Original Article

Patterns of opioid use after surgical discharge: a multicentre, prospective cohort study in 25 countries

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Summary

Background Excessive opioid prescribing following surgery contributes to the growing opioid crisis. Prescribing practices are modifiable, yet data to guide appropriate prescription of opioids at surgical discharge remain sparse. This study aimed to evaluate factors associated with opioid consumption following discharge from surgery.

Methods An international prospective multicentre cohort study was performed recruiting adult patients undergoing common general, orthopaedic, gynaecological and urological surgery, with follow-up 7 days after discharge. The primary outcome measures were the quantities of prescribed and consumed opioids in oral morphine milligram equivalents. Descriptive and multivariable analyses were performed to investigate factors associated with the primary outcome measures.

Results This analysis included 4273 patients from 144 hospitals in 25 countries. Overall, 1311 (30.7%) patients were prescribed opioids at discharge. For those patients prescribed opioids, mean (SD) 179 (240) oral morphine milligram equivalents were prescribed, yet only 81 (145) oral morphine milligram equivalents were consumed within the first 7 days after discharge. An increased dose of opioids prescribed at discharge was associated with an increased dose of opioids consumed during the follow-up period ($\beta = 0.33$ (95%CI 0.31–0.34), $p < 0.001$). The risk of prescribing more opioids than patients consumed increased as quantities of opioids prescribed at discharge exceeded 100 oral morphine milligram equivalents, independent of patient comorbidity, procedure and pain. Patients were prescribed more than twice the quantity of opioids they consumed in the first 7 days following discharge from surgery.

Conclusions Our data suggest that the current quantities of opioids provided at discharge exceed patient needs and may contribute to increasing community opioid use and circulation.

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Introduction

The opioid epidemic is a major public health crisis. The age-standardised prevalence of opioid dependence has been estimated to be 510 per 100,000, with the highest prevalence in the USA, Middle East and East Asia [1]. This translated to approximately 109,500 opioid overdose deaths worldwide in 2017 [1]. Post-surgical opioid prescribing is a significant contributor to the global opioid crisis [2], with overprescribing representing an ongoing source of community diversion of unused opioids, misuse, abuse and dependence [3, 4].

Opioid analgesia, though prescribed commonly to manage moderate to severe postoperative pain, has significant potential for harm and is facing increasing global scrutiny [5]. A recent systematic review of 47 randomised trials found that opioid prescribing at surgical discharge

following minor and moderate elective surgeries did not reduce pain intensity and was associated with an increased incidence of adverse events such as vomiting [6]. Amid growing awareness of the contribution of excessive and unsafe opioid prescribing to the current opioid crisis, further data are urgently required to guide clinical use following surgery [7–11]. As the second-highest prescribers of opioids, surgical teams are an important target group for improving prescribing practices [2].

The Opioid PrEscRiptions and Usage After Surgery (OPERAS) study aimed to quantify the current global practice of opioid prescribing and consumption patterns in patients after discharge from common surgical procedures, and to identify factors associated with increased opioid consumption.

Methods

Analyses were based on a prespecified, published protocol and other prespecified aims were addressed separately [12, 13]. Ethical approval was obtained for the lead site and local centres obtained approval according to the requirements of each participating centre. This was verified by the central steering committee. All hospitals that routinely performed general, orthopaedic, gynaecological and urological procedures were eligible to enrol. Prospective data were collected from inpatient clinical records and a standardised patient telephone interview was undertaken at 7 days following discharge [14]. Data collection took place over six predefined 14-day data collection periods. Centres could choose to participate in multiple 14-day consecutive recruitment periods.

Participating centres prospectively screened and approached all adult (age ≥ 18 y) patients who met eligibility criteria in the recruitment windows to obtain informed consent (when this was a requirement of the local site ethical approvals). Patients could withdraw at any stage. Patients undergoing either elective or emergency general surgery (cholecystectomy, appendicectomy, inguinal hernia repair, colon resection, fundoplication or sleeve gastrectomy); orthopaedic (total or reverse shoulder arthroplasty, rotator cuff or labral repair, anterior cruciate ligament repair or hip or knee arthroplasty); gynaecological (hysterectomy, oophorectomy or salpingectomy and oophorectomy); or urological procedures (prostatectomy, cystectomy or nephrectomy), were eligible if they were discharged home or to a non-healthcare setting [12]. We did not study patients meeting any of the following criteria: receiving medication-assisted treatment of opioid dependence with methadone, suboxone or buprenorphine; discharged to rehabilitation, nursing-supported care services, another hospital or with palliative intent; undergoing multivisceral resections; or who required a return to theatre.

The primary outcome was the proportion of prescribed opiates consumed within 7 days following discharge [15, 16]. This is in line with guideline-based recommendations for the duration of post-surgical discharge opioid prescriptions [16, 17]. Data were also collected on: patient characteristics (age, sex, tobacco use, vaping status, alcohol use, BMI, ASA physical status); comorbidities; diagnosis and procedure-specific details (indication, surgical approach and urgency); opioid use 24 h before hospital discharge; opioid prescription at the time of discharge from hospital (opioid type, dose and quantity of opioids); patient-reported outcomes; patient-reported opioid consumption (type, dose and quantity of opioids); postoperative complications; and requirement for additional analgesia. Data on opioid doses were converted to oral morphine milligram equivalents to account for varying potencies of different medications and enable comparison. Oral morphine milligram equivalent conversion ratios were calculated using conversion ratios defined by the Australian and New Zealand College of Anaesthetics Faculty of Pain Medicine [18]. Where these were absent, accepted conversion ratios were identified through a literature search and agreed on by consensus from members of the OPERAS Scientific Advisory Group [12]. For details of methods used see online Supporting Information Appendix S2 and Table S1. Cumulative oral morphine milligram equivalent doses were used to enable pragmatic comparisons; irrespective of intended duration of prescriptions this represents the quantity of opioids provided to patients. Opioid adverse effects were defined as ≥ 1 of the following: nausea or vomiting; drowsiness; itching; dizziness; or constipation. Patient characteristics and opioid prescribing practices were compared between high-income and low- and middle-income countries as defined by the Organisation for Economic Co-operation and Development [19]. Pain severity during the period post-discharge was measured at the 7-day follow-up phone call by asking patients to self-report on a scale of 0–100 how often they had been in severe pain since discharge (0 being none of the time and 100 being all the time).

