

Is the Preoperative Use of Antidepressants and Benzodiazepines Associated with Opioid and Other Analgesic Use after Hip and Knee Arthroplasty?

Running Title: Analgesic Use after Joint Arthroplasty

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1 **Abstract**

2 *Background* Mental health disorders can occur in patients with pain conditions, and there have been reports of
3 an increased risk of persistent pain after THA and TKA among patients who have psychological distress.
4 Persistent pain may result in the prolonged consumption of opioids and other analgesics, which may expose
5 patients to adverse drug events as well as narcotic habituation or addiction. However, the degree to which
6 preoperative use of antidepressants or benzodiazepines is associated with prolonged analgesic use after surgery
7 is not well quantified.

8 *Question/purposes* (1) Is the preoperative use of antidepressants or benzodiazepine medications associated with
9 a greater postoperative use of opioids, NSAIDs, or acetaminophen? (2) Is the proportion of patients still using
10 opioid analgesics 1 year after arthroplasty higher among patients who were taking antidepressants or
11 benzodiazepine medications before surgery, after controlling for relevant confounding variables? (3) Does
12 analgesic drug use decrease after surgery in patients with a history of antidepressant or benzodiazepine use? (4)
13 Does the proportion of patients using antidepressants or benzodiazepines change after joint arthroplasty
14 compared with before?

15 *Methods* Of the 10,138 patients who underwent hip arthroplasty and the 9930 patients who underwent knee
16 arthroplasty at Coxa Hospital for Joint Replacement, Tampere, Finland, between 2002 and 2013, those who had
17 primary joint arthroplasty for primary osteoarthritis (64% [6502 of 10,138] of patients with hip surgery and 82%
18 [8099 of 9930] who had knee surgery) were considered potentially eligible. After exclusion of another 8% (845
19 of 10,138) and 13% (1308 of 9930) of patients because they had revision or another joint arthroplasty within 2
20 years from the index surgery, 56% (5657 of 10,138) of patients with hip arthroplasty and 68% (6791 of 9930) of
21 patients with knee arthroplasty were included in this retrospective registry study. Patients who redeemed
22 prescribed antidepressants or benzodiazepines were identified from a nationwide drug prescription register, and
23 information on the redeemed prescriptions for opioids (mild and strong), NSAIDs, and acetaminophen were
24 extracted from the same database. For the analyses, subgroups were created according to the status of
25 benzodiazepine and antidepressant use during the 6 months before surgery. First, the proportions of patients
26 who used opioids and any analgesics (that is opioids, NSAIDs, or acetaminophen) were calculated. Then,
27 multivariable logistic regression adjusted with age, gender, joint, Charlson Comorbidity Index, BMI, laterality
28 (unilateral/same-day bilateral), and preoperative analgesic use was performed to calculate odds ratios for any
29 analgesic use and opioid use 1 year postoperatively. Additionally, the proportion of patients who used

30 antidepressants and benzodiazepines were calculated for 2 years before and 2 years after surgery.

31 *Results* At 1 year postoperatively, patients with a history of antidepressant or benzodiazepine use were more
32 likely to redeem prescriptions for any analgesics than were patients without a history of antidepressant or
33 benzodiazepine use (adjusted ORs 1.9 (95% CI 1.6 to 2.2]; $p < 0.001$) and 1.8 (95% CI 1.6 to 2.0]; $p < 0.001$),
34 respectively). Similarly, patients with a history of antidepressant or benzodiazepine use were more likely to
35 redeem opioids than patients without a history of antidepressant or benzodiazepine use (adjusted ORs 2.1 (95%
36 CI 1.7 to 2.7]; $p < 0.001$) and 2.0 (95% CI 1.6 to 2.4]; $p < 0.001$), respectively). Nevertheless, the proportion of
37 patients who redeemed any analgesics was smaller 1 year after surgery than preoperatively also in patients with
38 a history of antidepressant (42% (439 of 1038) vs 55% (568 of 1038); $p < 0.001$) and/or benzodiazepine use
39 (40% (801 of 2008) vs 55% (1098 of 2008); $p < 0.001$). The proportion of patients who used antidepressants
40 and/or benzodiazepines was essentially stable during the observation period.

41 *Conclusion* Surgeons should be aware of the increased risk of prolonged opioid and other analgesic use after
42 surgery among patients who were on preoperative antidepressant and/or benzodiazepine therapy, and they
43 should have candid discussions with patients referred for elective joint arthroplasty about this possibility.
44 Further studies are needed to find out which are the most effective methods to reduce prolonged postoperative
45 opioid use among these patients.

46 *Level of Evidence* Level III, therapeutic study.

47 **Introduction**

48 Hip and knee arthroplasties are highly effective surgical procedures for reducing pain in patients with late-stage
49 osteoarthritis [18, 35]. This reduction in pain should eventually be reflected in reduced consumption of
50 analgesic drugs. However, between 23% and 34% of patients who undergo hip or knee arthroplasty still use
51 analgesic drugs (opioids, NSAIDs, or acetaminophen) 1 to 2 years after surgery, and between 5% and 16% still
52 use opioids [11, 27, 36]. Moreover, although there may be other pain sites that patients and their physicians opt
53 to treat with analgesics, between 10% and 20% of patients who undergo hip or knee arthroplasty continue to
54 experience persistent postoperative pain, potentially explaining the increased consumption of opioids and other
55 analgesics in this patient group [6, 10, 40]. Recently, attempts have been made to identify patients undergoing
56 THA or TKA who do not benefit from surgery as well as expected and who continue to use analgesic drugs after
57 surgery [4, 16, 22, 39]. Earlier, we found that analgesic drug consumption is reduced after hip and knee
58 arthroplasty at the population level [36], and that obesity, a higher number of comorbidities, gender (women
59 more than men), and preoperative use of analgesics were associated with the postoperative use of opioids,
60 NSAIDs, or acetaminophen [38]. Previous studies have almost exclusively focused on opioid consumption, and
61 psychiatric disorders, worse preoperative pain, and catastrophizing have also been associated with increased
62 consumption of opioids after joint arthroplasty [4, 12, 22, 24, 25, 27, 32, 42, 43]. These factors have also been
63 correlated with persistent pain [10, 28–30, 37, 45].

