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Opioid tolerance impacts compliance with enhanced recovery pathway after major abdominal surgery

Oluwafemi P. Owodunni, MD, MPH[a], Mohammad H. Zaman, MD[b], Mehrnaz Ighani, MS[b], Michael C. Grant, MD[c], Dianne Bettick, MSN, CNS, RN[d], Sara Sateri, MD[c], Thomas Magnuson, MD[b], Susan Gearhart, MD, MEHP[b,*]

[a] Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD
[b] Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD
[c] Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, MD
[d] Department of Quality, Johns Hopkins Bayview Medical Center, Baltimore, MD

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ABSTRACT

Background: Opioid tolerant patients have been shown to have poor postoperative outcomes. Enhanced recovery pathways are evidence-based interventions that focus on optimizing recovery, and their effectiveness depends on the degree of compliance with the pathway. We wish to determine pathway compliance and its impact on postoperative outcomes in opioid tolerant patients undergoing abdominal surgery on an enhanced recovery pathway.

Methods: From December 2014 to June 2017, 646 patients undergoing major abdominal surgery on an enhanced recovery pathway were included. Patients <18 years and having emergency surgery were excluded. Compliance was measured to 14 perioperative pathway standards and high-compliance was defined as adhering to ≥75% standards. Opioid tolerance was defined as any patient taking a prescribed opioid medication equivalent to 60 mg of oral morphine per day for 1 week prior to surgery. The Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity was used for risk-adjusted analyses. Outcomes of interest include length of stay, major complications (Clavien-Dindo ≥2), 30-day readmission rates, and mortality.

Results: Overall, 114 (18%) patients were opioid tolerant and 532 (82%) were not opioid tolerant. Opioid tolerant patients were less likely to be highly compliant with enhanced recovery pathway standards than non-tolerant patients (35% vs 54%; $P < .001$); particularly postoperative care standards. On adjusted analysis, opioid tolerance was associated with a 2-fold increase in readmissions following major abdominal surgery. Examining only those patients with opioid tolerance, adjusted analysis demonstrated that high compliance with the enhanced recovery pathway standards was independently associated with a 26% reduction in length of stay, over a 90% reduction in major complications, and mitigated the effect on readmissions.

Conclusion: The authors provide evidence that opioid tolerance is associated with less favorable outcomes in patients undergoing major abdominal surgery on an enhanced recovery pathway, and this is likely due to a lack of pathway compliance. Establishing strategies to improve compliance in this challenging patient cohort may serve to mitigate the negative impact of opioid tolerance.

Introduction

Due to their versatility and effectiveness, intravenous and oral opioids have traditionally been used by healthcare professionals as their primary modality for acute pain management. However, opioid therapy is complicated by the loss of treatment effect leading to a decrease in ability to control pain and an increase in analgesic requirement. This condition is known as opioid-induced

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* Reprint requests: Susan L. Gearhart, MD, MEHP, Department of Surgery, Johns Hopkins Medical Institutions, A Building, 5th floor, 4940 Eastern Avenue, Baltimore, MD 21286.
E-mail address: sdemees1@jhmi.edu (S. Gearhart).

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hyperalgesia or opioid tolerance.[1] McAnally recently reported that as many as 33% to 70% of patients presenting for elective surgery of any type are using opioids chronically.[2] Patients on chronic opioids can be challenging for the physician trying to safely and adequately manage postoperative pain. Furthermore, Waljee et al recently demonstrated in a large cohort of general surgery patients that chronic preoperative opioid use was associated with a longer length of stay (LOS), higher 30-day readmissions rate, and increased costs.[3]

In an effort to improve postoperative outcomes and minimize opioid use, many hospitals in the United States have implemented an Enhanced Recovery After Surgery (ERAS) program. These enhanced recovery pathways (ERPs) are a set of evidence-based perioperative standards that focus on optimizing recovery and postoperative outcomes.[4] The authors have previously established the favorable effects of ERP on postoperative outcomes in gastrointestinal surgery, particularly among compliant patients.[5,6,7] Administration of multimodal postoperative analgesia after a major surgery is a key component in the ERPs. It is considered to be a vital step in facilitating the postoperative recovery process by supporting early mobility and return of bowel function as well as decreasing the risk of chronic postsurgical pain.[7]

There is a paucity of data regarding the impact of opioid tolerance on compliance with ERP standards in patients undergoing major abdominal surgery. Likewise, it is not known if opioid tolerant patients would benefit from an ERP, as demonstrated by improved postoperative outcomes. In this study, we sought to investigate the ability of opioid tolerant patients to comply with an ERP and the impact of opioid tolerance on postoperative outcomes including LOS, readmissions, and complications. We hypothesize that patients who are opioid tolerant may benefit from an ERP, if they remain compliant with the ERP standards.