All statistical analyses were performed with R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) using the tidyverse, rms and finalfit packages. An a priori sample size calculation was performed, necessitating a minimum sample size of 852 [12].

Factors collected for patients lost to follow-up (but not those who withdrew consent) were compared with the included cohort to assess any selection bias in those lost to

follow-up. Missing data were explored via visual inspection. The mice package was used to perform multiple imputation by chained equations for ASA physical status, alcohol consumption and BMI categories, which were assumed to be missing at random, and imputed models were pooled per Rubin's rules [20]. Descriptive statistics were used to compare patient characteristics and prescription-specific variables based on whether or not patients were prescribed opioids at discharge, using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. The univariable correlation between quantity of opioid in oral morphine milligram equivalents prescribed and consumed in the first 7 days after discharge was depicted using a generalised additive model. The risk of opioid-related adverse effects was modelled using binomial logistic regression and the independent variables; total oral morphine milligram equivalents prescribed at discharge and those consumed in the first 7 days after discharge were plotted with a spline term. Factors associated with the quantity of opioids prescribed and consumed were modelled using separate mixed-effects hierarchical linear regression with the country and hospital as the random effect. Beta coefficients are reported with 95%CI for linear regression models. This signifies the magnitude of change in the dependent variable per unit change in the independent variable and can be interpreted as the slope of the regression line. The model predicting `opioid quantity consumed´ was bootstrapped and applied at the patient level to quantify (with 95%CI) for the adjusted rate of overprescription. Residual, Q-Q plots and variance inflation factors were interrogated to assess model assumptions. Multivariable binary logistic regression models for the risk of overprescription (defined as prescribed oral morphine milligram equivalent quantity exceeding consumed oral morphine milligram equivalent quantity at follow-up) were generated. Sensitivity analyses for various thresholds of overprescription, including prescribed oral morphine milligram equivalent quantity exceeding 25%, 50% and 100% of consumed oral morphine milligram equivalent quantity, were also performed. Thereafter, the multivariable risk-adjusted odds ratio for overprescription was plotted against: the quantity of oral morphine milligram equivalents prescribed at discharge; quantity of oral morphine milligram equivalents consumed 24 h before discharge; and severity of pain experienced in the first 7 days after discharge, each with a spline term. Covariate selection for adjusted analyses was considered a priori and guided by: clinical plausibility; Akaike information criteria; and model parsimony [12]. A two-tailed α level was set at 5% for interpretation of significance.

Results

Between 4 April 2022 and 4 September 2022, data from 5476 patients were collected. Following exclusion, data from 4273 patients across 144 hospitals in 25 countries were analysed (2271 (53.1%) female, median (IQR [range]) age 50 (34–64 [18–96]) y; Fig. 1, and Table 1). Comparison of pre-discharge factors such as age, sex, indication and speciality showed similar proportions between those lost to follow-up and those included in analysis; however, there were minor differences in ASA physical status and BMI (online Supporting Information Table S2). There were 1923 (45.0%) patients recruited from high-income countries and 2350 (55.0%) from low- and middle-income countries (online Supporting Information Table S3). In total, 1311 patients (30.7%) were prescribed opioid analgesia at discharge (Table 1) and 184 patients (4.3%) were taking opioids pre-operatively (online Supporting Information Table S4). Patients were followed up at 7 (7–8 [5–15]) days.

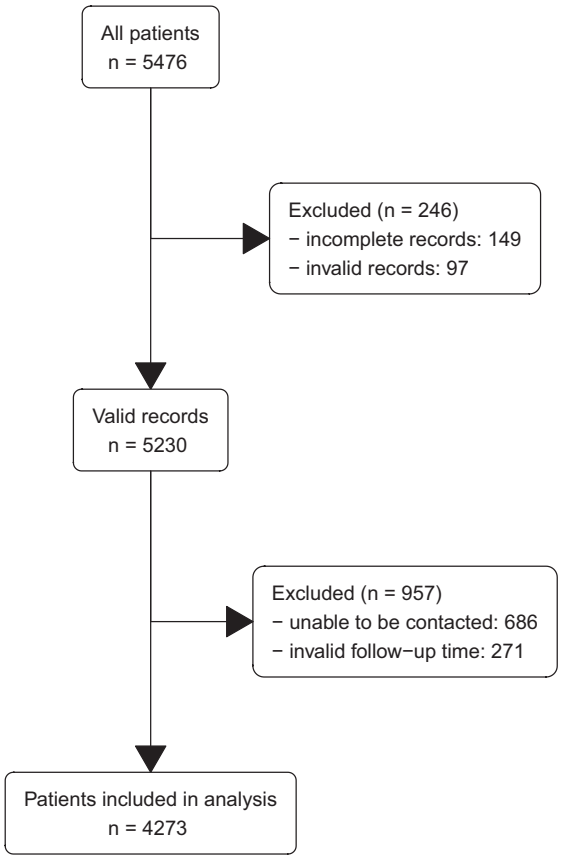

Figure 1 Flow diagram of included patients. Invalid records included patients with incongruous data, outside of study period or age < 18 y. Invalid follow-up time included < 5 days or > 15 days after discharge.

