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Original Article

Opioid analgesic effects on subjective well-being in the operating theatre*

M. Eikemo,[1,2] **I. M. Meier,**[3] **G. E. Løseth,**[4,5] **M. Trøstheim,**[6] **N. Ørstavik,**[4] **E. N. Jensen,**[7] **E. L. Garland,**[8,9] **C. Berna,**[10,11] **G. Ernst**[12,13] and **S. Leknes**[2,14]

1 Post-doctoral Fellow, 4 Clinical Psychologist, 5 PhD Student, 7 Dentist, 12 Associate Professor, 14 Professor, Department of Psychology, University of Oslo, Oslo, Norway
2 Senior Researcher, 3 Post-doctoral Fellow, 6 PhD Student, Department of Physics and Computational Radiology, Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway
8 Professor, College of Social Work, University of Utah, Salt Lake City, UT, USA
9 Director, Center on Mindfulness and Integrative Health Intervention Development, University of Utah, Salt Lake City, UT, USA
10 Professor, Center for Integrative and Complementary Medicine, Division of Anaesthesiology, Lausanne University Hospital, Lausanne, Switzerland
11 Professor, The Sense, Lausanne University, Switzerland
13 Senior Consultant, Kongsberg Hospital, Kongsberg, Norway

Summary

Exposure to opioid analgesics due to surgery increases the risk of new persistent opioid use. A mechanistic hypothesis for opioids' abuse liability rests on the belief that, in addition to pain relief, acute opioid treatment improves well-being (e.g. via euphoria) and relieves anxiety. However, opioids do not consistently improve mood in laboratory studies of healthy non-opioid users. This observational study determined how two commonly used opioid analgesics affected patients' subjective well-being in standard clinical practice. Day surgery patients rated how good and how anxious they felt before and after an open-label infusion of remifentanil (n = 159) or oxycodone (n = 110) in the operating theatre before general anaesthesia. One minute after drug injection, patients reported feeling intoxicated (> 6/10 points). Anxiety was reduced after opioids, but this anxiolytic effect was modest (remifentanil Cohen's d = 0.21; oxycodone d = 0.31). There was moderate to strong evidence against a concurrent improvement in well-being (Bayes factors > 6). After remifentanil, ratings of `feeling good´ were significantly reduced from pre-drug ratings (d = 0.28). After oxycodone, one in three participants felt better than pre-drug. Exploratory ordered logistic regressions revealed a link between previous opioid exposure and opioid effects on well-being, as only 14 of the 80 opioid-naïve patients reported feeling better after opioid injection. The odds of improved well-being ratings after opioids were higher in patients with previous opioid exposure and highest in patients with > 2 weeks previous opioid use (adjusted OR = 4.4). These data suggest that opioid-induced improvement of well-being is infrequent in opioid-naïve patients. We speculate that peri-operative exposure could increase risk of persistent use by rendering subsequent positive opioid effects on well-being more likely.

Correspondence to: M. Eikemo
Email: marie.eikemo@psykologi.uio.no
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Twitter: @Marie_Eikemo; @IM_Meier; @GuroLoseth; @martintrostheim; @Chantal_berna_; @sirileknes

Introduction

Millions of people receive opioids peri-operatively every year [1, 2]. The historical view that pain protects against the addictive properties of opioids [3, 4] has been abandoned [5] as the prevalence of opioid misuse and opioid use disorder among individuals initially treated for pain became evident. Moreover, postoperative pain management with opioid analgesics increases the risk of persistent opioid use well beyond the expected surgical recovery window [6, 7], which in turn is associated with increased mortality and poorer health outcomes [8].

Another widely held view on opioid analgesics is that opioids improve a patient's subjective experience of well-being. This is because euphoria, a feeling of intense well-being or elation, is a side effect of opioid analgesics [9]. However, such increases in subjective well-being (feeling good [10]) are far from ubiquitous. Individual responses to a given opioid dose are notoriously hard to predict due to variability in both analgesic effects and side-effects [11, 12]. For example, in 1955, Henry Beecher et al. reported dysphoric rather than euphoric effects after morphine and heroin injections in healthy, non-drug using men [13]. Many subsequent laboratory studies have established that acute opioid doses do not reliably improve healthy participants' mood or subjective well-being [13–18].

Somewhat surprisingly, laboratory studies also indicate a lack of efficacy of opioids for relieving anxiety and other negative emotions. While the opioid analgesics hydromorphone, morphine and buprenorphine have been shown to block cortisol responses to stress induction, none relieved subjective anxiety [14, 15, 19]. Moreover, and in line with the early findings by Beecher et al. [13], increased negative affect has been reported after morphine [19], oxycodone [16] and remifentanil [20] administration. Nevertheless, opioid analgesics are routinely used clinically with the aim of dampening subjective and physiological stress, e.g. before surgery [21]. Moreover, opioid-induced improvement in subjective well-being, both in the case of positive (euphoria, drug liking [22]) and negative reinforcement (stress and anxiety relief [23, 24]) is considered a key driver of misuse risk [22, 23]. Therefore, understanding how opioids affect well-being in opioid-naïve and opioid exposed patients is key to safer surgery related prescription practices.

In this observational study, we assessed how opioid analgesics impact on patients' well-being and anxiety when they are used in standard clinical practice, with no blinding or placebo control. In clinical care, both patients and treatment providers typically attribute any improvement in well-being or anxiety to the given treatment [24]. Studies of opioid analgesia have revealed that pain relief can be more than doubled when the physician [25] or the patient [26] believes the treatment is an opioid. Given these expectancy effects, despite the mixed evidence from placebo-controlled laboratory studies, we hypothesised that opioids would lead to anxiety relief and increased subjective well-being when administered according to standard, unblinded procedures in a clinical context.