64 In some studies, patients undergoing THA or TKA who had preoperative depression or anxiety used opioids
65 more frequently than patients without these disorders [4, 12, 14, 22, 25, 32, 34], whereas such an association has
66 not been reported in other studies [22, 34, 42, 43]. Although NSAIDs and acetaminophen are used frequently in
67 patients referred for joint arthroplasty [11, 20], as well, previous studies have not analyzed whether the prior use
68 of antidepressants and benzodiazepines is associated with the consumption of different types of analgesics
69 (opioids, NSAIDs, or acetaminophen) after joint arthroplasty. It is also unclear whether opioid and overall
70 analgesic use decrease after surgery in patients with a history of antidepressant or benzodiazepine use because
71 previous studies [4, 12, 14, 22, 25, 32, 34, 42, 43] have focused only on factors associated with increased
72 analgesic use, and no studies have reported whether or not analgesic drug use decrease after surgery also in
73 patients with a history of antidepressant or benzodiazepine therapy. Moreover, comorbidities and potential
74 adverse drug effects may influence the choice of analgesics (for example starting opioids to avoid use of
75 NSAIDs, or avoiding opioids in older patients). For these reasons, it is of interest to study both overall analgesic
76 use as well as opioid use. It is also important to note that most previous studies have determined depression and

77 anxiety from medical records based on diagnosis codes [3, 4, 25, 32, 34, 42, 43]. Information on antidepressant
78 or benzodiazepine use may capture a higher proportion of patients at risk for prolonged opioid use compared
79 with the use of diagnosis codes because hospital register data may be incomplete, and because it is not
80 uncommon that these agents are used without a specific diagnosis of a psychiatric condition. Furthermore,
81 benzodiazepines may be used for sleep disturbances related to chronic pain, and certain antidepressants are
82 indicated for the treatment of chronic pain [19, 48]. Therefore, consumption of antidepressants and
83 benzodiazepines might decrease after surgery [17, 26, 46]. We are aware of only one previous study on this
84 subject, in which there was a minimal decrease in the proportion of patients who used benzodiazepines while the
85 use of antidepressants remained stable, but this study included only hip arthroplasty patients [11].

86 To fill the gaps in previous studies, we asked: (1) Is the preoperative use of antidepressants or benzodiazepine
87 medications associated with a greater postoperative use of opioids, NSAIDs, or acetaminophen? (2) Is the
88 proportion of patients still using opioid analgesics 1 year after arthroplasty higher among patients who were
89 taking antidepressants or benzodiazepine medications before surgery, after controlling for relevant confounding
90 variables? (3) Does analgesic drug use decrease after surgery in patients with a history of antidepressant or
91 benzodiazepine use? (4) Does the proportion of patients using antidepressants or benzodiazepines change after
92 joint arthroplasty compared with before?

93 **Patients and Methods**

94 *Study Design and Participants*

95 We conducted a retrospective study of patients who underwent primary hip or knee arthroplasty for
96 osteoarthritis between September 2002 and December 2013 in a single orthopaedic hospital in Finland (Coxa
97 Hospital for Joint Replacement, Tampere, Finland). The study protocol has been described in detail [36]. The
98 inclusion criteria were a primary operation and primary osteoarthritis as the indication for surgery. Other
99 indications were excluded to maximize the homogeneity of our study group; for example, polyarticular
100 involvement in patients with rheumatoid arthritis could confound analysis of the use of analgesic drugs. Only
101 one procedure was included per patient (the first joint arthroplasty in the study period). Additionally, patients
102 with revisions or primary arthroplasties of other joints during the observation period (2 years before or 2 years
103 after the operation date of the index surgery) were excluded so that the potential perioperative peak in analgesic
104 consumption related to this latter operation would not hamper the results related to the index surgery.

105 Of the 10,138 hip arthroplasty patients (with 13,802 hip arthroplasties) and 9930 knee arthroplasty patients

106 (with 14,708 knee arthroplasties) operated on during the observation periods, 64% (6502 of 10,138) patients had
107 primary hip arthroplasty and 82% (8099 of 9930) patients had primary knee arthroplasty for primary
108 osteoarthritis. A further 8% (845 of 10,138) and 13% (1308 of 9930) were excluded because of revision or
109 another joint arthroplasty within 2 years from the index surgery, leaving 56% (5657 of 10,138) of hip and 68%
110 (6791 of 9930) of knee arthroplasty patients for analysis (altogether 12,448 joint arthroplasty patients) (Fig. 1).
111 Thanks to use of nationwide register data, no patients were lost to follow-up.

112 *Demographics*

113 The mean age was 68 years (67 years for patients undergoing hip arthroplasty and 69 years for patients
114 undergoing knee arthroplasty), and 61% were women (7550 of 12,448 patients) (53% [2971 of 5657] of patients
115 with hip arthroplasty and 67% [4579 of 6791] of those with knee arthroplasty). Among the 12,448 patients in
116 the study, the most common comorbidities were hypertension (31% [3866]), cardiac disease (12% [1454]), and
117 diabetes (9% [1168]). Preoperatively, antidepressants, benzodiazepines, or both were used by 5% (564), 12%
118 (1534), and 4% (474) of patients, respectively (Table 1). Antidepressant use was more common in women and
119 in patients who had a knee arthroplasty, unilateral joint replacement, higher Charlson Comorbidity Index score
120 (CCI), diabetes, cardiac disease, psychotic disorder, neurodegenerative disease, pulmonary disease, history of
121 malignancy, and epilepsy. Benzodiazepine use was associated with the same factors, as well as with
122 hypertension and older age (Supplementary Table 1; supplemental materials are available with the online
123 version of *CORR*[®]).

124 In the overall group of 12,448 patients, 3 months preoperatively, 42% (5281) of patients redeemed at least one
125 type of analgesic drug, most commonly NSAIDs (30% [3729]), followed by acetaminophen (12% [1484]), and
126 opioids (11% [1339]). One year after surgery, the proportion of patients who redeemed at least one type of
127 analgesic drug had decreased to 25% (3157), and NSAIDs were still the most common group of analgesics used
128 (15% [1927]), followed by acetaminophen (9% [1152]), and opioids (6% [777]).

129 *Data Sources and Outcome Measures*

130 Information on the drug use of these patients 2 years before and 2 years after surgery was gathered from
131 Finland's Drug Prescription Register, which is maintained by the Social Insurance Institution. Finland has a
132 national health insurance scheme that covers all permanent residents, and the Drug Prescription Register
133 contains information on all prescribed medications that have been dispensed from pharmacies in Finland.
134 Information on the Anatomical Therapeutic Chemical code of the dispensed drugs, the number of units

135 dispensed (tablets or patches), and the date of purchase regarding antidepressants (N06A), benzodiazepine
136 derivatives (N05BA or N05CD), benzodiazepine-related drugs (N05CF), acetaminophen (N02BE01), NSAIDs
137 (M01A), and opioids (N02A) was collected from the register. Benzodiazepine derivatives and benzodiazepine-
138 related drugs were analyzed together and are referred to in this paper as benzodiazepines.

139 We analyzed analgesic drugs in two groups: opioids and any analgesic drugs (acetaminophen, NSAIDs, and
140 opioids). Pooling all analgesic drugs was used to study overall need for analgesic drugs. Over-the-counter
141 analgesic drugs were not recorded in this study. In Finland, over-the-counter analgesic drugs come in small
142 packages of acetaminophen, ibuprofen, and ketoprofen, which are also dispensed by pharmacies, and are
143 relatively more expensive than those prescribed by a general practitioner or orthopaedic clinician. Although the
144 study does not include data from the last few years, the guidelines for the pharmacological management of OA
145 pain have remained essentially similar through the study period and thereafter until 2019 [2, 9].

