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Factors associated with use of opioid rescue medication after surgery

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ABSTRACT

Background Opioid exposure after surgery increases risk of persistent opioid use. Here, we characterize at-home use of opioid rescue medication during 1–2 days after outpatient surgery (N=270) in a postoperative opioid-sparing context at a Norwegian hospital.

Methods The postsurgical pain management plan included non-steroidal anti-inflammatory drugs and up to six pills of 5 mg oxycodone as rescue analgesics. In this observational study we assessed risk factors for taking rescue opioids after surgery, by comparing patients who did, with those who did not.

Results Only 35% (N=228) of patients reported taking rescue opioids 1–2 days after discharge. Patients taking rescue opioids after surgery (opioid-takers) differed from non-takers by prevalence of preoperative chronic pain (>3 months; 74% vs 48%), higher pain severity and interference before and after surgery, reporting lower ability to cope with postsurgical pain, higher nervousness about the surgery, being younger, and having received more opioid analgesics in the recovery room. Exploratory predictive modeling identified opioid administration in the recovery room as the most important predictor of at-home rescue medication use. Follow-up after >4 months indicated low acute pain levels (mean±SD = 1.1±1.8), with only four patients (2%, N=217) reporting opioid analgesic use.

Conclusion Factors related to at-home rescue medication use closely mirrored known risk factors for persistent opioid use after surgery, such as prior chronic pain, prior substance use, affective disturbances, and pain severity before surgery. These findings are potential targets in patient-centered care. Nevertheless, and reassuringly, findings are consistent with the idea that opioid-sparing postsurgical care can prevent large-scale chronic opioid use.

SWHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Growing evidence indicates that risk factors for persistent opioid use include acute and chronic pain, history of substance use, younger age and affective disorders.

WHAT THIS STUDY ADDS

⇒ The study demonstrates strong overlap between risk factors for persistent opioid use and acute use of opioids analgesics in an opioid sparing setting and highlights acute pain before surgery and frequency of opioid administration in the recovery room as relevant predictors for opioid rescue medication use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study demonstrates the feasibility of opioid sparing postoperative pain management after outpatient surgery and suggests potential targets for early, preventive patient-centered care.

INTRODUCTION

Opioid analgesics are a cornerstone of postsurgical pain treatment. Prolonged opioid use and large prescription sizes are associated with heightened prevalence of opioid misuse, addiction and mortality.[1–3] Over-prescription was a root cause for the first wave of the opioid epidemic in North America[4]; outside of the USA and Canada opioid-sparing postoperative analgesic regimens are more commonly chosen to prevent persistent opioid use. Overall, studies on acute postoperative opioid use and opioid sparing pathways are conducted in the North American context,[5–8] where opioid prescriptions as well as opioid prescription fillings are largely higher than internationally and opioid sparing prescription practice is scarce.[9 10]

In opioid-sparing postoperative care, non-opioid analgesics are the main treatment and limited opioid doses are provided to be taken as needed (ie, 'rescue medications'). In contrast to the growing evidence on predictors of persistent opioid use, which include history of substance use and chronic pain, affective disorders and pain severity,[1 11–13] little is currently known about which patient characteristics relate to postsurgical opioid use during the acute recovery phase when patients self-administer analgesics from home. Initial data on postoperative opioid use from home in a *voluntary* opioid-sparing postoperative pathway indicated that opioid-takers reported higher pain levels after surgery, lower coping ability and were on average younger than patients who did not take opioid rescue medication.[7]

Here, we used prospective observational data to investigate at-home use of opioid rescue medication after outpatient surgery at a Norwegian hospital, where postoperative opioid-sparing treatment is standard care. Patients who either did (N=81) or did not (N=147) self-administer opioid analgesics in the first 1–2 days after surgery were compared with the aim of identifying potential predictive

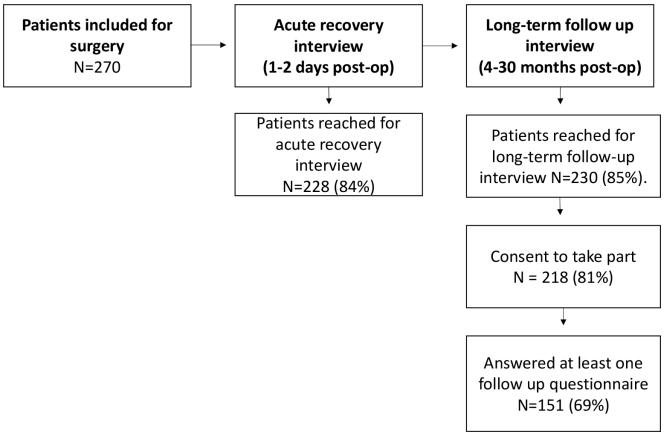

Figure 1 Inclusion flow chart. Of the 270 patients included in the study, 228 were reached for a phone interview during acute recovery (1–2 days after surgery). Of the 230 patients reached for long-term follow-up (4–30 months after surgery), 218 consented to take part in the phone interview and to receive questionnaires. From 186 of those 218 patients we also have information on postoperative opioid use during acute recovery. 151 of the 218 patients filled in at least one questionnaire.

measures of postoperative rescue opioid use. Since opioid use during acute recovery can be a first step in the development of persistent opioid use, we hypothesized that risk factors for persistent opioid use (eg, younger age, higher acute pain, history of chronic pain, prolonged opioid use) would also be related to postoperative use of rescue opioids in the 2 days after surgery (acute recovery phase). Unlike previous studies,[7 8] our prospective study assessed use of postoperative opioid rescue analgesics in a context where opioid sparing postoperative pain management is standard of care.

METHODS

Participants and procedure

A convenience sample of patients (N=270, 153 women, age mean±SD = 47.5±14.2) scheduled for outpatient surgery with general anesthesia was recruited at Kongsberg Hospital in Norway between April 2018 and June 2021. The participants were adult patients healthy enough to undergo minor outpatient surgery, classified as ASA-I–II (American Society of Anesthesiologists)[14] (see online supplemental file). Participants were invited to join the study and signed written informed consent on arrival at the hospital. Contact attempts for follow-up measures were limited to three times for phone interviews and three email reminders for online questionnaires resulting in varying response rates and a potential response bias. An inclusion flowchart for the different time points reported can be found in figure 1.

Participants received treatment as usual, that is, according to hospital routines. At discharge from the hospital after surgery, patients received two types of analgesics to take home: A fixed combination of naproxen (500 mg) with esomeprazole (20 mg) and as rescue medication up to six oxycodone pills (5 mg). The number of oxycodone pills was decided by the medical personnel, considering the likelihood of high pain and the accessibility of a pharmacy/general practitioner. Patients were instructed to rely on non-opioid analgesics as much as possible for pain management and to take one initial dose of paracetamol (1.5 g for <75 kg body weight and 2g for >75 kg body weight) followed by 1 g of paracetamol up to four times a day, non-steroidal anti-inflammatory drug if no contraindications were present, and opioids only if absolutely necessary. A detailed overview of the perioperative pain management can be found in the online supplemental material.

