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Opioid analgesic use after ambulatory surgery: A prospective, descriptive study of factors associated with quantities prescribed and consumed

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Patient and Public Involvement Statement

Patients were first involved in the research when recruited and informed verbally about the details of the study. Research questions and outcome measures were developed by several members of the research team (CWS, JML, OR, IH, DM). These questions and measures were informed by team members' priorities, experience, and preferences. Patients and the public were indirectly involved in the design of this study through careful monitoring of the issues and challenges associated with their recent surgeries and, when appropriate, specific questions were fashioned to optimally characterize their concerns. Patients were contacted and introduced to the study research assistant by the recruiting physician during their medical visits. Patients were provided a brief overview of the study; if they were interested in participating, they were referred to the study research assistant to receive more verbal information about the study. If interested, the patients underwent a formal informed consent process as previously approved by the Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB). Once consented, patients were enrolled into the study. As part of the study, participants were informed about the degree of burden of the intervention and time required to participate in the research. Participants were not involved in our wider plan to disseminate the study results to participants and relevant wider patient communities.

The purpose of this study was to pilot a procedure intended to recruit a larger number of subjects for use in a larger program of research. Simultaneously, we used other data gathered from this investigation to establish power calculations for a later and larger full-scale study. We have also used this work to evaluate the financial, technical, administrative, and logistic feasibility of a full-scale study, including issues of data collection, protocol adherence, and questionnaire design. The sample size was based on and justified by these results. This article will inform the probable impact that the pilot study will have on future research decisions.

ABSTRACT

Objectives: To prospectively characterize: (1) postoperative opioid analgesic prescribing practices; (2) experience of patients undergoing elective ambulatory surgeries; and (3) impact of patient risk for medication misuse on postoperative pain management.

Design: Longitudinal survey of patients seven days before and seven to 14 days after surgery.

Setting: Academic urban safety-net hospital.

Participants: 181 participants recruited, 18 surgeons, follow-up data from 149 participants (82% retention); 54% female; mean age: 49 years.

Interventions: None.

Primary and secondary outcome measures: Total morphine equivalent dose (MED) prescribed and consumed, percentage of unused opioids.

Results: Surgeons postoperatively prescribed a mean of 242 total MED per patient, equivalent to 32 oxycodone (5 mg) pills. Participants used a mean of 116 MEDs (48%), equivalent to 18 oxycodone (5 mg) pills (~145 mg of oxycodone remaining per patient). A 10-year increase in patient age was associated with 12 (95% CI [-2.05, -0.35]) total MED fewer prescribed opioids. Each one-point increase in the preoperative Graded Chronic Pain Scale was associated with an 18 (95% CI [6.84, 29.60]) total MED increase in opioid consumption, and 5% (95% CI [-0.09, -0.005]) fewer unused opioids. Prior opioid prescription was associated with a 55 (95% CI [5.38, -104.82]) total MED increase in opioid consumption, and 19% (95% CI [-0.35, -0.02]) fewer unused opioids. High-risk drug use trended towards 9% (95% CI [-0.19, 0.002]) fewer unused opioids. Pain severity in previous three months, high-risk alcohol and drug use, and prior opioid prescription were not associated with postoperative prescribing practices.

Conclusions: Participants with preoperative history of chronic pain, risky drug use, or prior opioid prescription are more likely to consume higher amounts of opioid medications postoperatively. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties, and patient education and monitoring.

ARTICLE SUMMARY (Strengths and limitations of this study)

The strengths of this study included:

1. The study population and setting were drawn from an academic urban safety-net hospital serving a majority of underserved persons.
2. The study was executed in a real-life setting and no guidance was given to prescribing surgeons about the study objectives.
3. We created and demonstrated a robust recruiting protocol.
4. We studied the postoperative pain management strategies across a variety of surgical subspecialties, surgeons drawn from those subspecialties, and a wide range of surgical procedures performed by those clinicians.