Table 1 Baseline characteristics and analgesic outcomes by opioid prescription at discharge. Values are median (IQR [range]) or number (proportion).

Variable	Category	Opioid prescribed at discharge		Total
		No n = 2962	Yes n = 1311	n = 4273
Age; y		48 (33–64 [18–96])	52 (37–66 [18–93])	50 (34–64 [18–96])
Sex	Female	1579 (53.3%)	692 (52.8%)	2271 (53.1%)
	Male	1383 (46.7%)	616 (47.0%)	1999 (46.8%)
	Other	0	3 (0.2%)	3 (0.1%)
ASA physical status	1–2	2558 (86.4%)	1051 (80.4%)	3609 (84.6%)
	3–4	402 (13.6%)	257 (19.6%)	659 (15.4%)
BMI; $kg.m^{-2}$	< 18.5	56 (2.1%)	13 (1.1%)	69 (1.8%)
	18.5–24.9	835 (31.1%)	327 (28.4%)	1162 (30.3%)
	25–30	1078 (40.2%)	385 (33.4%)	1463 (38.1%)
	31–40	603 (22.5%)	333 (28.9%)	936 (24.4%)
	> 40	111 (4.1%)	94 (8.2%)	205 (5.3%)
Myocardial infarction or congestive heart failure		154 (5.2%)	84 (6.4%)	238 (5.6%)
Peripheral vascular disease		85 (2.9%)	35 (2.7%)	120 (2.8%)
Cerebrovascular accident or transient ischemic attack		59 (2.0%)	26 (2.0%)	85 (2.0%)
Peptic ulcer disease		62 (2.1%)	26 (2.0%)	88 (2.1%)
Diabetes		403 (13.6%)	196 (15.0%)	599 (14.0%)
Chronic kidney disease		49 (1.7%)	43 (3.3%)	92 (2.2%)
Liver disease		52 (1.8%)	28 (2.1%)	80 (1.9%)
Comorbid cancer		213 (7.2%)	158 (12.1%)	371 (8.7%)
Smoking	Current smoker	550 (20.0%)	182 (15.0%)	732 (18.5%)
	Ex-smoker < 12 months	67 (2.4%)	37 (3.1%)	104 (2.6%)
	Ex-smoker > 12 months	288 (10.5%)	270 (22.3%)	558 (14.1%)
	Never smoked	1841 (67.0%)	723 (59.7%)	2564 (64.8%)
Vaping	Current vaper	55 (1.9%)	40 (3.1%)	95 (2.2%)
	Ex-vaper < 12 months	19 (0.6%)	3 (0.2%)	22 (0.5%)
	Ex-vaper > 12 months	20 (0.7%)	6 (0.5%)	26 (0.6%)
	Never vaped	2451 (82.7%)	834 (63.8%)	3285 (76.9%)
	Unknown	417 (14.1%)	425 (32.5%)	842 (19.7%)
Alcohol; units per week	0	2134 (81.0%)	585 (56.1%)	2719 (73.9%)
	1–5	406 (15.4%)	341 (32.7%)	747 (20.3%)
	6–10	72 (2.7%)	69 (6.6%)	141 (3.8%)
	≥ 11	24 (0.9%)	48 (4.6%)	72 (2.0%)

Patients who received opioids at discharge tended to: be slightly older (52 (18) vs. 49 (18), $p < 0.001$); have a higher ASA physical status (ASA 3–5, 257 (19.6%) vs. 402 (13.6%), $p < 0.001$); have an increased BMI (normal BMI 327 (28.4%) vs. 835 (31.1%), $p < 0.001$); have comorbid cancer (168 (12.1%) vs. 213 (7.2%), $p < 0.001$); have kidney disease (43 (3.3%) vs. 49 (1.7%), $p = 0.001$); be a current smoker (182 (15.0%) vs. 550 (20.0%), $p < 0.001$); be a current vaper (40 (3.1%) vs. 55 (1.9%), $p < 0.001$); and consume ≥ 11 units of alcohol per week (48 (4.6%) vs. 24 (0.9%), $p < 0.001$) (Table 1). After risk-adjustment, age (β = -0.30, 95%CI -0.57–0.03, $p = 0.031$), speciality of surgery compared with general surgery (gynaecological surgery $\beta = 20.11$ (95%CI 3.47–36.75), $p = 0.018$; orthopaedic surgery $\beta = 89.12$ (95%CI 75.29–102.94, $p < 0.001$; and urological surgery $\beta = 32.91$ (95%CI 12.39–53.43), $p = 0.002$)) and total oral morphine milligram equivalents consumed 24 h before discharge ($\beta = 0.16$ (95%CI 0.10–0.21), $p < 0.001$) were

Table 2 Patients prescribed an opioid at discharge stratified by speciality and surgical procedure (n = 4273). Values are number (proportion).