146 We divided patients into subgroups based on whether they had redeemed antidepressants or benzodiazepines 6
147 months preoperatively. Then, an exploratory analysis was made by calculating the proportions of patients who
148 redeemed opioids and any analgesics in these subgroups at 3-month intervals for a period of 2 years before and
149 2 years after surgery to illustrate the trends in drug use perioperatively. For the further statistical analyses, we
150 analyzed analgesic use 3 months before surgery (referred to as preoperative drug use) and for 3 months at 9 to
151 12 months after surgery (referred to as 1 year postoperatively). We chose the time period of 9 to 12 months after
152 surgery to exclude any analgesic consumption related to the acute postoperative period because analgesic
153 consumption was shown to stabilize at this timepoint in our previous analysis [36].

154 To examine our first and second research questions, we calculated multivariable logistic regression for the
155 probability of opioid and any analgesic use 3 months preoperatively and 1 year postoperatively. The
156 multivariable model was adjusted for potentially confounding factors such as age, gender, joint, BMI (missing
157 on 13% [1644 of 12,448] of patients), modified CCI, preoperative use of analgesics (categorical variable with
158 three groups: opioid, NSAID or acetaminophen but no opioid, none), and whether the patient had same-day
159 bilateral or unilateral surgery because these factors were associated with analgesic use in our previous analyses
160 with a threshold of $p < 0.05$ [38]. Information on comorbidities for the CCI was extracted from the nationwide
161 Special Reimbursement Register maintained by the Social Insurance Institution. A modified CCI score was
162 calculated, as in an earlier study [38]. A score of 1 was assigned for heart failure, coronary artery disease, Types
163 I or II diabetes, chronic asthma or other severe obstructive pulmonary disease, dementia, disseminated
164 connective tissue diseases, rheumatoid arthritis, and other comparable conditions. A score of 2 was assigned for

165 uremia resulting in dialysis, severe anemia in connection with chronic renal failure; leukemia and other
166 malignant diseases of the blood and bone marrow (including malignant diseases of the lymphatic system), and
167 cancer (including breast and prostate cancers, female genital tract cancer, and malignant neoplasms).

168 Additionally, because epilepsy and psychotic disorders are not components of the CCI, we performed an
169 additional analysis in which patients with these comorbidities were excluded, and the results were similar (this
170 additional analysis was performed because higher proportion of patients with epilepsy or psychosis used
171 antidepressants and/or benzodiazepines preoperatively compared with patients without epilepsy or psychosis)
172 (data not shown). The observed results were essentially the same among patients who had undergone hip or
173 knee arthroplasty, and therefore, the results are presented together (for opioid use, see Supplementary Table 2;
174 supplemental materials are available with the online version of *CORR*[®]).

175 For our third research question, we examined the exploratory trends of drug use in patients with a history of
176 antidepressant or benzodiazepine use, and we compared the proportions of patients who used opioids and other
177 analgesics preoperatively (0-3 months) and 1 year postoperatively. Finally, to answer question four, we have
178 descriptively reported the use of antidepressants and benzodiazepines preoperatively and postoperatively.

179 The analyses were performed using SPSS Statistics, version 25 (IBM Corp). Parametric variables are presented
180 as the mean and SD. We used a t-test to compare parametric variables and a chi-square test to compare
181 categorical variables. We used the McNemar test to compare proportions in paired groups. Multivariable logistic
182 regression analyses were used to calculate odds ratios with 95% confidence intervals for using analgesics. p
183 values of < 0.05 were considered statistically significant.

184 *Ethical Approval*

185 Because this was a retrospective register study, no approval from our ethical board or consent from patients was
186 required according to Finnish and EU legislation. The study was performed in accordance with the Declaration
187 of Helsinki.

188 **Results**

189 *Association Between Preoperative Antidepressants or Benzodiazepines and Postoperative Analgesic Use*

190 After controlling for potentially confounding variables such as age, number of comorbidities (CCI), and
191 preoperative use of analgesics, we found that patients with a history of antidepressant use were more likely to
192 redeem prescriptions for any analgesics than were patients without a history of antidepressant use (adjusted OR
193 1.9 [95% CI 1.6 to 2.2; $p < 0.001$) (Table 2). Similarly, patients with a history of benzodiazepine use were more

194 likely to redeem prescriptions for any analgesics than were patients without a history of benzodiazepine use
195 (adjusted OR 1.8 [95% CI 1.6 to 2.0]; $p < 0.001$) (Table 2). Moreover, the odds were the highest in patients with
196 a preoperative use of both antidepressants and benzodiazepines (Table 2). At 1 year postoperatively, analgesics
197 of all types were redeemed by 22% (2137 of 9876) of patients who had no history of preoperative use of
198 antidepressants or benzodiazepines, compared with 39% (219 of 564), 38% (581 of 1534), and 46% (220 of
199 474) of patients with prior use of antidepressants, benzodiazepines, or both, respectively ($p < 0.001$) (Fig. 2).
200 The proportion of patients who continued to use analgesics or started to use analgesics 1 year postoperatively
201 (those who did not use analgesics preoperatively but used them 1 year postoperatively) was higher in patients
202 with preoperative use of antidepressants or benzodiazepines (Table 3).

203 *Association Between Preoperative Antidepressants or Benzodiazepines and Persistent Opioid Use After Surgery*

204 In the multivariable logistic regression analysis, we found that patients with a history of antidepressant use were
205 more likely to redeem prescriptions for opioids than were patients without a history of antidepressant use
206 (adjusted OR 2.1 [95% CI 1.7 to 2.7]; $p < 0.001$). Patients with a history of benzodiazepine use were also more
207 likely to redeem prescriptions for opioids than were patients without a history of benzodiazepine use (adjusted
208 OR 2.0 [95% CI 1.6 to 2.4]; $p < 0.001$). At 1 year postoperatively, opioids were redeemed by 5% (455 of 9876)
209 of patients who had no history of preoperative use of antidepressants or benzodiazepines, compared with 13%
210 (72 of 564) of patients with a history of only antidepressant use, 11% (168 of 1534) of patients with a history of
211 only benzodiazepine use, and 17% (82 of 474) of patients with a history of both antidepressant and
212 benzodiazepine use ($p < 0.001$) (Fig. 3). The proportion of patients who continued to use opioids (those who
213 redeemed opioids preoperatively and postoperatively) or started to use opioids (those who did not use opioids
214 preoperatively but used them 1 year postoperatively) was higher in patients with preoperative use of
215 antidepressants or benzodiazepines (Table 3). The results were essentially the same among patients who had
216 undergone hip or knee arthroplasty (for opioid use, see Supplementary Table 2).

217 *Decrease in Analgesic Use After Surgery in Patients Taking Antidepressants or Benzodiazepines*

218 Among the 1038 patients with a history of using antidepressants, the proportion of patients who redeemed any
219 analgesics was smaller 1 year after surgery (42% [439 patients]), than preoperatively (55% [568 patients]; $p <$
220 0.001) (Fig. 2), and the proportion who redeemed a prescription for opioids was smaller 1 year after surgery
221 (15% [154 patients]), than preoperatively (20% [204 patients]; $p < 0.001$) (Fig. 3). Among the 2008 patients
222 with a history of using benzodiazepines, the proportion of patients who redeemed any analgesics was smaller 1

223 year after surgery (40% [801]), than preoperatively (55% [1098]; $p < 0.001$) (Fig. 2), and the proportion who
224 redeemed a prescription for opioids was smaller 1 year after surgery (12% [250]), than preoperatively (17%
225 [342]; $p < 0.001$) (Fig. 3).