Methods

This prospective observational study was conducted from April 2018 to June 2021 at Kongsberg Hospital in Norway, a regional non-university hospital with a largely rural catchment area. Procedures were approved by the local data protection officer and Regional Ethics Committee as part of a larger project where opioid use, pain and well-being outcomes were assessed during both acute and long-term recovery (Meier IM, preprint, https://psyarxiv.com/6s45a). Written informed consent was obtained from all participants. A convenience sample of 269 Norwegian-speaking patients (ASA physical status 1 or 2) scheduled to undergo day surgery with general anaesthesia (primarily minor abdominal, minor gynaecological, minor orthopaedics, otorhinolaryngology and colorectal surgery) were included. Any exclusion criteria for undergoing day surgery also excluded participation in the study (details in online Supporting Information Appendix S1). Inclusion occurred whenever patients were eligible and the anaesthetist (GE) had time to complete inclusion procedures. Data collection was discontinued whenever patients were unable to respond or to avoid interference with pre-oxygenation.

All participants received treatment-as-usual and were treated with an intravenous opioid analgesic 3–5 min before anaesthetic induction with propofol. According to standard procedures, they were informed by the medical personnel that they would be given medication for pain and for sleep while on the operating table. The first 159 patients (April 2018 and May 2019) received remifentanil (effect site concentration 5 $ng.ml^{-1}$ using a target-controlled infusion model (Minto) based on sex, age, weight and height [27] as per routine hospital practice). Interim analysis indicated

undesirable effects of remifentanil on subjective well-being, therefore the responsible anaesthetist (GE) switched to oxycodone as the pre-anaesthetic opioid, which is reported to cause fewer negative subjective effects [28]. Patients recruited between November 2019 and June 2021 received oxycodone. As per routine hospital practice, oxycodone was administered in a fixed dose of 5 mg. On the morning of their surgery, patients received 2 g acetaminophen (1.5 g for patients < 75 kg). If not contraindicated due to, e.g. history of gastric or duodenal ulcer, gastritis or significant gastroesophageal reflux disease, patients also received 500 mg naproxen, 20 mg esomeprazole and 12 mg dexamethasone. In the hour waiting for surgery, participants received detailed information about procedures, signed the consent form and completed a brief questionnaire regarding subjective mood and well-being, current pain and previous opioid use (see online Supporting Information Appendix S1). Items from a validated Norwegian translation of the Brief Pain Inventory (BPI) [29] were used to assess presence of any current pain (yes/no) and, if relevant, the severity of current pain was reported on an 11-point numerical rating scale (NRS) with anchors `no pain´ and `worst imaginable pain´. From the list of mood items, we calculated a negative affect score from the mean of the ratings of nervousness and anxiety, as these were strongly correlated (r = 0.77; both on a 11-point NRS; anchors: `not´ – `very´). Patients also read a brief medication list and indicated which, if any, commonly used opioid analgesics they had taken ever or for > 2–3 weeks.

To capture the subjective effects of opioid injection, we relied on items from instruments used in psychopharmacology and clinical studies of opioid treatment for pain and addiction [18, 30–32]. Questions were standardised and identical wording, scales and anchors were used across measurement times and formats (a complete list is included in online Supporting Information Appendix S1) having been piloted in patient populations. Single item questions are typically well-understood by respondents and can be completed within seconds, which was essential to capture the immediate effects of opioids [33–35]. An 11-point (0–10) NRS which transfers well between the written and the verbal response format was used for all key measures. Verbal responses were recorded manually on paper by the anaesthetist. On the operating table, we measured subjective well-being (feeling `good´) [10, 18] and anxiety (feeling `anxious´) [31, 36] immediately before and 1 min after opioid injection (anchors `not´ – `very´, see Fig. 1).

After injection of the drug, experience of a drug effect (yes/no), high/intoxication, liking and disliking/unpleasant effects were assessed with four items from a Norwegian translation of the Drug Effects Questionnaire (DEQ [32]) with the anchors `not´ – `very´ [30]. Two items were slightly adapted based on patient feedback. The `feel effect´ item was introduced from November 2018 and therefore recorded only in the last 64 remifentanil-treated patients and in most of the oxycodone sample. Heart rate was recorded shortly after connecting the patient to the ECG in the operating theatre (see Table 1 and online Supporting Information Appendix S1 for details), on average 2 min before the first questions were asked (see Fig. 1).

Additional clinical and demographic details were collected from the hospital database (type of surgery, pre-operative heart rate) and from a routine questionnaire sent to all patients before surgery, where patients reported age, sex, weight, tobacco use (yes/no) and pain duration (months, years), if relevant. Where pain had a duration of > 3 months it was categorised as chronic. Due to a change in hospital procedures, the pain duration item was omitted from the questionnaire in 73 patients in the oxycodone group (71%).

Analyses were conducted in R version 4.2.1 (R Foundation, Vienna, Austria). Detailed information about the statistical packages is outlined in online Supporting Information Appendix S2. In accordance with the non-randomised, observational study design, data from the two drug groups were used to test the main hypotheses separately in order to assess whether study findings could be replicated across two different opioids and were not directly compared. Paired-samples Welch's t-tests with Holm-Bonferroni correction (four tests) were used to assess the primary outcomes: differences between the ratings of feeling `good´ and `anxious´ pre- and post-drug injection. The distributions of change scores were symmetric and near bell-shaped but zero-inflated (high kurtosis due to the integer scales). Therefore, we also conducted permutation testing to assess sensitivity (see details in online Supporting Information Appendix S2). All permutation results aligned with results from t-tests (online Supporting Information Table S1). To assess robustness and the ratio of evidence between the alternative hypothesis (H1: drug effect) and the null-hypothesis (H0: no drug effect), we calculated a Bayes Factor for each t-test using the default prior (half-Cauchy, r = 0.707). Kendall's τ coefficient (τ_b, rank correlation) was used for associations between variables with non-normal distributions measured on the ordinal level. We also ran a set of ordered logistic regression models to explore whether known predictors of addiction also influence the probability of feeling better following acute opioid drug administration. These predictors included: drug; sex; age