Clinical and research specific data were collected over six time points: weeks before surgery, ~60 min before surgery, on the surgery table, in the recovery room, during acute recovery (1–2 days after discharge) and at long-term follow-up (4–30 months after surgery) (figure 2). Data on acute responses to opioids on the operating-table are reported elsewhere.[15]

Outcomes

The **grouping variable** *self-reported opioid use during acute recovery* was collected during the phone interview in the acute recovery phase (1–2 days after discharge) and defined as having taken (1) at least one pill of the oxycodone tablets provided by the hospital or (2) any other opioid analgesic patients had available. **Patient characteristics** were collected via self-report on paper questionnaires and the hospital database and include *sex, age, body mass index (BMI), operation category, opioid received on the surgery table, tobacco use, history of pain, history of*

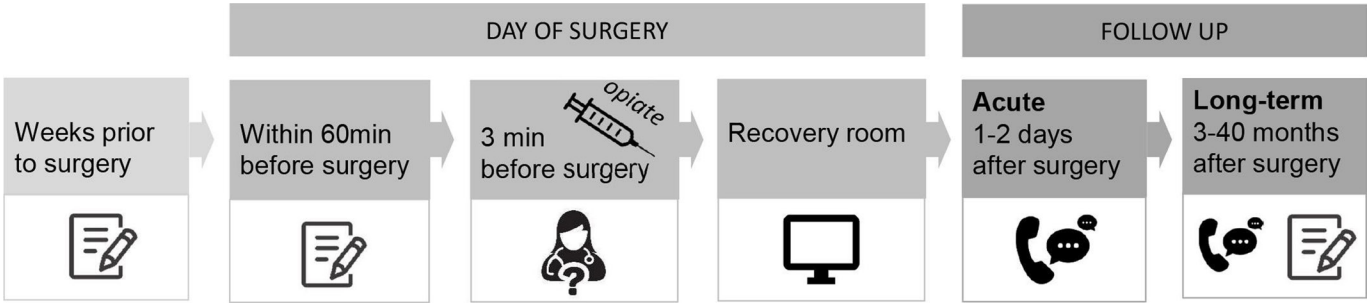

Figure 2 Timeline of data collection. 2–3 weeks prior to surgery: As part of the hospital routine, patients filled in a form on demographics, levels of nervousness before surgery, pain and pain interference. In the hour before surgery, patients completed questionnaires on mood, pain, pain interference and previous experience with opioids. In the operating room, patients rated their mood and acute drug effects verbally. Recovery room: Patients received opioid or non-opioid analgesics up to five times in the recovery room. Data was extracted from the hospital system. Acute recovery: 1–2 days after surgery. In a semi-structured phone interview, patients reported on their use of the analgesics, rated pain intensity, interference and coping as well as mood and satisfaction with the hospital treatment and stay. Follow-up: 4–30 months after surgery. In a second brief phone interview, patients reported on the extended recovery period after surgery (pain control, social support), current medication use and work status. We also included questionnaires on their substance use, experience of life stressors, pain and pain catastrophizing, life satisfaction, hedonic experience and mindfulness in day-to-day life. Long-term follow-up was an add-on to the project, leading to variability in the time since surgery (4–30 months).

opioid use and *analgesic use in the recovery room (number of doses administered*). **Subjective ratings** (0–10 rating scales) of *pain indices* and *nervousness* were collected via self-report on paper questionnaires in the weeks before surgery and on day of surgery and via phone interview during acute recovery and long-term follow-up; other state measures (*feeling good, feeling anxious*) were measured verbally on the operating table before and after induction of the opioid analgesic. *Patient satisfaction* was collected in the phone interview during acute recovery.

Subjective ratings

Patients rated their pain intensity and pain interference, nervousness about the surgery or recovery at three time points: weeks before surgery, morning of surgery and during the acute recovery phase 1–2 days after discharge from the hospital. Ratings of feeling good and anxious were collected on the surgery table before and after opioid injection. Patient satisfaction was measured during the acute recovery phase 1–2 days after discharge from the hospital. Details can be found in the online supplemental material.

Long-term follow-up questionnaire data

We measured pain[16] and pain catastrophizing,[17 18] depression and anxiety,[19] childhood trauma,[20 21] subjective perception of socio-economic status during childhood and adulthood,[22] potential substance abuse,[23 24] general life satisfaction,[25] hedonic experience,[26] and mindfulness in day-to-day life.[27] An overview of all questionnaires can be found in the online supplemental material.

Statistical analyses

All analyses were performed in R V.4.1.2.[28]

Primary analysis

To determine the relevance of factors previously associated with *persistent opioid use* (patient characteristics and subjective ratings) in this *acute recovery context* we compared patients who either did (N=81) or did not (N=147) self-administer opioid analgesics within the first 2 days after surgery using non-parametric repeated-measures analysis of variance (ANOVA) (rank-based)[29] as well as Welch's t-tests, Wilcoxon rank-sum test and χ^2 tests. Additionally, we tested whether the opioid type patients received on the surgery table influenced opioid use in the recovery room and at-home. Since we conducted a large number of pairwise comparisons, we chose a more conservative alpha level of 0.01 to lower the false-positive rate.

Exploratory analyses

To identify important variables for predicting opioid use after surgery, we used multimodel inference[30] implemented in *R*[31] with the *MuMIn* package.[32] Multimodel inference accounts for the uncertainty inherent in stepwise model selection by aggregating information from multiple models.[30] Stepwise methods for model selection were preferred historically due to limits in computational power. In contrast, the multimodel approach tests all possible models to determine the general importance (or usefulness) of each individual variable for predicting the outcome of interest. This is done by quantifying the tendency of each individual predictor to appear in good-performing models.

We used binary logistic regression with *opioid use after surgery* as outcome and fitted models for all 2048 possible combinations of a prespecified set of 11 predictors (*sex*, *age*, *BMI*, *previous opioid use*, *tobacco use*, *chronic pain*, *pain weeks before surgery*, *nervousness weeks before surgery*, *operation category*, *opioid administration in the recovery room*, and *pain on the day of surgery*), excluding interactions.

Akaike weights were calculated from Akaike information criteria (AIC) for all models to indicate the probability of each model being the best model.[33] The importance of each predictor across models was determined by calculating the sum of Akaike weights of all models containing the predictor.[30] To assess the overall significance of each predictor, we calculated the full-average model coefficients across all models.[30 34]

Due to missing data, we performed multimodel inference on the complete cases (n=118) and on all cases after imputation (n=228). Data for a total of 48% of incomplete cases were imputed. The percentage of imputed data varied by predictor with the lowest amount of imputed data for tobacco use (2%) to the highest amount of imputed data for chronic pain (33%). Multiple imputation by chained equations was implemented with the *mice* package.[35] We used a quadratic model[36] implemented with the *howManyImputations* package[37] to determine the required minimum number of 48 imputations for the analysis. All imputations were iterated 10 times.[38] We used the *mami* package[39 40] to pool multimodel inference results across imputations.