Methods

Study design

A retrospective analysis of adult (aged $\geq$18 years), 30-day postoperative outcomes entered in the American College of Surgeons National Surgical Improvement Program (ACS-NSQIP) with diagnosis codes for major abdominal surgery from 2015 to 2017 was performed. The application for the conduct of this study was approved by the Johns Hopkins Medicine institutional review board. This study was reported following the STROBE guidelines for retrospective studies.

Data source

Participants' data were obtained from the ACS-NSQIP database. Patients from Johns Hopkins Hospital (JHH) and the Johns Hopkins Bayview Medical Center (JHBMC), who underwent major gastrointestinal surgery on our colorectal/gastrointestinal services between December 15, 2014 (JHH) and July 1, 2015 (JHBMC) through June 15th, 2017 and participated in ERP, were identified in the ACS-NSQIP database and included for analysis. Procedures included were defined by the primary Current Procedural Terminology codes and All Patients Refined Diagnosis Related Groups 220 to 221 for elective, major abdominal procedures or International Classification of Diseases, Ninth Revision Procedure Codes (any position): 435, 436, 4389, and 4382. Patients <18 years of age and those whose procedures were emergent were excluded.

ERP protocols

A standardized ERP protocol was implemented throughout the Johns Hopkins Health System following the recommendations of the ERAS Society and the specific enhanced recovery standard requirements outlined in ACS-NSQIP. These variables are based on a multimodal approach, which captures perioperative components of patient-centered care specified for major abdominal procedures. Our institution's ERP items have been previously described and are applied to elective procedures only.[5] Additional best practices performed at JHH and JHBMC included in the ERP protocol but not included in this analysis were the following: standardized mechanical and oral antibiotic bowel preparation, preoperative skin cleansing with chlorhexidine wipes, and postoperative extended venous thromboembolism prophylaxis for patients with a Caprini score >5. The use of additional medications for prevention of pain (Bupivicaine Liposome Injectable Solution, Exparel) and postoperative nausea (Alvimopan, Entereg) were excluded as metrics for the ERP protocol as they are unavailable (not on the institutional formulary for use in this patient population).

Opioid tolerance

The US Food and Drug Administration's definition of opioid tolerance is receiving 60 milligrams of oral morphine per day or its equivalent for 1 week or longer.[8] Using this definition, the presence of opioid tolerance was determined by manual data abstraction from our electronic health record (EHR) as preoperative opioid use is not a variable recorded in ACS-NSQIP. To confirm opioid tolerance in our participants, preoperative opioid use was determined through review of the EHR for history and physical and medication reconciliation notes that were taken at the time of surgery registration.

Compliance metric

The primary outcome measurement was patient compliance with our ERP protocol. Our ERP protocol consisted of 14 perioperative ERAS standards, which are included in the NSQIP database as Enhanced Recovery in NSQIP (ERIN). All compliance standards were systematically recorded by trained nurses (Surgical Clinical Reviewers) through careful review of our EHR within in 90 days of the patient's procedure. The ERIN compliance definition allows for deviation from the standard should a "high risk" condition exist (ie, foley catheter removal after a low pelvic procedure). As previously reported, our individual compliance goal for each patient was set at 75% of ERIN standards.[5] Individual compliance assesses the total number of specific ERP items out of the 14 ERIN standards each patient received, regardless of high-risk status. The assessment of high individual compliance was defined as achieving $\geq$75%, or $\geq$11/14 of ERIN standards. Overall ERIN standard compliance, reported as a percentage, assesses the total number of patients that received the specific ERP item and met the standard definition. The denominator (total patients) excluded patients classified as "high risk" who did not receive the specific item as part of their care plan or patients with missing data on that specific standard. Compliance data per standard was noted to be complete in a minimum of 90% of patients, and missing data was recorded as noncompliant.