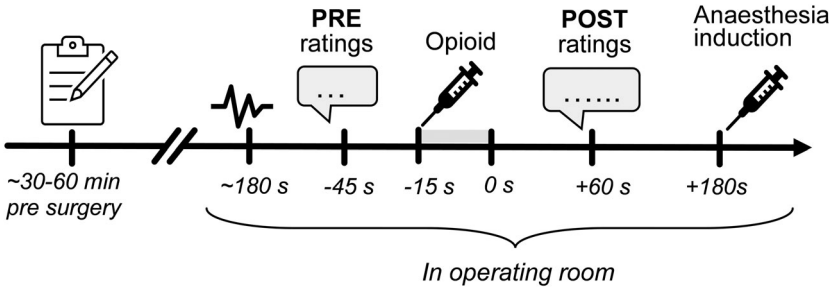

Figure 1 Study timeline for the day of surgery. Questionnaires were completed 30–60 min before surgery. On the operating table, patients gave two verbal ratings before the 15 s drug injection (PRE) and six verbal ratings 1–3 min after injection offset (POST). T = 0 is the opioid injection offset. Heart rate was recorded in the 2 min before drug administration.

Table 1 Patient characteristics and pre-operative data. Values are number (proportion), mean (SD) or median (IQR [range]).

	Remifentanil n = 159	**Oxycodone n = 110**	**Total n = 269**
Sex; female	95 (59.7%)	57 (51.8%)	152 (56.5%)
Age; y	46.4 (14.3)	48.9 (14.0)	47.4 (14.2)
Type of surgery			
Minor abdominal	41 (25.8%)	67 (60.9%)	108 (40.1%)
Minor gynaecological	50 (31.4%)	8 (7.3%)	58 (21.6%)
Colorectal	33 (20.8%)	15 (13.6%)	48 (17.8%)
Minor orthopaedics	20 (12.6%)	12 (10.9%)	32 (11.9%)
Otorhinolaryngology	5 (3.1%)	1 (0.9%)	6 (2.2%)
Other	10 (6.3%)	7 (6.4%)	17 (6.3%)
Weight; kg	80.7 (15.7)	81.9 (17.0)	81.2 (16.2)
Heart rate; bpm*	69.3 (13.2)	69.5 (13.0)	69.4 (13.1)
Tobacco use	34 (21.4%)	12 (10.9%)	46 (17.1%)
Current pain score 0/10	63 (46.3%)	52 (53.1%)	115 (49.1%)
Current pain severity given any pain	2 (1–4 [1–8])	3 (1–4 [1–9])	2 (1–4 [1–9])
Chronic pain	79 (53.7%)	22 (68.8%)	101 (56.4%)
Previous opioid use			
Opioid naïve	40 (27.8%)	42 (43.3%)	82 (34.0%)
Some experience	96 (66.7%)	49 (50.5%)	145 (60.2%)
Prolonged use (> 2 weeks)	8 (5.6%)	6 (6.2%)	14 (5.8%)
Current negative affect (0–10)	3.5 (1.5–5.5 [0–10])	3.3 (1–6 [0–9.5])	3.5 (1–6 [0–10])

*Beats per minute from pre-surgery heart rate recording.

(included in all models); surgical category; chronic pain history; current pain severity; tobacco use; previous opioid use; and negative affect on the day of surgery, each tested in separate models. An ordinal outcome variable with three levels (feeling worse, same or better) was computed from the change in ratings (post-pre drug) of feeling good and anxious. Ordered logistic regressions were performed using the polr function in the R-package MASS [37]. Models reported passed standard criteria for goodness-of-fit (Lipsitzs test) and the proportional odds assumption (Brant-Wald test).

For the two the main outcomes, 6 (2.2%) of the `feeling good´ and 13 (4.8%) of the anxiety ratings were missing (the number of observations per measure is listed in online Supporting Information Table S2). To assess whether missing data for explanatory variables biased the results, we used multiple imputation via multivariable imputation by chained equations (MICE) [38] as a sensitivity analysis (see