Speciality	Surgical procedure	Opioids prescribed at discharge	
		No n = 2962	Yes n = 1311
General surgery	Appendicectomy	522 (68.4%)	241 (31.6%)
	Cholecystectomy	880 (71.8%)	346 (28.2%)
	Colorectal resection	271 (69.0%)	122 (31.0%)
	Inguinal hernia repair	440 (76.4%)	136 (23.6%)
	Fundoplication	23 (82.1%)	5 (17.9%)
	Sleeve gastrectomy	49 (70.0%)	21 (30.0%)
Orthopaedic surgery	Anterior cruciate ligament repair	57 (73.1%)	21 (26.9%)
	Hip arthroplasty	110 (54.7%)	91 (45.3%)
	Knee arthroplasty	110 (42.8%)	147 (57.2%)
	Rotator cuff repair	11 (50.0%)	11 (50.0%)
	Shoulder arthroplasty	9 (45.0%)	11 (55.0%)
	Shoulder labral repair	12 (92.3%)	1 (7.7%)
Gynaecology	Hysterectomy	228 (79.4%)	59 (20.6%)
	Oophorectomy and salpingectomy	28 (68.3%)	13 (31.7%)
	Oophorectomy only	21 (87.5%)	3 (12.5%)
	Salpingectomy only	35 (85.4%)	6 (14.6%)
Urology	Cystectomy	28 (87.5%)	4 (12.5%)
	Nephrectomy	62 (62.0%)	38 (38.0%)
	Prostatectomy	66 (65.3%)	35 (34.7%)

associated with an increased quantity of opioids prescribed at discharge (online Supporting Information Table S5).

Following all procedures except for arthroplasty, fewer than 50% of patients were prescribed an opioid at discharge (Table 2). The mean of the imputed models for the quantity of opioids prescribed had a good fit with a conditional $R^2 = 0.39$. Online Supporting Information Table S5 has a summary of the pooled model. Of the 1952 patients who received no opioids in the 24 h before discharge, 197 (10.1%) received an opioid prescription on discharge.

Patients prescribed opioids at discharge tended to have: longer surgery (median (IQR [range]) 98 (66–135 [18–1150]) min vs. 80 (55–120 [5–900]) min, $p < 0.001$); more complications (no complications 1025 (78.2%) vs. 2450 (82.8%), $p < 0.001$); and were more frequently referred to an acute pain service (108 (8.2%) vs. 139 (4.7%), $p < 0.001$). However, these patients had similar duration of hospital stay (2 (1–3 [0–18]) days vs. 2 (1–3 [0–92]) days, $p = 0.698$) to those not prescribed opioids. Regarding co-analgesics, patients prescribed opioids were more often discharged with: paracetamol (1172 (89.4%) vs. 2113 (71.4%), $p < 0.001$); gabapentinoids (60 (4.6%) vs. 38 (1.3%), $p < 0.001$); and tricyclic antidepressants (31 (2.4%) vs. 14 (0.5%), $p < 0.001$). In the first 7 days following discharge those patients prescribed opioids experienced more time in severe pain (median (IQR [range]) NRS 20 (5–40 [0–100]) vs. 10 (0–30 [0–100]), $p < 0.001$; Table 3).

Of those patients prescribed opioids, the majority received a single opioid (1174 (89.5%)). Over three-quarters of these patients used this prescription (1035 (79%)) and the majority (1114 (85%)) also used paracetamol. Of the patients prescribed an opioid at discharge 485 (37%) were prescribed laxatives and 295 (22.5%) were prescribed anti-emetics (online Supporting Information Table S6). Less than one-third of patients (377 (30.5%)) received documented advice regarding safe disposal of unused opioids.

Median (IQR [range]) quantity of opioids prescribed in oral morphine milligram equivalents was 100 (60–200 [1–2550]). In the first 7 days following discharge the quantity of opioids consumed in oral morphine milligram equivalents was 40 (7.5–100 [0–2000]) and was significantly lower than the quantities prescribed (Fig. 2). The average ratio of the quantity of oral morphine milligram equivalents predicted to be consumed compared with what was prescribed was 2.22 (95%CI 2.13–2.30). This trend of prescribing more opioids than were consumed in the first

Table 3 Surgical factors and analgesic outcomes by opioid prescription at discharge. Values are number (proportion) or median (IQR [range]).

Variable	Category	Opioids prescribed at discharge		Total
		No n = 2962	Yes n = 1311	n = 4273
Surgical indication	Benign	2601 (87.8%)	1144 (87.3%)	3745 (87.7%)
	Malignancy	360 (12.2%)	167 (12.7%)	527 (12.3%)
Urgency	Elective	2098 (70.9%)	818 (62.4%)	2916 (68.3%)
	Emergency	863 (29.1%)	493 (37.6%)	1356 (31.7%)
Procedure	Anterior cruciate ligament repair	57 (1.9%)	21 (1.6%)	78 (1.8%)
	Appendicectomy	522 (17.6%)	241 (18.4%)	763 (17.9%)
	Cholecystectomy	880 (29.7%)	346 (26.4%)	1226 (28.7%)
	Colorectal resection	271 (9.1%)	122 (9.3%)	393 (9.2%)
	Cystectomy	28 (0.9%)	4 (0.3%)	32 (0.7%)
	Hip arthroplasty	110 (3.7%)	91 (6.9%)	201 (4.7%)
	Hysterectomy	228 (7.7%)	59 (4.5%)	287 (6.7%)
	Inguinal hernia repair	440 (14.9%)	136 (10.4%)	576 (13.5%)
	Knee arthroplasty	110 (3.7%)	147 (11.2%)	257 (6.0%)
	Nephrectomy	62 (2.1%)	38 (2.9%)	100 (2.3%)
	Fundoplication	23 (0.8%)	5 (0.4%)	28 (0.7%)
	Oophorectomy and salpingectomy	28 (0.9%)	13 (1.0%)	41 (1.0%)
	Oophorectomy only	21 (0.7%)	3 (0.2%)	24 (0.6%)
	Prostatectomy	66 (2.2%)	35 (2.7%)	101 (2.4%)
	Rotator cuff repair	11 (0.4%)	11 (0.8%)	22 (0.5%)
	Salpingectomy only	35 (1.2%)	6 (0.5%)	41 (1.0%)
	Shoulder arthroplasty	9 (0.3%)	11 (0.8%)	20 (0.5%)
	Shoulder labral repair	12 (0.4%)	1 (0.1%)	13 (0.3%)
	Sleeve gastrectomy	49 (1.7%)	21 (1.6%)	70 (1.6%)
Pain severity*		10 (0–30 [0–100])	20 (5–4 [0–100])	10 (1–30 [0–100])
Duration of surgery; min		80 (55–120 [5–900])	98 (66–135 [18–1150])	87 (60–120 [5–1150])
Postoperative complications (Clavien-Dindo grade)	1	380 (12.8%)	218 (16.6%)	598 (14.0%)
	2	107 (3.6%)	47 (3.6%)	154 (3.6%)
	3a/3b/4a/4b	21 (0.7%)	20 (1.5%)	41 (1.0%)
	None	2450 (82.8%)	1025 (78.2%)	3475 (81.4%)
Duration of stay; days		2 (1–3 [0–92])	2 (1–3 [0–18])	2 (1–3 [0–92])
Referral to acute pain service		139 (4.7%)	108 (8.2%)	247 (5.8%)
Discharged with paracetamol		2113 (71.4%)	1172 (89.4%)	3285 (76.9%)
Discharged with NSAIDs		1458 (49.3%)	623 (47.6%)	2081 (48.7%)
Discharged with gabapentinoids		38 (1.3%)	60 (4.6%)	98 (2.3%)
Discharged with tricyclic antidepressants		14 (0.5%)	31 (2.4%)	45 (1.1%)

