.6 \pm 24.8$  vs  $58.7 \pm 18.2$ ;  $p=0.004$ ). Concurrent back pain was reported by 11.9% of  
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17 230 participants (7.3% vs 16.7% for the intervention vs control group resp.,  $p=0.151$ ). The incidence  
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19 231 of other pain conditions (migraine, irritable bowel syndrome, fibromyalgia, and chronic neck  
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21 232 pain) was below 10%, with no significant differences between the groups. Detailed information  
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23 233 regarding loss to follow-up, protocol violations, adverse events, and missing data can be found in  
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25 234 supplementary file 5. Complete follow-up of all post-operative time points up to 1 year after  
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27 235 surgery was retrieved in 92 cases (82.9%).  
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32 236 ***Please insert figure 1 here***  
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**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.*

239 *Postoperative Pain*

240 Table 2 presents the mean scores and standard deviations of the pain outcome scores on different  
 241 postoperative time points. Baseline scores and scores after 7 weeks of targeted preoperative  
 242 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*

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244 The KOOS and HOOS pain subscales showed a skewed distribution 6 months after surgery.

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

251 Based on the mixed model for repeated measures as described above, table 3 presents the  
 252 estimated means and differences in pain on different time points between treatment groups, and  
 253 Figure 2 shows the course of the KOOS/HOOS pain subscale over different time points for both  
 254 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

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256 **Please insert figure 2 here**

257

258 *Chronic residual pain*

259 When looking at proportions of patients with moderate chronic residual pain, at 6 months after  
 260 surgery, 32.6% of the intervention group and 31.9% of the control group scored a KOOS/HOOS  
 261 pain scale < 70 points. This percentages decreased to 27.3% and 31.3% at 12 months after surgery  
 262 for the intervention group and control group resp. When looking at hip and knee patients  
 263 separately, 14.3% of the hip patients and 47.1% of the knee patients had a KOOS/HOOS pain scale  
 264 <70 points 6 months after arthroplasty. Twelve months after arthroplasty this was 19% for hip  
 265 patients and 38% for knee patients.

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## 267 Discussion

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

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

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

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3 293 phase. However, this difference does not seem clinically relevant compared to literature although  
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5 294 reports regarding the clinically important differences in hip and knee OA patients specifically  
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7 295 following conservative treatment is scarce<sup>50,56,57</sup>. If the effect of desensitization is too small to  
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9 296 make a clinically relevant difference immediately following the treatment phase, this could  
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11 297 explain the lack of effect on chronic residual pain after TJA. A detailed analysis of the treatment  
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13 298 effect in the pre-operative study period was published earlier<sup>58</sup>. As more extensively described in  
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15 299 this previous publication, effects of duloxetine found in previous literature are similar to the effect  
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17 300 in the present study regarding knee OA, although comparison is only possible to a limited extent  
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19 301 due to the more controlled-nature of previous studies and only knee OA study populations<sup>33-36,38-</sup>  
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21 302 <sup>40</sup>. There is a lack of studies concerning hip OA patients. Moreover, due to the enriched nature of  
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23 303 the present study, a greater effect of duloxetine could have been expected when comparing to  
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25 304 previous studies. The applied duloxetine regiment was in accordance with the recommended  
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27 305 treatment-dose based on previous literature although the applied treatment time can be  
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29 306 considered relatively short compared to literature<sup>33,34,47,48</sup>. Future studies could investigate  
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31 307 whether a longer pre-operative treatment duration would show more effect on chronic residual  
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33 308 pain after TJA. As described in the subanalysis in supplementary file 4, the found effect of  
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35 309 duloxetine treatment can be principally attributed to the knee OA group of the study population.  
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37 310 No effect of duloxetine treatment was found in the hip OA study population. The cause of the lack  
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39 311 of effect in the hip OA subgroup of patients can only be speculated<sup>58</sup>. Also, for hip OA patients,  
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41 312 despite having screened for signs of sensitization, we found a relatively low percentage of chronic  
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43 313 residual pain, 14.3% after 6 months and 19% after 12 months, whereas literature reports up to  
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45 314 23%<sup>19,20</sup>. Consequently, the association between sensitization in hip OA and development of  
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47 315 chronic residual pain after THA is less prominent in the present study. The proportion of patients  
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49 316 with chronic residual pain is relatively high in the knee OA patients after TKA, 47.1% after 6  
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51 317 months and 38% after 12 months, compared to up to 34% in literature<sup>16-20,23</sup>. This was expected  
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53 318 due to the enriched nature of our study population. However, the numbers of the subgroups of  
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55 319 knee and hip OA patients are low, rendering generalizability of these findings limited.  
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3 320 Thirdly, it is possible that the effect of duloxetine treatment diminishes after tapering of  
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5 321 the treatment dose and that the desensitization is becoming undone in the (short) interval period  
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7 322 between tapering and surgery. This interval period was imposed due to safety reasons (see  
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9 323 methods section). In the previous publication focusing on the pre-operative study period, a  
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11 324 decrease in the treatment effect could be observed after the tapering phase <sup>58</sup>. This could be a  
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14 325 possible explanation for the lack of treatment effect on chronic residual pain. In a recent study by  
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16 326 Koh et al. a 30 mg duloxetine regimen was administered 1 day prior up to 6 weeks after TKA in  
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18 327 knee OA patients with signs of sensitization. In this study, perioperative duloxetine treatment  
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20 328 significantly reduced pain up to 12 weeks postoperatively <sup>38</sup>. Maybe the timing of duloxetine  
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22 329 treatment would be more prudent in the perioperative period. However, Koh et al. do not report  
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24 330 any information regarding more than 12 weeks postoperatively. Future studies are needed to  
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26 331 determine whether a different timing of pre-operative duloxetine treatment continued up to (or  
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28 332 shortly after) TJA has a different effect on chronic residual pain compared to the present study.

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32 333 Fourthly, the present study is formed around the hypothesis that treatment of  
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34 334 sensitization in OA patients leads to less development of chronic residual pain after THA/TKA.  
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36 335 Although signs of sensitization are a known predictor in literature for developing chronic residual  
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38 336 pain after TJA, that does not necessarily imply that treatment of the first prevents the development  
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40 337 of the latter. Our present findings could therefore be in line with a theory by Neogi et al <sup>12,13</sup>. Rather  
41  
42 338 than being induced by nociceptive input from the OA pathology, sensitization should possibly be  
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44 339 seen as a 'trait' related to a person's genetic/systemic predisposition to increased pain perception  
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46 340 which is being unmasked once nociceptive input is supplied by structural OA pathology. Maybe  
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48 341 sensitization in OA and chronic residual pain after TJA are both traits of an underlying  
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50 342 proneness/vulnerability to enhanced pain experience which explains why people who develop  
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52 343 sensitization in OA are at risk to also develop chronic residual pain, but that treatment of the first  
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54 344 does not influence the underlying vulnerability and therefore does not lessen the development of  
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56 345 chronic residual pain. As this is the first study known to us to investigate the direct effect of  
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58 346 treatment of sensitization in OA on chronic residual pain, future research is needed to re-assess

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3 347 the present findings and to further investigate the complex causal pathways in the development  
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5 348 of chronic residual pain.

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8 349 *Strengths and limitations*

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11 350 This study contributes important pragmatic insights to the existing literature. There is an  
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13 351 increasing demand for pragmatic studies in the field of OA research<sup>59-61</sup>. Pragmatic trials try to  
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15 352 demonstrate whether an intervention works in the reality of daily practice rather than under  
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17 353 highly controlled circumstances. Pragmatic dimensions of the DOA study are specified in detail in  
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19 354 our design study<sup>41</sup>.

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23 355 There are also limitations to this study. Firstly, the substantial difference in treatment  
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25 356 effect of duloxetine in the two different joint-groups was not anticipated and somewhat lessens  
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27 357 the interpretability of our results for the total study group because the study population was  
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29 358 underpowered to analyse the hip and knee OA patients separately. However, by designing a mixed  
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31 359 model for repeated measures including joint as a fixed variable (see subanalysis in supplement 3),  
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33 360 we were able to assess the effect of joint-group in the study population as a whole. Secondly, by  
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35 361 comparing duloxetine treatment with usual care, we can only assess the combination of the  
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37 362 pharmacological effect together with the accompanying placebo and nocebo effects. However, to  
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39 363 some extent these factors would also play a role in daily application of this treatment and  
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41 364 therefore are relevant for assessing the effectiveness of the total intervention.

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45 365 *Applicability*

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48 366 Considering applicability of duloxetine in the targeted treatment population, the percentage of  
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50 367 AEs was high in the intervention group. 21.1% of intervention participants discontinued the study  
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52 368 treatment due to AEs. In a previous study, the incidence and nature of the AEs in the treatment  
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54 369 period are described in more detail<sup>58</sup>. Also, due to the risk of side effects a substantial proportion  
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56 370 of patients had a disinclination to participating in the study. This, in combination with the  
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371 substantial number of contra-indications for duloxetine on medical reasons lessens the practical  
372 applicability of duloxetine in general practice of OA patients with accompanying co-morbidity.

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

385

### 386 **Figure Legends:**

387 **Figure 1.** Flow chart of screening and inclusion process.

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

390

### 391 **Competing Interests**

392 There are no competing interests for any authors

393

### 394 **Author Contributions**

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

397 Acquisition, analysis and interpretation of data: Wietske Rienstra, Tim Blikman, Sjoerd K.  
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4 400 Stewart, Wierd P. Zijlstra, Tom M. van Raaij, Anita J. ten Hagen, Sjoerd K. Bulstra, Inge van den  
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### 16 17 408 **Patient and Public involvement statement**

18  
19 409 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination  
20 410 plans of our research.

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431 **References**

- 432 1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement.  
433 *Lancet*. 2007. doi:10.1016/S0140-6736(07)60457-7
- 434 2. Räsänen P, Paavolainen P, Sintonen H, *et al*. Effectiveness of hip or knee replacement  
435 surgery in terms of quality-adjusted life years and costs. *Acta Orthop*. 2007.  
436 doi:10.1080/17453670610013501
- 437 3. Ravi B, Croxford R, Reichmann WM, *et al*. The changing demographics of total joint  
438 arthroplasty recipients in the United States and Ontario from 2001 to 2007. *Best Pract Res Clin*  
439 *Rheumatol*. 2012. doi:10.1016/j.berh.2012.07.014
- 440 4. Kurtz SM, Ong KL, Lau E, *et al*. Impact of the economic downturn on total joint replacement  
441 demand in the United States: Updated projections to 2021. *J Bone Jt Surg - Am Vol*. 2014.  
442 doi:10.2106/JBJS.M.00285
- 443 5. Kurtz S, Ong K, Lau E, *et al*. Projections of primary and revision hip and knee arthroplasty  
444 in the United States from 2005 to 2030. *J Bone Jt Surg - Ser A*. 2007. doi:10.2106/JBJS.F.00222
- 445 6. Inacio MCS, Graves SE, Pratt NL, *et al*. Increase in Total Joint Arthroplasty Projected from  
446 2014 to 2046 in Australia: A Conservative Local Model With International Implications. *Clin*  
447 *Orthop Relat Res*. 2017. doi:10.1007/s11999-017-5377-7
- 448 7. Beswick AD, Wylde V, Goberman-Hill R, *et al*. What proportion of patients report long-  
449 term pain after total hip or knee replacement for osteoarthritis? A systematic review of  
450 Prospective studies in unselected patients. *BMJ Open*. 2012. doi:10.1136/bmjopen-2011-000435
- 451 8. Scott CEH, Howie CR, MacDonald D, *et al*. Predicting dissatisfaction following total knee  
452 replacement: A prospective study of 1217 patients. *J Bone Jt Surg - Ser B*. 2010. doi:10.1302/0301-  
453 620X.92B9.24394

