Preoperative Opioid and Benzodiazepine Use: Influence on Abdominal Surgical Outcomes

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BACKGROUND: Preoperative opioid use has shown association with worse outcomes after surgery. However, little is known about the effect of preoperative benzodiazepines with and without opioids. The aim of this study was to determine the influence of preoperative substance use on outcomes after abdominal surgery.

STUDY DESIGN: Patients undergoing abdominal operations including ventral hernia, colectomy, hysterectomy, cholecystectomy, appendectomy, nephrectomy, and hiatal hernia were identified in an opioid surgical steward program by a regional NSQIP consortium between 2019 and 2021. American College of Surgeons NSQIP data were linked with custom substance use variables created by the collaborative. Univariable and multivariable analyses were performed for 30-day outcomes.

RESULTS: Of 4,439 patients, 64% (n = 2,847) were women, with a median age of 56 years. The most common operations performed were hysterectomy (22%), ventral hernia repair (22%), and colectomy (21%). Preoperative opioid use was present in 11% of patients (n = 472), 10% (n = 449) were on benzodiazepines, and 2.3% (n = 104) were on both. Serious morbidity was significantly ($p < 0.001$) increased in patients on preoperative opioids (16% vs 7.9%) and benzodiazepines (14% vs 8.3%) compared with their naïve counterpart and this effect was amplified in patients on both substances (20% vs 7.5%). Multivariable regression analyses reveal that preoperative substance use is an independent risk factor ($p < 0.01$) for overall morbidity and serious morbidity.

CONCLUSIONS: Preoperative opioid and benzodiazepine use are independent risk factors that contribute to postoperative morbidity. This influence on surgical outcomes is exacerbated when patients are on both substances. (J Am Coll Surg 2023;236:925–934. © 2023 by the American College of Surgeons. Published by Wolters Kluwer Health, Inc. All rights reserved.)

The opioid epidemic has become a national health problem contributing to a significant burden on the US heath system.[1,2] Chronic opioid use is prevalent and traverses the socioeconomic landscape, impacting nearly every surgical specialty.[3] In recent years, the literature regarding opioid use in the medical and surgical world has grown exponentially in response to this health crisis. Some of the first reports of the negative impact of chronic opioid use on surgical outcomes comes from the orthopedic and spine literature.[4,5] Numerous studies have shown that preoperative opioid use is associated with increased complications, emergency department visits, lengths of stay, and readmissions after major abdominal surgery, as well as higher costs.[6-14] Previous work has shown that patients taking preoperative opioids are more likely to be prescribed opioids postoperatively, and those on opioids have higher

Disclosure Information: Nothing to disclose.

Support: This study was supported by the AmerisourceBergen Foundation.

Presented at the Southern Surgical Association 134th Annual Meeting, Palm Beach, FL, December 2022.

Received December 12, 2022; Accepted December 12, 2022.

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Supplemental digital content is available for this article.

https://doi.org/10.1097/XCS.0000000000000572
ISSN 1879-1190/22

Abbreviations and Acronyms
ACS = American College of Surgeons
ASA = American Society of Anesthesiologists

healthcare costs up to 1 year after surgery.[15,16] Despite these known associations, only few initiatives have been made to standardize opioid prescriptions and address opioid use in the preoperative setting.[17-21]

Benzodiazepines represent a class of drugs used to treat anxiety, insomnia, and epilepsy, and are increasingly prescribed in the US.[22,23] Benzodiazepines are more likely to be prescribed to females and older patients.[24] In recent years, the US has seen an increase in the number of benzodiazepine-related overdoses and deaths both with and without concurrent opioid use.[25-28] Similar to opioids, preoperative benzodiazepine use has been associated with increased complications, hospital length of stay, and readmissions in medical and surgical populations.[9,26,29-31] However, limited data are available, and much work is still to be done regarding the impact of benzodiazepines on postoperative outcomes. Studies have identified that multiple substances, including benzodiazepine and opioids, have a cumulative effect on morbidity and mortality.[25-29,32] Therefore, the aim of this analysis was to determine the influence of preoperative substance use on outcomes after abdominal surgery utilizing the NSQIP platform with custom substance use variables created by a surgical opioid stewardship.

METHODS

Study population

Patients undergoing major abdominal surgery were identified in the American College of Surgeons (ACS) NSQIP custom consortium Participant Use File from September 2019 to August 2021. Abdominal operations included ventral hernia repair, colectomy, hysterectomy, cholecystectomy, appendectomy, nephrectomy, and hiatal hernia repair. These data were then linked by patient ID with 10 custom substance use variables created by the Pennsylvania NSQIP Consortium. Among the 10 variables were data on preoperative opioids and benzodiazepines used during the 6 months preoperatively.