The limitations of this study included:

1. Generalizability of this study may be limited because of the study's small size at a single academic urban safety-net hospital.
2. We obtained data on the amount of medication taken or effectiveness of medication taken via patient report (i.e., there were no objective tests to ascertain accuracy of self-reported data).
3. We did not differentiate between preexisting pain and pain directly related to the indication for surgery.

INTRODUCTION

Prescription opioid misuse is a major public health problem. Therapeutically prescribed opioid analgesics constitute the single largest source of misused opioids, and opioid prescribing by physicians increased dramatically from the late 1990s until the mid-2010s when it began to level off.[1–4] Opioid analgesics prescribed for postoperative and acute pain management can lead to patients' long-term opioid use,[5–12] which may be associated with development of opioid use disorder and other opioid medication adverse events.[12–23]

In addition to inducing long-term use and potential addiction, unused opioid pills prescribed for surgical procedures are available for misuse by the patient, friends, or family. In fact, most individuals who misuse opioids obtain them from friends or family.[24, 25] Numerous studies have found that a majority of patients reported having unused or unfilled prescriptions postoperatively.[26–30] Wide variations in opioid prescribing for the same procedure also support the concept that postoperative opioid prescribing is not evidence-based and may result in excess opioid prescribing with unknown benefits in pain outcomes.[31]

In a national survey of adults prescribed opioids, nearly half reported having no recollection of receiving information on safe medication storage or disposal.[32] Among those with leftover medications, 62% reported keeping them for future use.[33–35] Bicket and colleagues (2017) performed a systematic review of unused opioid analgesics postoperatively and found that 67–97% of patients report unused opioids, with 42–71% of prescribed opioid tablets remaining unused.[26] Furthermore, two prior studies that examine storage of excess medications found that a minority of patients stored the medications in safe manner, and even fewer planned to dispose of unused medications using U.S. Food and Drug Administration (FDA)-recommended methods.[23, 24]

Patient-associated factors may potentially impact surgeons' postoperative prescribing practices, as well as patients' opioid medication-taking behaviors. A history of chronic pain is associated with more opioid medication use postoperatively.[36–39] There is also evidence of racial and ethnic disparities in opioid prescribing (e.g., black race has been shown to be associated with fewer opioids prescribed compared to white race).[40] A history of chronic opioid use is associated with greater postoperative opioid use.[41, 42] Opioid-tolerant patients require longer durations of higher dosage of postoperative opioid use to achieve the same level of pain relief as non-opioid-tolerant patients taking opioids postoperatively.[43, 44] Patients reporting depression are more likely to use opioids postoperatively in an non-prescribed manner,[45, 46, 47] and anxiety is associated with prolonged postoperative opioid usage.[44] Moreover, little is known about if, what, and to what degree patient-associated factors impact surgeons' postoperative prescribing practices.

Using data collected prospectively from patients undergoing elective ambulatory surgery, we analyzed the associations between participants' sociodemographic factors, high-risk substance use, and chronic pain on (1) surgeons' opioid prescribing patterns, (2) participants' plans for postoperative opioid use, and (3) plans for remaining opioid

disposal. To assess potential risk factors for postoperative medication misuse and look for correlations with surgeons' postoperative pain prescribing practices, we collected preoperative data on participants' baseline mental health status, prior prescription opioid use, and high-risk substance use.

METHODS

Study Design

This was a one-year, prospective pre-post study of surgeons' postoperative opioid prescribing practices for participants undergoing elective ambulatory surgery in Spring 2015. A study research assistant (RA) assessed participants over the phone or in person in the seven days leading up to the scheduled surgery. Follow-up assessment occurred between seven and 14 days postoperatively via telephone. The Boston University Medical Center (BUMC) Institutional Review Board (IRB) approved the study. We used the STROBE cohort checklist when writing our report.[48]

Sample

We recruited 18 surgeons among nine surgical specialties (colorectal surgery, general surgery, gynecology, oral surgery, orthopedic surgery, otolaryngology, podiatry, trauma, and urology) from a single academic urban safety-net hospital. We included surgical procedures that were most likely to generate at least moderate postoperative pain. We excluded cancer-related procedures and those not expected to generate significant postoperative pain (e.g., endoscopy).