- 1  
2  
3 454 9. Anakwe RE, Jenkins PJ, Moran M. Predicting Dissatisfaction After Total Hip Arthroplasty:  
4  
5 455 A Study of 850 Patients. *J Arthroplasty*. 2011. doi:10.1016/j.arth.2010.03.013  
6  
7  
8 456 10. Mannion AF, Kämpfen S, Munzinger U, *et al*. The role of patient expectations in predicting  
9  
10 457 outcome after total knee arthroplasty. *Arthritis Res Ther*. 2009. doi:10.1186/ar2811  
11  
12  
13 458 11. Baker PN, van der Meulen JH, Lewsey J, *et al*. The role of pain and function in determining  
14  
15 459 patient satisfaction after total knee replacement. Data from the national joint registry for England  
16  
17 460 and Wales. *J Bone Jt Surg - Ser B*. 2007. doi:10.1302/0301-620X.89B7.19091  
18  
19  
20 461 12. Neogi T. Structural correlates of pain in osteoarthritis. *Clin Exp Rheumatol*. 2017.  
21  
22  
23 462 13. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthr Cartil*. 2013.  
24  
25 463 doi:10.1016/j.joca.2013.03.018  
26  
27  
28 464 14. Gwilym SE, Keltner JR, Warnaby CE, *et al*. Psychophysical and functional imaging evidence  
29  
30 465 supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis*  
31  
32 466 *Care Res*. 2009. doi:10.1002/art.24837  
33  
34  
35 467 15. Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: Nociceptive or neuropathic? *Nat*  
36  
37 468 *Rev Rheumatol*. 2014. doi:10.1038/nrrheum.2014.47  
38  
39  
40 469 16. Skou ST, Graven-Nielsen T, Rasmussen S, *et al*. Facilitation of pain sensitization in knee  
41  
42 470 osteoarthritis and persistent post-operative pain: A cross-sectional study. *Eur J Pain (United*  
43  
44 471 *Kingdom)*. 2014. doi:10.1002/j.1532-2149.2013.00447.x  
45  
46  
47  
48 472 17. Lundblad H, Kreicbergs A, Jansson KÅ. Prediction of persistent pain after total knee  
49  
50 473 replacement for osteoarthritis. *J Bone Jt Surg - Ser B*. 2008. doi:10.1302/0301-620X.90B2.19640  
51  
52  
53 474 18. Wylde V, Palmer S, Learmonth ID, *et al*. The association between pre-operative pain  
54  
55 475 sensitisation and chronic pain after knee replacement: An exploratory study. *Osteoarthr Cartil*.  
56  
57 476 2013. doi:10.1016/j.joca.2013.05.008  
58  
59  
60

- 1  
2  
3 477 19. Wylde V, Sayers A, Lenguerrand E, *et al.* Preoperative widespread pain sensitization and  
4  
5 478 chronic pain after hip and knee replacement: A cohort analysis. *Pain.* 2015.  
6  
7 479 doi:10.1016/j.pain.0000000000000002  
8  
9  
10 480 20. Wylde V, Hewlett S, Learmonth ID, *et al.* Persistent pain after joint replacement:  
11  
12 481 Prevalence, sensory qualities, and postoperative determinants. *Pain.* 2011.  
13  
14 482 doi:10.1016/j.pain.2010.11.023  
15  
16  
17 483 21. Ohtori S, Orita S, Yamashita M, *et al.* Existence of a neuropathic pain component in patients  
18  
19 484 with osteoarthritis of the knee. *Yonsei Med J.* 2012. doi:10.3349/ymj.2012.53.4.801  
20  
21  
22 485 22. Valdes AM, Doherty SA, Zhang W, *et al.* Inverse relationship between preoperative  
23  
24 486 radiographic severity and postoperative pain in patients with osteoarthritis who have undergone  
25  
26 487 total joint arthroplasty. *Semin Arthritis Rheum.* 2012. doi:10.1016/j.semarthrit.2011.07.002  
27  
28  
29 488 23. Valdes AM, Suokas AK, Doherty SA, *et al.* History of knee surgery is associated with higher  
30  
31 489 prevalence of neuropathic pain-like symptoms in patients with severe osteoarthritis of the knee.  
32  
33 490 *Semin Arthritis Rheum.* 2014. doi:10.1016/j.semarthrit.2013.10.001  
34  
35  
36 491 24. Finan PH, Buenaver LF, Bounds SC, *et al.* Discordance between pain and radiographic  
37  
38 492 severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization.  
39  
40 493 *Arthritis Rheum.* 2013. doi:10.1002/art.34646  
41  
42  
43 494 25. Hochman JR, French MR, Birmingham SL, *et al.* The nerve of osteoarthritis pain. *Arthritis*  
44  
45 495 *Care Res.* 2010. doi:10.1002/acr.20142  
46  
47  
48 496 26. Mease PJ, Hanna S, Frakes EP, *et al.* Pain mechanisms in osteoarthritis: Understanding the  
49  
50 497 role of central pain and current approaches to its treatment. *J Rheumatol.* 2011.  
51  
52 498 doi:10.3899/jrheum.100759  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 499 27. Murphy SL, Phillips K, Williams DA, *et al.* The role of the central nervous system in  
4  
5 500 osteoarthritis pain and implications for rehabilitation. *Curr Rheumatol Rep.* 2012.  
6  
7 501 doi:10.1007/s11926-012-0285-z  
8  
9  
10 502 28. Lluch E, Torres R, Nijs J, *et al.* Evidence for central sensitization in patients with  
11  
12 503 osteoarthritis pain: A systematic literature review. *Eur J Pain (United Kingdom).* 2014.  
13  
14 504 doi:10.1002/j.1532-2149.2014.499.x  
15  
16  
17 505 29. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. *Clin Exp Rheumatol.* 2017.  
18  
19  
20 506 30. Fingleton C, Smart K, Moloney N, *et al.* Pain sensitization in people with knee  
21  
22 507 osteoarthritis: A systematic review and meta-analysis. *Osteoarthr Cartil.* 2015.  
23  
24 508 doi:10.1016/j.joca.2015.02.163  
25  
26  
27 509 31. Imamura M, Imamura ST, Kaziyama HHS, *et al.* Impact of nervous system hyperalgesia on  
28  
29 510 pain, disability, and quality of life in patients with knee osteoarthritis: A controlled analysis.  
30  
31 511 *Arthritis Care Res.* 2008. doi:10.1002/art.24120  
32  
33  
34 512 32. Hochman JR, Gagliese L, Davis AM, *et al.* Neuropathic pain symptoms in a community knee  
35  
36 513 OA cohort. *Osteoarthr Cartil.* 2011. doi:10.1016/j.joca.2011.03.007  
37  
38  
39 514 33. Wang G, Bi L, Li X, *et al.* Efficacy and safety of duloxetine in Chinese patients with chronic  
40  
41 515 pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. *Osteoarthr*  
42  
43 516 *Cartil.* 2017. doi:10.1016/j.joca.2016.12.025  
44  
45  
46  
47 517 34. Wang ZY, Shi SY, Li SJ, *et al.* Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain:  
48  
49 518 A Meta-Analysis of Randomized Controlled Trials. *Pain Med (United States).* 2015.  
50  
51 519 doi:10.1111/pme.12800  
52  
53  
54 520 35. Frakes EP, Risser RC, Ball TD, *et al.* Duloxetine added to oral nonsteroidal anti-  
55  
56 521 inflammatory drugs for treatment of knee pain due to osteoarthritis: Results of a randomized,  
57  
58  
59  
60

- 1  
2  
3 522 double-blind, placebo-controlled trial. *Curr Med Res Opin.* 2011.  
4  
5 523 doi:10.1185/03007995.2011.633502  
6  
7  
8 524 36. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic  
9  
10 525 review and meta-analysis. *Korean J Intern Med.* 2019. doi:10.3904/kjim.2018.460  
11  
12  
13 526 37. Hochberg MC, Wohlreich M, Gaynor P, *et al.* Clinically relevant outcomes based on analysis  
14  
15 527 of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. *J Rheumatol.* 2012.  
16  
17 528 doi:10.3899/jrheum.110307  
18  
19  
20 529 38. Koh IJ, Kim MS, Sohn S, *et al.* Duloxetine Reduces Pain and Improves Quality of Recovery  
21  
22 530 Following Total Knee Arthroplasty in Centrally Sensitized Patients: A Prospective, Randomized  
23  
24 531 Controlled Study. *J Bone Jt Surg - Am Vol.* 2019. doi:10.2106/JBJS.18.00347  
25  
26  
27  
28 532 39. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older  
29  
30 533 adults with knee osteoarthritis: Randomised placebo-controlled trial. *Age Ageing.* 2012.  
31  
32 534 doi:10.1093/ageing/afs072  
33  
34  
35 535 40. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain:  
36  
37 536 What is the number needed to treat, number needed to harm, and likelihood to be helped or  
38  
39 537 harmed? *Postgrad Med.* 2012. doi:10.3810/pgm.2012.01.2521  
40  
41  
42 538 41. Blikman T, Rienstra W, Van Raaij TM, *et al.* Duloxetine in osteoarthritis (DOA) study: Study  
43  
44 539 protocol of a pragmatic open-label randomised controlled trial assessing the effect of preoperative  
45  
46 540 pain treatment on postoperative outcome after total hip or knee arthroplasty. *BMJ Open.* 2016.  
47  
48 541 doi:10.1136/bmjopen-2015-010343  
49  
50  
51 542 42. Hochman J, Elkayam J, Gagliese L, *et al.* The relationship between neuropathic pain  
52  
53 543 symptoms on the modified pain detect and signs of central sensitization in knee osteoarthritis.  
54  
55 544 *Osteoarthr Cartil.* 2012. doi:10.1016/j.joca.2012.02.430  
56  
57  
58  
59  
60

- 1  
2  
3 545 43. Hochman JR, Davis AM, Elkayam J, *et al.* Neuropathic pain symptoms on the modified  
4  
5 546 painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthr Cartil.*  
6  
7 547 2013. doi:10.1016/j.joca.2013.06.023  
8  
9  
10 548 44. Rienstra W, Blikman T, Mensink FB, *et al.* The modified painDETECT Questionnaire for  
11  
12 549 patients with hip or knee osteoarthritis: Translation into Dutch, cross-cultural adaptation and  
13  
14 550 reliability assessment. *PLoS One.* 2015. doi:10.1371/journal.pone.0146117  
15  
16  
17 551 45. Rienstra W, Blikman T, Dijkstra B, *et al.* Validity of the Dutch modified painDETECT  
18  
19 552 questionnaire for patients with hip or knee osteoarthritis. *Disabil Rehabil.* 2019.  
20  
21 553 doi:10.1080/09638288.2017.1413429  
22  
23  
24  
25 554 46. Cymbalta (duloxetine hydrochloride) FULL PRESCRIBING INFORMATION.  
26  
27 555 <http://pi.lilly.com/us/cymbalta-pi.pdf> (accessed 18 Nov 2013).  
28  
29  
30 556 47. Chappell AS, Ossanna MJ, Liu-Seifert H, *et al.* Duloxetine, a centrally acting analgesic, in the  
31  
32 557 treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled  
33  
34 558 trial. *Pain.* 2009. doi:10.1016/j.pain.2009.06.024  
35  
36  
37  
38 559 48. Chappell AS, Desai D, Liu-Seifert H, *et al.* A Double-blind, Randomized, Placebo-  
39  
40 560 controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain Due to  
41  
42 561 Osteoarthritis of the Knee. *Pain Pract.* 2011. doi:10.1111/j.1533-2500.2010.00401.x  
43  
44  
45 562 49. de Groot IB, Favejee MM, Reijman M, *et al.* The dutch version of the knee injury and  
46  
47 563 osteoarthritis outcome score: A validation study. *Health Qual Life Outcomes.* 2008.  
48  
49 564 doi:10.1186/1477-7525-6-16  
50  
51  
52 565 50. Collins NJ, Prinsen CAC, Christensen R, *et al.* Knee Injury and Osteoarthritis Outcome Score  
53  
54 566 (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthr Cartil.*  
55  
56 567 2016;24(8):1317-1329. doi:10.1016/j.joca.2016.03.010  
57  
58  
59  
60