226 *Change in Antidepressant or Benzodiazepine Use After Arthroplasty*

227 The proportion of patients using antidepressants did not change from the preoperative period (7% [844 of
228 12,448]) to 1 year after surgery (7% [845 of 12,448]; $p > 0.99$) (Fig. 4). The proportion of patients who
229 redeemed benzodiazepines was slightly smaller 1 year postoperatively compared to the preoperative period
230 (12% [1501 of 12,448]) versus 13% [1566 of 12,448]; $p = 0.04$) (Fig. 4).

231 Altogether, the proportion of patients who redeemed antidepressants was essentially stable over the study period
232 (Fig. 4). The proportion of patients using benzodiazepines increased slightly preoperatively, peaked
233 immediately after surgery, and decreased thereafter to a lower level than that seen at 3 months preoperatively
234 (Fig. 4). The results were similar between patients treated with hip arthroplasty and those treated with knee
235 arthroplasty.

236 **Discussion**

237 Persistent postoperative pain affects between 10% and 20% of patients who undergo hip or knee arthroplasty,
238 which may result in the prolonged consumption of opioids and other analgesics in this patient group [6, 10, 40].
239 Because of the ongoing opioid epidemic, attempts have been made to identify especially those patients
240 undergoing THA or TKA who continue to use opioids after surgery, but disagreement persists as to whether
241 preoperative depression and anxiety are associated with persistent opioid use after surgery [4, 12, 14, 22, 25, 32,
242 34, 42, 43]. In this large registry study, we found that patients with a history of antidepressant or benzodiazepine
243 use were more likely to redeem prescriptions for opioids and other analgesics 1 year after surgery than were
244 patients without a history of antidepressant or benzodiazepine use. The increased possibility of prolonged opioid
245 and other analgesic use should be considered and discussed before performing joint arthroplasty on these
246 patients.

247 *Limitations*

248 The most important limitation of this registry study is that we were not able to control for all potentially
249 confounding variables, although major confounders, such as the preoperative use of analgesics and
250 comorbidities were included in the adjusted regression model. Another limitation is that we pooled all analgesic
251 drugs (acetaminophen, NSAIDs, and opioids) together in order to study overall need for analgesic drugs.

252 Although this approach may enable to capture a greater proportion of patients who suffer from pain after
253 surgery, there is most likely a great difference in the intensity of pain between patients with irregular use of
254 acetaminophen and patients with regular use of strong opioids. Additionally, the risks related to prolonged use
255 of opioids are at a completely different level compared to use of acetaminophen. Therefore, we analyzed opioid
256 use also separately. Some patients may have entered drug treatment programs/detox, but it is unlikely that this
257 would have confounded the results. Opioid abuse has been very rare in Finland; even across the country there
258 would have been very few, if any, patients having joint arthroplasty during drug treatment programs/detox,
259 although it may be more common in patients with antidepressants or benzodiazepines. In addition, we did not
260 analyze amounts of drugs used. Therefore, the results only present whether there is need or no need for opioids
261 or other analgesic drugs. Another limitation is the inability to assess the indications for the prescribed
262 analgesics. Therefore, we were not able to determine whether patients redeemed analgesics because of pain in
263 the operated joint or because of pain in other sites, although we tried to reduce confounding by excluding
264 patients with revisions or other joint arthroplasties during the study period, and by excluding patients with other
265 indications than primary osteoarthritis. But even if some patients had arthritis in other joints (besides the one
266 operated for primary osteoarthritis), this should not undermine our results considering the prolonged usage of
267 analgesics in patients with history of antidepressant and benzodiazepine use. Inability to assess medication
268 adherence is another limitation, and we were not able to find out whether the redeemed drugs were actually
269 taken by the patient and when. The data that we used were relatively old (they span the period from 2002 to
270 2013). However, we do not believe that this would confound the association with preoperative
271 antidepressant/benzodiazepine and analgesic use, or the other questions studied.

272 Another limitation is that the use of over-the-counter drugs was not analyzed, which may have underestimated
273 the actual use of acetaminophen and NSAIDs. It is unlikely, however, that this would have substantially
274 confounded the drug use patterns or the risk factors analyzed. Furthermore, not all postoperative complications
275 were analyzed. However, the major complications leading to revision surgery of the index joint were excluded.
276 Pain variables, such as the intensity of preoperative and postoperative pain, the prevalence of persistent pain, or
277 pain catastrophizing, were not analyzed in this study. It was not possible to determine the severity of mental
278 health problems and whether the medication used was sufficient. The generalizability of the results may be
279 limited, because all surgical procedures were performed in the same hospital. However, although there may be
280 some variation in the indications for joint replacement and prescription practices in other centers, we believe the
281 results apply to osteoarthritis patients also in other countries because the national guidelines for treatment of

282 osteoarthritis are similar in Finland and in other western countries.

283 *Association Between Preoperative Antidepressants or Benzodiazepines and Postoperative Analgesic Use*

284 The coexistence of depression and chronic pain often aggravates the severity of both disorders [41], and up to
285 85% of patients with chronic pain are affected by severe depression [1, 21, 41]. In our study, there was a clear
286 association between a history of antidepressant or benzodiazepine use and the use of any of the studied
287 analgesics (that is opioids, NSAIDs, and acetaminophen), both preoperatively and postoperatively. Only a few
288 studies have analyzed the association between depression and analgesics other than opioids, and a greater use of
289 NSAIDs has been found after hip and knee arthroplasty [42, 43], although there is a synergistic risk of
290 gastrointestinal bleeding between serotonin reuptake inhibitors and NSAIDs [7]. In the present study, a history
291 of benzodiazepine use was associated with the postoperative use of not only opioids but also NSAIDs and
292 acetaminophen, which to our knowledge has not been described before. Benzodiazepine use has been associated
293 with pain severity and catastrophizing in patients with chronic pain, and this may be one explanation for this
294 finding [15, 33].