RESULTS

Patient characteristics

Descriptive data of the full patient population are available in table 1. Approximately half of the participants reported previous pain that lasted more than 3 months (56% of N=180). Previous experience with opioids was limited: Of 242 patients 34% reported no prior opioid experience (opioid-naïve), 60% had taken an opioid analgesic at least once. Only 6% of N=232 reported to have used opioids for more than 2 weeks at a time. In the interview 1–2 days after surgery (N=228), most patients (99%) reported to be satisfied with their treatment and stay at the hospital.

Analgesic use after surgery

Recovery room

Of the 270 patients, 200 (74%) received an analgesic (opioid or non-opioid) in the recovery room. Of these, 110 patients (55%) received at least one opioid dose. Only 54 (49%) of these 110 patients received more than one opioid analgesic dose. We found no difference of the opioid administration in the recovery room depending on the history of opioid use. Among the patients who provided information on their opioid history (N=242), 39% of opioid-naïve patients received opioids in the recovery room, compared with 40% of patients with a history of opioid use (χ^2=0.01(1), p=0.92). A larger proportion of patients receiving preoperative oxycodone compared with remifentanil received opioids in the recovery room (note that preoperative opioids were not randomized). Detailed results can be found in the online supplemental material.

Acute recovery at home

Most patients (93.2%, N=265) received one to six pills of 5 mg oxycodone as rescue medication (median=5, IQR=2–5). Only 35.5% of patients reached at 1–2 days postsurgery (N=228) reported use of oxycodone (32%) or another opioid analgesic they already had at home (3.5%).

Long-term analgesic use

In the long-term follow-up phone interview, 24 (11%) of the patients reaching and consenting to take part (N=218) reported

Table 1 Overview of patient characteristics for the full sample and the two subsamples

	Full sample	Opioid-takers	Non-opioid-takers	P value
N	270	81	147	
Sex, n (%)	153 women (57)	52 women (64)	80 women (54)	0.2*
Age, mean (SD)	47.5 (14.2)	44.5 (13.4)	49.7 (13.8)	**0.006**†
BMI, mean (SD)	27 (5.1)	28.4 (6.2)	26.5 (4.3)	0.3‡
Surgery type, n (%)				
Colorectal	48 (18)	9 (11)	26 (18)	0.26*
Minor abdominal	108 (40)	36 (44)	54 (37)	0.3*
Minor gynecological	59 (22)	14 (1)	41 (28)	0.1*
Otorhinolaryngology	6 (2)	2 (3)	2 (1)	0.9*
Minor orthopedics	32 (12)	14 (17)	15 (10)	0.2*
Other	17 (6)	6 (7)	9 (6)	0.9*
Analgesics received in the recovery room, n (%)				
No analgesic	70 (26)	13 (16)	48 (33)	**<0.001***
Non-opioid analgesic	89 (33)	14 (17)	61 (42)	
Opioid analgesic	111 (41)	54 (67)	38 (26)	
Prior pain,>3 months, n (%)	101 (56)	36 (72)	49 (48)	**0.007***
Tobacco use (yes/no), n (%)	46 (17)	15 (19)	21 (15)	0.5*
History of opioid exposure				
Opioid-naive, n (%)	82 (34)	20 (27)	52 (41)	0.07*
Opioid use >2 weeks, n (%)	14 (6)	5 (7)	5 (4)	0.5*
Satisfied w/treatment, n (%)	223 (99)	78 (96)	145 (99)	0.6*
Opioid use at long-term follow-up, n (%)	4 (2)	4 (6)	0	0.2*

Total counts (n), percentages (%) and averages (mean) for the full sample (n=270) and per group for the patients reached during acute recovery (n=228). Opioid use at long-term follow-up was measured in the subsample of n=218 who consented to take part in the follow-up part of the study. Percentage of missing data for group comparisons: pain >3 months: 33%; tobacco: 2%; previous opioid use: 11%; opioid use >2 weeks: 15%; opioid use long-term follow-up: 19%.
P values reflect comparisons of opioid-takers vs non-takers.
Bold p values indicate p<.01.
*χ^2 test.
†Welch's t-test.
‡Wilcoxon rank-sum test.
BMI, body mass index.

current pain medication use, of which only 4 patients reported opioid analgesic use (1.8%).

Comparison of patients who did and did not use rescue opioids during acute recovery

Characteristics of opioid-takers and non-takers are listed in table 1. Results on acute opioid effects on the surgery table can be found in online supplemental material.

Pain and pain coping

A significantly higher percentage of the opioid-takers reported having had pain for more than 3 months before surgery (72%) compared with the non-takers (48%, N=228, likelihood-ratio chi-square (χ2)=7.2, p=0.007). Opioid-takers were also more likely to have received opioids in the recovery room (N=228; 67% vs 26%, (χ2)=36.3, p<0.001).

The non-parametric repeated-measures ANOVA on pain intensity ratings (N=228) revealed a significant main effect of group (opioid-takers vs non-takers; $F(1)=36.5$, p<0.0001) and time (weeks before surgery, day of surgery, acute recovery, long-term follow-up; $F(2.8)=68.9$, p<0.0001). No significant group×time interaction effect was found ($F(2.8)=2.0$, p=0.12). As illustrated in figure 3, opioid-takers reported significantly higher pain intensity weeks before surgery, on the day of surgery and during acute recovery, but not at long-term follow-up when low levels of current pain were reported (online supplemental table 2).

The pattern of pain interference ratings strongly resemble pain intensity ratings across time and groups (online supplemental table 2).

Wilcoxon rank-sum tests showed that during acute recovery, both groups reported experiencing high pain relief from the analgesic medications ingested (N=210, mean±SD: opioid-takers: 6.8±2.3; non-takers: 7.1±2.8; W=5719, p=0.2). While pain coping was rated high overall, opioid-takers' ratings were significantly lower (N=225, opioid-takers: 7.9±2.0; non-takers: 8.9±1.5; W=7778, p<0.001).