Pennsylvania–New Jersey Surgical Opioid Stewardship

Pennsylvania NSQIP Consortium's Surgical Opioid Stewardship program is a quality improvement project focusing on preventing chronic opioid use among surgical patients. The program involves quality improvement champions from 10 hospitals among 5 health systems: Jefferson Health, Main Line Health, Penn Medicine, Temple Health, and WellSpan. Pennsylvania NSQIP Consortium's Surgical Opioid Stewardship program includes NSQIP Surgeon Champions and Surgical Clinical Reviewers from these health systems. The Surgeon Champions and Surgical Clinical Reviewers collected and entered substance-related data into the NSQIP registry on patients undergoing selected operations.

Patients were classified as being on preoperative opioids if they had filled an opioid prescription within 180 days of their operation. Preoperative opioids included codeine, hydrocodone, hydromorphone, oxycodone, tramadol, or oral morphine. Patients on preoperative benzodiazepines filled a prescription within 180 days of the operation for any of the following: alprazolam, clorazepate, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, oxazepam, temazepam, or triazolam. Other custom use variables included chronic pain disorders, the use of an intraoperative block, multimodal pain management (NSAIDs, acetaminophen, gabapentin, ketamine, clonidine), and postoperative opioid prescription at discharge along with prescription fill and refill.

Surgical outcomes

The standard 30 postoperative outcomes as collected by NSQIP were measured. Composite morbidity variables including overall and serious morbidity were created as previously described.[33] Overall morbidity included the occurrence of any postoperative complication. Serious morbidity was defined in a similar fashion with the omission of minor complications including superficial surgical site infection, urinary tract infection, deep vein thrombosis or progressive renal insufficiency. A complete list of all surgical outcomes is listed in Table 1.

Statistical analysis

Continuous variables were expressed as median with the interquartile range and were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. Multivariable analyses were performed for overall and serious morbidity using backward selection regression analysis. Patient demographics that were clinically and statistically relevant on univariable analysis were entered into the multivariable regression and included the following: age, sex, race, Hispanic ethnicity, BMI, ASA class, tobacco use, and preoperative substance use. Results are reported as odds ratio (OR), 95% CI, and p value. Statistical significance was set at $p < 0.05$, and all analysis were performed using SPSS version 25 (IBM).

Table 1. Postoperative Outcomes

Variable	Data (N = 4,439)
Mortality, n (%)	13 (0.3)
Overall morbidity, n (%)	512 (12)
Serious morbidity, n (%)	395 (8.9)
Superficial SSI, n (%)	76 (1.7)
Deep incisional SSI, n (%)	10 (0.2)
Organ space infection, n (%)	91 (2.1)
Dehiscence, n (%)	9 (0.2)
Pneumonia, n (%)	35 (0.8)
Reintubation, n (%)	26 (0.6)
Pulmonary embolism, n (%)	21 (0.5)
Ventilator dependence >48 h, n (%)	34 (0.8)
Progressive renal insufficiency, n (%)	20 (0.5)
Acute renal failure, n (%)	9 (0.2)
Urinary tract infection, n (%)	88 (2.0)
Stroke/CVA, n (%)	8 (0.2)
Cardiac arrest, n (%)	6 (0.1)
Myocardial infarction, n (%)	7 (0.2)
Deep vein thrombosis, n (%)	23 (0.5)
Sepsis, n (%)	63 (1.4)
Septic shock, n (%)	43 (1.0)
Reoperation, n (%)	79 (1.8)
Length of stay, d, median (IQR)	2 (0-3)
Readmission, n (%)	239 (5.4)

CVA, Cerebrovascular accident; IQR, interquartile range; SSI, Surgical site infection.

RESULTS

Patient demographics

From 2019 to 2021, 4,439 patients undergoing major abdominal surgery were identified (see complete demographics outlined in Table 2). Of the entire cohort, the median age was 56 years and 64% were female. The most common operations performed were ventral hernia repair (22%), hysterectomy (22%), and colectomy (21%). Patients taking preoperative opioids represented 11% of the cohort (n = 472), while 10% (n = 449) were taking benzodiazepines and 2.3% (n = 104) were on both substances preoperatively. The median opioid daily dose in oral morphine equivalents (in mg) was 38. In addition, 70% (n = 3,121) of patients received multimodal pain management perioperatively: 79% (n = 3,439) were prescribed an opioid after their operation, 59% (n = 2,634) filled their prescription, and 7.8% (n = 347) had their opioid prescription refilled. Opioid-naïve patients were younger, less likely to be White, had fewer comorbidities, and lower ASA scores when compared to those on preoperative opioids (p < 0.05) (Table 1, **Supplemental Digital Content**, http://links.lww.com/JACS/A201). Similar findings were observed when comparing benzodiazepine-naïve patients to those on benzodiazepines preoperatively (Table 2, **Supplemental Digital Content**, http://links.lww.com/JACS/A201), as well as opioid and benzodiazepine-naïve patients compared with those taking both substances (Table 3, **Supplemental Digital Content**, http://links.lww.com/JACS/A201).