Outcome measure

The secondary outcome measures were the specific 30-day postoperative outcomes, which include LOS, the incidence of major complications, and the readmission rate post-discharge. The 30-day postoperative outcomes captured in ACS-NSQIP include

Table I
Baseline demographic, clinical, operative characteristics, and postoperative outcomes of ERP patients stratified by opioid tolerance status

Characteristic	Total ERP (N = 646)	Nonopioid tolerant (n = 532)	Opioid tolerant (n = 114)	P value*	Opioid tolerant low compliance (n = 74)	Opioid tolerant high compliance (n = 40)	P value†
Age in y median (IQR)	59.0 (49.0, 69.0)	60.0 (49.3, 69.8)	56.8 (47.6, 64.2)	.02	55.7 (47.6, 63.1)	59.0 (48.6, 64.8)	.29
Sex n (%)							
Male	329 (51.0%)	278 (52.3%)	51 (44.7%)	.15	38 (51.0%)	13 (32.0%)	.08
Female	317 (49.0%)	254 (47.7%)	63 (55.3%)		36 (49.0%)	27 (68.0%)	
Race n (%)							
White	484 (75.0%)	401 (75.4%)	83 (72.8%)	.64	51 (69.0%)	32 (80.0%)	.47
Black	96 (15.0%)	76 (14.3%)	20 (17.5%)		15 (20.0%)	5 (13.0%)	
Others‡/unknown	66 (10.0%)	55 (10.3%)	11 (9.6%)		8 (11.0%)	3 (8.0%)	
Current smoker n (%)	76 (12.0%)	62 (11.7%)	14 (12.3%)	.87	12 (16.0%)	2 (5.0%)	.13
Disseminated malignancies n (%)	43 (7.0%)	32 (6.0%)	11 (9.6%)	.15	6 (8.0%)	5 (13.0%)	.51
BMI (kg/m^2) median (IQR)	27.0 (23.0, 31.0)	26.5 (23.2, 30.8)	26.3 (23.0, 30.8)	.66	26.2 (21.8, 30.7)	26.4 (23.3, 31.1)	.62
CR-POSSUM median (IQR)	1.9 (1.0, 3.6)	1.9 (1.0, 3.6)	1.9 (1.0, 3.6)	.63	1.8 (1.0,3.6)	1.9 (1.0, 3.6)	.76
Operative approach n (%)							
Open	356 (55.1)	290 (54.5%)	66 (57.9%)	.53	45 (61.0%)	21 (52.0%)	.43
Laparoscopic	290 (44.9)	242 (45.5%)	48 (42.1%)		29 (39.0%)	19 (48.0%)	
Postoperative outcomes							
LOS (d) median (IQR)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)	5.0 (3.0, 9.0)	.02	5.0 (4.0, 9.0)	3.0 (3.0, 7.0)	<.01
Complications CD n (%)							
0–I	543 (84.0%)	449 (84.4%)	94 (85.5%)	.58	55 (74.0%)	39 (97.0%)	<.01§
II–IV	103 (16.0%)	83 (15.6%)	20 (17.5%)		19 (26.0%)	1 (3.0%)	
Complication grade II–IV (%)							
II	71 (11%)	58 (11%)	13 (11.4%)	.01	13 (17.6%)	0	.65
III	26 (4%)	20 (3.8%)	6 (5.3%)		5 (6.8%)	1 (2.5%)	
IV	6 (1%)	5 (1%)	1 (1%)		1 (1.4%)	0	
Readmissions n (%)	98 (15%)	71 (13.3%)	27 (23.7%)		19 (36%)	8 (20%)	

BMI, body mass index; *IQR*, interquartile range.
* Comparison of total ERP patients that are opioid and nonopioid tolerant.
† Comparison of opioid tolerant ERP patients who were high and low compliers to the ERP protocol.
‡ Asian-Native Hawaiian/Pacific Islander-American Indian/Alaska Native.
§ Comparison between CD 0–1 and CD II–IV.

deviations from the expected postoperative course. All adverse events which developed within the inpatient period following surgery or discharge were recorded as postoperative morbidity and mortality. LOS recorded in days is the postoperative time interval from the first day following the operation to the day of discharge from inpatient, acute hospital care.

Postoperative occurrences were graded according to the Clavien-Dindo (CD) classification. Occurrences graded as II to IV require an intervention and may be life threatening were considered as major complications. These complications include deep/organ space infection, pneumonia, venothrombotic event, renal insufficiency, urinary tract infection, cerebral vascular accident, cardiac abnormalities, bleeding requiring transfusion, sepsis, and C. difficile infection. The CD classification grade V is considered as death. For the purpose of this analysis, no occurrences and grade 1 occurrences were assigned a "0," while grade II to IV were assigned a "1" or yes. Readmission rate was the proportion of patients readmitted to the hospital within 30 days from discharge.