Nervousness

A non-parametric repeated-measures ANOVA revealed a significant main effect of group (N=228, opioid taker vs non-taker; $F(1)=8.3$, p=0.004) and time (weeks before surgery, on the day of surgery and acute recovery; $F(1.8)=69.3$, p<0.0001),

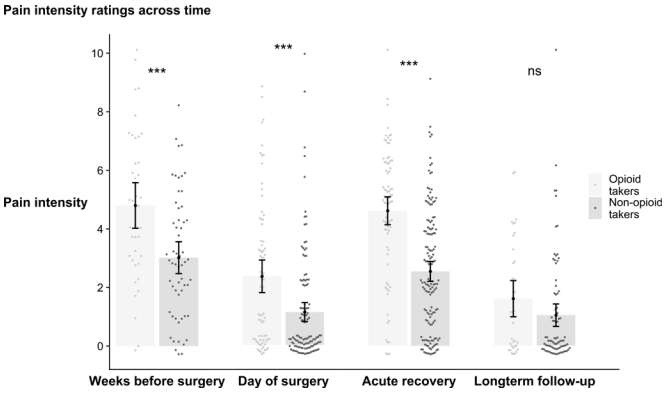

Figure 3 Pain intensity ratings for opioid-takers and non-takers. Opioid-takers reported significantly higher pain intensity before surgery and during acute recovery compared with non-takers. The plots display groupwise means, 95% CIs, dots depict individual numeric ratings indicated via questionnaire (weeks before surgery, day of surgery, long-term follow-up) and verbally via phone interview (acute recovery). Numeric ratings were always given as discrete numbers on a scale from 0 to 10. Error bars represent 95% CIs. ***p≤0.001; ns, not significant.

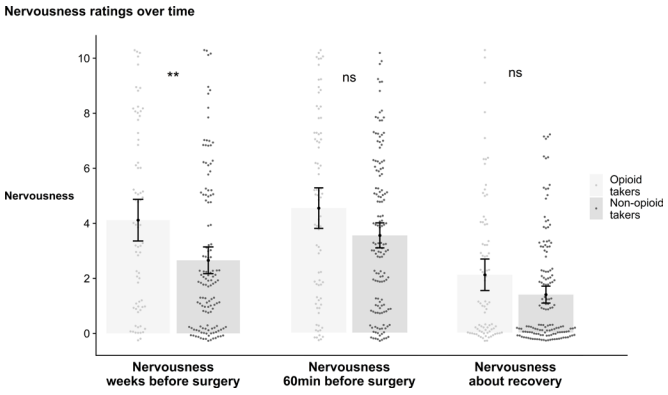

Figure 4 Nervousness ratings for opioid-takers and non-takers. Opioid-takers were significantly more nervous about the surgery in the weeks before but did not differ significantly from non-takers in nervousness on the day of surgery or about recovery in the 2 days after surgery. Groupwise means, 95% CIs, dots depict individual numeric ratings indicated via questionnaire (nervousness about surgery, weeks before and day of surgery) and verbally via phone interview (nervousness about recovery, 1–2 days after surgery). Numeric ratings were always given as discrete numbers on a scale from 0 to 10. Error bars represent 95% CIs. **p<0.01, ns, not significant.

however no significant interaction effect ($F(1.8)=1.6$, $p=0.20$). Opioid-takers rated on average significantly greater nervousness about the surgery weeks before surgery, but not in the hour before surgery and in the acute recovery interview (figure 4).

Long-term follow-up questionnaire data

For questionnaires collected in the 4–30 months after surgery reporting on early trauma, alcohol misuse, drug misuse, pain catastrophizing, pain intensity, depression and anxiety, life satisfaction, perceived socioeconomic status during childhood and adulthood, anhedonia, and mindfulness, no significant differences were found between opioid-takers and non-takers (online supplemental table 3).

Predictors of acute opioid use after surgery

Opioid administration in the recovery room was identified as the most important and only significant predictor of opioid use after surgery in the averaged models using multimodel inference, when analyzing both complete cases (N=118, ORs for complete cases (OR_{comp}) (95% CI) = 2.89 (1.70 to 4.93), $p_z<0.0001$, *Importance*=1) and all cases after imputation (N=228, ORs for imputed cases (OR_{imp}) (95% CI) = 2.68 (1.86 to 3.86), $p_z<0.0001$, *Importance*=1; figure 5; online supplemental table 4). A forest plot including model-averaged ORs and indicators of importance for each predictor per model can be found in figure 5. Overall, the pattern of results was similar for multimodel analysis of complete cases and the 48 imputed data sets. Although not significant, the second most important predictor of opioid use after surgery was pain in the weeks before surgery (OR_{imp} (95% CI) = 1.23 (0.98 to 1.54), $p_z=0.07$, *Importance*=0.88), followed by age, BMI and history of opioid use (*Importance* imputed cases: >0.5; see online supplemental table 4).

DISCUSSION

Here, we described opioid rescue medication use in 270 outpatient surgery patients in an opioid-sparing postoperative context. Opioid-sparing postoperative analgesic regimens aim to prevent persistent opioid use. Patients received opioids immediately

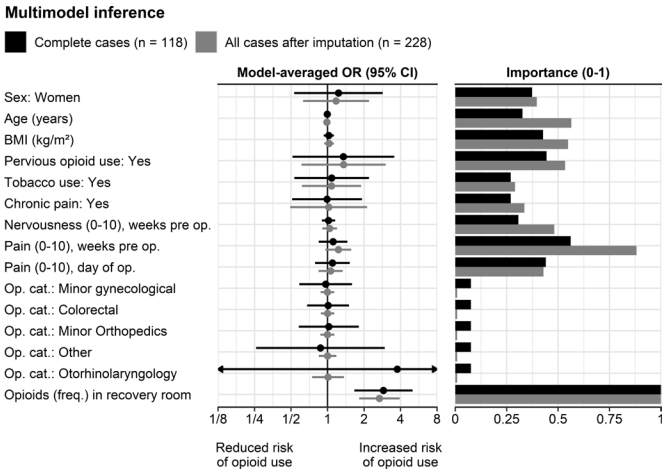

Figure 5 Identification of important predictors of opioid use after surgery through multimodel inference (2048 possible models). Results based on complete cases before imputation (n=118) are displayed in black while results based on all cases after imputation (n=228) are displayed in gray. As a reference category, we used *Men* for the predictor *Sex*, *No* for the predictors *Tobacco use* and *Chronic pain*, and *Minor abdominal surgery* for the predictor *Operation category* (*Op. cat.*). Black dots and horizontal lines indicate model-averaged ORs and 95% CIs, respectively. Arrows indicate that the 95% CI exceeds the limits of the x-axis. ORs >1 indicate increased risk of opioid use after surgery while ORs <1 indicate reduced risk of opioid use after surgery. Horizontal bars indicate the importance of each predictor, calculated as the sum of Akaike weights for models containing the predictor. Models containing predictors of high importance tend to perform better at predicting opioid use after surgery compared with models not containing these predictors.

before and during surgery (remifentanil during anesthesia), but only 41% received opioids in the recovery room. While most patients (93.2%) received one to six pills of 5 mg oxycodone as rescue medication for at-home postoperative pain management, 65% of the interviewed patients had not taken any opioid analgesic 1–2 days after discharge. Since the risk of persistent use hinges on initial use, we compared the rescue opioid-takers to the non-takers, focusing on known risk factors for persistent postsurgical opioid use. Consistent with these known risk factors, we found that opioid-takers were of significantly younger age, more likely to have chronic pain, had higher levels of pain before surgery and during acute recovery, lower pain coping ability after surgery, higher nervousness about the surgery in the weeks before, and were more likely to have received opioids in the recovery room.