Outcomes

Postoperative outcomes for the entire cohort are depicted in Table 1. Mortality was low: only 13 patients (0.3%) died within 30 days from the operation. Overall morbidity was 12% (n = 512) and 8.9% (n = 395) had a serious complication. The median length of stay for the cohort was 2 days (interquartile range, 0 to 2) and 5.4% (n = 239) of patients were readmitted to the hospital within 30 days of their operation. Postoperative outcomes stratified by preoperative substance use are shown in Figure 1. Serious morbidity was significantly higher in patients on preoperative opioids (16% vs 7.9%, p < 0.001) and in patients on preoperative benzodiazepines (14% vs 8.3%, p < 0.001). For the small subset of patients on both substances (opioid/BDZ), serious morbidity was even higher (20% vs 7.5%, p < 0.001) when compared to their naïve counterpart (Figure 1A). The length of stay was 2 days longer for patients on opioids (3 days vs 1 day, p < 0.001) and 1 day longer for those on benzodiazepine (2 days vs 1 day, p < 0.001) and opioids/BDZ (2 days vs 1 day, p < 0.001) (Figure 1B). In addition, readmissions were significantly higher among patients on preoperative opioids (11% vs 4.8%, p < 0.001), benzodiazepine (9.1% vs 4.9%, p < 0.001) and Opioid/BDZ (14% vs 4.7%, p < 0.001) compared to naïve patients (Figure 1C). Pulmonary complications including unplanned reintubations (1.3% vs 0.4%, p < 0.05) and ventilator dependence (1.7% vs 0.6%, p < 0.05) were also significantly higher in patients on preoperative opioids. A comprehensive list of all surgical outcomes among the groups is shown in Table 3.

Multivariable analyses

Multivariable analyses for overall and serious morbidity are shown in Table 4. In both analyses, preoperative substance use was an independent risk factor for postoperative morbidity. Preoperative opioid use was independently associated with overall morbidity (OR 1.58, p = 0.003) and serious morbidity (OR 1.70, p = 0.002). Preoperative benzodiazepine also was an independent risk factor for overall morbidity (OR 1.65, p = 0.002) and serious morbidity (OR 1.61, p = 0.008). Additionally, patients on both opioids and benzodiazepine had a 2-fold

Table 2. Patient Demographics, Preoperative and Perioperative Characteristics

Variable	Data (n = 4,439)
Age, y, median (IQR)	56 (42–67)
Sex, f	2,847 (64)
Race	
White	2,943 (66.3)
Black	975 (22.0)
Other	521 (11.7)
Hispanic	396 (8.9)
BMI, kg/m^2, median (IQR)	29.6 (25.4–35.0)
ASA class III to V	2,069 (47)
Diabetes	643 (15)
Hypertension	1,860 (42)
Current smoker	640 (14)
Perioperative blood transfusion	237 (5.3)
Operative time, min, median (IQR)	131 (75–196)
Pain control data	
Positive preoperative opioid use screen	535 (12)
Chronic pain syndrome	219 (4.9)
Fibromyalgia	24 (0.5)
Substance use disorder	60 (1.4)
Preoperative opioid use	472 (11)
Preoperative opioid daily dose, OME, median (IQR)	38 (20–60)
Preoperative benzodiazepine use	449 (10)
Preoperative opioid and benzodiazepine use	104 (2.3)
Intraoperative regional block	937 (21)
Abdominal	864 (20)
Epidural	58 (1.3)
Multimodal pain management	3,121 (70)
Opioid prescription at discharge	3,439 (79)
Postoperative opioid prescription filled	2,634 (59)
Postoperative opioid refilled	347 (7.8)
Case type	
Ventral hernia repair	991 (22.3)
Hysterectomy	970 (21.9)
Colectomy	951 (21.4)
Cholecystectomy	638 (14.4)
Appendectomy	487 (11.0)
Nephrectomy	351 (7.9)
Hiatal hernia repair	51 (1.1)

All data expressed as n (%), except where indicated.
ASA, American Society of Anesthesiologists; IQR, interquartile range; OME, oral morphine equivalent.

risk of overall morbidity (OR 2.31, p = 0.002) and serious morbidity (OR 2.65, p < 0.001) which was higher than if they were on one substance alone. In addition, patients who were ASA class III or greater had the highest risks of a postoperative morbidity. The complete results of the multivariable regression analyses and other risk factors are shown in Table 4.