We utilized the Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) to risk stratify our patient population. This is a validated tool designed to predict postoperative morbidity and mortality in colorectal surgery. To calculate the CR-POSSUM for each patient, we utilized both the NSQIP database and the EHR.

Statistical analysis

Baseline characteristics and perioperative continuous variables were compared using a Student's t-test or the Mann-Whitney U test as indicated. Categorical variables were analyzed using frequency and proportions, χ^2, and Fisher's exact tests. Patients were risk-stratified using the CR-POSSUM. Independent variables (age, sex, race, surgery approach, and CR-POSSUM mortality risk) were selected based on the literature and Akaike criteria.

Quasi-likelihood Poisson models evaluated postoperative LOS as incidence rate ratios , while multivariable logistic regression models evaluated compliance with the protocol and 30-day postoperative outcomes (CD and readmission) as odds ratios (OR). A P value of $< .05$ was considered statistically significant in all analyses. All analyses were performed using STATA 14.0 (StataCorp, College Station, TX).

Results

Study population demographics and procedure characteristics

From December 15, 2014 until June 2017, 646 patients at JHH and JHBMC met the inclusion criteria. Overall, 532 (82%) patients were not opioid tolerant and 114 (18%) were opioid tolerant. Patient level demographic and operative characteristics for the cohort are delineated in Table I. Patients who were opioid tolerant were younger than non-opioid tolerant patients (60 vs 56.8 years; $P = .02$).

ERP standard compliance

Among the ERP cohort, opioid tolerant patients had a significantly lower compliance rate with the postoperative standards of mobilization on postoperative day (POD)# 0 (50.9% vs 64.5%; $P = .01$) and receiving a solid diet on POD# 1 (27.2% vs 43.9%; $P = .002$) than non-opioid tolerant patients (Table II.) Risk-adjusted analysis was performed to look for predictors of poor compliance among all patients for the ERIN standards of mobilization POD# 0 and solid meal given POD# 1. Being non-white (OR 0.66; 95% confidence interval [CI] 0.58–0.75, $P < .001$) and opioid tolerant (OR 0.58; 95%

Table II
Observed ERIN standard compliance rates among ERP stratified by opioid tolerance

Variable (*%)	ERP nonopioid tolerant ($n = 532$)	ERP opioid tolerant ($n = 114$)	*P* value (NonOT vs OT)
Preoperative processes			
Preadmission counseling	403 (80.3%)	83 (76.9%)	.43
Allow clear liquids up to 3 h before induction†	404 (78.0%)	87 (78.4%)	1.00
Day of surgery processes			
Use of multimodal pain management	516 (99.4%)	110 (99.1%)	.54
Use of regional anesthetic‡	225 (43.9%)	55 (50.0%)	.25
Normal temperature upon arrival to PACU	503 (97.7%)	109 (97.3%)	.74
Use of goal-directed fluid therapy	288 (55.6%)	57 (51.4%)	.46
Use of antiemetic prophylaxis	499 (97.1%)	109 (97.3%)	1.00
Postoperative processes			
Mobilization on POD# 0	332 (64.5%)	55 (50.9%)	.01
Patient was given clear liquids on POD# 0	452 (88.5%)	98 (89.1%)	1.0
IV fluids discontinued POD# 0	387 (76.9%)	77 (72.6%)	.38
Mobilization BID POD# 1	376 (73.2%)	71 (65.1%)	.10
Solids given POD# 1	206 (43.9%)	28 (27.2%)	<.01
Foley removed on/before POD# 1§	370 (72.3%)	70 (64.2%)	.10
Mobilization BID POD# 2	429 (84.3%)	88 (82.2%)	.57

BID, twice daily; *PACU*, postoperative anesthesia care unit.
* % reflects the number of patients meeting the compliance measure over the denominator of patients with available data.
† Total excludes high-risk patients for impaired gastric emptying per NSQIP data definition.
‡ Total reflects open cases only.
§ Total excludes high-risk patients with concurrent urinary tract procedures per NSQIP data definition.