Exploratory predictive modeling identified frequency of opioids received in the recovery room after surgery as the most important predictor for at-home use of opioid rescue medication, pointing to postoperative pain management in the recovery room as a relevant target for preventive care. Other factors identified as important in a large proportion of models tested, though not significant in the average model, included pain severity in the weeks before surgery, age, BMI, and history of opioid use. Nevertheless, only 2% of patients were still on opioids at long-term follow-up, supporting the idea of efficient prevention through the postoperative opioid-sparing scheme.

Compared with a Northern-American non-opioid-sparing context, where over 75% of patients fill opioid prescriptions after surgery[2 10] and 4.5% take opioids over 3 months or longer,[1] the current patient population had very little opioid exposure.

Patient endorsement of treatment satisfaction was high in both groups. This is consistent with findings from studies introducing the opioid-sparing approach in the USA.[7 8] The overall pain level at long-term follow-up was low and significantly reduced in comparison to presurgery and acutely postsurgery. Taken together, the high satisfaction, low levels of persistent pain and analgesic use months after surgery, validate the opioid-sparing approach as an efficient pain management scheme within this population, in line with the idea that opioid-sparing post-surgical care can prevent large-scale chronic opioid use.

The aim of this study was to identify whether known risk factors of persistent opioid use can also explain rescue opioid use after surgery. In line with previous studies indicating that elevated levels of acute and chronic pain are major vulnerability factors for persistent opioid use,[11 41] we found that patients who self-administered opioids during acute recovery (opioid-takers) were more likely to have chronic pain, and reported higher levels of acute pain before surgery, on the day of surgery, and in the 2 days after surgery. Consistent with their elevated pain ratings, opioid-takers were also more likely to receive opioids in the recovery room. While the recovery room staff were not blinded to the patients' opioid history which can result in a potential bias, we found no significant association between opioid history and opioid administration in the recovery room.

Both frequency of opioid administration in the recovery room and pain severity in the weeks before surgery emerged as relevant predictors for at-home use of opioid analgesics, making them interesting targets for preventive care. Patients who took opioids after surgery also reported to cope less well with postsurgical pain, although the overall reported pain relief in the two groups was comparable. This is in line with research demonstrating that improving pain coping skills significantly reduced opioid craving in adults with chronic pain and opioid dependency,[42] and post-operative opioid use in surgery patients.[6]

Age has previously been identified as an important predictor of postoperative opioid requirements, with younger patients requesting substantially higher doses of morphine.[43] In line with these findings, although the age range for the two groups was similar, opioid-takers were on average 5 years younger than non-takers. Opioid-takers and non-takers did not differ significantly in sex, BMI and history of tobacco use. All patients were selected for minor ambulatory surgery, hence excluding those with massive noxious input such as thoracotomy or major abdominal surgery. Despite potential systematic differences in the noxious input of the surgery, there was no significant difference in acute opioid use depending on the surgery type, nor was surgery type a significant predictor of postoperative opioid use in our sample. This is in line with prior evidence that new persistent opioid use and postoperative opioid use in the 2 months after surgery was not dependent on the type or severity of surgery patients received (eg, minor vs major surgery).[6 7 11]

Undergoing surgery is considered a major stressor and anxiety is reported as the worst aspect of the perioperative experience.[44] Opioid-takers were on average significantly more nervous about the surgery weeks before compared with non-takers. When asked how nervous they felt on the day of surgery and later about their recovery in the postoperative phone interview, the opioid-takers and non-takers reported comparably low numbers. We speculate that the limited nervousness in the postoperative period could be a consequence of their positive experience at the hospital, as documented by the overall high satisfaction rate.

Anxiety, depression[11 41 45] and catastrophizing[12 13 46] have been reported to be independently associated with persistent opioid use after surgery, unrelated to factors such as severity of injury, treating surgeon or surgery type.[13] We found no differences in anxiety, depression or catastrophizing scores in our long-term follow-up data, however it is possible that differences were present before surgery and/or during acute recovery. We found no significant differences between opioid-takers and non-takers in history of trauma, perceived socioeconomic status, or experience of loneliness.

LIMITATIONS

The study had several limitations. While the purely observational data ensure high ecological validity, relying on self-reports of rescue opioid use in the postsurgical phone interview could result in bias by desirability effects. Some questionnaires were only administered months or years after surgery, limiting the ability to interpret any lack of association with opioid self-administration. The low overall opioid exposure of the sample limits our ability to test the relationship between prior opioid use and opioid taking in the days after surgery. Similarly, some of the comparisons between subgroups were underpowered (eg, opioid use at long-term follow-up). Since we aimed for a descriptive approach, we conducted a high number of statistical tests with no correction for multiple comparison beyond a more stringent alpha level ($\alpha=0.01$). We tested for the predictive value of several factors collected before surgery using a multimodel approach with logistic regressions. While our findings align with and add to previous retrospective data,[8] we recommend that our findings should be replicated.

CONCLUSION

With opioid exposure being a large risk factor for persistent use, we need to understand what predicts the intake of rescue medication. Overall, only 36% of patients reported opioid analgesic use within 1–2 days after surgery. Opioid-takers were younger, more likely to have chronic pain and reported higher nervousness before surgery as well as higher pain levels and worse pain coping skills overall. Pain severity before surgery and frequency of opioids administered before discharge are relevant predictors of opioid use after surgery in an opioid-sparing context and could be targets for patient-centered care. The data reported here demonstrate the feasibility and utility of the opioid-sparing postsurgical care, with high patient satisfaction throughout, adequate postoperative pain control and very low incidence of persistent opioid analgesic use.

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Supplementary material

Methods

Inclusion and exclusion criteria

The participants recruited for the study were adult patients healthy enough to undergo minor day surgery, classified as ASA-I-II defined in line with the American Society of Anesthesiologists' Physical Status Classification System[1]. Very few patients invited to participate declined (n<10, exact number was not recorded). Excessive anxiety or a language barrier were criteria for not inviting otherwise eligible patients to take part in the study (small minority, number not recorded).

Surgery categories

The surgical categories consisted of colorectal (e.g., haemorrhoid resection, anal fissures), gynaecological (e.g., hysteroscopy, conisation, dilatation and curettage, minor abdominal (e.g., open and laparoscopic herniotomy, laparoscopic cholecystectomy), otorhinolaryngology (adenectomy, tonsillectomy, septum operations), minor orthopaedics (arthroscopy, arthrodesis) and other surgeries.