*Time spent in severe pain since discharge on a scale of 0 (none) to 100 (all of the time). NSAIDs, non-steroidal anti-inflammatory drugs.

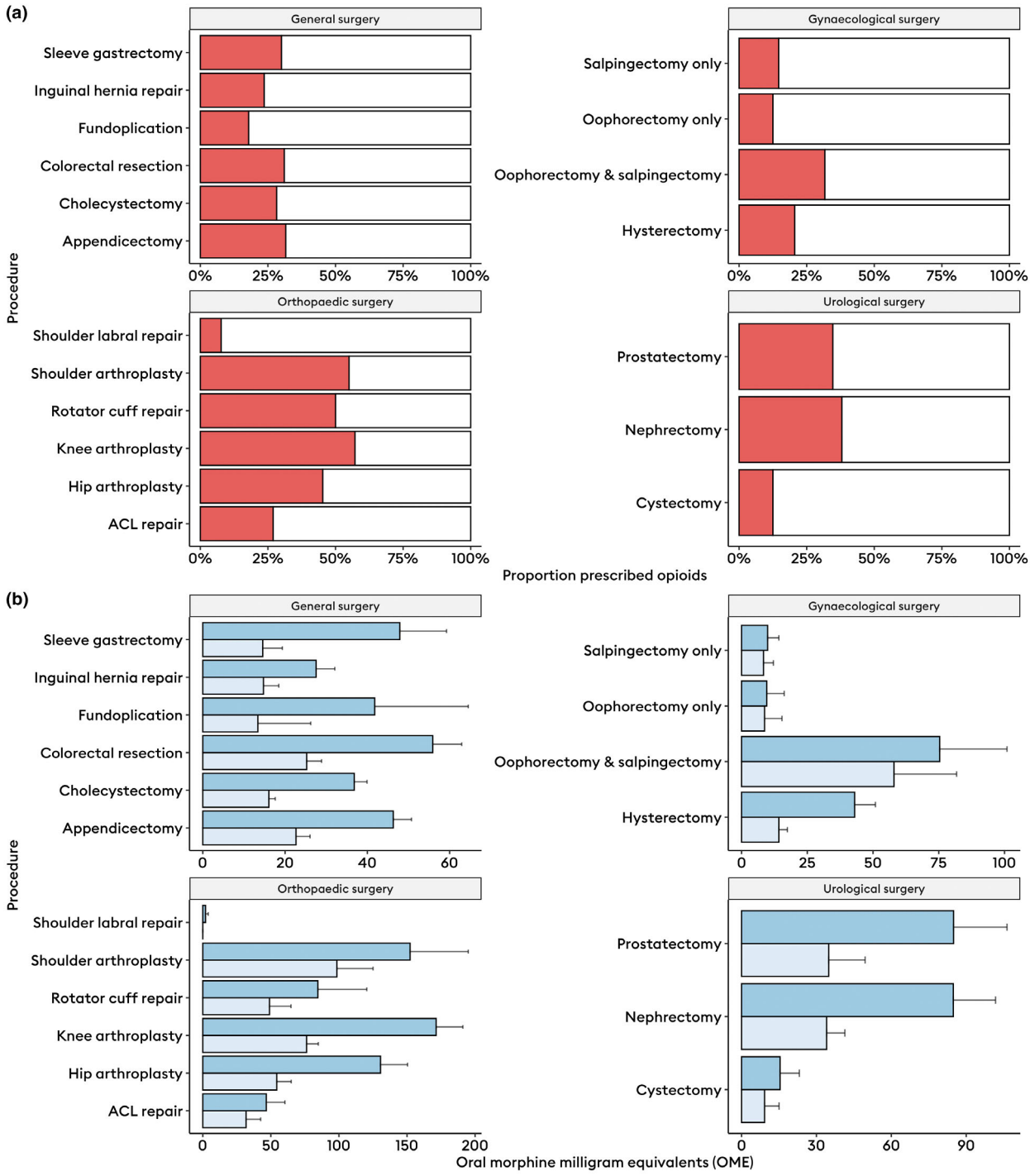

Figure 2 (a) Proportion of patients prescribed an opioid at discharge stratified by speciality and surgical procedure (n = 4273). (b) Mean and standard error of the mean (whiskers) for oral morphine milligram equivalents of opioids prescribed at discharge after surgery (dark blue) and consumed in the first 7 days after discharge (light blue) stratified by speciality and surgical procedure (n = 4273). ACL, anterior cruciate ligament.