DISCUSSION

In this analysis from 10 Pennsylvania NSQIP Consortium hospitals, patients undergoing major abdominal surgery on preoperative substances including opioids, benzodiazepines, or both had significantly worse outcomes. Of 4,439 patients, 11% (488) were taking opioids preoperatively and 10% (444) were on benzodiazepines, while a small subset of patients were taking both substances (2.3.% [102]). Length of stay is significantly longer when patients are on preoperative substances (2 days longer if on opioids and 1 day longer for benzodiazepine and Opioids/BDZ). Readmissions were increased 2-fold when patients were taking a single substance and were 3-fold higher when patients were on both opioids and benzodiazepines preoperatively. These patients represent a unique subset of the surgical population who exemplify an opportunity for improvement in surgical quality and outcomes.

Preoperative opioid use has been associated with increased morbidity after multiple surgical specialties with the effect ranging from 10% to 40%. The present study corroborates these findings as patients on preoperative opioids (11%) had higher rates of overall morbidity (19% vs 11%, p < 0.001) and serious morbidity (16% vs 7.9%, p < 0.001) compared to opioid-naïve patients. These associations were first reported in orthopedic and spine literature related to patients with chronic osteoarthritis and degenerative spine disease who have chronic pain which has been deemed the *fifth vital sign*.[34] Given these observations, studies document that preoperative reduction of opioid use is possible and those who wean from opioids before knee arthroplasty have improvement in postoperative physical pain.[21] In addition, evidence exists to show that nonpharmacologic methods including acupuncture and electrotherapy can reduce postoperative opioid consumption after total knee arthroplasty.[20]

With respect to abdominal surgery, investigators from Michigan were among the first to report the impact of opioids on surgical outcomes. In their analysis of the Michigan Surgical Quality Collaborative database, Cron and colleagues found that 21% of 2,413 patients undergoing abdominal surgery were on preoperative opioids.[6] They reported an increased rate of complications (25% vs 14%), reintubations (2.6% vs 1.3%), lengths of stay (2 days longer), and readmissions (11% vs 6%) in opioid users. The current findings from Pennsylvania mirror the

Table 3. Postoperative Outcomes Stratified by Preoperative Substance Use

Variable	Opioid-naïve (n = 3,499)	Opioid use (n = 472)	Benzodiazepine-naïve (n = 3,722)	Benzodiazepine use (n = 449)	Opioid and Benzodiazepine-naïve (n = 3,050)	Opioid and Benzodiazepine use (n = 104)
Mortality	11 (0.3)	0 (0)	13 (0.3)	0 (0)	11 (0.4)	0 (0)
Overall morbidity	376 (11)	91 (19)*	400 (11)	79 (18)*	311 (10)	24 (23)*
Serious morbidity	276 (7.9)	76 (16)*	308 (8.3)	64 (14)*	230 (7.5)	21 (20)*
Superficial SSI	64 (1.8)	10 (2.1)	56 (1.5)	16 (3.6)†	51 (1.7)	4 (3.8)
Deep incisional SSI	6 (0.2)	3 (0.6)	6 (0.2)	4 (0.9)†	4 (0.1)	1 (1.0)
Organ space infection	63 (1.8)	18 (3.8)*	75 (2.0)	14 (3.1)	55 (1.8)	4 (3.8)
Dehiscence	6 (0.2)	3 (0.6)	6 (0.2)	1 (0.2)	5 (0.2)	0 (0)
Pneumonia	28 (0.8)	4 (0.8)	28 (0.8)	7 (1.6)	23 (0.8)	1 (1.0)
Reintubation	14 (0.4)	6 (1.3)†	25 (0.7)	1 (0.2)	13 (0.4)	0 (0)
Ventilator dependence	22 (0.6)	8 (1.7)†	29 (0.8)	4 (0.9)	18 (0.6)	1 (1.0)
Pulmonary embolism	18 (0.5)	1 (0.2)	19 (0.5)	1 (0.2)	16 (0.5)	0 (0)
Progressive renal insufficiency	17 (0.5)	2 (0.4)	16 (0.4)	3 (0.7)	15 (0.5)	0 (0)
Acute renal failure	6 (0.2)	3 (0.6)	6 (0.2)	3 (0.7)	5 (0.2)	2 (1.9)†
Urinary tract infection	69 (2.0)	17 (3.6)†	67 (1.8)	15 (3.3)†	55 (1.8)	5 (4.8)†
Stroke/CVA	8 (0.2)	0 (0)	8 (0.2)	0 (0)	8 (0.3)	0 (0)
Cardiac arrest	5 (0.1)	0 (0)	6 (0.2)	0 (0)	5 (0.2)	0 (0)
Myocardial infarction	6 (0.2)	1 (0.2)	6 (0.2)	1 (0.2)	6 (0.2)	1 (1.0)
Deep vein thrombosis	16 (0.5)	2 (0.4)	18 (0.5)	3 (0.7)	13 (0.4)	1 (1.0)
Sepsis	43 (1.2)	7 (1.5)	44 (1.2)	16 (3.6)*	32 (1.0)	2 (1.9)
Septic shock	33 (0.9)	7 (1.5)	36 (1.0)	7 (1.6)	28 (0.9)	2 (1.9)
Reoperation	47 (1.3)	20 (4.2) *	63 (1.7)	11 (2.4)	40 (1.3)	3 (2.9)
Length of stay, d, median (IQR)	1 (0–3)	3 (1–5)*	1 (0–3)	2 (1–4)*	1 (0–3)	2 (1–5)*
Readmission	169 (4.8)	51 (11)*	183 (4.9)	41 (9.1)*	142 (4.7)	14 (14)*