295 *Association Between Preoperative Antidepressants or Benzodiazepines and Persistent Opioid Use After Surgery*

296 Although opioids are effective drugs for treating chronic pain, major risks, such as dependence and addiction,
297 are associated with their use; in general, opioids are not a good choice for treating arthritic pain in most patients.
298 There is emerging evidence suggesting that opioids do not provide benefit when compared with NSAIDs to
299 manage noncancer pain (such as arthritis pain), but opioids are associated with higher risk for adverse events,
300 such as dependence and addiction [13]. Additionally, preoperative opioid use is associated with worse patient
301 outcomes after total joint replacement [23]. The latest Osteoarthritis Research Society International (OARSI)
302 guidelines for the nonsurgical management of osteoarthritis pain do not recommend the use of opioids in
303 osteoarthritis patients [2]. However, opioid prescriptions have been increasing so that recently around 24% to
304 60% of patients are being prescribed opioids before total joint replacement [4, 5, 27, 32]. Some studies have
305 found that patients undergoing hip and knee arthroplasty who have depression preoperatively use opioids more
306 frequently after surgery than patients without depression [4, 12, 22, 25, 32], whereas no such association has
307 been reported in other studies [34, 43]. Similarly, in some earlier studies, anxiety and the preoperative use of
308 benzodiazepines was associated with greater use of opioids after hip and knee arthroplasty [4, 12, 14, 25, 32, 34,
309 43], whereas such an association has not been reported in other studies [22, 42].

310 In our study, after adjusting for possible confounders such as preoperative analgesic use and comorbidities,
311 there was a clear association between a history of antidepressant or benzodiazepine use and the prolonged use of
312 opioids after surgery. Moreover, the probability of prolonged opioid use was greatest in patients with a
313 preoperative use of both antidepressants and benzodiazepines. Most earlier studies have determined depression
314 and anxiety from preoperative medical records according to registered diagnosis codes. However, it limits the
315 analysis to specific psychiatric conditions although especially benzodiazepines are used more widely as
316 anxiolytics and sleep medicines without a specific psychiatric diagnosis. Our approach may have helped to
317 capture a higher proportion of patients at risk for prolonged opioid use compared with the use of diagnosis
318 codes. Based on the results of our study, surgeons should be aware of the increased possibility of prolonged
319 opioid and other analgesic use among patients who have surgery while on preoperative antidepressant and/or
320 benzodiazepine therapy. Further studies are needed to find ways to reduce the risk for prolonged opioid
321 consumption in these patients; these might, for example, explore the effects of more intensive preoperative
322 management of depression and anxiety, alternative pain management techniques, more intensive monitoring,
323 and patient counseling.

324 *Decrease in Analgesic Use After Surgery in Patients Taking Antidepressants or Benzodiazepines*

325 The proportion of patients who used opioids and other analgesics decreased after surgery to a lower level than
326 that observed preoperatively. This was also true for patients undergoing antidepressant or benzodiazepine
327 therapy, although the proportion of patients who used opioids and other analgesics remained higher in these
328 patients than in patients without a history of antidepressant or benzodiazepine use. Surprisingly, we did not find
329 any previous studies on this subject because earlier studies only analyzed depression and anxiety as risk factors
330 for increased analgesic use. Some previous studies have found that patients with depression or anxiety are often
331 satisfied after joint arthroplasty, and that surgery has positive effects on the pain levels of patients with
332 depression [8, 26]. Our study adds to these previous studies; that the consumption of opioids and other
333 analgesics is reduced after surgery in patients with a history of antidepressant or benzodiazepine therapy.
334 However, these patients should be informed of the greater possibility of prolonged opioid and other analgesic
335 use after surgery, and depression and anxiety should be managed as effectively as possible in advance to
336 elective joint arthroplasty surgery.

337 *Change in Antidepressant or Benzodiazepine Use After Arthroplasty*

338

339 In accordance with the findings of a study on patients undergoing hip arthroplasty [11], the proportion of
340 patients using antidepressants remained essentially stable throughout the study period, except for a minor drop
341 immediately after surgery. Following the evidence-based recommendations [19], serotonin-noradrenaline
342 reuptake inhibitors (duloxetine and venlafaxine) and tricyclic antidepressants may be used in treatment of
343 chronic neuropathic pain. In Finland, as well as in many other countries, they are also used in patients with
344 mixed pain patterns if the treating clinician believes there are both nociceptive and neuropathic components of
345 pain involved. However, our findings suggest that these patients most probably used antidepressants for
346 indications other than chronic pain related to osteoarthritis of the index joint, because the proportion of patients
347 who redeemed antidepressants remained essentially stable throughout the study period. The proportion of
348 patients using benzodiazepines increased before surgery, peaked immediately postoperatively, and then
349 decreased. However, the amplitude of the changes in the proportion of patients using benzodiazepines was
350 minimal and was similar to that reported in a previous study [11]. There was a slight increase in the long-term
351 proportions during the observation period from 2 years preoperatively to 2 years postoperatively. The
352 preoperative increase of benzodiazepine use in patients waiting for elective joint arthroplasty may be related to
353 the link between pain and sleep or between pain and anxiety [11, 44, 47]. Generally, the preoperative use of
354 benzodiazepines in our study was in line with an earlier study [11], but the preoperative use of antidepressants
355 (9%) was slightly higher than in a previous study [27] and in a Finnish population study [31]. Neither the use of
356 antidepressants nor benzodiazepines changed markedly in the long-term after joint arthroplasty. Based on
357 present results, the proportion of patients who use antidepressants or benzodiazepines should not be expected to
358 change very much after joint arthroplasty.

359 *Conclusion*

360 In this large, register-based study with comprehensive drug prescription data, we found that the preoperative use
361 of antidepressants and benzodiazepines was associated with more sustained postoperative use of opioids and
362 other analgesics. Sustained opioid and other analgesic use was more common in patients who redeemed both
363 antidepressants and benzodiazepines preoperatively than it was in patients who used only one of those two drug
364 classes before surgery, and more common than in patients who redeemed neither antidepressants nor
365 benzodiazepines. Based on the results of this study, surgeons should be aware of the increased possibility of
366 prolonged opioid and other analgesic use among patients undergoing preoperative antidepressant and/or
367 benzodiazepine therapy, and they should have candid discussions with patients referred for elective joint
368 arthroplasty about this possibility. Further studies are needed to identify the most effective methods to reduce

369 prolonged opioid consumption among these patients.