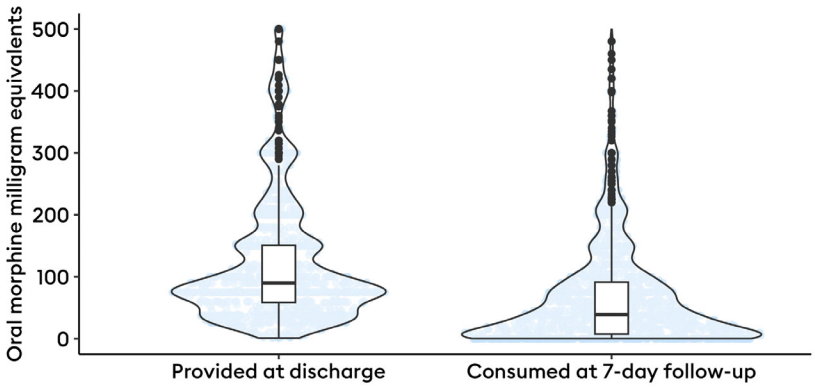

Figure 3 Box and violin plots of total amount of oral morphine milligram equivalents of opioids prescribed at discharge after surgery and consumed in the first 7 days after discharge.

7 days following discharge was evident across most procedures (Fig. 3 and online Supporting Information Table S7). Increasing quantities of opioids prescribed at discharge were associated with a linear increase in risk of opioid adverse effects (online Supporting Information Figure S1a).

There was a steep increase in the risk of patients experiencing opioid-related adverse effects with increasing opioid consumption (up to approximately 50 oral morphine milligram equivalents). At doses higher than this, the risk of adverse effects was roughly triple that found for doses < 10 oral morphine milligram equivalents (online Supporting Information Figure S1b). Consumption of opioids at follow-up increased linearly with the quantity of opioids prescribed at discharge ($r = 0.57$, $p < 0.001$, online Supporting Information Figure S2). After risk-adjustment: pain severity ($\beta = 0.19$ (95%CI 0.10–0.27), $p < 0.001$); total amount of opioids prescribed ($\beta = 0.33$ (95%CI 0.31–0.34), $p < 0.001$); and total amount of opioids consumed 24 h before discharge ($\beta = 0.07$ (95%CI 0.04–0.10), $p < 0.001$) were independently and positively associated with increased opioid consumption. The mean of the imputed models for the quantity of opioids consumed had a good fit with conditional $R^2 = 0.60$ and the pooled model is summarised in online Supporting Information Table S8.

Overprescription of opioids compared with consumption was evident after 12 of the 17 surgeries assessed (Table 4, Fig. 3 and online Supporting Information Table S7). There were 59 (1.4%) patients who consumed more opioids than they were initially prescribed (for example, had sources other than the discharge prescription). The risk of overprescribing opioids increased linearly as larger quantities were prescribed at discharge. This was particularly evidenced in doses > 100 oral morphine milligram equivalents, below which the risk of overprescribing progressively reduced (Fig. 4a). Similarly, consumption of < 35 oral morphine milligram equivalents in the 24 h before discharge was predictive of likely overprescription (Fig. 4b). Risk of overprescription reduced when pain severity scores were more than 30/100 after discharge (Fig. 4c). These findings persisted in subgroup analyses where overprescription was defined as prescriptions 25%, 50% and 100% more than what was consumed (online Supportive Information Figure S3).

Overall, 53.7% (1033/1923) of patients from high-income countries were prescribed opioids with a median (IQR [range]) quantity of oral morphine milligram equivalents of 37.5 (0–112.5 [0–2100]). In comparison, 11.8% (278/2350) of patients from low- and middle-income countries were prescribed opioids (online Supporting Information Table S9). Median (IQR [range]) quantity of oral morphine milligram equivalents was 0 (0–0 [0–2550]). This was significantly lower in dose than that prescribed in high-income countries. Despite a statistically significant difference in the median consumption of opioids in the first 7 days after discharge in oral morphine milligram equivalents, the quantitative median (IQR [range]) difference of 0 (0–0 [0–2000]) in low- and middle-income countries vs. 0 (0–50 [0–1015]) ($p < 0.001$) in high-income countries, was not clinically significant. Notably, there was significant variation in rates of opioid prescription by hospital centre. After adjusting for patient factors, clear differences between low- and middle-income countries and high-income countries centres were evident, with higher adjusted rates of opioid prescribing in high-income countries (online Supporting Information Figures S4 and S5, Tables S4 and S9).

Table 4 Difference between quantities of opioids prescribed at discharge and those consumed in the first 7 days after discharge stratified by procedure, in oral morphine milligram equivalents. Multiple comparison adjustment of p-values was via the Benjamini-Hochberg correction.