All data expressed as n (%), except where indicated.
*p < 0.001 vs naïve.
†p < 0.05 vs naïve.
CVA, cerebrovascular accident; IQR, interquartile range; SSI, surgical site infection.

Michigan results and these associations are likely happening throughout the country. The same Michigan group has repeated analyses across different databases (including Truven Health Marketscan, Optums private insurance claims, Clinformatics DataMart Database, and Medicare claims data) and have reported similar results with respect to increased hospital costs, lengths of stay, and readmissions in preoperative opioid users.[7,8] Walijee and colleagues have also shown that these negative health impacts correlate with preoperative dose effect when stratified by oral morphine equivalent.[7] Additionally, preoperative opioid use is associated with second refills and persistent postoperative opioid consumption, which exacerbate the problem.[15,16]

Minimizing perioperative opioid use also has been a focus among colorectal surgeons as an avenue to improve postoperative outcomes.[35] Enhanced recovery after surgery (ERAS) pathways employ multimodal pain regimens with acetaminophen (Tylenol), nonsteroidal anti-inflammatory agents and gabapentin with utilization of anesthetic blocks.[36] In the present analysis 70% of patients were prescribed a perioperative multimodal pain regimen, and 21% had an intraoperative regional block. These findings represent an area for continued improvement in postoperative pain control. In the present cohort, 22% of the patient population underwent colectomy. Although the focus of the current analysis is not limited to colorectal procedures, patients on preoperative opioids who underwent colectomy had significantly increased morbidity (data not shown). Previous single center studies within the colorectal literature are limited and are conflicting. Gan and colleagues analyzed their institution's patients NSQIP colorectal data and found that 30% of 1,201 patients were on opioids preoperatively. These opioids use patients had increased infectious and pulmonary complications as well as long length of stay and more readmissions.[9] In comparison, Ogilvie and colleagues in their single-center review reported 923 patients of whom 23% were on preoperative opioids. The opioid use patients had no