370

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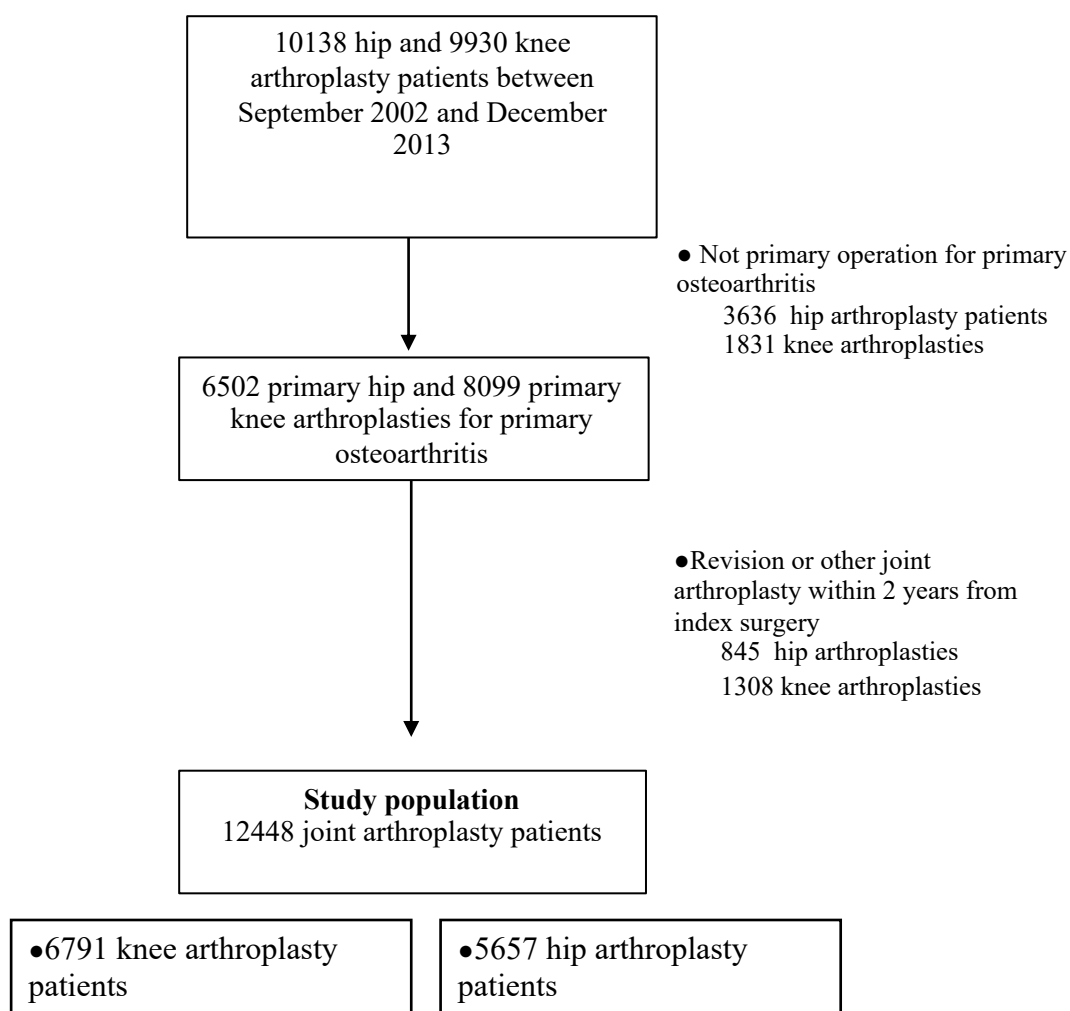
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Fig. 1 The patients who were included in this study; OA = osteoarthritis.

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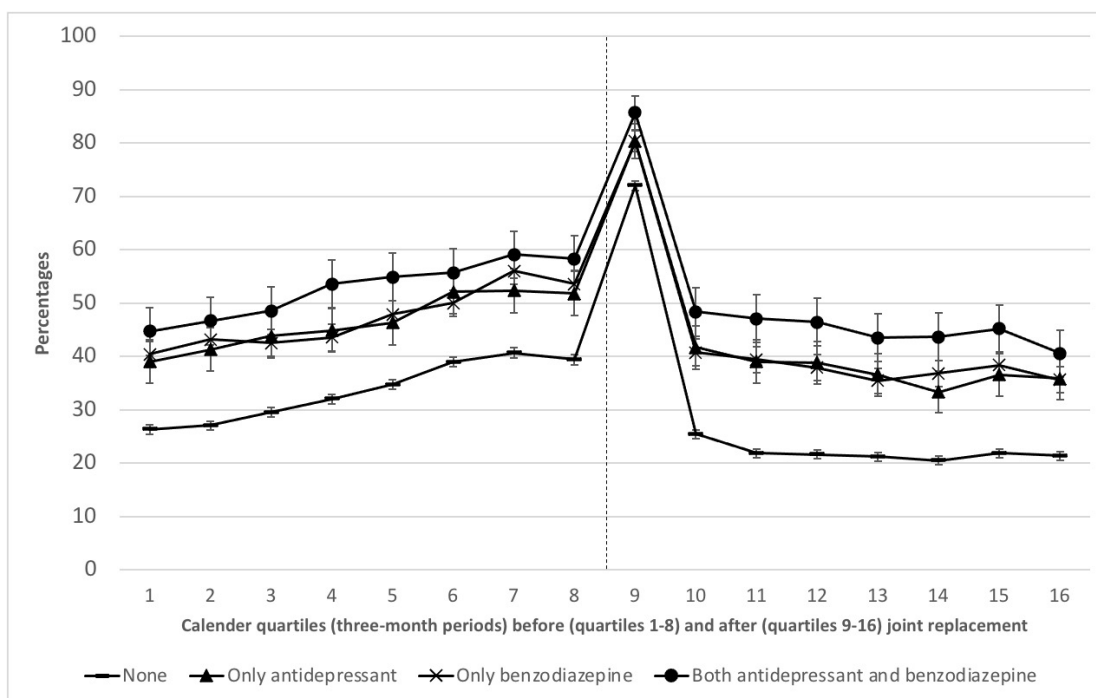


Fig. 2 The proportions (with 95% CI) of patients with any analgesic drug use according to the preoperative use of antidepressants and benzodiazepines, in 3-month intervals.

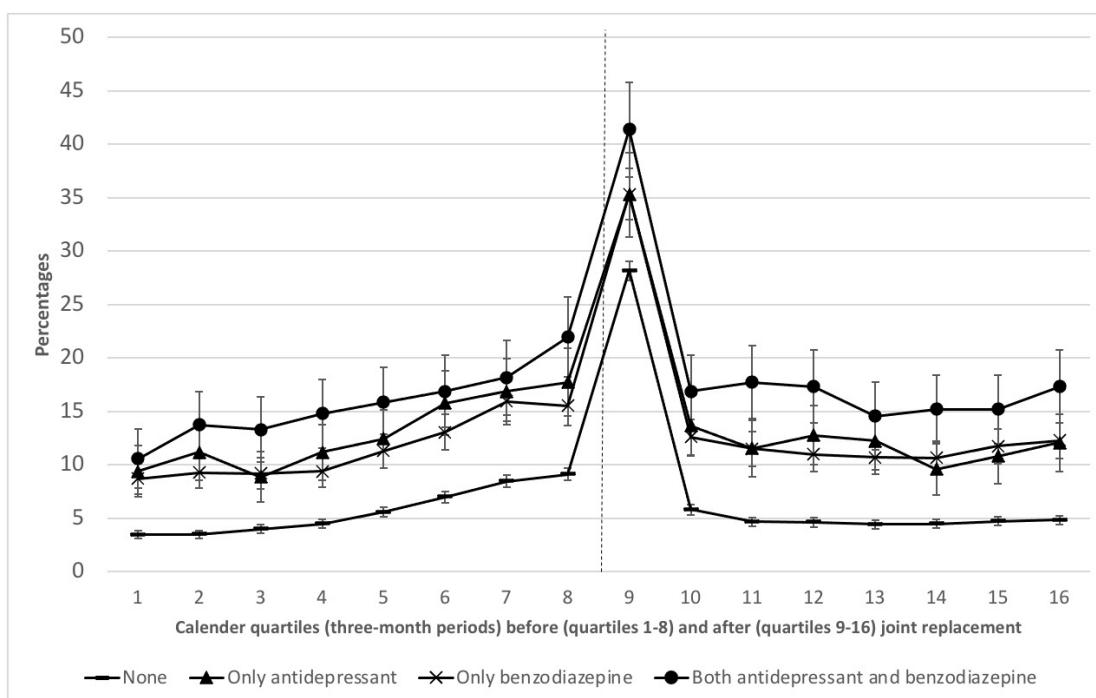


Fig. 3 The proportions (with 95% CI) of patients with opioids according to the preoperative use of antidepressants and benzodiazepines, in 3-month intervals.