CI 0.57–0.58, $P < .001$) increased the likelihood of noncompliance to mobilization POD# 0, while undergoing a laparoscopic approach significantly increased the likelihood of compliance (OR 2.3; 95% CI 2.0–2.5, $P < .001$). Similar findings were seen for solid meal given on POD# 1. Non-white patients (OR 0.9; 95% CI 0.87–0.9, $P < .001$) and opioid tolerant patients (OR 0.48; 95% CI 0.24–0.9, $P = .04$) were less likely to be compliant with consuming a solid meal on POD# 1. However, being female (OR 1.45; 95% C 1.1–1.8, $P < .001$) and having a laparoscopic procedure (OR 1.7; 95% CI 1.2–2.5, $P = .004$) was associated with an increased likelihood of compliance.

Opioid tolerant patients also had a significantly lower rate of high compliance with ERP standards than nontolerant patients (35% vs 54%; $P < .001$). When comparing standard compliance for opioid tolerant and nonopioid tolerant ERP patients with high individual compliance to those patients with low individual compliance, a significant difference was only noted for the use of epidural anesthesia (Table III). However, it was most notable when comparing high compliance and low compliance among patients with opioid tolerance. Significantly lower rates of compliance were found in 6 out of the 7 postoperative ERP standards among opioid tolerant patients not achieving high compliance (see Table III).

Analysis of 30-day postoperative outcomes

Comparing our nonopioid tolerant ERP patients to our opioid tolerant patients demonstrated that opioid tolerant patients had an increased LOS (5 vs 4 days; $P = .015$) and a higher readmission rate (23.7% vs 13.3%; $P = .009$, Table I) than nonopioid tolerant patients. On adjusted analysis among all ERP patients, opioid tolerance identified preoperatively was associated with a 2-fold increase in readmissions following major abdominal surgery (OR 2.0, 95% CI 1.26, 3.29; Table IV). Furthermore, high compliance with ERP standards was associated with a 66% reduction in the likelihood for major complications and a 21% reduction in risk of readmission. In addition, having a laparoscopic procedure was independently associated with a decrease in LOS and major complications. However, non-white patients, independent of opioid use or high compliance, had an increased LOS (OR 1.23; 95% CI 1.09–1.37, $P < .001$) but a decreased likelihood of readmission (OR 0.83; 95% CI 0.69–0.99, $P = .04$).

Examining those patients with opioid tolerance, adjusted analysis demonstrated that high compliance with the ERP standard was independently associated with a 26% reduction in LOS (incidence rate ratio 0.72, 95% CI 0.58, 0.90), over 90% reduction in major complications (OR 0.04, 95% CI 0.02, 0.10, Table V). Furthermore, the female sex was independently associated with a significant decrease in LOS. Laparoscopic surgery was independently associated with a reduction in LOS and major complications. In addition, opioid tolerant non-white patients, independent of high compliance status, were less likely to be readmitted (OR 0.78, 95% CI 0.76–0.80, $P<.001$).

Discussion

The impact of chronic opioid use on postoperative outcomes has been well described, particularly in the orthopedic surgery population where its use has been linked to not only increase in complications but poor functional outcomes.[9,10] More recently, Waljee et al utilized Truven Health Marketscan Databases to identify over 200,000 adults undergoing elective abdominal surgery and evaluated preoperative opioid use on postoperative health care utilization.[3] This study demonstrated that 1 out of 10 patients were using 10 to 100 oral morphine equivalents per day, preoperatively. Adverse effects on postoperative outcomes were noted, including increased LOS, greater likelihood of being discharged to a rehabilitation facility, higher readmission rate, and overall greater expenditure within 1 year of surgery.

To our knowledge, this is the first study examining the impact of preoperative opioid use defined as tolerance on outcomes in the era of enhanced recovery. In our patient population, patients with preoperative opioid tolerance were significantly less compliant with ERP standards than nontolerant patients. After adjusting for other risk factors, we found that opioid tolerance was independently associated with a 2-fold increase in the likelihood of readmissions. However, high compliance with the ERP standards among opioid tolerant patients was independently associated with a reduction in LOS and complications and mitigated the effect on readmissions, thus indicating that opioid tolerant patients can benefit from an ERP if they comply with the pathway standards.