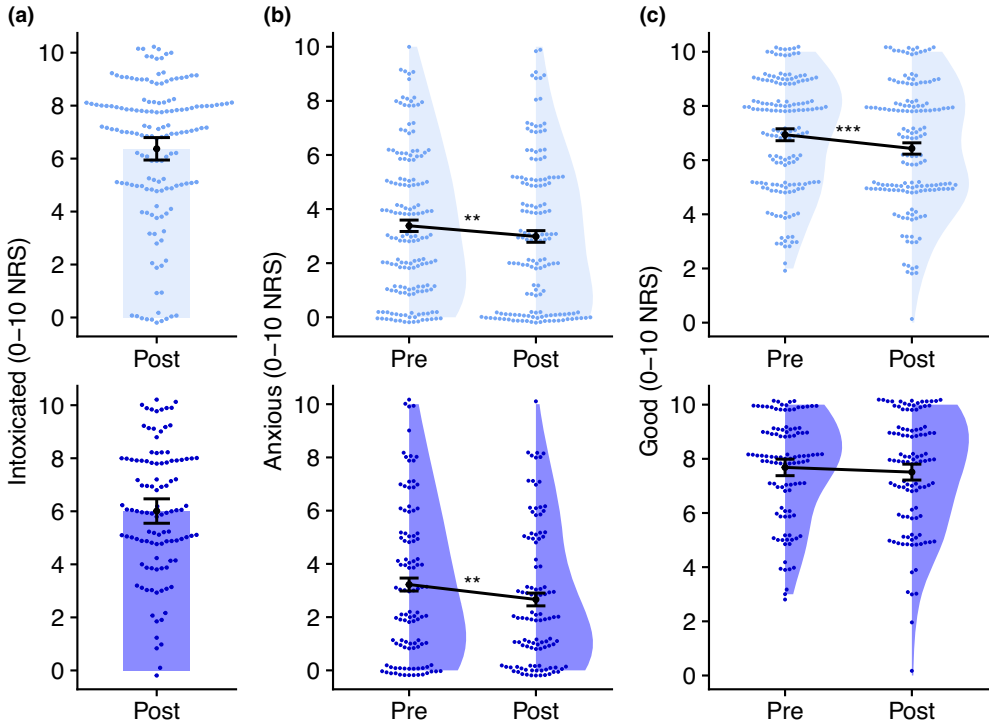

Figure 2 Subjective effects of a single dose of pre-operative opioids in the operating theatre. (a) Ratings of `feeling intoxicated´ by drug; (b) ratings of `feeling anxious´ before (pre-) and after (post-) drug injection; (c) ratings of `feeling good´ before (pre-) and after (post-) drug injection. Group-wise means and 95%CI in black, dots represent individual verbal numeric ratings. Remifentanil (light blue, n = 159); oxycodone (dark blue, n = 110). A jitter is added to points on the y and x-axis in the swarm plot due to overlapping ratings. **p < 0.01; ***p < 0.001.

online Supporting Information Appendix S2). The results from the complete case regression were compared with pooled imputed results (across imputations). Multivariable imputation by chained equations was deemed suitable for the sample size and type of explanatory variables (mainly categorical and ordinal). Number of imputations was set to the same as the highest proportion missing for any regression variable (k = 33) and number of iterations was set to 30. Complete case analyses were compared to the pooled imputed results.

Results

A total of 269 patients provided informed consent. Patient characteristics and self-reported pain, opioid use and negative affect are displayed in Table 1. Overall, patients reported limited previous use of opioid analgesics, moderate levels of negative affect and little pain in the hour before surgery.

After drug administration, most participants reported feeling drug effects (remifentanil n = 64 (81%) and oxycodone n = 91 (85%)). On average, participants also reported feeling intoxicated (> 6 on a 10-point NRS) at this time-point (Fig. 2a and online Supporting Information Table S2). Although oxycodone was given at a fixed dose, patients' weight was not significantly associated with the level of reported intoxication (adjusted for *sex*, β = 0.004, p = 0.77).

Anxiety ratings were significantly lower after opioid injection compared with immediately before (Fig. 2b; mean (SD) anxiety for remifentanil; pre- 3.4 (2.7), post-surgery 3.0 (2.8), p = 0.01, p_{adj} = 0.02; mean (SD) anxiety for oxycodone; pre- 3.2 (2.9), post-surgery 2.7 (2.6), p = 0.002, p_{adj} = 0.005, online Supporting Information Table S3). These anxiolytic effects were of modest size (remifentanil Cohen's d = 0.21, oxycodone d = 0.31). For both drugs, approximately 35% reported lower anxiety (remifentanil n = 53, oxycodone n = 36, online Supporting Information Tables S4 and S5). Bayes factors indicated inconclusive evidence for anxiolytic effects after remifentanil (BF_{10} = 2.2), but strong evidence for oxycodone (BF_{10} = 12.9).

There was no increased subjective well-being after either drug (Fig. 2c). Patients' ratings of `feeling good´ were significantly decreased after remifentanil (mean (SD), pre- 6.9 (2.1), post-surgery 6.4 (2.3), p = 0.0007, p_{adj} = 0.003,

d = 0.28) and decreased after oxycodone (pre- 7.7 (1.9), post-surgery 7.5 (2.2), p = 0.40, p_{adj} = 0.4, d = 0.08). Bayes factors indicated strong support that remifentanil reduced well-being (BF_{10} = 24.2), and moderate support for the absence of an oxycodone effect (BF_{10} = 0.15). The majority of patients reported the same or reduced levels of `feeling good´ after injection; 36 (23%) felt better after remifentanil and 36 (34%) after oxycodone (online Supporting Information Table S4).

Average drug liking and disliking (`unpleasant effect´) were comparable in the remifentanil group (mean (SD) liking 4.8 (3.1), disliking 4.9 (3.0), p = 0.9, BF_{10} = 0.09), whereas the ratio of drug liking to disliking was positive for oxycodone (liking 5.4 (3.0), disliking 3.8 (3.1), p = 0.002, BF_{10} = 13.8). For both opioids, drug liking and disliking were inversely correlated (remifentanil, Kendall's $\tau_b = -0.38$, $z = -6.2$, $p < 0.001$; oxycodone, $\tau_b = -0.44$, $z = -5.8$, $p < 0.001$). Drug liking was also positively associated with opioid effects on well-being (τ_b = 0.148, z = 3, p = 0.002). Patients who felt better after opioids also liked the drug effects (mean (SD) 5.7 (2.8)) whereas patients whose well-being decreased also indicated less drug liking (4.3 (3.2)).

For the exploratory analyses of predictors of increased well-being, there was a main effect of drug type; the odds for feeling better (by one category: worse, same, better) was 1.6 times greater in the oxycodone group (adjusted odds ratio (aOR), (95%CI) 1.6 (1.0–2.5), χ^2 = 4.0, p = 0.047) compared with remifentanil-treated patients. There were no significant effects of sex (aOR 95%CI 0.97 (0.6–1.5), p = 0.9) or age (aOR 1.0 (0.98–1.0), p = 0.59) on the change in feeling good following opioids. Of the exploratory variables, the number (proportion) of missing datapoints was: tobacco use n = 4 (1.5%); previous opioid use n = 28 (10.4%); heart rate n = 21 (7.8%); negative affect scores n = 5 (1.9%); current pain n = 35 (13.0%); and chronic pain status n = 90 (33.5%).