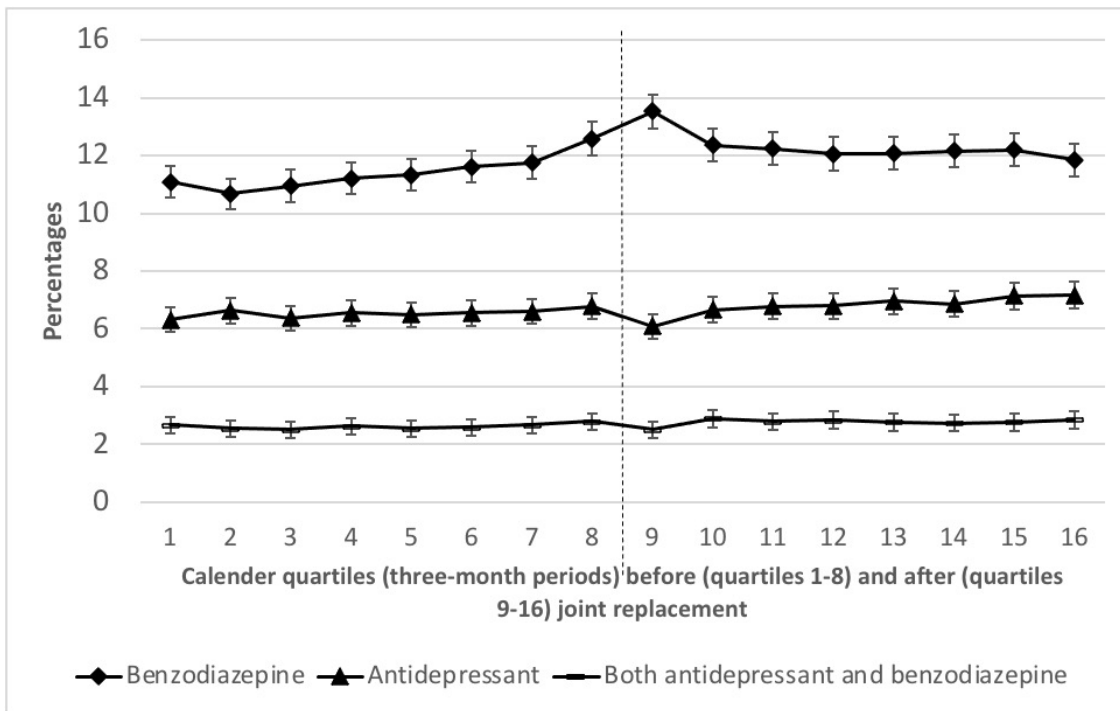


Fig. 4 The proportions (with 95% CI) of patients with antidepressants or benzodiazepines, in 3-month intervals.

Table 1. Demographic characteristics (n = 12,448 patients)

Factor	Value
Age in years, mean \pm SD	68 \pm 10
Women, % (n)	61% (7550)
Type of joint arthroplasty, % (n)	
Hip	45% (5657)
TKA	51% (6326)
Unicompartmental knee arthroplasty	4% (465)
Bilateral operation, % (n)	13% (1615)
BMI in kg ² , mean \pm SD ^a	29 \pm 5
Charlson comorbidity index, % (n) ^b	
0	71% (8887)
1	21% (2562)
> 2	8% (999)
Diabetes, % (n)	9% (1168)
Cardiac disease, % (n) ^c	12% (1454)
Psychotic disorder, % (n)	2% (216)
Neurodegenerative disease (Alzheimer's or Parkinson's), % (n)	1% (181)
Pulmonary disease, % (n)	7% (931)
Hypertension, % (n)	31% (3866)
History of malignancy, % (n)	3% (424)
Epilepsy, % (n)	1% (132)
Preoperative antidepressant or benzodiazepine, % (n)	
None	79% (9876)
Only antidepressant	5% (564)
Only benzodiazepine	12% (1534)
Both antidepressant and benzodiazepine	4% (474)

^aBMI missing on 13% (1644) of patients. ^bModified Charlson comorbidity index. ^cIncludes coronary artery disease, heart failure, and chronic arrhythmia.

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Table 2. Multivariable adjusted ORs for analgesic consumption by patients with preoperative use of antidepressants or benzodiazepines

Factor	Preoperative (0-3 months)	Postoperative (9-12 months)	
	Any analgesic ^a Adjusted OR ^{b, d}	Any analgesic ^a Adjusted OR ^{c, d}	Opioid Adjusted OR ^{c, d}
Antidepressants and benzodiazepines			
None	1	1	1
Only antidepressant	1.6 (1.3-1.9)	1.9 (1.5-2.3)	2.2 (1.6-3.0)
Only benzodiazepine	1.9 (1.7-2.1)	1.8 (1.5-2.0)	1.9 (1.6-2.4)
Both antidepressant and benzodiazepine	2.2 (1.8-2.7)	2.4 (1.9-2.9)	2.8 (2.0-3.8)
Antidepressant (reference: no antidepressant)	1.7 (1.5-1.9)	1.9 (1.6-2.2)	2.1 (1.7-2.7)
Benzodiazepine (reference: no benzodiazepine)	1.9 (1.7-2.1)	1.8 (1.6-2.0)	2.0 (1.6-2.4)

^aAcetaminophen, NSAID, or opioid.^bOR (95% CI) adjusted for age, gender, joint, Charlson comorbidity index score, BMI, and laterality (unilateral versus simultaneous bilateral).^cOR (95% CI) adjusted for age, gender, joint, Charlson comorbidity index score, BMI, laterality (unilateral versus simultaneous bilateral), and preoperative use of opioids or other analgesics.^dAll p values < 0.001.

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Table 3. Continuation of analgesic use according to preoperative antidepressant and benzodiazepine use

		Use of any analgesics				p value
		Continued ^a	Stopped after surgery ^b	Started after surgery ^c	No use pre- or postoperatively ^d	
Antidepressant preoperatively	Yes (n=1038)	30% (314)	25% (254)	12% (125)	33% (345)	< 0.001
	No (n=11410)	16% (1778)	26% (2935)	8% (940)	50% (5757)	
Benzodiazepine preoperatively	Yes (n=2008)	28% (570)	26% (528)	12% (231)	34% (679)	< 0.001
	No (10440)	15% (1522)	26% (2661)	8% (834)	52% (5423)	
		Use of opioids				
		Continued	Stopped after surgery	Started after surgery	No use pre- or postoperatively	p value
Antidepressant preoperatively	Yes (n=1038)	9% (92)	11% (112)	6% (62)	74% (772)	< 0.001
	No (n=11410)	2% (270)	8% (865)	3% (353)	87% (9922)	
Benzodiazepine preoperatively	Yes (n=2008)	6% (126)	11% (216)	6% (124)	77% (1542)	< 0.001
	No (n=10440)	2% (236)	7% (761)	3% (291)	88% (9152)	

^aRedeemed medications 3 months preoperatively and 1 year postoperatively.