Procedure	n	Mean difference	Adjusted p value
Anterior cruciate ligament repair	78	-1.66	0.101
Appendicectomy	763	-5.99	< 0.001
Cholecystectomy	1226	-8.28	< 0.001
Colorectal resection	393	-5.54	< 0.001
Cystectomy	32	-1.30	0.205
Hip arthroplasty	201	-5.52	< 0.001
Hysterectomy	287	-4.51	< 0.001
Inguinal hernia repair	576	-5.11	< 0.001
Knee arthroplasty	257	-6.13	< 0.001
Nephrectomy	100	-3.63	< 0.001
Fundoplication	28	-2.07	0.048
Oophorectomy and salpingectomy	41	-2.79	0.008
Oophorectomy only	24	-1.00	0.328
Prostatectomy	101	-3.96	< 0.001
Rotator cuff repair	22	-1.62	0.121
Salpingectomy only	41	-1.06	0.295
Shoulder arthroplasty	20	-1.46	0.159
Shoulder labral repair	13	-1.00	0.337
Sleeve gastrectomy	70	-3.00	0.004

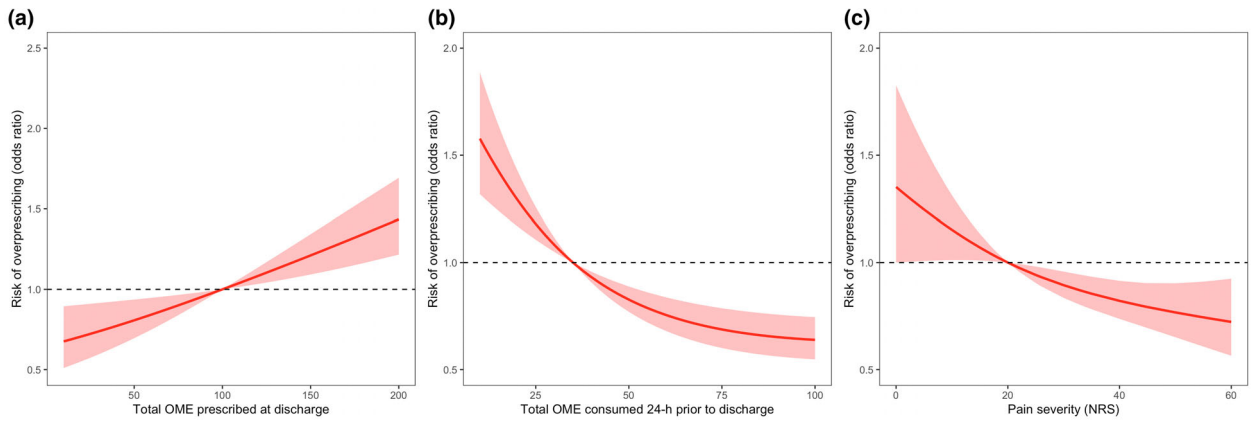

Figure 4 Restricted cubic spline plots with three knots for a binary logistic regression model for the risk (odds ratio) of overprescribing opioids (prescribing more than what was consumed in the first 7 days after discharge). (a) Risk of overprescription across the range of oral morphine milligram equivalents prescribed at discharge; (b) risk of overprescription across a spectrum of oral morphine milligram equivalents of opioids consumed 24 h before discharge; (c) risk of overprescription across a spectrum of the pain severity numeric rating scale scores (measure how often the patients had been in severe pain since discharge where 0 is none of the time and 100 being all the time). OME, oral morphine milligram equivalents; NRS, numerical rating scale.

Discussion

This multinational observational cohort study shows that opioids were widely prescribed in doses that exceeded those which patients had consumed in the first 7 days after discharge from common general, urological, gynaecological and orthopaedic surgical procedures.

Prescribing higher quantities of opioids after discharge from surgery was associated with a higher risk of experiencing opioid-related adverse effects. Higher quantities of opioids prescribed by clinicians at discharge were associated with increased opioid consumption by patients, even after adjusting for post-discharge pain severity and pre-discharge opioid consumption. Excess opioid prescribing was evident across a geographically diverse cohort, particularly in high-income countries. These findings confirm that urgent improvements in prescribing practice are needed to mitigate the globally escalating opioid crisis.

Excess opioid prescribing has been described across many surgical specialities [4, 9–11, 21–24]. Our data corroborate a vast literature predominantly originating from the USA, showing that excess volumes of opioids are prescribed at surgical discharge globally (frequently in excess of 100 oral morphine milligram equivalents) [7, 10, 23–25]. We found fewer than 50% of opioids prescribed are consumed within 7 days of discharge from hospital. These findings are similar to the results of a systematic review of USA studies, which found that only 29–58% of prescribed opioids were consumed following discharge [9]. This shows that opioid overprescribing at surgical discharge is more widespread than previously accepted. This work also highlights important inequities in global opioid prescribing practice with individuals from high-income countries being more likely to be prescribed opioids at higher quantities compared with patients from low- and middle-income countries. As efforts are put in place to improve opioid stewardship globally, care must be taken to ensure equitable global prescribing practices at surgical discharge [26].

Overprescription poses a key risk for increased unregulated circulation of opioids in the community. Safe disposal of excess opioids is known to be low and this is evidenced by our findings that fewer than one-third of patients received documented advice about safe disposal of opioids [27]. The retention of what is frequently 60% of an individual's prescription quantity in the community significantly increases the risk of opioid misuse. Lipari et al. have shown that peers and family remain a much more widespread source of opioids for non-medical use in the community than the black market or `doctor shopping´ strategies [28]. This highlights the responsibility that falls on clinicians to ensure appropriate prescribing.

When prescribing opioids after surgery, clinical care standards emphasise a patient-centred approach, limiting the duration of usual discharge opioid prescriptions to < 7 days of short-acting opioids for acute pain [17, 29]. This is consistent with the most recently published international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients [30]. Providing large quantities of opioids for longer durations poses a substantially increased risk for chronic use, misuse and overdose [15]. The duration of the first opioid analgesic prescription has been found to be more strongly related to misuse in the early postoperative period than the dosage, with each refill and week of opioid analgesic prescription associated with a 20% increase in opioid misuse among opioid-naïve patients [31].