- 1  
2  
3 568 51. <http://www.koos.nu>. Instructions Hip disability and Osteoarthritis Outcome Score  
4  
5 569 (HOOS) Scoring instructions. 2013;(accessed april 2021)  
6  
7  
8 570 52. <http://www.koos.nu>. Knee Osteoarthritis Outcome Score, Scoring. KOOS Excel scoring  
9  
10 571 files. (accessed april 2021)  
11  
12  
13 572 53. Freynhagen R, Baron R, Gockel U, *et al*. painDETECT: A new screening questionnaire to  
14  
15 573 identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006.  
16  
17 574 doi:10.1185/030079906X132488  
18  
19  
20 575 54. Price DD, McGrath PA, Rafii A, *et al*. The validation of visual analogue scales as ratio scale  
21  
22 576 measures for chronic and experimental pain. *Pain*. 1983. doi:10.1016/0304-3959(83)90126-4  
23  
24  
25 577 55. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): From  
26  
27 578 joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003. doi:10.1186/1477-7525-1-64  
28  
29  
30  
31 579 56. Çelik D, Çoban Ö, Kılıçoğlu Ö. Minimal clinically important difference of commonly used  
32  
33 580 hip-, knee-, foot-, and ankle-specific questionnaires: a systematic review. *J Clin Epidemiol*.  
34  
35 581 2019;113:44-57. doi:10.1016/j.jclinepi.2019.04.017  
36  
37  
38 582 57. Roos EM, Boyle E, Frobell RB, *et al*. It is good to feel better, but better to feel good: Whether  
39  
40 583 a patient finds treatment successful' or not depends on the questions researchers ask. *Br J Sports*  
41  
42 584 *Med*. 2019. doi:10.1136/bjsports-2018-100260  
43  
44  
45 585 58. Blikman T. Neuropathic-like symptoms in hip and knee osteoarthritis. [2020] University  
46  
47 586 of Groningen ISBN 978-94-6419-011-3  
48  
49  
50 587 59. Zhang W, Moskowitz RW, Nuki G, *et al*. OARSI recommendations for the management of  
51  
52 588 hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines.  
53  
54 589 *Osteoarthr Cartil*. 2008. doi:10.1016/j.joca.2007.12.013  
55  
56  
57  
58  
59  
60

1  
2  
3 590 60. Thorpe KE, Zwarenstein M, Oxman AD, *et al*. A pragmatic-explanatory continuum indicator  
4  
5 591 summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. 2009.  
6  
7 592 doi:10.1016/j.jclinepi.2008.12.011  
8  
9

10 593 61. Zwarenstein M, Treweek S, Gagnier JJ. CONSORT group; Pragmatic Trials in Healthcare  
11  
12 594 (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT  
13  
14 595 statement. *Bmj*. 2008;337(December):a2390. doi:10.1136/bmj.a2390  
15  
16

17 596  
18  
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21  
22  
23  
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For peer review only



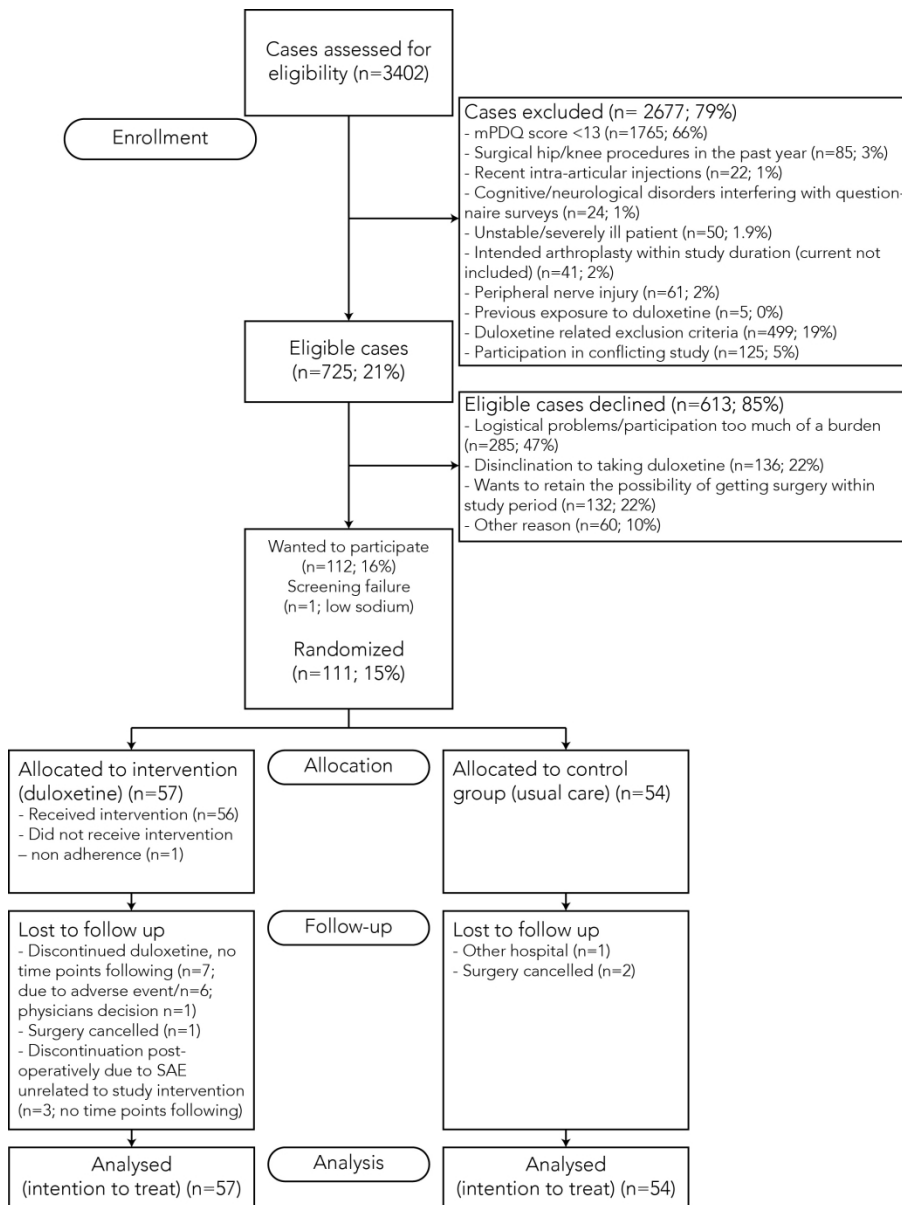


Figure 1. Flow chart of screening and inclusion process.

192x254mm (300 x 300 DPI)

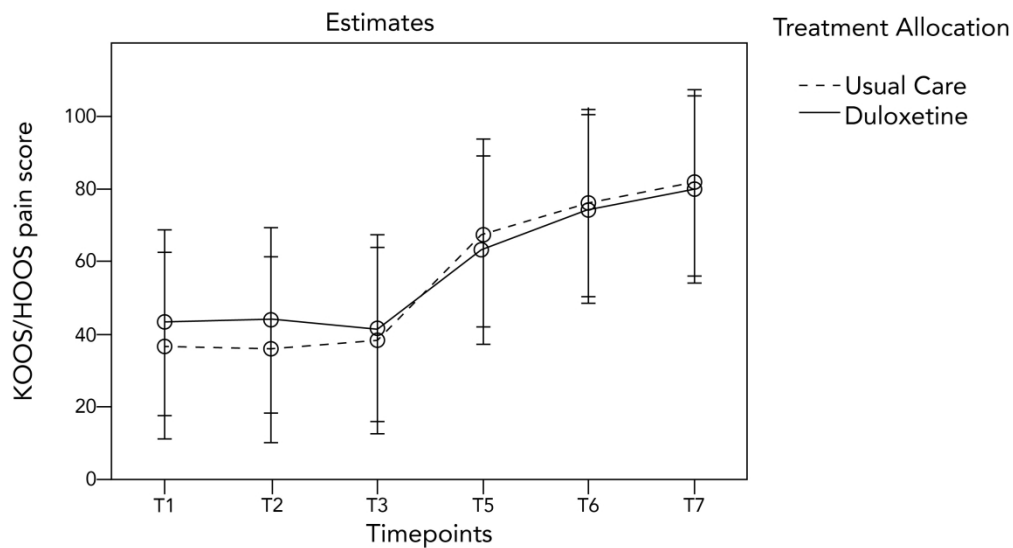


Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

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**Supplementary 1/5: 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  $\leq 12$

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

### 22 23 *Visual Analogue Scale Pain (VAS pain)*

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25 Visual Analogue Scales (VAS) are widely used to measure pain. Patients place a marking on a  
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27 100-mm horizontal line that represents their pain. The left ending of the line represents 'no  
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29 pain at all' and the right ending 'worst pain imaginable'. The distance between the marking  
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31 and the left ending of the line is measured in whole millimetres and represents the pain score.  
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33 Patients were asked to note their present pain status and their mean pain status over the last  
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35 week; at rest (VAS-R: defined as pain in rest while sitting, standing or lying down) and during  
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37 movement (VAS-M defined as pain during regular walking). VAS have been reported as valid  
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39 and reliable measures for the intensity of pain 54.  
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### 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:*

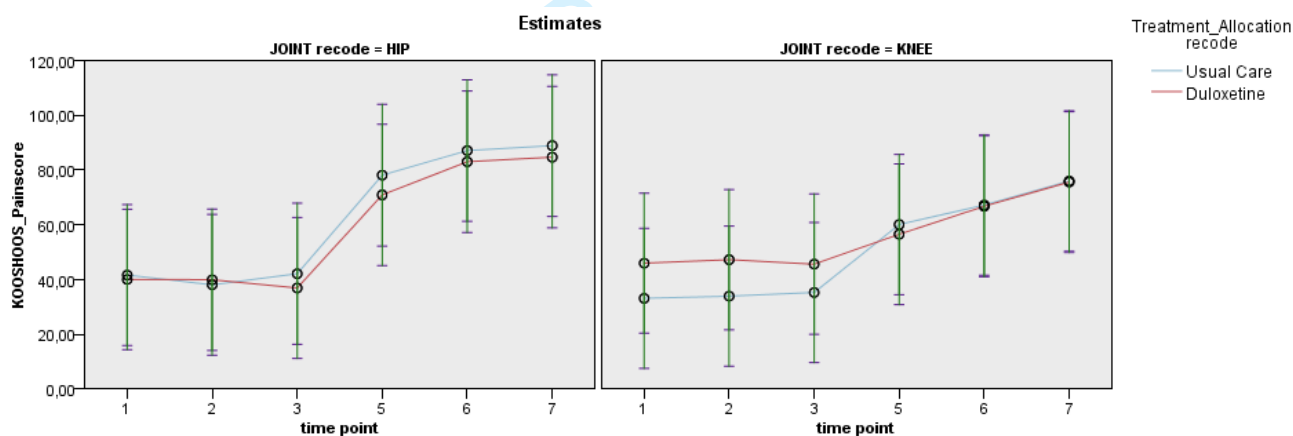
Sub analysis mixed model for repeated measures including joint as a fixed variable.