Separate analyses showed no significant effects of type of surgery, chronic pain status, current pain level or tobacco use (all $\chi^2 < 2.1$, $p > 0.15$). For previous opioid use, we observed a significant `dose–response´ relationship such that the probability of increased well-being based on model predictions was low for opioid-naïve patients (n = 14 (18%)), higher for those with some previous use (n = 43 (30%)) and highest in patients with previous prolonged (> 2 weeks) opioid use (n = 8 (57%)). The odds for feeling better was 4.4 times greater for the patients with a history of long-term opioid use than for patients reporting no previous opioid use (aOR 95%CI 4.4 (1.4–14.8), p = 0.012, see Fig. 3 for probabilities based on the unadjusted model and online Supporting Information Table S4). Since only 14 patients

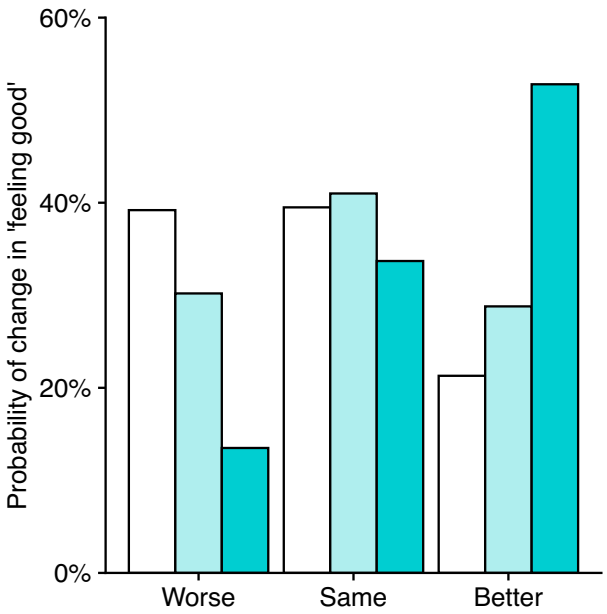

Figure 3 Effect of previous opioid use on the likelihood of feeling worse, same or better following opioid injection (change in `feeling good´ ratings). Bars depict predicted probabilities based on the bivariate (unadjusted) ordered logistic regression model. Opioid naïve (white); some previous opioid use (light blue); prolonged (> 2 weeks) opioid use (turquoise).

reported long-term opioid use, we conducted a robustness analysis with only the opioid-naïve and `some experience´ groups; the effect of opioid exposure was significant (aOR 1.7 (1.1–2.9), p = 0.046) and the overall pattern of results did not change. The degree of negative affect before surgery was also a significant predictor of increased well-being; for each additional point of negative affect the odds of feeling better increased with 9% (aOR 1.09 (1.0–1.2), p = 0.039). The effect is illustrated in Figure 4a with a categorical negative affect variable (negative state low (0–2), medium (2.1–5), high (5.1–10)).

The predictive value of the same variables for change in anxiety ratings from pre- to post-opioid injection was explored. In the base model (drug, sex, age) we did not observe significant effects of drug (aOR 95%CI 1.12 (0.7–1.8), p = 0.65) or age (aOR 95%CI 1.01 (0.99–1.02), p = 0.50), but a significant effect of sex, with 1.7 times higher odds for anxiety relief in women (aOR 95%CI 1.7 (1.04–2.7), X^2 = 4.5, p = 0.033). However, women also had higher pre-drug anxiety ratings (mean (SD) women 3.9 (3.0), men 2.6 (2.3)). Negative affect before surgery was also predictive of change in anxiety relief following an opioid: for each additional point of negative affect, the odds of feeling less anxious increased by 12% (aOR 95%CI 1.12 (1.03–1.23),

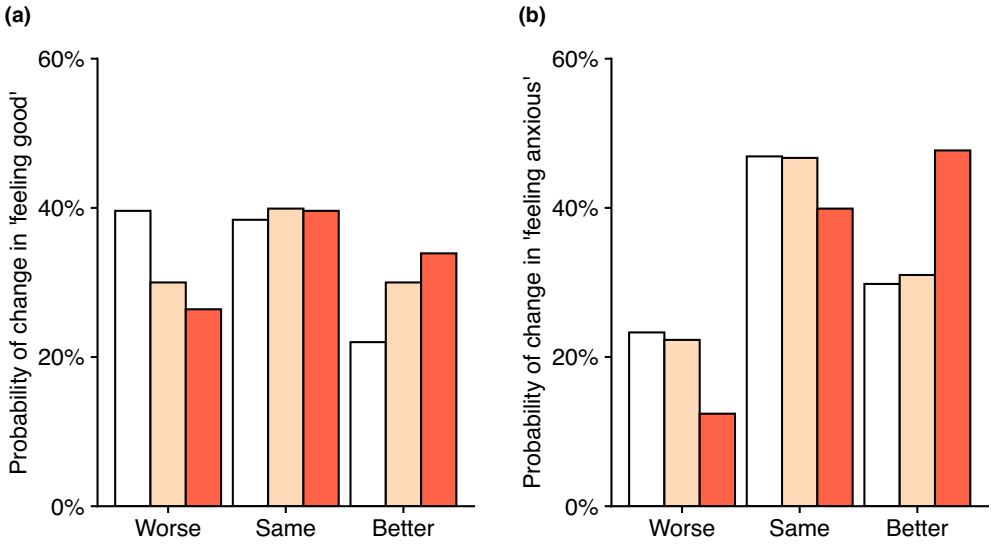

Figure 4 Effect of negative affect before surgery on the likelihood of feeling worse, same or better following opioid injection. Bars depict probability of change in (a) `feeling good´ and (b) `feeling anxious´. Negative affect categories from scores given 30–60 min before surgery: low; 0–2 (white), medium; 2.1–5 (peach) or high; 5.1–10 (orange).