Perioperative pain management

Preoperative pain management: As part of the standard procedure at Kongsberg hospital patients were instructed to take 2 g acetaminophen (1.5 <70 kg) at home before surgery. If no contraindications were present, e.g. history of gastric or duodenal ulcer, significant gastroesophageal reflux disease (GERD), or kidney disease, patients also received an NSAID (500mg naproxen, 20mg esomeprazol and 12mg dexamethasone).

Intraoperative pain management: Regarding intraoperative pain management, all patients received a Target Controlled Infusion (TCI) of Propofol (Schneiders model - effect site control (4-6µg/ml) at the induction. Patients received Remifentanil (Mintos model - effect

site concentration 5 ng/ml) or 5 mg oxycodone as a pre-anesthetic opioid in the three to five minutes before propofol induction. If the patient had not fallen asleep within 2 - 3 min, propofol was increased to 8.0 µg/ml. Patients received either a laryngeal mask or were intubated. For intubation, patients received either Rocuronium 0.6 mg/kg or Mivacurium 0.2mg/kg. To maintain the anesthesia, propofol was administered in the range of 3 - 5 µg/ml and remifentanil to 2 - 4 ng/ml for all patients, but with individual adjustments. Intraoperatively, in some cases fentanyl was given on a case-by-case basis. No regional anesthesia was used, but infiltration of the wounds with local anesthesia was conducted in some patients.

Recovery room pain management: The overall goal of pain management in the recovery room was for patients to reach a pain score below 3 points on a numeric rating scale. If the patient scored above 3 points on the pain scale or the pain left them unable to relax, patients received 5 mg oxycodone per oral + 2.5 mg oxycodone iv up to 4 times (total 10 mg iv). If the patient remained in pain, the anesthetist was contacted for further treatment.

Subjective ratings

Pain

Patients rated pain intensity and pain interference at three time points: weeks before surgery (average pain last week), morning of surgery (pain right now) and during the acute recovery phase after discharge from the hospital (pain right now). Pain was rated on a numeric rating scale (NRS) from 0 to 10 with the ankers ‘no pain’ to ‘worst imaginable pain’ for pain intensity and ‘no interference’ to ‘worst interference’ for pain interference. They also indicated the duration of pain before surgery in months and years, and pain coping as well as analgeisc effect and associated pain relief after surgery on a NRS (0-10, ‘coping very badly’ to ‘coping very well’; ‘no pain relief’ to ‘full pain relief’).

Nervousness

Nervousness was measured at several time points. Patients indicated their nervousness about surgery in the weeks before surgery, state nervousness on the day of surgery, and their nervousness about recovery during the post-surgery phone interview on a NRS (0-10, 'not nervous' to 'very nervous').

Feeling good & feeling anxious in the operating room

Ratings of how good and anxious patients felt on the surgery table before and one minute after opioid injection were collected verbally on a NRS (0-10, 'not good/anxious' to 'very good/anxious').

Patient satisfaction

Patients were asked to indicate treatment satisfaction as a binary outcome variable (yes/no) at the post-surgery interview.

Long-term follow-up questionnaire data

We measured catastrophic thinking around pain (*Pain Catastrophizing Scale*, PCS)[2,3], pain (*Brief Pain Inventory*, BPI)[4], depression and anxiety (*Hospital Anxiety and Depression Scale,* HADS)[5], occurrence of traumatic experiences during childhood (*Childhood Trauma Questionnaire – short form*, CTQ-SF)[6,7], subjective perception of socio-economic status during child- and adulthood (*MacArthur Scale of Subjective Social Status*)[8], potential substance abuse (*Alcohol Use Disorders Identification Test*, AUDIT[9] and *Drug Use Disorders Identification Test*, DUDIT)[10], life satisfaction (*Life Satisfaction Questionnaire*, LISAT-11)[11], hedonic experience (*Snaith Hamilton Pleasure Scale*, SHAPS)[12], and mindfulness relating to thoughts, experiences and actions in day-to-day life (*Five Facet Mindfulness Questionnaire*, FFMQ-15)[13]. All questionnaires were administered online and in Norwegian.

Results

Comparison of patients who did and did not use rescue opioids during acute recovery

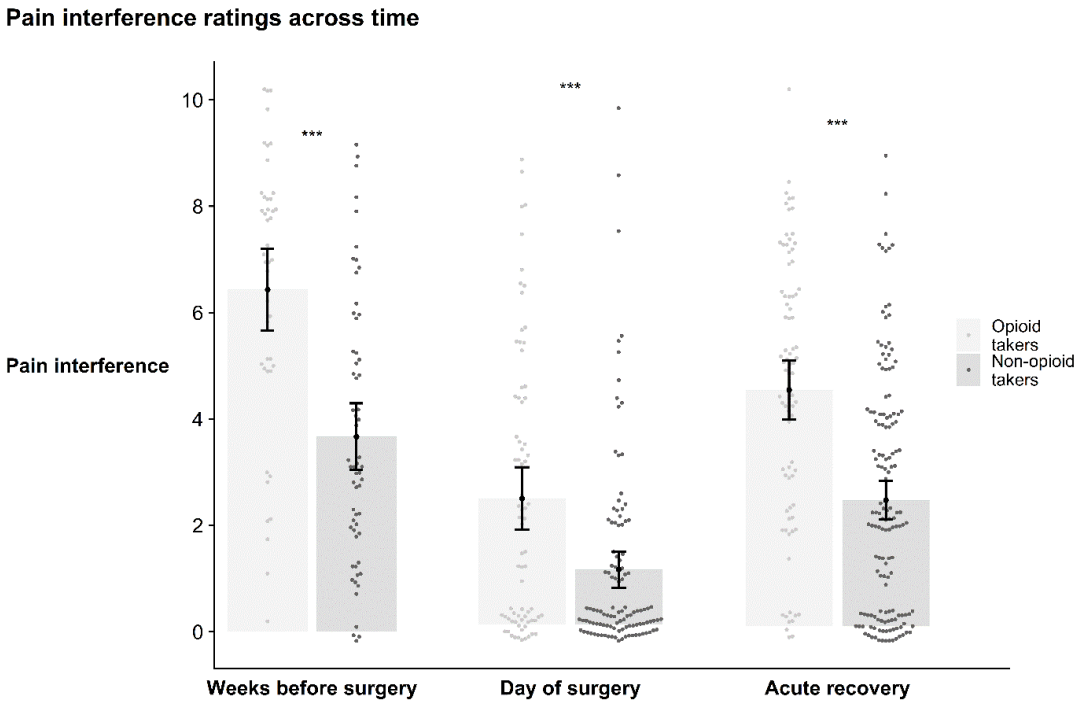
An overview of pain and mood ratings can be found in **Table 2**.