Table III
Observed ERIN standard compliance rates among ERP stratified by individual compliance (high vs low) among the opioid tolerant and nonopioid tolerant patients

Variable (*%)	Low compliance (nonOT only) ($n = 247$)	Low compliance (OT only) ($n = 74$)	*P* value (OT versus nonOT)	High compliance (nonOT only) ($n = 285$)	High compliance (OT only) ($n = 40$)	*P* value (OT versus nonOT)	*P* value high vs low (OT only)†
Preoperative processes							
Preadmission counseling	150 (67.6%)	46 (66.7%)	.88	253 (90.4%)	37 (94.9%)	.55	<.01
Allow clear liquids up to 3 h before induction‡	152 (65.0%)	53 (74.6%)	.15	252 (88.7%)	34 (85.0%)	.44	.24
Day of surgery processes							
Use of multimodal pain management	232 (99.1%)	70 (98.6%)	.55	284 (99.6%)	40 (100%)	1	1
Use of regional anesthetic§	83 (35.5%)	35 (50%)	.04	142 (51.1%)	20 (50%)	1	.52
Normal temperature upon arrival to PACU	222 (95.7%)	70 (97.2%)	.74	281 (99.3%)	39 (97.5%)	.33	1
Use of goal-directed fluid therapy	104 (44.4%)	31 (43.7%)	1	184 (64.8%)	26 (65.0%)	1	.05
Use of antiemetic prophylaxis	219 (95.6%)	70 (97.2%)	.74	280 (98.2%)	39 (97.5%)	.55	1
Postoperative processes							
Mobilization on POD# 0	96 (41.7%)	23 (33.8%)	.26	236 (82.8%)	32 (80.0%)	.66	< .001
Patient was given clear liquids on POD# 0	174 (77.0%)	60 (85.7%)	.13	278 (97.5%)	38 (95.0%)	.31	.21
IV fluids discontinued POD# 0	144 (64.6%)	43 (63.2%)	.89	243 (86.8%)	34 (89.5%)	.80	< .01
Mobilization BID POD# 1	118 (51.5%)	35 (50.7%)	1	258 (90.5%)	36 (90.0%)	1	< .001
Solids given POD# 1	37 (18.1%)	10 (15.2%)	.71	169 (63.8%)	18 (48.6%)	.1	< .001
Foley removed on/before POD# 1‖	113 (49.6%)	34 (49.3%)	1	257 (90.5%)	36 (90.0%)	1	< .001
Mobilization BID POD# 2	154 (68.1%)	49 (72.1%)	.65	275 (97.2%)	39 (100%)	.6	< .001

BID, twice daily; *PACU*, postoperative anesthesia care unit.
* % reflects the number of patients meeting the compliance measure over the denominator of patients with available data.
† Comparison between OT patients only ($n = 114$).
‡ Total excludes high-risk patients for impaired gastric emptying per NSQIP data definition.
§ Total reflects open cases only.
‖ Total excludes high-risk patients with concurrent urinary tract procedures- per NSQIP data definition.

Table IV
Multivariable analysis examining the association between high compliance, opioid tolerance, and 30-day outcomes (LOS, major complications, and readmissions) among all ERP patients ($N = 646$)

Variable	LOS		CD (II–IV)		Readmission	
	IRR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
High compliance	0.88 (0.54, 1.43)	.61	0.36 (0.14, 0.90)	.03	0.78 (0.68, 0.89)	<.001
Opioid tolerance	1.06 (0.95, 1.18)	.32	1.01 (0.79, 1.30)	.93	2.00 (1.26, 3.29)	<.01
Age	1.00 (1.00, 1.00)	< .01	1.02 (1.00, 1.03)	< .01	1.00 (1.00, 1.00)	.02
Sex						
Male	[REF]		[REF]		[REF]	
Female	1.09 (0.94, 1.27)	.24	1.11 (0.64, 1.91)	.71	0.82 (0.66, 1.01)	.06
Race						
White	[REF]		[REF]		[REF]	
Non-white	1.23 (1.09, 1.37)	< .001	1.09 (0.89, 1.32)	.40	0.83 (0.69, 0.99)	.04
Operative approach						
Open	[REF]		[REF]		[REF]	
Laparoscopic	0.60 (0.49, 0.74)	< .001	0.60 (0.43, 0.84)	< .01	0.94 (0.73, 1.21)	.63
CR-POSSUM risk	1.00 (0.99, 1.00)	.03	1.00 (1.00, 1.00)	< .01	1.03 (1.03, 1.04)	<.001