^bRedeemed medications 3 months preoperatively but not 1 year postoperatively.

^cDid not redeem medications 3 months preoperatively but redeemed 1 year postoperatively.

^dDid not redeem medications 3 months preoperatively or 1 year postoperatively.

Supplementary Table 1. Demographic characteristics of patients with antidepressants and those with benzodiazepines

Factor	Antidepressant preoperatively (altogether 1038 of 12,448)	p value	Benzodiazepine preoperatively (altogether 2008 of 12,448)	p value
Age in years, mean \pm SD (reference: no antidepressant, or benzodiazepine)	68 \pm 11 (vs 68 \pm 10)	0.34	72 \pm 10 (vs 68 \pm 10)	<0.001
BMI in kg/m ² , mean \pm SD (reference: no antidepressant or benzodiazepine)	30 \pm 5 (vs 29 \pm 5)	<0.001	29 \pm 5 (vs 29 \pm 5)	0.19
Female, % (n)	10% (764 of 7550)		19% (1418 of 7550)	
Male	6% (274 of 4898)	<0.001	12% (590 of 4898)	<0.001
Type of joint arthroplasty, % (n)				
Hip	7% (423 of 5657)		14% (777 of 5657)	
Knee	9% (615 of 6791)	0.01	18% (1231 of 6791)	<0.001
TKA	9% (574 of 6326)		18% (1161 of 6326)	
Unicompartmental knee arthroplasty	9% (41 of 465)	0.85	15% (70 of 465)	0.07
Bilateral operation, % (n)	7% (109 of 1615)		13% (217 of 1615)	
Unilateral	9% (929 of 10,833)	0.01	17% (1791 of 10,833)	<0.001
Charlson comorbidity index, % (n) ^a				
0	7% (635 of 8887)		14% (1209 of 8887)	
1	10% (264 of 2562)		21% (536 of 2562)	
> 2	14% (139 of 999)	<0.001	26% (263 of 999)	<0.001
Diabetes, % (n)	10% (122 of 1168)		21% (251 of 1168)	
No diabetes	8% (916 of 11,280)	0.01	16% (1757 of 11,280)	<0.001
Cardiac disease, % (n) ^b	10% (142 of 1454)		25% (369 of 1454)	
No cardiac disease	8% (896 of 10,994)	0.04	15% (1639 of 10,994)	<0.001
Psychotic disorder, % (n)	44% (94 of 216)		41% (89 of 216)	
No psychotic disorder	8% (944 of 12,232)	<0.001	16% (1919 of 12,232)	<0.001
Neurodegenerative disease (Alzheimer or Parkinson), % (n)	23% (42 of 181)		26% (47 of 181)	
No neurodegenerative disease	8% (996 of 12,267)	<0.001	16% (1961 of 12,267)	<0.001
Pulmonary disease, % (n)	13% (125 of 931)		23% (215 of 931)	
No pulmonary disease	8% (913 of 11,517)	<0.001	16% (1793 of 11,517)	<0.001
Hypertension, % (n)	9% (344 of 3866)		20% (790 of 3866)	
No hypertension	8% (694 of 8582)	0.13	14% (1218 of 8582)	<0.001
History of malignancy, % (n)	13% (57 of 424)		25% (105 of 424)	
No malignancy	8% (981 of 12,024)	<0.001	16% (1903 of 12,024)	<0.001
Epilepsy, % (n)	18% (24 of 132)		23% (31 of 132)	
No epilepsy	8% (1014 of 12,316)	<0.001	16% (1977 of 12,316)	0.02

^aModified Charlson comorbidity index.^bCoronary artery disease, heart failure, and chronic arrhythmia.

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Supplementary Table 2. Proportions of patients with opioid use and multivariable adjusted ORs for opioid consumption after hip and knee replacement by patients with preoperative use of antidepressants or benzodiazepines

Factor	Preoperative (0-3 months) use of opioids				Postoperative (9-12 months) use of opioids			
	Hip replacement		Knee replacement		Hip replacement		Knee replacement	
	Proportion (n) ^a	Adjusted OR ^{a,b}	Proportion (n) ^a	Adjusted OR ^{a,b}	Proportion (n) ^a	Adjusted OR ^{a,c}	Proportion (n) ^a	Adjusted OR ^{a,c}
Antidepressant and benzodiazepines								
None	12% (540 of 4636)	1	7% (357 of 5240)	1	4% (185 of 4636)	1	5% (270 of 5240)	1
Only antidepressant	24% (58 of 244)	2.1 (1.5-2.9)	13% (42 of 320)	1.9 (1.3-2.7)	14% (34 of 244)	2.8 (1.7-4.3)	12% (38 of 320)	2.0 (1.3-3.0)
Only benzodiazepine	20% (119 of 598)	1.8 (1.4-2.3)	13% (119 of 936)	2.1 (1.6-2.6)	10% (62 of 598)	2.1 (1.5-2.9)	11% (106 of 936)	1.9 (1.4-2.5)
Both antidepressant and benzodiazepine	26% (46 of 179)	2.5 (1.7-3.6)	20% (58 of 295)	3.1 (2.2-4.4)	13% (24 of 179)	2.6 (1.6-4.5)	20% (58 of 295)	2.8 (1.9-4.1)
Antidepressant								
No	13% (659 of 5234)	1	8% (476 of 6176)	1	5% (247 of 5234)	1	6% (376 of 6176)	1
Yes	25% (104 of 423)	2.0 (1.6-2.7)	16% (100 of 615)	2.1 (1.6-2.7)	14% (58 of 423)	2.3 (1.6-3.3)	16% (96 of 615)	2.1 (1.5-2.7)
Benzodiazepine								
No	12% (598 of 4880)	1	7% (399 of 5560)	1	4% (219 of 4880)	1	6% (308 of 5560)	1
Yes	21% (165 of 777)	1.9 (1.5-2.3)	14% (177 of 1231)	2.2 (1.8-2.7)	11% (86 of 777)	2.0 (1.4-2.7)	13% (164 of 1231)	2.0 (1.6-2.5)

^aAll p values < 0.001.^bOR (95% CI) adjusted for age, gender, Charlson comorbidity index score, BMI, and laterality (unilateral versus simultaneous bilateral).^cOR (95% CI) adjusted for age, gender, Charlson comorbidity index score, BMI, laterality (unilateral versus simultaneous bilateral), and preoperative use of opioids and other analgesics.

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