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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
<b>Methods</b>			
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
<b>Randomisation:</b>			
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

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
2				
3		11b	If relevant, description of the similarity of interventions	NA
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9 and 10 + suppl 3
5				
6		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10 and Suppl 4
7				
8				
9	<b>Results</b>			
10	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
11		13b	For each group, losses and exclusions after randomisation, together with reasons	11 and suppl 5
12				
13	Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
14		14b	Why the trial ended or was stopped	6
15				
16	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
17	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
18				
19	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
20		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
21	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Suppl 4
22				
23	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11 and suppl 5
24				
25				
26	<b>Discussion</b>			
27	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19 and 20
28	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19 and 20
29	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16 to 19
30				
31	<b>Other information</b>			
32	Registration	23	Registration number and name of trial registry	6
33	Protocol	24	Where the full trial protocol can be accessed, if available	6
34	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6
35				
36				
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1 \*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  
2 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.  
3 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
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# BMJ Open

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

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3 1 **Effect of preoperative duloxetine treatment on postoperative chronic residual pain after**  
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5 2 **total hip or knee arthroplasty: A Randomised Controlled Trial**  
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## 18 **Abstract**

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

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

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

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

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

41 **Results** Mean improvement in the KOOS/HOOS pain subscale at six months postoperatively was  
42 37 (SD 28.1) in the intervention group and 43 (SD 26.5) in the control group. No statistically



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3 43 significant difference was found in change score six months postoperatively between the two  
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5 44 groups ( $p=0.280$ ). 12 patients from the intervention group (21%) discontinued duloxetine due to  
6  
7 45 adverse effects.  
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10 46 **Conclusions** Preoperative targeted treatment with duloxetine in end-stage knee and hip OA  
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12 47 patients with sensitisation does not influence postoperative chronic residual pain after TKA/THA.  
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15 48 **Trial Registration** Netherlands Trial Register on 15-August-2014 (trial ID NTR4744).  
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21 50 **Keywords:** Pain Management, Sensitization, Orthopaedic Hip and Knee surgery, Clinical  
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23 51 Pharmacology  
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### 28 29 53 **Strengths and limitations of this study**

- 30  
31  
32 54 – Broad screening of all patients who were planned for total knee or hip arthroplasty, creating a  
33  
34 55 representative study population.  
35  
36 56 – Using patient-reported outcome measures relevant for clinical practice.  
37  
38 57 – Comparing to usual care, which varied among clinicians and participating centres, thereby  
39  
40 58 increasing generalizability.  
41  
42 59 – Long-term follow-up focusing on clinical relevance of the efficacy of duloxetine treatment from  
43  
44 60 prior to arthroplasty to postoperative outcome.  
45  
46 61 – The substantial difference in treatment effect of duloxetine between hip and knee OA patients  
47  
48 62 was not anticipated and somewhat lessens the interpretability of our results for the total study  
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50 63 group.  
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## 64 Introduction

65 Total hip and knee arthroplasties are among the most performed procedures in orthopaedic  
66 surgery for the treatment of patients with severe osteoarthritis (OA).<sup>1,2</sup> Projections show that the  
67 number of performed procedures will dramatically rise in the future.<sup>3-5</sup> In light of this, the high  
68 prevalence of residual pain after these procedures must be considered a highly relevant problem.  
69 Chronic residual pain is pain that persists after the postoperative recovery process is over. Up to  
70 23% of patients after total hip arthroplasty (THA) and up to 34% after total hip arthroplasty (TKA)  
71 experience chronic residual pain,<sup>6-10</sup> which leads to declining patient satisfaction, functioning, and  
72 quality of life.<sup>11-14</sup>

73 Numerous studies have demonstrated that pain in OA is a highly complex phenomenon  
74 that seems to involve both intra-articular and extra-articular mechanisms<sup>1,7,13-16</sup> like modification  
75 of pain transmission in both the peripheral and the central nervous system, leading to  
76 sensitisation of the pain pathways. Several mechanisms have been described leading to  
77 sensitisation, among which modulation of the inhibitory descending control pathways of the  
78 central nervous system seems to play an important role.<sup>7,17</sup> Sensitisation in OA expresses itself  
79 through neuropathic-like symptoms such as allodynia, hyperalgesia, and spreading of the pain.  
80 Signs of sensitisation seem to be among the key predictors for poorer outcome after total joint  
81 arthroplasty (TJA), especially for chronic residual pain.<sup>18-22</sup> Up to 19% of patients with hip OA and  
82 19-37% of patients with knee OA experience signs of sensitisation and are therefore at a higher  
83 risk of developing chronic residual pain after TJA.<sup>7,10-14,16,23</sup>

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

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3 90 perioperatively (1 day before up to 6 weeks after surgery) in sensitised knee OA patients has  
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5 91 positive effects on pain up to 12 weeks postoperatively.<sup>27</sup> To our knowledge, it is unknown  
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7 92 whether this beneficial effect remains in long-term follow-up. Specifically selecting OA patients  
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9 93 with signs of sensitisation rather than the general knee and hip OA population will enable a better  
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11 94 assessment of the effectiveness of pre-THA/TKA desensitisation on the development of chronic  
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14 95 residual pain. Until now, the effect of duloxetine on pain in OA patients has solely been  
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16 96 investigated compared to placebo. It is of clinically relevant value to assess the added effect of  
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18 97 duloxetine in OA patients compared to usual care.  
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21 98 Aim of this study is therefore to investigate whether preoperative treatment with  
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23 99 duloxetine of hip and knee OA patients with signs of sensitisation reduces postoperative chronic  
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25 100 residual pain up to one year post-TJA.  
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## 101 **Methods**

### 102 *Design*

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

110 This work is supported by the Dutch Arthritis Foundation *Reumafonds* (grant number BP  
111 12-357 3-401), [www.reumafonds.nl](http://www.reumafonds.nl). The funders had no role in study design, data collection and  
112 analysis, decision to publish, or preparation of the manuscript. The study was approved by the  
113 Medical Ethics Committee of University Medical Center Groningen (2014/087). The procedures  
114 followed were in accordance with the ethical standards of the responsible committee on human  
115 experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

### 116 *Patient and public involvement*

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

### 119 *Participants and screening*

120 Patients were recruited between December 2014 and June 2018; follow-up was completed in  
121 2019. During the study period, all patients with primary hip or knee OA planned for THA or TKA  
122 were screened using a self-report tool for neuropathic-like pain symptoms in hip and knee OA, the  
123 modified PainDETECT Questionnaire (m-PDQ). The m-PDQ is a self-administered questionnaire  
124 consisting of 12 items on neuropathic pain symptoms in the left/right knee or hip during the past  
125 week. The questions ask about presence of pain radiation; pattern of pain over time; pain quality,

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3 126 including burning, tingling or prickling sensation; pain at light touch; sudden pain attacks; pain at  
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5 127 cold or warm stimulus; numbness; and pain at light pressure. The total score ranges from -1 to 38  
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7 128 points. Analogously to the original PainDETECT Questionnaire, scoring  $\leq 12$  indicates a  
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9 129 nociceptive pain profile, 13-18 a possible neuropathic pain profile, and  $\geq 19$  a likely neuropathic  
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11 130 pain profile. Apart from nociceptive discrimination from neuropathic pain, m-PDQ scores  $>12.0$   
12  
13 131 are associated with greater odds of having signs of sensitisation.<sup>8,29-32</sup> The supplementary file  
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15 132 includes more detailed information on the m-PDQ. Patients who reported m-PDQ scores  $>12.0$   
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17 133 and were eligible based on the inclusion and exclusion criteria were invited to participate.

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21 134 Exclusion criteria were: surgical hip or knee joint procedures in the past year; intra-  
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23 135 articular hip/knee injection/arthroscopy in the past 3 months; cognitive or neurological disorders  
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25 136 that could strongly interfere with questionnaire surveys; a history of significant peripheral nerve  
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27 137 injury; serious or unstable physical or mental medical conditions that could interfere with study  
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29 138 participation; intended THA/TKA to another joint within the study period; previous exposure to  
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31 139 duloxetine or a medical contraindication for usage of duloxetine. A complete list of inclusion and  
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33 140 exclusion criteria can be found in the design paper.<sup>28</sup>

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37 141 Patients received oral and written information plus two weeks' consideration time.  
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39 142 Patients willing to participate were invited to visit the outpatient clinic of their orthopaedic  
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41 143 department, where the last safety-related exclusion criteria were ruled out based on laboratory  
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43 144 testing and physical examination. Patients who complied with the inclusion and exclusion criteria  
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45 145 and were still willing to participate, provided written informed consent and their visit to the  
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47 146 outpatient clinic extended into a baseline visit.

#### 48 49 50 51 147 *Randomisation*

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53 148 Randomisation took place with a 1:1 allocation ratio. The ALEA online randomisation program  
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55 149 (ALEA, FormsVision, Abcoude, The Netherlands) localised on the secured servers of the local Trial  
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57 150 Coordination Centre of UMCG was used. Participants were stratified by type of arthroplasty to be  
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59 151 performed (hip or knee), with block sizes of 4 and 6.

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3 152 *Procedure*  
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6 153 Demographic information, patient characteristics and medical history were collected using  
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8 154 patient records (see Table 1), and all patients received their first set of questionnaires at baseline.  
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10 155 The preoperative treatment period was divided into three timepoints. As the risk of side effects  
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12 156 was highest at initiation of treatment, the dosage of duloxetine was built up from 30 mg/day in  
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14 157 week 1 to 60 mg/day in week 2. The first timepoint, two weeks after baseline, was therefore  
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16 158 primarily instated for safety reasons and to assess side effects. The second timepoint was eight  
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18 159 weeks after baseline, right after the 7-week treatment period with 60 mg/day duloxetine. This  
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20 160 timepoint aimed to measure the effect of duloxetine on pain directly after treatment. Before  
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22 161 surgery the dosage of duloxetine was tapered for two weeks to 30 mg/day, to reduce  
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24 162 discontinuation symptoms. For safety reasons related to possible influence of duloxetine on  
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26 163 platelet function, there was a window of 5-8 days between ending the duloxetine treatment period  
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28 164 and surgery. The third and last preoperative timepoint took place one day prior to surgery.  
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30 165 Patients in the care-as-usual group were mailed identical sets of questionnaires at the same  
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32 166 timepoints.  
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37 167 Surgery and the postoperative recovery process followed local protocols. No study-related  
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39 168 measures were needed. All participants of the two study groups were mailed identical sets of  
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41 169 questionnaires at 48 hours, 6 weeks, 6 months and 12 months postoperatively, to assess the effect  
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43 170 of the duloxetine treatment on the endpoints at different follow-up stages. A detailed description  
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45 171 of all measurement instruments used and the timepoints at which they were administered can be  
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47 172 found in the design paper and in the supplementary file.<sup>28</sup>  
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51 173 *Intervention*  
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54 174 Patients randomised for the intervention group received duloxetine added to their usual care for  
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56 175 10 weeks preoperatively. The recommended dosage for chronic musculoskeletal pain is 60  
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58 176 mg/day when considering maximal effectiveness and minimal side effects.<sup>33</sup> Based on previous  
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60 177 studies a 7-week treatment period with 60 mg/day was considered sufficient to establish a

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3 178 relevant effect on pain.<sup>34,35</sup> The total intervention period was 10 weeks, including one week of  
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5 179 build-up and two weeks of tapering off the medication dose as described above. See the  
6  
7 180 supplementary file for a visual illustration of the intervention phase.  
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### 10 181 *Usual Care*