X^2 = 7.2, p = 0.007, see Fig. 4b). There were no significant effects of the remaining predictors (previous opioid use, tobacco use, chronic and current pain and type of surgery, all $X^2 < 4.5$, $p > 0.10$). Information about chronic pain was missing for most patients in the oxycodone group. Therefore, regression analyses with this predictor (for feeling `good´ and `anxious´) with remifentanil data only, were performed as a robustness check. The results aligned with the main analyses (see online Supporting Information Tables S6 and S7).

Results from the regression analyses using imputed data yielded very similar results and identical interpretations. Consequently, the more conservative complete case results are reported here while imputed results can be found in the dedicated OSF repository (details in online Supporting Information Appendix S2).

Discussion

Pain is the primary indication for opioid analgesics. However, treatment providers [21] and patients [39–41] also use these medications to relieve stress and discomfort and to increase well-being. Positive opioid effects are in turn linked to abuse liability [22]. In this open-label observational study, intravenous injection of remifentanil or oxycodone rapidly yielded reports of intoxication and modestly reduced anxiety ratings. However, we found robust evidence against the hypothesised increase in subjective well-being in the minutes after opioid injection. Surprisingly, only a minority of patients reported increased well-being immediately following opioid administration, and subjective well-being was significantly reduced after remifentanil. Exploratory analysis indicated that the probability of improvement in well-being increased with the degree of previous opioid exposure.

Euphoria and drug liking are considered key predictors of a drug's abuse liability [22]. Here, increased well-being after opioids was significantly associated with higher drug liking and previous opioid exposure, but not with current or persistent pain. The probability of increased well-being after opioids was low (18%) for opioid-naïve patients. The odds for increased well-being after opioids were over four times higher in patients with > 2 weeks of previous opioid exposure. Our results dovetail with findings from studies of opioid abuse liability, where liking and euphoria from opioids is most consistently observed in people with extensive previous opioid use/misuse [22]. Moreover, pre-clinical studies show that brain responses to opioids can change even after a single opioid dose [42]. Consistent with this finding, a robustness analysis including only opioid-naïve patients and those with short-term exposure (< 2 weeks) showed that mere exposure was associated with a doubling of the odds of increased well-being from a single dose of opioids. These intriguing results are exploratory in nature and warrant replication in independent samples.

Several factors influence the effects of opioids, including the speed of absorption into the bloodstream and into the brain. Intravenous administration typically yields the strongest subjective effects [43]. In the current study, subjective well-being was measured after the remifentanil infusion had reached plateau [27], but before the expected

Tmax of oxycodone at 2–8 min [44, 45]. Nevertheless, a comparable proportion of patients reported feeling a drug effect 1 min after injection of either drug (> 80%). Average ratings of intoxication and drug liking were also comparable after remifentanil and oxycodone. Moreover, a distinct, though modestly sized, anxiolytic effect was observed after both opioids compared with pre-drug ratings. The lack of randomisation inherent in an observational study limits our ability to directly compare the effects of these two commonly used opioid analgesics. The ratio of drug liking to disliking was 1 after remifentanil but positive after oxycodone, consistent with previous reports that this drug induces relatively fewer negative side effects than other opioid analgesics [28]. Although only a minority of patients reported increased well-being after this drug in the current study, exploratory regression analyses indicated a significantly higher probability of increased well-being after oxycodone than after remifentanil.

Surgery is a major stressor, and patients cite anxiety as the worst aspect of the peri-operative experience [46]. Using opioids to reduce presurgical anxiety was standard practice [47] until head-to-head comparison revealed that opioids were inferior to benzodiazepines due to side-effects [48]. Opioids are still administered peri-operatively to ensure unconsciousness and analgesia throughout procedures. Initiating opioid treatment in the minutes before propofol is thought to relieve the stress and discomfort of intubation [21]. The present results indicate that modest anxiety relief is observed as early as 1 min after the opioid injection. However, the magnitude of the observed effect (0.5 reduction on an 11-point scale) may not be clinically relevant [49], particularly not for pre-surgical remifentanil where ratings of `feeling good´ showed a reduction of similar size.

Two recent studies of pain treatment in the Emergency Department indicated that positive ratings of an opioid drug were largely explained by pain relief [33, 34]. In contrast with the Emergency Department studies, here opioids were given when pain levels were overall very low, with half of the patients reporting no current pain, likely partly due to premedication with acetaminophen. We did not find a significant association between current or chronic pain status and opioid effects in this sample. However, consistent with the notion that relief from negative states may drive appreciation of opioids [50], the probability of increased well-being and anxiety relief was somewhat higher in patients reporting higher negative affect on the day of surgery. These links between pain/negative affect and subsequent subjective opioid effects in the operating theatre should however be considered preliminary and hypothesis-generating given the study's observational design and the substantial portion missing data for the chronic pain outcome.

The study site was a regional non-university hospital with a largely rural catchment area. Data from the two drug groups were collected sequentially by the same anaesthetist (GE), with the majority of the oxycodone group included after the start of the COVID-19 pandemic. The lack of randomisation reduces the generalisability of the results, but the strength of an observational study is its ecological validity. The lack of an observed increase in well-being from pre-surgery opioids cannot be attributed to differences between the study setup and common clinical practice, since only minimal alterations from standard clinical care were made. Future studies are needed to determine whether these and different opioids given at different time-points and varying doses are associated with similar subjective effects. Since no placebo control was included, we cannot exclude the possibility that effects on anxiety and well-being were influenced by the passage of time or by the anaesthetist's supervision, e.g. with lower well-being as the time of surgery approached, reduced anxiety from receiving care, regression to the mean and/or a potential `floor effect´ for the participants with low pre-drug anxiety levels.