Ongoing pain management in the community beyond the first post-discharge week should involve the transfer of care to primary healthcare professionals, who are well-positioned to ensure appropriate review and to implement weaning plans as appropriate [17]. Additionally, guideline-based strategies to optimise analgesia at surgical discharge should include using non-opioid analgesia as first-line and utilising multimodal analgesia [30, 32]. Though we found paracetamol was co-prescribed with opioids in close to 90% of patients discharged with opioids, non-steroidal anti-inflammatory drugs were co-prescribed in only 50%. It is concerning that we found that 10% of patients not requiring opioids before discharge were discharged with opioid analgesia. As previously reported, this variability suggests prescribing practices remain dogmatic, habit-driven and are in urgent need of reform [11, 33].

We have also shown that a key driver of excess opioid prescribing is prescriber choices, as the quantity of opioids consumed was associated with the quantity prescribed, even after adjusting for pre-discharge opioid consumption and post-discharge pain severity. Numerous regional series have identified this trend [7, 34–36] and we verified this in an international multi-speciality cohort. Our data show the risk of overprescription increases significantly once discharge doses > 100 oral morphine milligram equivalents are prescribed, even when we conservatively defined overprescription as being double the quantity of opioids prescribed that the patients actually consumed (further discussed in online Supporting Information Appendix S3).

In this global prospective multi-speciality study we had high levels of data completion and minimal loss to follow-up (< 20%). This was encouraging in a study that required telephone interviews of patients. Nevertheless, there are several limitations that include the need for care interpreting association rather than causality owing to the observational nature of the data. In addition, elements of subjectivity and recall bias are inevitable with patient-reported data points, but we aimed to mitigated these through the short, 7-day follow-up time-point after

discharge to contact patients. Guidelines recommend no longer than a 7-day supply of opioids should be prescribed after surgery, to encourage patients with inadequately managed pain to seek help and to mitigate large opioid prescription volumes [16, 17]. Hence, our 7-day follow-up is both clinically and pragmatically optimal [15, 16]. Analysis of pre-operative chronic pain was beyond the scope of this study, but this is an important limitation given this can impact on opioid requirements and pain responses. However, we did evaluate whether patients received opioids before admission. This was only found in 4.3% of the population and therefore was unlikely to significantly contribute to postoperative opioid use. Similarly, while this study found that patients prescribed opioids were more often discharged with other modes of analgesia such as gabapentinoids and tricyclic antidepressants, it was not captured whether these prescriptions were new, perhaps as part of an effort to utilise multimodal analgesia post-discharge or if these reflected pre-operative chronic pain, which similarly could have impacted the results. We did not explore long-term clinical outcomes beyond patient-reported pain severity in the acute post-discharge setting and data regarding the wider patient experience would be useful to place opioid use in context. Finally, these data also amalgamate a geographically diverse cohort where opioid prescribing practices vary, but this is also a strength of the study that adds to the generalisability of the findings.

Our findings have direct implications for clinical practice, highlighting the importance of appropriate post-discharge opioid prescribing to reduce opioid-related harm. As suggested by Howard et al., our multicentre data can define ``*consumption norms*'' thus helping to generate procedure-specific guidelines for widespread use, that could then be disseminated through professional bodies to improve clinical practice [7]. Targeting prescribing education and change interventions at early career prescribers, who frequently organise post-surgical discharges, also represents a pivotal point to impact on practice as, more often than not, it is these professionals who produce discharge prescriptions.

Opioid prescribing after surgery is a global issue with significant implications for patients. Our data highlight that double the quantity of opioids patients consume in the post-discharge period are prescribed at discharge, exposing them to risk of opioid-related harm. Individualised opioid prescribing at discharge remains important as excess prescriptions are driving increased consumption of opioids by patients. While patient pain levels and pre-discharge opioid consumption influence opioid consumption at discharge, the quantity of opioids prescribed remains a modifiable factor to curtailing excessive prescriptions of unused opioids.

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Supporting Information

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

Appendix S1. TASMAN collaborators.

Appendix S2. Supplementary methods.

Appendix S3. Supplemental discussion.

Figure S1. Restricted cubic splines with four knots plotting odds ratios of the risk of opioid-related side effects against a spectrum of oral morphine milligram equivalent totals prescribed at discharge and consumed at follow-up.

Figure S2. Total amount of oral morphine milligram equivalents consumed within 7 days and total amount prescribed at discharge.

Figure S3. Restricted cubic spline plots with 3 knots for a binary logistic regression model for the risk of over-prescribing opioids.

Figure S4. Global variation in rate of opioid prescription by centre, stratified by country income group.

Figure S5. Global variation in prescription, consumption and differences in prescription and consumption quantities of opioids in oral morphine milligram equivalents.

Table S1. Opioid oral morphine milligram equivalent conversion factors used in OPERAS and corresponding source.

Table S2. Comparison of those lost-to-follow-up versus those included in the final cohort.

Table S3. Contributions to study by country.

Table S4. Variations in demographics by region.

Table S5. Mixed effects hierarchical linear regression model for the quantity of opioids (OME) prescribed to patients at discharge after surgery.

Table S6. Prescribing factors of those prescribed an opioid at discharge.

Table S7. Raw data from Figure 2, mean and standard error for oral morphine milligram equivalents of opioid prescribed at discharge after surgery and consumed within 7-days follow-up stratified by speciality and surgical procedure.

Table S8. Mixed effects hierarchical linear regression model for the quantity of opioids (OME) consumed by patients at follow-up after surgical discharge.

Table S9. Opioid prescription and consumption quantities by country income group.