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13 182 Patients in the usual-care group remained on the waiting list for arthroplasty. They were allowed  
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15 183 to continue with any pain medication they were already taking as well as any other ongoing  
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17 184 treatment (like physiotherapy). Since the use of neuropathic pain medication is not registered for  
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19 185 OA pain in the Netherlands, none of the participants had a prescription for such medication in the  
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21 186 preoperative stage. Usual-care patients received regular preoperative care following local  
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23 187 protocols, without imposed procedures. No restrictions were imposed on usage of escape pain  
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25 188 medication in either study group – with one exception, that of agents specifically targeted for  
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27 189 neuropathic pain, like gabapentinoids perioperatively.  
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### 31 190 *Measurement instruments*

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34 191 Primary endpoint is the mean difference between the intervention and control groups in hip- or  
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36 192 knee-specific pain six months postoperatively, assessed with the pain subscale of the *Knee injury*  
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38 193 *and Osteoarthritis Outcome Score (KOOS)* or the *Hip disability and Osteoarthritis Outcome Score*  
39  
40 194 (HOOS). Both KOOS and HOOS use a 0-100 scale, where 0 represents extreme symptoms and 100  
41  
42 195 no symptoms. In literature a score <70 points on the KOOS or HOOS pain subscale is considered a  
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44 196 moderate amount of joint-specific pain.<sup>36,37</sup> Missing items in the KOOS/HOOS were handled  
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46 197 according to the KOOS/HOOS manual.<sup>36,37</sup> This primary outcome measure was chosen at 6  
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48 198 months, as in practice this was considered the first possible timepoint to evaluate chronic residual  
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50 199 pain after arthroplasty. Because it is known from practice that the amount of chronic residual pain  
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52 200 is not likely to change after one year postop, we aimed to follow up to one year postop in order to  
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54 201 be as thorough as possible.  
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58  
59 202 Secondary study endpoints included:  
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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.<sup>28</sup> 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.<sup>38</sup> 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



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3 229 and standard deviation or median and percentiles in case of continuous variables, based on  
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5 230 normality assessment by histogram. For normally distributed data, differences between  
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7 231 treatment groups were assessed using an independent samples student T-test. For non-normally  
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9 232 distributed data a Mann-Whitney U-test was performed. Our planned analysis was the inferential  
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11 233 test between difference in KOOS/HOOS pain subscale between the intervention and the control  
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13 234 group at six months after surgery. Proportions and percentages were described for discrete data,  
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16 235 In case of discontinued participation in the study, all data obtained up to the participant's  
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18 236 discontinuation was analysed according to the intention-to-treat principle. All participants with  
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20 237 at least one measurement after baseline were included in the study analyses. The data was not  
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22 238 imputed. We decided to use a Full Information Maximum Likelihood technique using multilevel  
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24 239 mixed model analysis for repeated measures. Multilevel models have the ability to handle models  
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26 240 by using all available data, which is an advance over traditional repeated-measures analysis,  
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28 241 where the usual treatment is to remove the entire patient if one of the outcomes is missing. With  
29  
30 242 the multilevel model, we use as estimated strategy Full information maximum likelihood, where  
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32 243 we get parameter estimates even in the presence of missing data. Missing items in the primary  
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34 244 outcome scores, the pain subscales of the KOOS/HOOS questionnaires, were handled according to  
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36 245 the KOOS/HOOS manual.<sup>36,37</sup>

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40 246 A multilevel mixed model analysis for repeated measures was performed on the  
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42 247 longitudinal data to determine whether there is a difference in the modification of pain over time  
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44 248 between the two groups. A mixed model was constructed that included time, treatment allocation  
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46 249 and baseline KOOS/HOOS pain subscale (in order to correct for the differences between groups at  
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48 250 baseline). A variable was added differentiating between preoperative and postoperative  
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50 251 timepoints (coded 0 or 1, respectively), thereby creating a piece-wise analysis. This way the  
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52 252 postoperative effect of duloxetine treatment could be distinguished while including the data from  
53  
54 253 all timepoints. Apart from the baseline KOOS/HOOS pain subscale, interaction terms between this  
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56 254 piece-wise variable and all other separate variables were added, as well as a three-way interaction  
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58 255 term between time, treatment and the piece-wise variable. A random intercept was added for

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3 256 individual subjects. The model was designed based on the best fit, Schwartz's Bayesian  
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5 257 Information Criterion was 4976.818, and Akaike Corrected Information Criterion was 4968.141.  
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7 258 Once the model was constructed for the HOOS/KOOS pain subscale, it was also applied to the other  
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9 259 pain outcome measures (VAS-R, VAS-M, m-PDQ).

10  
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12 260 As a sub-analysis, another mixed model for repeated measures was constructed  
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14 261 comparing the influence of duloxetine on the development of pain over time for knee and hip OA  
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16 262 patients. In this model a fixed variable for joint was added to the above-mentioned model. This  
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18 263 way, the difference explained by whether the hip or the knee was the affected joint could be taken  
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20 264 into consideration. Further information, as well as the results of this sub-analysis, can be found in  
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22 265 the supplementary file.

## 26 266 **Results**

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29 267 Screening took place over a total number of 3402 patients, 34.1% of whom had a possible or likely  
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31 268 neuropathic pain profile, indicating sensitisation. Of this population, 725 patients were eligible  
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33 269 and therefore invited to participate (see Figure 1 for the flowchart of the screening and inclusion  
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35 270 process). The 112 patients who consented to participate did not differ from non-participants in  
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37 271 mean m-PDQ-score ( $p=0.999$ ) or hip-versus-knee ratio ( $p=0.184$ ). On average, participants were  
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39 272 older than non-participants (mean difference: 5.2 years;  $p<0.0001$ ) and more often male (38%  
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41 273 males among participants vs 28% males among non-participants;  $p=0.031$ ).

### 42 274 *Non-eligibility and disinclination to participate*

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45 275 The main reason for declining to participate was the time investment and practical/logistical  
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47 276 burden that participation in the study required. Also, disinclination to take duloxetine and having  
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49 277 to relinquish the option of another TJA within the one-year follow-up period were major reasons  
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51 278 not to participate in the study.

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54 279 One patient failed to pass the baseline screening due to a low sodium level, so ultimately  
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56 280 111 patients were included. Baseline characteristics are shown in Table 1. Slightly more females

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3 281 (62.2%) participated and the average participant was 62.7 (SD 8.5) years old. Median duration of  
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5 282 symptoms was 42 months (IQR 18-72). After randomisation, 57 patients were placed in the  
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7 283 intervention group and 54 in the control group. Despite randomisation, there were significant  
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9 284 differences in baseline HOOS/KOOS pain subscales ( $38.0 \pm 14.0$  in the duloxetine group vs  
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11 285  $30.6 \pm 12.7$  in the control group;  $P=0.004$ ) and mean VAS at rest ( $46.6 \pm 24.8$  in the duloxetine group  
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13  
14 286 vs  $58.7 \pm 18.2$  in the control group;  $p=0.004$ ). Concurrent back pain was reported by 11.9% of  
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16 287 participants (7.3% vs 16.7% for the intervention vs control group, respectively;  $p=0.151$ ). The  
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18 288 incidence of other pain conditions (migraine, irritable bowel syndrome, fibromyalgia, chronic  
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20 289 neck pain) was below 10%, with no significant differences between the groups.  
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23 290 ***Please insert figure 1 here***  
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**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*

293 *Postoperative Pain*

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

303 ***Please insert figure 2 here***

304 Based on the multilevel mixed model for repeated measures as described above, Table 2  
 305 presents the estimated means and differences in pain at different timepoints between treatment  
 306 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
<i>Preoperatively</i>					
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
<i>Postoperatively</i>					
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
<b>6 months post- arthroplasty</b>	<b>KOOS/HOOS-p</b>	<b>74.5 (48.8-100.2)</b>	<b>76.0 (50.3-101.7)</b>	<b>1.5 (-5.8-8.8)</b>	<b>0.690</b>
	<b>mPDQ</b>	<b>7.2 (-1.7-16.1)</b>	<b>7.1 (-1.8-16.02)</b>	<b>0.1 (-2.5-2.6)</b>	<b>0.952</b>
	<b>VAS-R</b>	<b>21.4 (-8.6-51.4)</b>	<b>15.5 (-14.5-45.5)</b>	<b>5.9 (-2.6-14.4)</b>	<b>0.173</b>
	<b>VAS-M</b>	<b>25.3 (-5.7-56.3)</b>	<b>21.3 (-9.7-52.2)</b>	<b>4.0 (-4.8-12.8)</b>	<b>0.370</b>
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.**

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### 308 *Results of sub-analysis:*

309 The study group consisted of 61 knee OA patients and 50 hip OA patients. The table in the  
 310 supplementary file presents the estimated means and difference based on the mixed model for  
 311 repeated measures using a piece-wise design including joint as a fixed variable. A significant effect  
 312 was seen in knee OA patients after 7 weeks of targeted treatment with duloxetine compared to  
 313 usual care, with an estimated mean KOOS pain subscale score of 47.2 (95% CI 21.6-72.8) for  
 314 duloxetine and 33.9 (95% CI 8.3-59.5) for usual care (estimated difference 13.3, 95% CI 4.4-22.3;  
 315  $p=0.004$ ). As seen in the table in the supplementary file, the duloxetine treatment does not show  
 316 a similar effect in hip OA patients, with an estimated mean HOOS pain subscale score of 39.9 (95%  
 317 CI 14.0-65.7) for duloxetine and 38.0 (95% CI 12.3-63.7) for usual care (estimated difference 1.8,  
 318 95% CI -8.0-11.7;  $p=0.714$ ). For both subgroups there was no significant effect of duloxetine  
 319 treatment on any of the postoperative timepoints (estimated differences of 4.1 (95% CI -6.1-14.3  
 320  $p=0.432$  for hip OA patients and estimated differences of 0.5 (95% CI -9.1-10.0  $p=0.924$  for knee  
 321 OA patients at six months postoperatively. Supplementary Figure 3 shows the course of the  
 322 KOOS/HOOS pain subscale for the different treatment groups based on the mixed model for  
 323 repeated measures including joint groups.