In summary, these ecologically valid findings add substantially to the literature on how acute opioid treatment affects subjective well-being [13, 14, 16–18]. We find that while opioid injection on the operating table yielded a mean intoxication above 6/10, the medications were associated with only a modest anxiolytic effect. We report evidence against opioid-induced well-being at the group level, with most patients reporting the same or lower levels of `feeling good´ after opioids. Exploratory analyses showed that the odds of improved well-being after opioids increased as a function of previous opioid exposure. We conclude that increased well-being from opioids is relatively rare, and as such it is difficult to explain the undeniable abuse liability of opioid analgesics. Researchers and clinicians should instead consider exposure-related processes and opioid effects on the brain's `wanting´ circuits [51], acute withdrawal symptoms [52–54] or the high value of acute relief from intense [33, 34] or long-term physical [55, 56] or emotional [39, 40] pain.

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References

1. Deyo RA, Hallvik SE, Hildebran C, et al. Association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients: a statewide retrospective cohort study. *Journal of General Internal Medicine* 2017; **32**: 21–7.
2. Larach DB, Waljee JF, Hu H-M, Lee JS, Nalliah R, Englesbe MJ, Brummett CM. Patterns of initial opioid prescribing to opioid-naive patients. *Annals of Surgery* 2020; **271**: 290–5.
3. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; **25**: 171–86.
4. Porter J, Jick H. Addiction rare in patients treated with narcotics. *New England Journal of Medicine* 1980; **302**: 123–3.
5. Barnett ML. Opioid prescribing in the midst of crisis — myths and realities. *New England Journal of Medicine* 2020; **382**: 1086–8.
6. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *Journal of the American Medical Association Surgery* 2017; **152**: e170504.
7. Howard R, Brown CS, Lai Y-L, et al. Postoperative opioid prescribing and new persistent opioid use: the risk of excessive prescribing. *Annals of Surgery* 2023; **277**: e1225–31.
8. Santosa KB, Priest CR, Oliver JD, Kenney B, Bicket MC, Brummett CM, Waljee JF. Long-term health outcomes of new persistent opioid use after surgery among medicare beneficiaries. *Annals of Surgery* 2022. Epub 14 November. https://doi.org/10.1097/SLA.0000000000005752.
9. Hewson DW, Struys MMRF, Hardman JG. Opioids: refining the perioperative role of God's own medicine. *British Journal of Anaesthesia* 2019; **122**: e93–5.
10. Diener E, Oishi S, Tay L. Advances in subjective well-being research. *Nature Human Behaviour* 2018; **2**: 253–60.
11. Angst MS, Lazzeroni LC, Phillips NG, et al. Aversive and reinforcing opioid effects: a pharmacogenomic twin study. *Anesthesiology* 2012; **117**: 22–37.
12. Angst MS, Phillips NG, Drover DR, et al. Pain sensitivity and opioid analgesia: a pharmacogenomic twin study. *Pain* 2012; **153**: 1397–409.
13. Lasagna L, von Felsinger JM, Beecher HK. Drug-induced mood changes in man: 1. Observations on healthy subjects, chronically ill patients, and ``postaddicts''. *Journal of the American Medical Association* 1955; **157**: 1006–20.
14. Bershad AK, Miller MA, Norman GJ, de Wit H. Effects of opioid- and non-opioid analgesics on responses to psychosocial stress in humans. *Hormones and Behavior* 2018; **102**: 41–7.
15. Bershad AK, Jaffe JH, Childs E, de Wit H. Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans. *Psychoneuroendocrinology* 2015; **52**: 281–8.
16. Wardle MC, Fitzgerald DA, Angstadt M, Rabinak CA, de Wit H, Phan KL. Effects of oxycodone on brain responses to emotional images. *Psychopharmacology* 2014; **231**: 4403–15.
17. Zacny JP, de Wit H. The prescription opioid, oxycodone, does not alter behavioral measures of impulsivity in healthy volunteers. *Pharmacology Biochemistry and Behavior* 2009; **94**: 108–13.
18. Zacny JP, Lichtor SA. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers. *Psychopharmacology* 2008; **196**: 105–16.
19. Massaccesi C, Willeit M, Quednow BB, et al. Opioid-blunted cortisol response to stress is associated with increased negative mood and wanting of social reward. *Neuropsychopharmacology* 2022; **47**: 1–10.
20. Wagner K, Valet M, Kochs E, Kriner M, Tölle T, Sprenger T. The μ-opioid receptor agonist remifentanil induces acute dysphoria irrespective of its analgesic properties. *Journal of Psychopharmacology* 2010; **24**: 355–61.
21. Shanthanna H, Ladha KS, Kehlet H, Joshi GP. Perioperative opioid administration: a critical review of opioid-free versus opioid-sparing approaches. *Anesthesiology* 2021; **134**: 645–59.
22. Comer SD, Zacny JP, Dworkin RH, et al. Core outcome measures for opioid abuse liability laboratory assessment studies in humans: IMMPACT recommendations. *Pain* 2012; **153**: 2315–24.
23. Koob GF. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry* 2007; **164**: 1149–59.
24. Hartman SE. Why do ineffective treatments seem helpful? A brief review. *Chiropractic and Osteopathy* 2009; **17**: 10.
25. Gracely R, Dubner R, Deeter W, Wolskee P. Clinicians' expectations influence placebo analgesia. *Lancet* 1985; **325**: 43.
26. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nature Reviews. Neuroscience* 2005; **6**: 545–52.
27. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33.
28. Kibaly C, Alderete JA, Liu SH, Nasef HS, Law PY, Evans CJ, Cahill CM. Oxycodone in the opioid epidemic: high `liking´, `wanting´, and abuse liability. *Cellular and Molecular Neurobiology* 2021; **41**: 899–926.
29. Klepstad P, Loge JH, Borchgrevink PC, Mendoza TR, Cleeland CS, Kaasa S. The Norwegian Brief Pain Inventory Questionnaire: translation and validation in cancer pain patients. *Journal of Pain and Symptom Management* 2002; **24**: 517–25.
30. Comer S, Cooper Z, Kowalczyk W, et al. Evaluation of potential sex differences in the subjective and analgesic effects of morphine in normal, healthy volunteers. *Psychopharmacology* 2010; **208**: 45–55.
31. Eikemo M, Loseth GE, Johnstone T, Gjerstad J, Willoch F, Leknes S. Sweet taste pleasantness is modulated by morphine and naltrexone. *Psychopharmacology* 2016; **233**: 3711–23.
32. Morean ME, de Wit H, King AC, Sofuoglu M, Rueger SY, O'Malley SS. The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology* 2013; **227**: 177–92.
33. Abril Ochoa L, Naeem F, White DJ, Bijur PE, Friedman BW. Opioid-induced euphoria among emergency department patients with acute severe pain: an analysis of data from a randomized trial. *Academic Emergency Medicine* 2020; **27**: 1100–5.
34. Friedman BW, Latev A, Campbell C, White D. Opioid-induced ``likeability'' and ``feeling good'' are not associated with return visits to an ED among migraine patients administered IV hydromorphone. *Headache: The Journal of Head and Face Pain* 2018; **58**: 750–4.
35. Sapkota A, Takematsu M, Adewunmi V, Gupta C, Williams AR, Friedman BW. Oxycodone induced euphoria in ED patients