The authors' previous work has evaluated the effect of age[6], frailty[11], and depression (in review) on 30-day postoperative outcomes following major abdominal surgery and demonstrated that high compliance (>75%) with ERP standards can mitigate the impact of these "high risk" features on postoperative outcomes. It is interesting to note that the race status of "non-white" was associated with an increased LOS but decrease readmission rate independent of opioid tolerance and compliance. The finding of decreased readmissions persisted when examining the opioid tolerant population alone. These findings may reflect the findings of worse ERP compliance to some variables among non-white patients and have implications for access to care and caregiver support. Similar findings regarding lower compliance rates to ERAS standards have been reported by Wahl et al, who noted that Black patients were less likely to adhere to their preop fasting protocol and remain normothermic.[12] Further studies are necessary to examine this association with greater granularity.

Other studies have also highlighted the impact of compliance on outcomes. Gustafsson et al demonstrated in a cohort of over 900 colorectal surgical cancer patients that there was a significant relationship between protocol adherence and postoperative outcomes.[13] In this study, patients who were highly adherent to an ERP had a 25% lower risk of postoperative complications, a 50% reduction of symptoms, and a reduction of readmissions. More recently, Arrick et al demonstrated in 500 colorectal surgical patients that high compliance (≥75%) with the ACS-NSQIP ERIN standards was associated with a significant decrease in both the complication rate and mean hospital LOS when compared to patients who were less compliant.[14]

In the current study, opioid tolerant patients were notably less likely to comply with the postoperative pathway standards. Particularly among those opioid tolerant patients with lower compliance, the rate of postoperative ambulation, advancing diet, removal of Foley catheters, and discontinuing intravenous fluids was significantly lower. Other studies examining outcomes in opioid tolerant patients have demonstrated poorer outcomes but fail to demonstrate causality.[3] It is plausible that patients who have opioid tolerance may have poorly controlled postoperative pain, which prohibits adherence to the ERP. Increased postoperative opioid use likely results in more adverse effects, such as nausea,

Table V
Multivariable analysis examining the association between high compliance and 30-day outcomes (LOS, major complications, and readmissions) among opioid tolerant ERP patients ($n = 114$)

Variable	LOS		CD (II-IV)		Readmission	
	IRR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
High compliance	0.72 (0.58, 0.90)	<.01	0.04 (0.02, 0.10)	<.001	0.68 (0.43, 1.07)	.10
Age	0.99 (0.98, 0.99)	.03	1.01 (0.98, 1.04)	.40	1.04 (1.04, 1.04)	<.001
Sex						
Male	[REF]		[REF]		[REF]	
Female	0.73 (0.71, 0.75)	< .001	0.73 (0.09, 5.74)	.77	0.65 (0.13, 3.27)	.60
Race						
White	[REF]		[REF]		[REF]	
Non-white	0.95 (0.91, 0.98)	<.01	0.97 (0.76, 1.22)	.80	0.78 (0.76, 0.80)	<.001
Operative approach						
Open	[REF]		[REF]		[REF]	
Laparoscopic	0.81 (0.68, 0.96)	.01	0.53 (0.32, 0.89)	.02	1.35 (0.46, 3.98)	.59
CR-POSSUM risk	1.02 (1.00, 1.07)	.03	1.23 (1.16, 1.30)	<.001	0.97 (0.85, 1.10)	.68

vomiting, sedation, and ileus, leading to an inability to ambulate and impediment of normal bowel function restoration. Further studies looking closely at causality are warranted.

This study is not without limitations. These results are from a single institutional practice and may not accurately represent national patterns. Nevertheless, our rate of opioid tolerance is in keeping with other studies which examined the rate of opioid use preoperatively.[3] Secondly, the EHR was utilized to identify preoperative opioid use, which depends on patient reported use and accurate review of the medication list by providers prior to the operation. However, we do not believe this would greatly alter the significant findings in this study. We did not evaluate the postoperative use of opioids. In particular, early postoperative use of opioids while hospitalized was not evaluated, and this information may be helpful in the future for determining causality for differences in outcomes. Finally, compliance data was lacking on some study participants; however, no standard was lacking in more than 10% of the study population.

In conclusion, we provide evidence that opioid tolerance is associated with less favorable outcomes in patients undergoing major abdominal surgery on an ERP, and this is likely due to a lack of compliance with the pathways. Interventions that increase patient compliance with the ERP protocol may mitigate the harmful effects of opioid tolerance and improve postoperative outcomes in this challenging patient cohort.

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Conflict of interest/Disclosure

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