### 324 *Chronic residual pain*

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

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3 329 14.3% of hip patients and 47.1% of knee patients had a KOOS/HOOS pain subscale <70 six months  
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5 330 post-arthroplasty. Twelve months post-arthroplasty this was 19% for hip patients and 38% for  
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7 331 knee patients.  
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### 10 332 **Loss to follow-up, Protocol violations, Adverse effects, and Missing data**

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13 333 Within the intervention group, 12 patients (21.1%) discontinued duloxetine due to adverse effects  
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15 334 (AEs). No subsequent timepoints were retrieved after these patients' discontinuation, so they  
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17 335 were lost to follow-up. Other losses to follow-up constituted approximately 5% of participants  
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19 336 (see Figure 1). There were 10 registered protocol violations, nine from another TJA within the  
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21 337 follow-up year (two in the intervention group vs seven in the usual-care group). These patients  
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23 338 all remained in the study up to one-year follow-up. Three patients from the intervention group  
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25 339 discontinued participation during the follow-up period due to serious AEs not related to the  
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27 340 intervention. One patient (intervention group) developed post-TKA infection and underwent  
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29 341 extensive additional treatment involving surgery and antibiotics. This patient did remain in the  
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31 342 follow-up process up to the end of the study. Another patient (intervention group) suffered from  
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33 343 post-TKA aseptic loosening of the tibial component, also remained in the study up to the last  
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35 344 follow-up timepoint, and later on underwent revision surgery. Apart from these discontinuations,  
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37 345 some patients did not return their questionnaires for any of the follow-up timepoints despite  
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39 346 phone and/or mail reminders. Complete follow-up of all postoperative timepoints up to 1 year  
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41 347 postoperatively was retrieved in 92 cases (82.9%).  
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## 350 Discussion

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

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

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



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3 376 difference does not seem clinically relevant compared to reported minimally important changes  
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5 377 (MIC) of 10 points in literature.<sup>40-42</sup> It should be noted that these MIC values are mostly reported  
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7 378 after operative treatments and therefore cannot automatically be extrapolated to relevant  
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9 379 changes following conservative treatment. If the effect of desensitisation is too small to make a  
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11 380 clinically relevant difference immediately following the treatment phase, this could explain the  
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13 381 lack of effect on chronic residual pain after TJA. A detailed analysis of the treatment effect in the  
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15 382 preoperative study period was published earlier,<sup>43</sup> describing more extensively how effects of  
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17 383 duloxetine found in previous literature are similar to the effect in the present study for knee OA.  
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19 384 Still, comparison is only possible to a limited extent due to the more controlled nature of previous  
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21 385 studies and investigating only knee OA populations.<sup>24-27</sup> There is a lack of studies on hip OA  
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23 386 patients. Thanks to the enriched nature of the present study a greater effect of duloxetine could  
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25 387 have been expected when comparing to previous studies. The administered duloxetine regimen  
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27 388 was in accordance with the recommended treatment dose based on previous literature, although  
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29 389 the treatment duration can be considered relatively short compared to literature.<sup>24,25,34,35</sup> Future  
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31 390 studies could investigate whether a longer preoperative treatment duration would show more  
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33 391 effect on chronic residual pain post-TJA. As described in the sub-analysis in the supplementary  
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35 392 file, the found effect of duloxetine treatment can be principally attributed to the knee OA group of  
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37 393 the study population. No effect of duloxetine treatment was found in the hip OA study population.  
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39 394 The cause of the lack of effect in the hip OA subgroup of patients can only be speculated on.<sup>43</sup> Also,  
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41 395 for hip OA patients, despite having screened for signs of sensitisation, we found a relatively low  
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43 396 percentage of chronic residual pain – 14.3% after 6 months and 19% after 12 months – whereas  
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45 397 literature reports up to 23%.<sup>21,22</sup> Consequently, the association between sensitisation in hip OA  
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47 398 and development of chronic residual pain after THA is less prominent in the present study. The  
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49 399 proportion of patients with chronic residual pain is relatively high in knee OA patients after TKA,  
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51 400 47.1% after 6 months and 38% after 12 months, compared to up to 34% in literature.<sup>10,18,20,21</sup> This  
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53 401 was expected due to the enriched nature of our study population. And yet the numbers of the  
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3 402 subgroups of knee and hip OA patients are low, rendering generalisability of these findings  
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5 403 limited.

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8 404 Third, it is possible that the effect of duloxetine treatment diminishes after tapering of the  
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10 405 treatment dose and that the desensitisation is becoming undone in the (short) interval period  
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12 406 between tapering and surgery. This interval period was imposed for safety reasons (see Methods  
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14 407 section). In the previous publication focusing on the preoperative study period, a decrease in  
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16 408 treatment effect could be observed after the tapering phase.<sup>43</sup> This could explain the lack of  
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18 409 treatment effect on chronic residual pain. In a recent study a 30mg duloxetine regimen was  
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20 410 administered one day before up to six weeks after TKA to knee OA patients with signs of  
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22 411 sensitisation; the perioperative duloxetine treatment significantly reduced pain up to 12 weeks  
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24 412 postoperatively.<sup>27</sup> Maybe the treatment timing should have been more suitability and safety of the  
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26 413 perioperative period, but no information is reported beyond 12 weeks postoperatively. Studies  
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28 414 are needed to determine whether a different timing of preoperative duloxetine treatment  
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30 415 continuing up to (or shortly after) TJA has a different effect on chronic residual pain compared to  
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32 416 the present study.  
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37 417 Fourth, this study centres around the hypothesis that treatment of sensitisation in OA  
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39 418 patients curbs development of chronic residual pain after THA/TKA. Although in literature signs  
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41 419 of sensitisation are a known predictor for developing chronic residual pain post-TJA, that does not  
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43 420 necessarily imply that treatment of the first prevents development of the latter. Our present  
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45 421 findings could therefore be in line with a theory by Neogi et al.<sup>1,14</sup> rather than being induced by  
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47 422 nociceptive input from the OA pathology, sensitisation should be seen as a trait related to a  
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49 423 person's genetic/systemic predisposition to increased pain perception, which is unmasked once  
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51 424 nociceptive input is supplied by structural OA pathology. Maybe sensitisation in OA and chronic  
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53 425 residual pain post-TJA are both traits of an underlying proneness/vulnerability to enhanced pain  
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55 426 experience, which explains why people who develop sensitisation in OA are also at risk of  
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57 427 developing chronic residual pain, but treatment of the first does not influence the underlying  
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3 428 vulnerability and therefore does not lessen the development of chronic residual pain. As to our  
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5 429 knowledge this is the first study to investigate the direct effect of treatment of sensitisation in OA  
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7 430 on chronic residual pain, additional research is needed to reassess the present findings and to  
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9 431 further investigate the complex causal pathways in the development of chronic residual pain.  
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### 12 432 *Strengths and limitations*

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15 433 This study contributes important pragmatic insights to the existing literature. There is an  
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17 434 increasing demand for pragmatic studies in the field of OA research.<sup>44-46</sup> Pragmatic trials attempt  
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19 435 to demonstrate whether an intervention works in the reality of daily practice rather than under  
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21 436 highly controlled conditions. Pragmatic dimensions of the DOA study are specified in detail in our  
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23 437 design study.  
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27 438 There are also limitations to this study. First, the substantial difference in treatment effect  
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29 439 of duloxetine in the two different joint groups was not anticipated and somewhat lessens the  
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31 440 interpretability of our results for the total study group, as the study population was  
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33 441 underpowered to analyse hip and knee OA patients separately. However, by designing a mixed  
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35 442 model for repeated measures including joint as a fixed variable (see sub-analysis in  
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37 443 supplementary file) we were able to assess the effect of joint group in the study population as a  
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39 444 whole. Second, by comparing duloxetine treatment with usual care we can only assess the  
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41 445 combination of the pharmacological effect together with the accompanying placebo and nocebo  
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43 446 effects. However, to some extent these factors would also play a role in daily administration of this  
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45 447 treatment and are therefore relevant for assessing the effectiveness of the total intervention. Due  
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47 448 to lack of blinding and the high percentage of AEs in the duloxetine treatment group, there is a  
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49 449 possibility of a nocebo effect, especially during and shortly after the intervention period. Still, due  
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51 450 to the extensive time period between the actual study intervention and the surgery that took place  
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53 451 in-between, this effect is not very likely to have influenced the primary endpoint of this study at  
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55 452 six months post-arthroplasty.  
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### 60 453 *Suitability and safety*

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3 454 Regarding suitability and safety of duloxetine in the targeted treatment population, the  
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5 455 percentage of AEs was high in the intervention group, with 21.1% of intervention participants  
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7 456 discontinuing the study treatment due to AEs. The incidence and nature of the AEs in the  
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9 457 treatment period are described in more detail elsewhere.<sup>43</sup> Also, due to the risk of side effects a  
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11 458 substantial proportion of patients was disinclined to participate in the study. This, in combination  
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13 459 with the substantial number of contraindications for duloxetine for medical reasons, lessens the  
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15 460 practical applicability of duloxetine in general practice for OA patients with accompanying  
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17 461 comorbidity.  
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21 462 **In conclusion**, based on the results of the present study, preoperative targeted treatment  
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23 463 with duloxetine in end-stage hip and knee OA patients with sensitisation does not influence  
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25 464 postoperative chronic residual pain after arthroplasty. Duloxetine does seem to have a treatment  
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27 465 effect on pain in end-stage knee OA patients suffering from sensitisation, but clinically relevant  
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29 466 thresholds were not met and applicability seems limited. No treatment effect was found in end-  
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31 467 stage hip OA patients with sensitisation. The percentage of patients with chronic residual pain in  
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33 468 this sensitised study population was relatively high for knee patients (38%, 12 months post-TKA)  
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35 469 but relatively low for hip patients (19%, 12 months post-THA). Additional studies are needed,  
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37 470 especially regarding timing and duration of duloxetine treatment. Other treatment options for OA  
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39 471 patients with sensitisation as well as for chronic residual pain should be explored. Dedicated  
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41 472 studies specifically addressing these issues in hip OA patients are indicated, considering the  
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43 473 apparent differences between hip and knee OA patients found in the present study.  
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#### 49 475 **Figure Legends:**

50 476 **Figure 1.** Flowchart of screening and inclusion process.

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52 477 **Figure 2.** Course of KOOS/HOOS pain subscale per treatment group based on the mixed model  
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54 478 for repeated measures using a piece-wise design.  
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#### 58 59 480 **Competing Interests**

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3 481 There are no competing interests for any of the authors.  
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5 482

6  
7 483 **Author Contributions**

8  
9 484 Conception and design of the study: Wietske Rienstra, Tim Blikman, Roy Stewart, Sjoerd K.  
10 485 Bulstra, Inge van den Akker-Scheek, Martin Stevens.

11  
12 486 Acquisition, analysis and interpretation of data: Wietske Rienstra, Tim Blikman, Sjoerd K.  
13 487 Bulstra, Inge van den Akker-Scheek, Martin Stevens.

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15 488 Drafting and revision of the manuscript: Wietske Rienstra, Tim Blikman, Baukje Dijkstra, Roy  
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17 490 Akker-Scheek, Martin Stevens.

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20  
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25 495 and analysis, decision to publish, or preparation of the manuscript.

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29 497 **Data Sharing**

30  
31 498 Data are available upon reasonable request.  
32 499

33  
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1  
2  
3 519 **References**  
4  
5

- 6 520 1. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthr Cartil*. Published  
7  
8 521 online 2013. doi:10.1016/j.joca.2013.03.018  
9  
10  
11 522 2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. Published online 2019.  
12  
13 523 doi:10.1016/S0140-6736(19)30417-9  
14  
15  
16 524 3. Kurtz SM, Ong KL, Lau E, Bozic KJ. Impact of the economic downturn on total joint  
17  
18 525 replacement demand in the United States: Updated projections to 2021. *J Bone Jt Surg - Am*  
19  
20 526 *Vol*. Published online 2014. doi:10.2106/JBJS.M.00285  
21  
22  
23 527 4. Inacio MCS, Graves SE, Pratt NL, Roughead EE, Nemes S. Increase in Total Joint Arthroplasty  
24  
25 528 Projected from 2014 to 2046 in Australia: A Conservative Local Model With International  
26  
27 529 Implications. *Clin Orthop Relat Res*. Published online 2017. doi:10.1007/s11999-017-5377-  
28  
29 530 7  
30  
31  
32  
33 531 5. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and  
34  
35 532 knee arthroplasty in the United States from 2005 to 2030. *J Bone Jt Surg - Ser A*. Published  
36  
37 533 online 2007. doi:10.2106/JBJS.F.00222  
38  
39  
40 534 6. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients  
41  
42 535 report long-term pain after total hip or knee replacement for osteoarthritis? A systematic  
43  
44 536 review of Prospective studies in unselected patients. *BMJ Open*. Published online 2012.  
45  
46 537 doi:10.1136/bmjopen-2011-000435  
47  
48  
49 538 7. Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: Nociceptive or neuropathic? *Nat*  
50  
51 539 *Rev Rheumatol*. Published online 2014. doi:10.1038/nrrheum.2014.47  
52  
53  
54  
55 540 8. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on  
56  
57 541 the modified painDETECT correlate with signs of central sensitization in knee  
58  
59 542 osteoarthritis. *Osteoarthr Cartil*. Published online 2013. doi:10.1016/j.joca.2013.06.023  
60