with acute musculoskeletal pain. A secondary analysis of data from a randomized trial. *American Journal of Emergency Medicine* 2022; **53**: 240–4.
36. Collins ED, Vosberg SK, Ward AS, Haney M, Foltin RW. The effects of acute pretreatment with high-dose memantine on the cardiovascular and behavioral effects of cocaine in humans. *Experimental and Clinical Psychopharmacology* 2007; **15**: 228–37.
37. Venables WN, Ripley BD. *Modern Applied Statistics with S*, 4th edn. New York: Springer, 2002.
38. Newman DA. Missing data: five practical guidelines. *Organizational Research Methods* 2014; **17**: 372–411.
39. McHugh RK, Weiss RD, Cornelius M, Martel MO, Jamison RN, Edwards RR. Distress intolerance and prescription opioid misuse among patients with chronic pain. *Journal of Pain* 2016; **17**: 806–14.
40. Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD. The association between negative affect and prescription opioid misuse in patients with chronic pain: the mediating role of opioid craving. *Journal of Pain* 2014; **15**: 90–100.
41. Blatt JM. Implications of hedonic effects of opioids in clinical practice. *Pain* 2022; **163**: e608–9.
42. Fields HL, Margolis EB. Understanding opioid reward. *Trends in Neurosciences* 2015; **38**: 217–25.
43. Marsch LA, Bickel WK, Badger GJ, Rathmell JP, Swedberg MD, Jonzon B, Norsten-Höög C. Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. *Journal of Pharmacology and Experimental Therapeutics* 2001; **299**: 1056–65.
44. Hao G-T, Zhou H-Y, Gao H-Z, et al. Pharmacokinetics of oxycodone hydrochloride and three of its metabolites after intravenous administration in Chinese patients with pain. *Pharmacological Reports* 2014; **66**: 153–8.
45. Kokki H, Rasanen I, Reinikainen M, Suhonen P, Vanamo K, Ojanperä I. Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clinical Pharmacokinetics* 2004; **43**: 613–22.
46. Walker EMK, Bell M, Cook TM, Grocott MPW, Moonesinghe SR. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. *British Journal of Anaesthesia* 2016; **117**: 758–66.
47. Pandit SK, Kothary SP. Intravenous narcotics for premedication in outpatient anaesthesia. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 353–8.
48. Raeder JC, Breivik H. Premedication with midazolam in outpatient general anaesthesia. A comparison with morphine-scopolamine and placebo. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 509–14.
49. Eaton TA, Comer SD, Revicki DA, Trudeau JJ, van Inwegen RG, Stauffer JW, Katz NP. Determining the clinically important difference in visual analog scale scores in abuse liability studies evaluating novel opioid formulations. *Quality of Life Research* 2012; **21**: 975–81.
50. Cabanac M. Sensory pleasure. *Quarterly Review of Biology* 1979; **54**: 1–29.
51. Berridge KC, Robinson TE. Parsing reward. *Trends in Neurosciences* 2003; **26**: 507–13.
52. June HL, Stitzer ML, Cone E. Acute physical dependence: time course and relation to human plasma morphine concentrations. *Clinical Pharmacology and Therapeutics* 1995; **57**: 270–80.
53. Heishman SJ, Stitzer ML, Bigelow GE, Liebson IA. Acute opioid physical dependence in humans: effect of varying the morphine-naloxone interval. *Journal of Pharmacology and Experimental Therapeutics* 1989; **250**: 485–91.
54. Coloma-Carmona A, Carballo JL, Rodríguez-Marín J, Pérez-Carbonell A. Withdrawal symptoms predict prescription opioid dependence in chronic pain patients. *Drug and Alcohol Dependence* 2019; **195**: 27–32.
55. Wilsey BL, Fishman S, Li C-S, Storment J, Albanese A. Markers of abuse liability of short- vs long-acting opioids in chronic pain patients: a randomized cross-over trial. *Pharmacology Biochemistry and Behavior* 2009; **94**: 98–107.
56. Garland EL. Psychosocial intervention and the reward system in pain and opioid misuse: new opportunities and directions. *Pain* 2020; **161**: 2659–66.

Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Methodological details and questionnaires.

Appendix S2. Statistical details, multiple imputation, and robustness checks.

Table S1. The output of paired permutation tests (of the mean).

Table S2. Descriptive ratings reported from the operating theatre.

Table S3. Statistics for the four main hypothesis tests.

Table S4. Numbers and proportions of patients who felt worse, better or the same after the opioid administration grouped by drug and history of opioid use.

Table S5. Average and median change score within each change group.

Table S6. Robustness check for chronic pain effect on change in ``feeling good´´ with remifentanil data only.

Table S7. Robustness check for chronic pain effect on change in ``feeling anxious´´ with remifentanil data only.