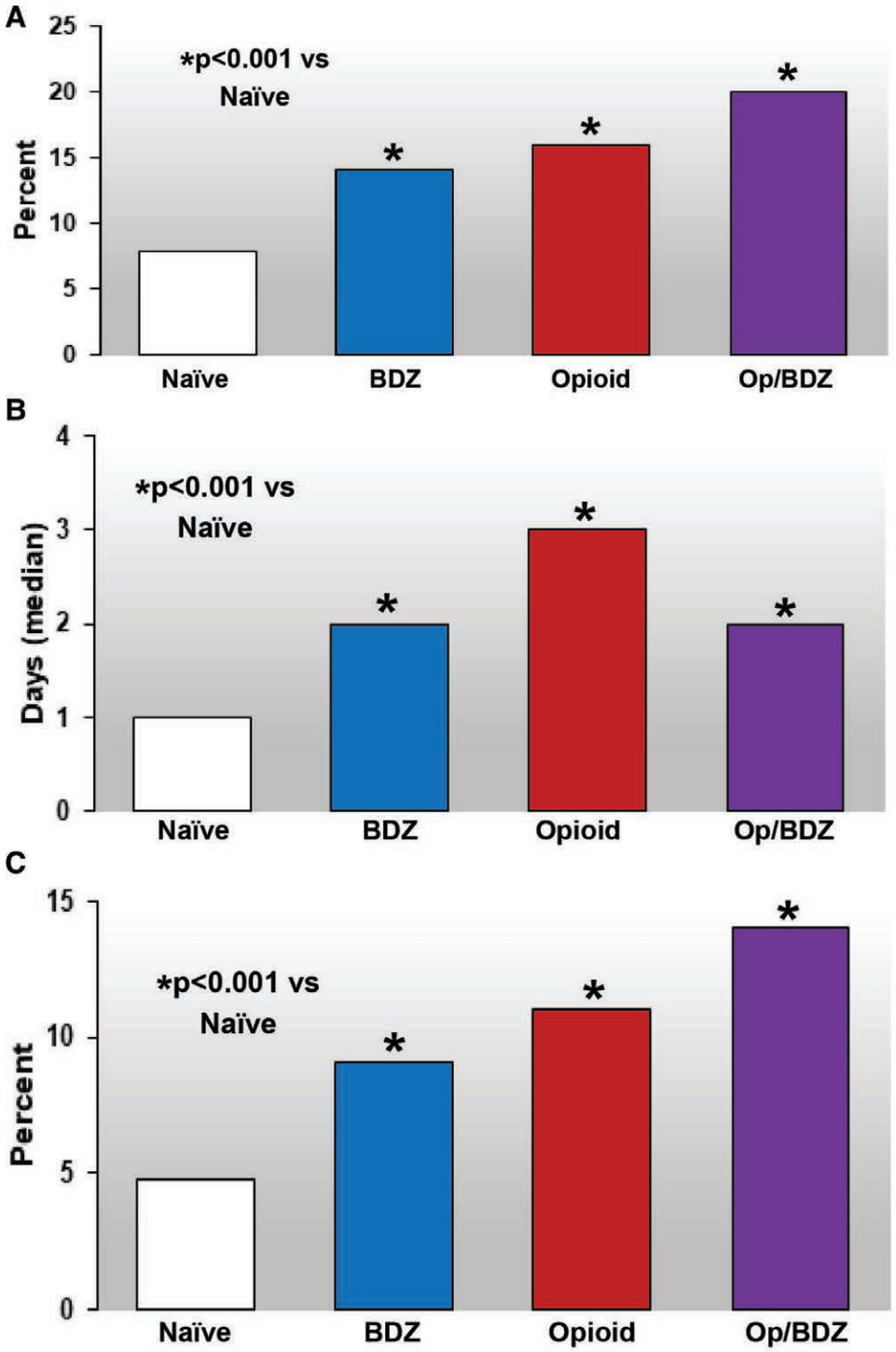

Figure 1. Postoperative outcomes stratified by preoperative substance for (A) serious morbidity, (B) length of stay, and (C) readmission. BDZ, benzodiazepine; OP, opioid.

difference in surgical site infections or readmissions but experienced a slight increase in length of stay.[11] Li and colleagues reported a cohort of patients with Crohn's disease who commonly experience chronic pain. They found that opioid-use patients had more complications and longer lengths of stay.[14]

Table 4. Multivariable Logistic Regression Analyses

Variable	Odds ratio	95% CI	p Value
Overall morbidity			
ASA class ≥III	2.34	1.76–3.10	<0.001*
Preoperative opioid and benzodiazepine use	2.31	1.37–3.88	0.002*
Hispanic	1.88	1.13–3.11	0.016*
Preoperative benzodiazepine use	1.65	1.20–2.27	0.002*
Preoperative opioid use	1.58	1.17–2.13	0.003*
Age >65, y	1.44	1.12–1.84	0.004*
Sex, f	0.79	0.63–1.00	0.045*
Current smoker	1.09	0.79–1.50	0.596
BMI >30, kg/m^2	1.09	0.87–1.37	0.438
Black	0.87	0.66–1.14	0.303
Serious morbidity			
ASA class ≥III	3.26	2.31–4.58	<0.001*
Preoperative opioid and benzodiazepine use	2.65	1.52–4.63	<0.001*
Preoperative opioid use	1.70	1.22–2.35	0.002*
Preoperative benzodiazepine use	1.61	1.13–2.30	0.008*
Sex, f	0.65	0.49–0.87	0.004*
Hispanic	1.30	0.63–2.70	0.484
Age >65, y	1.10	0.73–1.67	0.646
Black	0.96	0.68–1.35	0.799
BMI >30, kg/m^2	0.95	0.71–1.28	0.750
Current smoker	0.80	0.51–1.25	0.321

Results of backward stepwise multivariable logistic regression presented in table.
*Statistically significant.
ASA, American Society of Anesthesiologists.