- 1  
2  
3 543 9. Ohtori S, Orita S, Yamashita M, et al. Existence of a neuropathic pain component in patients  
4  
5 544 with osteoarthritis of the knee. *Yonsei Med J*. Published online 2012.  
6  
7 545 doi:10.3349/ymj.2012.53.4.801  
8  
9  
10 546 10. Valdes AM, Suokas AK, Doherty SA, Jenkins W, Doherty M. History of knee surgery is  
11  
12 547 associated with higher prevalence of neuropathic pain-like symptoms in patients with  
13  
14 548 severe osteoarthritis of the knee. *Semin Arthritis Rheum*. Published online 2014.  
15  
16 549 doi:10.1016/j.semarthrit.2013.10.001  
17  
18  
19  
20 550 11. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee  
21  
22 551 osteoarthritis: A systematic review and meta-analysis. *Osteoarthr Cartil*. Published online  
23  
24 552 2015. doi:10.1016/j.joca.2015.02.163  
25  
26  
27 553 12. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients  
28  
29 554 with osteoarthritis pain: A systematic literature review. *Eur J Pain (United Kingdom)*.  
30  
31 555 Published online 2014. doi:10.1002/j.1532-2149.2014.499.x  
32  
33  
34 556 13. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity  
35  
36 557 in knee osteoarthritis: Trait or state? *Ann Rheum Dis*. Published online 2015.  
37  
38 558 doi:10.1136/annrheumdis-2013-204191  
39  
40  
41  
42 559 14. Neogi T. Structural correlates of pain in osteoarthritis. *Clin Exp Rheumatol*. Published online  
43  
44 560 2017.  
45  
46  
47 561 15. Dimitroulas T, Duarte R V., Behura A, Kitas GD, Raphael JH. Neuropathic pain in  
48  
49 562 osteoarthritis: A review of pathophysiological mechanisms and implications for treatment.  
50  
51 563 *Semin Arthritis Rheum*. Published online 2014. doi:10.1016/j.semarthrit.2014.05.011  
52  
53  
54 564 16. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. *Clin Exp Rheumatol*. Published online  
55  
56 565 2017.  
57  
58  
59 566 17. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence  
60



- 1  
2  
3 567 supporting the presence of central sensitization in a cohort of osteoarthritis patients.  
4  
5 568 *Arthritis Care Res.* Published online 2009. doi:10.1002/art.24837  
6  
7  
8 569 18. Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L.  
9  
10 570 Facilitation of pain sensitization in knee osteoarthritis and persistent post-operative pain:  
11  
12 571 A cross-sectional study. *Eur J Pain (United Kingdom)*. Published online 2014.  
13  
14 572 doi:10.1002/j.1532-2149.2013.00447.x  
15  
16  
17 573 19. Lundblad H, Kreicbergs A, Jansson KÅ. Prediction of persistent pain after total knee  
18  
19 574 replacement for osteoarthritis. *J Bone Jt Surg - Ser B*. Published online 2008.  
20  
21 575 doi:10.1302/0301-620X.90B2.19640  
22  
23  
24 576 20. Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain  
25  
26 577 sensitisation and chronic pain after knee replacement: An exploratory study. *Osteoarthr*  
27  
28 578 *Cartil*. Published online 2013. doi:10.1016/j.joca.2013.05.008  
29  
30  
31 579 21. Wylde V, Sayers A, Lenguerrand E, et al. Preoperative widespread pain sensitization and  
32  
33 580 chronic pain after hip and knee replacement: A cohort analysis. *Pain*. Published online  
34  
35 581 2015. doi:10.1016/j.pain.0000000000000002  
36  
37  
38  
39 582 22. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement:  
40  
41 583 Prevalence, sensory qualities, and postoperative determinants. *Pain*. Published online  
42  
43 584 2011. doi:10.1016/j.pain.2010.11.023  
44  
45  
46 585 23. Murphy SL, Phillips K, Williams DA, Clauw DJ. The role of the central nervous system in  
47  
48 586 osteoarthritis pain and implications for rehabilitation. *Curr Rheumatol Rep*. Published  
49  
50 587 online 2012. doi:10.1007/s11926-012-0285-z  
51  
52  
53 588 24. Wang G, Bi L, Li X, et al. Efficacy and safety of duloxetine in Chinese patients with chronic  
54  
55 589 pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study.  
56  
57 590 *Osteoarthr Cartil*. Published online 2017. doi:10.1016/j.joca.2016.12.025  
58  
59  
60



- 1  
2  
3 591 25. Wang ZY, Shi SY, Li SJ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain:  
4  
5 592 A Meta-Analysis of Randomized Controlled Trials. *Pain Med (United States)*. Published  
6  
7 593 online 2015. doi:10.1111/pme.12800  
8  
9  
10 594 26. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic  
11  
12 595 review and meta-analysis. *Korean J Intern Med*. Published online 2019.  
13  
14 596 doi:10.3904/kjim.2018.460  
15  
16  
17 597 27. Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine Reduces Pain and Improves  
18  
19 598 Quality of Recovery Following Total Knee Arthroplasty in Centrally Sensitized Patients: A  
20  
21 599 Prospective, Randomized Controlled Study. *J Bone Jt Surg - Am Vol*. 2019;101(1).  
22  
23 600 doi:10.2106/JBJS.18.00347  
24  
25  
26  
27 601 28. Blikman T, Rienstra W, Van Raaij TM, et al. Duloxetine in osteoarthritis (DOA) study: Study  
28  
29 602 protocol of a pragmatic open-label randomised controlled trial assessing the effect of  
30  
31 603 preoperative pain treatment on postoperative outcome after total hip or knee arthroplasty.  
32  
33 604 *BMJ Open*. Published online 2016. doi:10.1136/bmjopen-2015-010343  
34  
35  
36 605 29. Hochman J, Elkayam J, Gagliese L, Davis A, Hawker G. The relationship between neuropathic  
37  
38 606 pain symptoms on the modified pain detect and signs of central sensitization in knee  
39  
40 607 osteoarthritis. *Osteoarthr Cartil*. Published online 2012. doi:10.1016/j.joca.2012.02.430  
41  
42  
43  
44 608 30. Rienstra W, Blikman T, Mensink FB, et al. The modified painDETECT Questionnaire for  
45  
46 609 patients with hip or knee osteoarthritis: Translation into Dutch, cross-cultural adaptation  
47  
48 610 and reliability assessment. *PLoS One*. Published online 2015.  
49  
50 611 doi:10.1371/journal.pone.0146117  
51  
52  
53 612 31. Rienstra W, Blikman T, Dijkstra B, et al. Validity of the Dutch modified painDETECT  
54  
55 613 questionnaire for patients with hip or knee osteoarthritis. *Disabil Rehabil*. Published online  
56  
57 614 2019. doi:10.1080/09638288.2017.1413429  
58  
59  
60

- 1  
2  
3 615 32. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to  
4  
5 616 identify neuropathic components in patients with back pain. *Curr Med Res Opin*. Published  
6  
7 617 online 2006. doi:10.1185/030079906X132488  
8  
9  
10 618 33. Of H, Information P, Capsules DD, et al. Prescribing Information. Cymbalta. Eli Lilly, 2006.  
11  
12 619 2004;(3).  
13  
14  
15 620 34. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the  
16  
17 621 treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-  
18  
19 622 controlled trial. *Pain*. Published online 2009. doi:10.1016/j.pain.2009.06.024  
20  
21  
22  
23 623 35. Chappell AS, Desai D, Liu-Seifert H, et al. A Double-blind, Randomized, Placebo-  
24  
25 624 controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain  
26  
27 625 Due to Osteoarthritis of the Knee. *Pain Pract*. Published online 2011. doi:10.1111/j.1533-  
28  
29 626 2500.2010.00401.x  
30  
31  
32 627 36. <http://www.koos.nu>. Hip Disability and Osteoarthritis Outcome Score, Scoring. HOOS  
33  
34 628 Excel scoring files. 2013;(June):2-4.( assessed april 2021)  
35  
36  
37 629 37. <http://www.koos.nu> Knee Osteoarthritis Outcome Score, Scoring. KOOS Excel scoring files.  
38  
39 630 2012;(August):4-6. (assessed april 2021)  
40  
41  
42 631 38. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): From  
43  
44 632 joint injury to osteoarthritis. *Health Qual Life Outcomes*. Published online 2003.  
45  
46 633 doi:10.1186/1477-7525-1-64  
47  
48  
49 634 39. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic  
50  
51 635 severity in knee osteoarthritis: Findings from quantitative sensory testing of central  
52  
53 636 sensitization. *Arthritis Rheum*. Published online 2013. doi:10.1002/art.34646  
54  
55  
56  
57 637 40. Collins NJ, Prinsen CAC, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and  
58  
59 638 Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of  
60