Pain interference

For pain interference, the non-parametric repeated measures ANOVA revealed a significant main effect of group (N=228; opioid takers vs. non-takers; $F(1) = 62.1$, $p < 0.0001$) and time (weeks before surgery, day of surgery, acute recovery; $F(2.0) = 99.2$, $p < 0.0001$). No significant group*time interaction effect was found ($F(2.0) = 1.2$, $p = 0.32$). Opioid takers self-reported higher pain interference weeks before surgery, on the day of surgery and during acute recovery (see supplementary **Figure 6** and **Table 2**).

State measures on the surgery table

The acute effects of opioid injection on the operating table are reported in Eikemo et al.[14]. Here, we compared these effects between opioid-takers and non-takers. When patients were asked to rate how good they felt right before and 1 minute after opioid induction on the surgery table, there was a significant main effect of time (N=227; before vs. after opioid injection, $F(1)=7.4$, $p=0.007$), but not of group (opioid-takers vs. non-takers, $F(1)=0.57$, $p=0.45$) nor a significant interaction effect ($F(1)=0.04$, $p=0.84$). After opioid injection, both patient subgroups reported feeling on average slightly less good (opioid-takers: pre: 7.2±2.1 vs. post: 6.7±2.3; non-takers: pre: 7.4±1.9 vs. post: 7.0±2.3; mean±SD). For ratings of feeling anxious on the surgery table, a non-parametric rmANOVA revealed a significant main effect of time (N=227; $F(1)=13.0$, $p<0.001$), but no significant effect of group ($F(1)=3.2$, $p=0.08$) nor a significant interaction effect ($F(1)=1.2$, $p=0.27$). Both opioid-takers and non-takers reported somewhat lower anxiety after opioid induction on the surgery table (opioid-takers: pre: 3.8±2.9 vs. post: 3.2±2.8; non-takers: pre: 2.9±2.7 vs. post: 2.6±2.6).



Supplementary Figure 6: Pain interference ratings for opioid takers and non-takers. Opioid-takers reported significantly higher pain interference before surgery and during acute recovery compared to non-takers. Groupwise means, 95% confidence intervals, dots depict individual numeric ratings indicated via questionnaire (weeks before surgery and day of surgery) and verbally via phone interview (acute recovery). Numeric ratings were always given as discrete numbers on a scale from 0 to 10. Error bars represent 95% confidence intervals. *** = $p \leq .001$.

Effect of intraoperative opioid on recovery room- and at home opioid use

More patients receiving oxycodone in the minutes before propofol induction received opioid analgesics vs. non-opioid analgesics in the recovery room (N=269; oxycodone: 51%; remifentanil: 35%; χ^2 = 13(2), p=.002). Rescue opioid use at home was not affected by intraoperative opioid choice (opioid takers: oxycodone 24%; remifentanil 20%; χ^2 = 0.6(2), p=0.73).

Supplementary Table 2. Overview of subjective ratings

	Full sample	Opioid takers	Non-opioid takers	*p*
Pain intensity (mean, SD)				
Weeks before surgery	3.7 (2.4)	4.8 (2.5)	3.0 (2.1)	**< 0.001**[b]
On day of surgery	1.4 (2.0)	2.2 (2.3)	1.0 (1.7)	**< 0.001**[c]
Post-surgery Day 1 or 2	3.2 (2.3)	4.5 (2.2)	2.5 (2.1)	**< 0.001**[c]
Long-term follow up: Pain right now	1.2 (1.8)	1.6 (1.9)	1.0 (1.8)	0.06[c]
Long-term follow up: Worst pain 24h	2.0 (2.3)	2.5 (2.5)	1.8 (2.3)	0.2[c]
Pain interference (mean, Sd)				
Weeks before surgery	5.0 (2.8)	6.4 (2.6)	3.7 (2.5)	**< 0.001**[b]
On day of surgery	1.4 (2.0)	2.2 (2.4)	0.9 (1.7)	**< 0.001**[c]
Post-surgery Day 1 or 2	3.1 (2.5)	4.4 (2.5)	2.3 (2.2)	**< 0.001**[c]
Pain relief acute recovery (mean, SD)	7.0 (2.5)	6.8 (2.3)	7.1 (2.6)	0.2[c]
Pain coping acute recovery (mean, SD)	8.5 (1.7)	7.9 (2.0)	8.9 (1.5)	**<0.001**[c]
Nervousness				
Nervousness before surgery	3.3 (3.0)	4.1 (3.3)	2.7 (2.8)	**0.002**[c]
Nervousness day of surgery	4.0 (3.0)	4.5 (3.3)	3.5 (2.8)	0.04[c]
Nervousness about recovery	1.6 (2.2)	2.1 (2.6)	1.4 (1.9)	0.1[c]

Notes. Overview of subjective ratings for full sample (N=270) and the two subgroups reached for the acute recovery interview (N=228). Overview of pain intensity and interference at three different time points, before surgery, on day of surgery and during acute recovery. In addition, pain intensity ratings were collected in the longterm-follow up phase (N=218). Pain relief and pain coping were collected during acute recovery. Nervousness ratings were collected before surgery, on the day of surgery and during acute recovery. Numeric ratings were always given as discrete numbers on a scale from 0 to 10. Groupwise means indicated for non-missing data. Percentage of missing data for group comparisons of pain intensity: weeks before surgery: 57%, day of surgery: 14%, long-term follow up: 44%; and of pain interference: weeks before surgery: 54%, day of surgery: 17%; pain relief: 8%; pain coping: 1%; Nervousness before surgery: 12%, day of surgery: 3%. SD= standard deviation. b= Welch's t-test, c= Wilcoxon sum of ranks test.

Long-term follow-up

Consistent with the acute post-surgery data, patients reported low concern about recovery after being released from the hospital (N=218; mean±SD: 2.2±1.2; Likert scale 1-6) and very high satisfaction with treatment at the hospital (N=218; mean±SD: 5.6±0.9; Likert scale 1-6). Sixty-nine percent of patients reported to have received support from close others during the acute recovery period. One person preferred not to disclose information on support and 67 of 218 (30.7%) patients reported to not have received support during acute recovery. Out of the patients who reported no support during recovery, 27 indicated that they did not need any support and 2 patients that they would have needed support but did not receive any. None of the other 38 patients who reported no support commented on their need of support.

Supplementary Table 3. Overview of long-term follow-up questionnaire outcomes.