Benzodiazepines also represent a class of drugs that have the potential for abuse and are associated with increased morbidity and mortality.[23] Similar to the opioids findings, the current analysis reports that patients taking preoperative benzodiazepine (10%) had significantly higher overall and serious morbidity, superficial surgical site infections, length of stay and readmissions. After risk adjustment, preoperative benzodiazepine use was independently associated with increased overall morbidity (OR 1.65, p = 0.002) and serious morbidity (OR 1.61, p = 0.008). These results are some of the first to report the influence of preoperative benzodiazepine use on abdominal surgical outcomes. Gaulton and colleagues utilized the Optum database (US health insurance) to query a wide variety of procedures including orthopedic and general operations. They found that 12% were taking benzodiazepine preoperatively and reported a slight increased risk for adverse postoperative event (OR 1.07).[29] Sidurdsson and colleagues reported a cohort of 41,000 patients undergoing noncardiac surgery in Iceland. They found that 7.4% were on benzodiazepines preoperatively, but benzodiazepine use conferred no risk on short- or long-term mortality.[25] However, when patients were on both benzodiazepines and opioids, 30-day mortality was higher (3.2% vs 1.8%, p = 0.004) with increased risk of mortality (HR 1.41, p < 0.001). Other single-center studies in patients on benzodiazepines preoperatively undergoing colorectal surgery[9] and ventral hernia repair[31] reported higher composite morbidity, lengths of stay, and readmissions compared to naïve patients.

Patients taking both opioids and benzodiazepine in the current study represented the highest risk population. The overall morbidity rates increased by 2-fold and nearly 3-fold for serious morbidity with triple the number of readmissions. After multivariable regression, concurrent opioid and benzodiazepine use was independently associated with overall morbidity (OR 2.31, p = 0.002) and serious morbidity (OR 2.65, p < 0.001). This effect was significantly greater than if a patient were taking only one substance. ASA class III or greater conferred a higher risk of a postoperative morbidity; this association is well described in the literature.[37,38] Patients taking both substances represent an extremely high-risk population vulnerable to increased morbidity. These patients need to be identified and counseled preoperatively.

Concurrent opioid and benzodiazepine use are on the rise, and as many as 30% of opioid-related deaths involve simultaneous benzodiazepine use.[28] Although the current analysis did not reveal any associations with mortality, this potential connection cannot be ignored. Guidelines for geriatric populations have been published by the ACS advising discontinuation and tapering of benzodiazepines before surgery[39]; however, this plan is not always possible. One must be cognizant of patients taking both substances and plan for postoperative pain control, focusing on reduction in opioids. Although not always possible in emergency surgery, the elective setting is the ideal situation for reduction of substances with collaboration from psychiatry, psychology, and pain specialists. In fact, in their cluster randomized trial, Tannenbaum and colleagues showed that benzodiazepine reduction is achievable: 27% of the intervention group discontinued benzodiazepines at 6 months with patient-physician conversations.[40]

The current study is not without limitations. These data are from NSQIP which is limited to 30-day outcomes. In addition, preoperative opioid and benzodiazepine variables were created as binary options; specific substances were not analyzed. Additionally, patients on preoperative opioids were not stratified by oral morphine equivalent because of the small sample size. Data exist suggesting that increased quantity and duration of opioid use preoperatively are associated with increased morbidity.[7] In this analysis, patients who may have been on substances illegally were not captured. Also, subanalyses based on procedure type were not performed because of the sample size, and we acknowledge the inherent bias that may occur when grouping patients. The patients in this analysis were primarily from southeast Pennsylvania and southern New Jersey, an area with a significant opioid-use problem. Whether these data are generalizable to other regions is unknown; however, these patients come from a mix of urban academic and suburban community hospitals. Finally, despite these limitations, NSQIP is a well validated database and includes data collected by trained surgical clinical reviewers.

CONCLUSIONS

Patients undergoing major abdominal operations and taking preoperative opioids, benzodiazepines, or both have significantly higher postoperative morbidity when compared to their naïve counterparts. This high-risk patient population necessitates attention by surgeons if future outcomes are to be improved.

Author Contributions

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Project administration: Braun
Validation: Pitt