- 1  
2  
3 639 measurement properties. *Osteoarthr Cartil.* Published online 2016.  
4  
5 640 doi:10.1016/j.joca.2016.03.010  
6  
7  
8 641 41. Çelik D, Çoban Ö, Kılıçoğlu Ö. Minimal clinically important difference of commonly used  
9  
10 642 hip-, knee-, foot-, and ankle-specific questionnaires: a systematic review. *J Clin Epidemiol.*  
11  
12 643 2019;113:44-57. doi:10.1016/j.jclinepi.2019.04.017  
13  
14  
15 644 42. Roos EM, Boyle E, Frobell RB, Lohmander LS, Ingelsrud LH. It is good to feel better, but  
16  
17 645 better to feel good: Whether a patient finds treatment successful' or not depends on the  
18  
19 646 questions researchers ask. *Br J Sports Med.* Published online 2019. doi:10.1136/bjsports-  
20  
21 647 2018-100260  
22  
23  
24  
25 648 43 [http://hdl.handle.net/\(...\)6a-997f-0fd5826319ce](http://hdl.handle.net/(...)6a-997f-0fd5826319ce). Blikman T. Neuropathic-like symptoms  
26  
27 649 in hip and knee osteoarthritis. [2020] University of Groningen ISBN 978-94-6419-011-3  
28  
29  
30 650 44. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip  
31  
32 651 and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines.  
33  
34 652 *Osteoarthr Cartil.* Published online 2008. doi:10.1016/j.joca.2007.12.013  
35  
36  
37 653 45. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator  
38  
39 654 summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol.* Published online 2009.  
40  
41 655 doi:10.1016/j.jclinepi.2008.12.011  
42  
43  
44  
45 656 46. Zwarenstein M, Treweek S, Gagnier JJ. CONSORT group; Pragmatic Trials in Healthcare  
46  
47 657 (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT  
48  
49 658 statement. *Bmj.* 2008;337(December):a2390. doi:10.1136/bmj.a2390  
50  
51  
52  
53 659  
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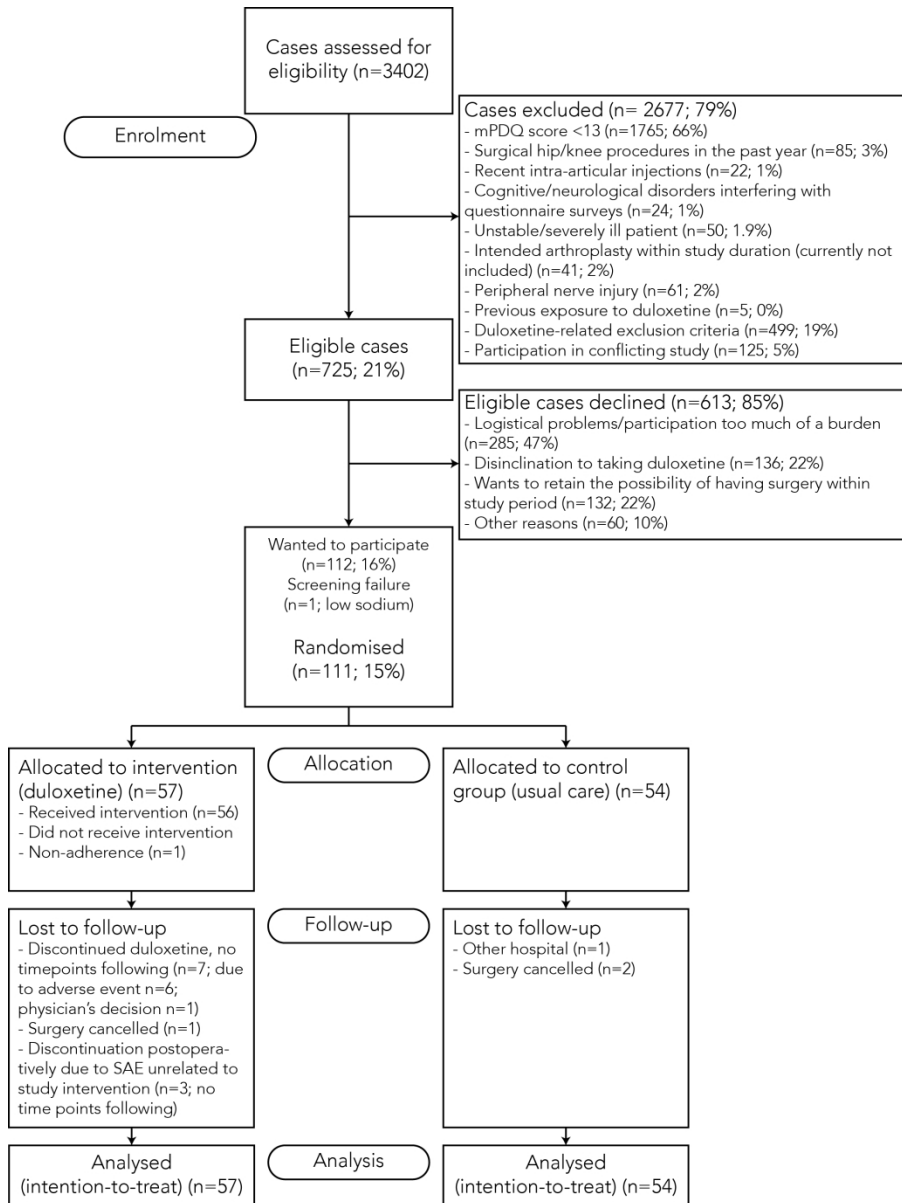


Figure 1. Flowchart of screening and inclusion process.

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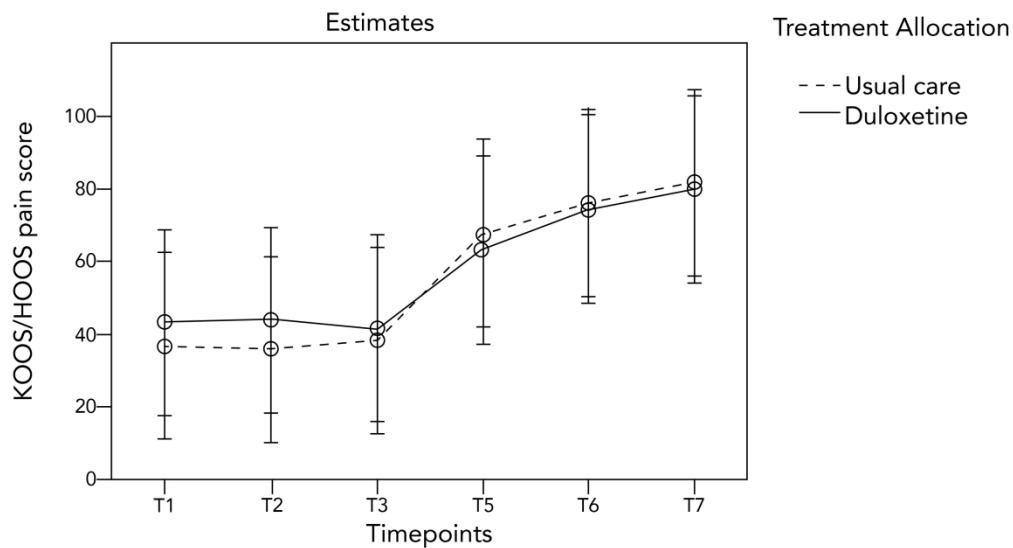
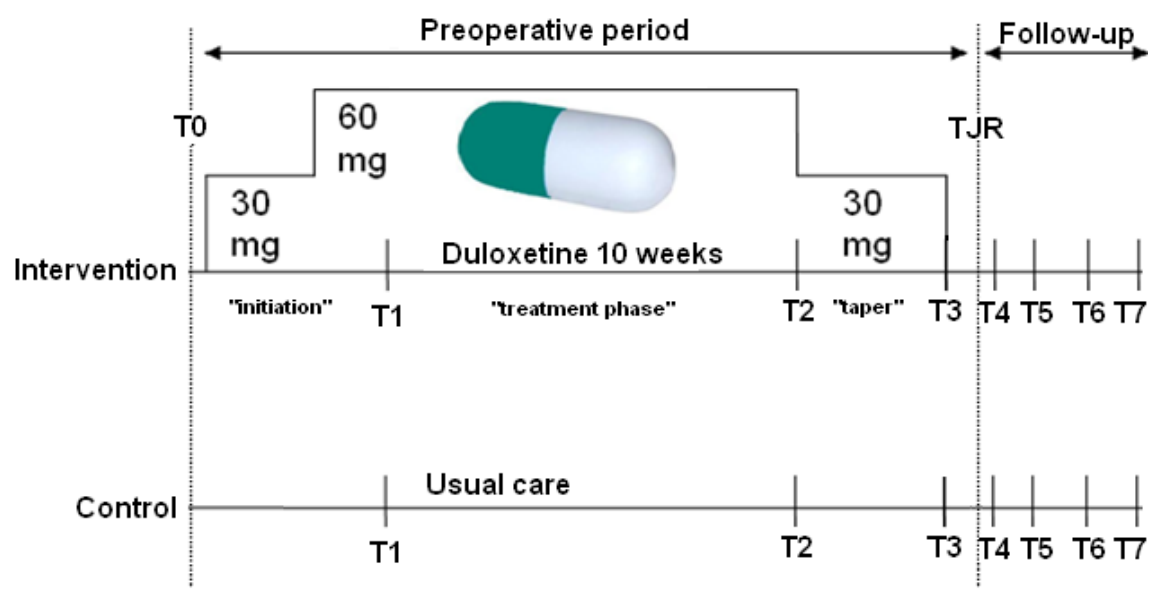


Figure 2. Course of KOOS/HOOS pain subscale per treatment group based on the mixed model for repeated measures using a piece-wise design.

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### Supplementary 1/3: Scheme of the DOA trial



Peer review only

### 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.<sup>13,49,50</sup> Missing items in the KOOS/HOOS were imputed according to the KOOS/HOOS manual.<sup>51,52</sup>

#### *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  $\leq 12$  indicates a nociceptive pain profile, 13-18 a

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3 possible neuropathic pain profile, and  $\geq 19$  a likely neuropathic pain profile.<sup>43,53</sup> m-PDQ scores  
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5 >12.0 were associated with greater odds of having signs of sensitisation. Correcting for age,  
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7 knee OA patients with m-PDQ scores >12.0 were almost six times more likely to have signs of  
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9 sensitisation (on Quantitative Sensory Testing) than those with scores  $\leq 12$ .<sup>43</sup> Gwilym et al.  
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11 found significant positive correlations between PainDETECT scores and functional MRI  
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13 activity, indicating central sensitisation among hip OA patients.<sup>14</sup> The Dutch version of the m-  
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15 PDQ is considered to be a reliable and valid self-report instrument in patients with hip and  
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17 knee OA.<sup>44,45</sup>

#### 25 *Visual Analogue Scale Pain (VAS pain)*

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27 Visual Analogue Scales (VAS) are widely used to measure pain. Patients place a marking on a  
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29 100-mm horizontal line that represents their pain. The left ending of the line represents 'no  
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31 pain at all' and the right ending 'worst pain imaginable'. The distance between the marking  
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33 and the left ending of the line is measured in whole millimetres and represents the pain score.  
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35 Patients were asked to note their present pain status and their mean pain status over the last  
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37 week, at rest (VAS-R: defined as pain at rest while sitting, standing or lying down) and during  
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39 movement (VAS-M defined as pain during regular walking). VAS have been reported as valid  
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41 and reliable measures for pain intensity.<sup>54</sup>



### 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.

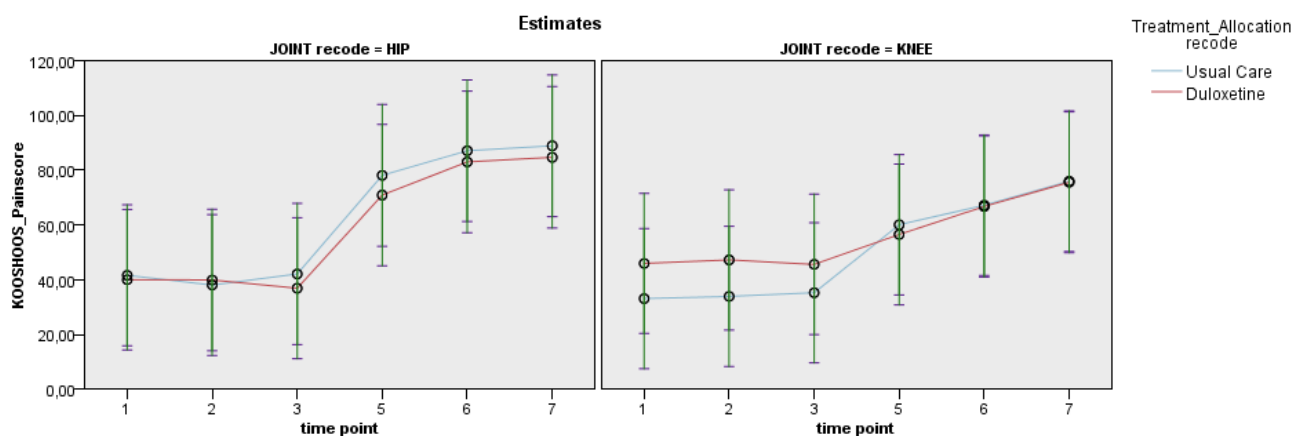
#### *Results of sub-analysis:*

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 treatment	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 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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
<b>Methods</b>			
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
<b>Randomisation:</b>			
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

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
2				
3		11b	If relevant, description of the similarity of interventions	NA
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9 and 10 + suppl 3
5				
6		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10 and Suppl 4
7				
8				
9	<b>Results</b>			
10	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
11		13b	For each group, losses and exclusions after randomisation, together with reasons	11 and suppl 5
12				
13	Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
14		14b	Why the trial ended or was stopped	6
15				
16	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
17	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
18				
19	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
20		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
21	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Suppl 4
22				
23	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11 and suppl 5
24				
25				
26	<b>Discussion</b>			
27	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19 and 20
28	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19 and 20
29	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16 to 19
30				
31	<b>Other information</b>			
32	Registration	23	Registration number and name of trial registry	6
33	Protocol	24	Where the full trial protocol can be accessed, if available	6
34	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6
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1 \*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  
2 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.  
3 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
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