	OPIOID TAKERS N=67	**NON-OPIOID TAKERS** N=119	***p***
CTQ total			
Mean (SD)	38.2 (10.4)	36.4 (8.4)	0.7[c]
Median (min - max)	34.0 (28-49)	34.0 (29-67)	
AUDIT total (N=			
Mean (SD)	4.9 (2.7)	3.7 (2.5)	0.2[c]
Median (min - max)	4 (1-14)	3 (0-12)	
DUDIT total			
Mean (SD)	0.6 (1.7)	0.07 (0.4)	0.6[c]
Median (min - max)	0 (0-8)	0 (0-3)	
BPI intensity total			
Mean (SD)	1.5 (1.7)	1.2 (0.3)	0.2[c]
Median (min - max)	1 (0-5)	0 (0-9)	
PCS total			
Mean (SD)	7.3 (7.9)	5.2 (6.4)	0.1[c]
Median (min - max)	5 (0-27)	3 (0-26)	
HADS total			
Mean (SD)	8.3 (6.0)	6.4 (4.4)	0.1[c]
Median (min - max)	8.0 (0-24)	6.0 (0-21)	
LISAT total			
Mean (SD)	4.4 (1.0)	4.8 (0.7)	0.09[b]
Median (min - max)	4.6 (1-5.8)	4.9 (2.9-6)	
SES childhood			
Mean (SD)	5.7 (1.6)	5.6 (1.6)	0.7[b]
Median (min - max)	5.5 (2-10)	6 (2-9)	
SES now			
Mean (SD)	6.8 (1.4)	7.1 (1.1)	0.4[c]
Median (min - max)	7 (4-10)	7 (4-10)	
SHAPS total			
Mean (SD)	0.9 (1.5)	0.8 (1.9)	0.6[b]
Median (min - max)	0 (0-6)	0 (0-14)	
FFMQ total			
Mean (SD)	2.6 (0.5)	2.5 (0.5)	1.0[b]
Median (min - max)	2.6 (1.5-3-3)	2.6 (1.3-3-5)	

Note: Total scores of all questionnaires were calculated for opioid takers and non-takers in the follow-up subsample. Out of 218 patients who took part in the long-term follow-up part of the study, data on opioid use during acute recovery was available in N=186 patients. The two groups did not differ significantly on any of the measures. Groupwise means and medians indicated, reflecting non-missing data. Percentage of missing data for N=186 in CTQ: 40%; AUDIT: 44%; DUDIT: 40%; BPI: 32%; PCS: 37%; HADS: 34%; LISAT: 40%; SESyoung: 35%; SESnow: 34%; SHAPS: 35%; FFMQ: 41%. SD= standard deviation. b= Welch's t-test, c= Wilcoxon sum of ranks test.

Supplementary Table 4. Results from multimodel inference.

Data set and predictor	Model-averaged OR [95% CI]	Model-averaged B (SE)	z	p_z	Importance
Complete cases (n = 118)					
Sex: Women	1.23 [0.54, 2.80]	0.21 (0.42)	0.49	0.62	0.37
Age (years)	0.99 [0.97, 1.02]	-0.01 (0.01)	-0.41	0.68	0.33
BMI	1.02 [0.95, 1.10]	0.02 (0.04)	0.59	0.55	0.43
Pervious opioid use: Yes	1.35 [0.52, 3.48]	0.30 (0.48)	0.62	0.53	0.44
Tobacco use: Yes	1.08 [0.54, 2.15]	0.08 (0.35)	0.22	0.82	0.27
Chronic pain: Yes	0.99 [0.52, 1.89]	-0.01 (0.33)	-0.03	0.98	0.27
Pain weeks before surgery (0-10)	1.11 [0.86, 1.43]	0.11 (0.13)	0.82	0.41	0.56
Nervousness weeks before surgery (0-10)	1.02 [0.92, 1.13]	0.02 (0.05)	0.35	0.73	0.31
Operation cat.: Minor gynecological	0.96 [0.60, 1.56]	-0.04 (0.24)	-0.15	0.88	0.08
Operation cat.: Colorectal	1.01 [0.69, 1.47]	0.01 (0.19)	0.05	0.96	0.08
Operation cat.: Minor Orthopedics	1.02 [0.59, 1.77]	0.02 (0.28)	0.08	0.93	0.08
Operation cat.: Other	0.87 [0.26, 2.91]	-0.13 (0.61)	-0.22	0.83	0.08
Operation cat.: Otorhinolaryngology	3.76 [0.00, Inf]	1.32 (401.54)	0.00	1.00	0.08
Opioid admin. in recovery room (freq.)	2.89 [1.70, 4.93]	1.06 (0.27)	3.91	**< 0.0001**	1.00
Pain day of surgery (0-10)	1.10 [0.81, 1.50]	0.09 (0.16)	0.59	0.55	0.44
All cases after imputation (n = 228)					
Sex: Women	1.18 [0.64, 2.16]	0.16 (0.31)	0.52	0.60	0.40
Age (years)	0.99 [0.96, 1.02]	-0.01 (0.01)	-0.83	0.41	0.56
BMI	1.03 [0.96, 1.11]	0.03 (0.04)	0.79	0.43	0.55
Pervious opioid use: Yes	1.36 [0.62, 2.95]	0.30 (0.40)	0.77	0.44	0.53
Tobacco use: Yes	1.08 [0.63, 1.86]	0.07 (0.28)	0.27	0.79	0.29
Chronic pain: Yes	1.02 [0.50, 2.08]	0.02 (0.36)	0.06	0.95	0.34
Pain weeks before surgery (0-10)	1.23 [0.98, 1.54]	0.21 (0.11)	1.79	0.07	0.88
Nervousness weeks before surgery (0-10)	1.04 [0.92, 1.17]	0.04 (0.06)	0.67	0.50	0.48
Operation cat.: Minor gynecological	1.00 [0.90, 1.11]	0.00 (0.06)	-0.03	0.98	0.01
Operation cat.: Colorectal	1.00 [0.90, 1.11]	0.00 (0.05)	0.00	1.00	0.01
Operation cat.: Minor Orthopedics	1.00 [0.89, 1.12]	0.00 (0.06)	-0.03	0.98	0.01
Operation cat.: Other	1.00 [0.86, 1.16]	0.00 (0.07)	0.01	0.99	0.01
Operation cat.: Otorhinolaryngology	1.01 [0.76, 1.34]	0.01 (0.14)	0.06	0.95	0.01
Opioid admin. in recovery room (freq.)	2.68 [1.86, 3.86]	0.99 (0.19)	5.30	**< 0.0001**	1.00
Pain day of surgery (0-10)	1.06 [0.86, 1.31]	0.06 (0.11)	0.54	0.59	0.43

Note. As reference category, we used *Men* for the predictor *Sex*, *No* for the predictors *Tobacco use* and *Chronic pain*, and. *Minor abdominal surgery* for the predictor *Operation category*. Odds ratios > 1 indicate increased risk of opioid use after surgery while odds ratios < 1 indicate reduced risk of opioid use after surgery. All p-values are from two-tailed z-tests. The importance of each predictor was calculated as the sum of Akaike weights for models containing the predictor. Models containing predictors of high importance tend to perform better at predicting opioid use after surgery compared to models not containing these predictors.

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