Acknowledgment: The ACS NSQIP and its participating hospitals are the source of the data used herein; they have not verified, and are not responsible for, the statistical validity of the data analysis or the conclusions derived by the authors. The Surgeon Champions and Surgical Clinical Reviewers at the 10 participating Pennsylvania NSQIP Consortium hospitals are greatly appreciated for variable development as well as data gathering and integrity. Abington Memorial Hospital, Jefferson Health: Kristin M Noonan, MD, FACS, Surgeon Champion; Jeannine Gerolamo, MSN, BSN, CPPS, Surgical Clinical Reviewer; Judith DellaPorta, BSN, RN, Surgical Clinical Reviewer. Fox Chase Cancer Center, Temple Health: Stephanie Greco, MD, FACS, Surgeon Champion; Dawn Stack, RN, ASN, Surgical Clinical Reviewer; Erin Costello, RN, Surgical Clinical Reviewer. Hospital of University of Pennsylvania, Penn Medicine: Rachel Kelz, MD, MSCE, MBA, FACS, Surgeon Champion; James Rowe, RN, MSN, BA, CNOR, Surgical Clinical Reviewer. Jeanes Hospital, Temple Health: Eric Velazquez, MD, MBA, FACS, Surgeon Champion; Kimberly Morgan, RN, Surgical Clinical Reviewer. Methodist Hospital, Jefferson Health: Francesco Palazzo, MD, FACS, Surgeon Champion; Kathleen Shindle, BSN, RN, Surgical Clinical Reviewer. Penn Presbyterian Medical Center, Penn Medicine: Patrick Kim, MD, MHCI, FACS, Surgeon Champion; Kim Daniels, DNP, ACNS-BC, RN, GERO-BC; Surgical Clinical Reviewer; Mary Kathleen Wood, MSN, RN, Surgical Clinical Reviewer. Pennsylvania Hospital, Penn Medicine: Nicole Saur, MD, FACS, FACSR, Surgeon Champion; Stephanie Diem, MSMI, RN- BC, CAHIMS, Surgical Clinical Reviewer; Jillian Blackwell, BSN, RN, corln, Surgical Clinical Reviewer. Temple University Hospital, Temple Health: Matthew Philp, MD, FACS, FACSR, Surgeon Champion; Cindy Blank-Reid, MSN, RN, TCRN, CEN, Surgical Clinical Reviewer; Kathleen Campbell, BSN, RN, Surgical Clinical Reviewer. Thomas Jefferson University Hospital, Jefferson Health: Harish Lavu, MD, FACS, Surgeon Champion; Christine

Schleider, MSN, RN, Surgical Clinical Reviewer. York Hospital, WellSpan Health: Richard Damewood, MD, FACS, Surgeon Champion; Kelly Gemmill, BA, RN, Surgical Clinical Reviewer; Pamela Emig, BSN, RN, Surgical Clinical Reviewer; Debra Sigel, RN, Surgical Clinical Reviewer.

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Discussion

DR EDWARD E CORNWELL III (Washington, DC): The finding in more than 4,400 patients undergoing major abdominal surgical procedures at 10 Pennsylvania Consortium hospitals participating in NSQIP that patients using preoperative opioids or benzodiazepines had more complications and longer lengths of stay is important, fruitful, and deserving of careful scrutiny of the multivariate logistic regression analysis. For example, the 10% to 11% subset of patients taking these drugs preoperatively were older with more comorbidities and higher ASA scores than their drug-naïve counterparts. The confluence of some of these factors on surgical outcomes form the basis for my comments and questions.

I concur with the illuminating discussion in your manuscript on the enhanced recovery after surgery pathways that the colorectal community has promoted to improve postoperative outcomes. These protocols emphasize anti-inflammatory alternatives to opioids. While most would assume this to be the case, can your study confirm that those patients receiving opioids and benzodiazepines preoperatively were also receiving them in greater abundance postoperatively?

The second question is a natural follow-up to the first. Three of the most common complications after major abdominal surgery—atelectasis, ileus, deep vein thrombosis—are directly affected by postoperative ambulation and mobility. Patients receiving large amounts of postoperative benzodiazepines and opioids are less likely to be mobile and ambulatory. Are there any parameters that allow us to measure these variables in your NSQIP study? Do we know what percentage of patients had minimally invasive operations, and were there associations with outcomes?

Please comment on next steps and how committed you are by the findings reported in this paper. For example, would you delay an elective operation for a few months and employ the use of psychiatrists, psychologists, and pain specialists in the management of a patient taking substantial doses of opioids or benzodiazepines in order to seek perioperative alternatives?

All told, I am excited by this study for its potential to further determine pursuits that can offer improved outcomes for our surgical patients. While I suspect that the subset of elective surgical patients here receiving preoperative opioids and benzodiazepines are an older, sicker cohort who may receive more of the same drugs postoperatively and thus be more sedentary, I applaud the authors for their work in teasing out an adjustable surrogate for substantial risk factors for postoperative complications.

DR DAVID T EFRON (Baltimore, MD): This is an extraordinarily important topic. Opiate and benzodiazepine substance abuse are at epidemic proportions. You do not need an operation to suffer the ravages of these substances, yet both are vital adjuncts to our treatment armamentarium.

This study reinforces previous data implication that preoperative use of opiates and benzodiazepines, individually or in combination, is associated with adverse postoperative outcomes and morbidity. The question that remains in my mind is why, or perhaps more precisely, how?

In the comparison of the types of outcomes associated with use, not surprisingly, opioid use affects respiratory outcomes such as ventilator days and reintubation. That makes sense. Benzodiazepines alone are not associated, but they are, however, associated with surgical site infections and deep surgical infections. Both are associated with urinary tract infections. Why do you think this is? Is there a possible alteration in the biome or immune response, or is this a reflection of the patient? These are patients who were prescribed these drugs without evidence noting abuse. Does this reflect the patient's poor investment in their perioperative or preoperative care, health optimization,