We identified potential participants via their electronic health records (EHRs). An RA generated a list of patients who were scheduled to have elective surgery in predesignated categories between 14 and 23 days in the future. Eligibility criteria were: Age 18 to 89 years, English comprehension, an active telephone line in the EHR, and availability to complete a follow-up telephone interview two weeks after surgery. We generated a personalized study introduction letter for each patient. The letter was signed by the patient's surgeon then mailed to the patient. This process enabled surgeons to efficiently remove any patients they did not feel would be appropriate for the study. The letter included a description of the study, with an "opt-out" choice that required the patient to call the study team one week before the planned surgery to avoid undesired contact. The letter included a study brochure and a "pain diary," which the participant was advised to use to record pain, prescription medicine use, and over-the-counter medicine use during the 10 days after the surgery if he or she was eventually enrolled in the study.

Starting seven days before planned surgical procedures, the RA contacted patients to obtain their consent to participate in the study and administer the baseline assessment. The RA reminded participants to fill out the pain diary to improve recall and accuracy at the follow-up assessment. The RA collected follow-up data over the phone between seven and 14 days postoperatively using an interviewer-administered questionnaire. Patients were contacted and introduced to the study research assistant by the recruiting

physician during their medical visits. Patients were provided a brief overview of the study; if they were interested in participating, they were referred to the study research assistant to receive more verbal information about the study. If still interested, the patients underwent a formal informed consent process as previously approved by the Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB).

Data Collection

Preoperative baseline patient-reported data included: demographics (age, gender, race/ethnicity); chronic pain severity and function in the past three months per the Graded Chronic Pain Scale's (GCPS's) standard categories of disability, intensity, and functional limitations; and high-risk alcohol and drug use (Alcohol Use Disorders Identification Test [AUDIT] and Drug Use Disorders Identification Test [DUDIT], respectively).[48–50] Postoperative patient reported data included: postoperative pain via a postoperative pain scale with a 0 (no pain relief) to 10 (complete pain relief) scale, adapted from Albi-Feldzer, et al (2013);[51–54] Timeline-Follow-Back (TLFB) of total opioids consumed and pain rating on each day; prescription opioid misuse via the Prescription Opioid Misuse Index (POMI)[55] and Prescription Misuse Questionnaire (PMQ);[56] substance use since surgery; and intentions for leftover medication storage and disposal (concepts based on Winstock et al, 2007).[57] In addition, participants verified pain medication data extracted from the EHR.

EHR data included date of surgery, surgery type, and detailed opioid prescriptions, as well as any history of opioid prescription prior to surgery. To determine the total amount of opioid medications prescribed at the time of surgery, we calculated a total morphine equivalent dose (total MED) for all prescribed opioid medications as the number of pills multiplied by the MED of the opioid.[58]

Dependent Variable

The dependent variables for this analysis included: (1) amount of opioid analgesic medications prescribed for postoperative pain management as calculated by total MED (source: EHR); (2) opioids consumed over the 10-day postoperative period (total MED) (source: TLFB); and (3) percent of unused opioids after the 10-day postoperative period (sources: EHR and TLFB). We obtained the percent of unused opioids by subtracting reported total MED consumed from total MED prescribed for each participant, then divided by total MED prescribed. We converted opioid amounts from total MED back to oxycodone-equivalent 5 mg pills to make the data more clinically accessible. We used the highest possible dose interpretable when surgeons prescribed a dosing range for these analyses.

Independent Variable

Independent variables included age, gender, race/ethnicity (white, black, and "other" [i.e., mixed race/ethnicity]), and high-risk alcohol and drug use in the past month (AUDIT score greater than 15, DUDIT score greater than 9).

Analysis

We included only participants for whom we had follow-up data in this analysis. The available number of patients recruited from 18 surgeons during the study period determined the size of this convenience sample. Two-sided type-I error rates of 0.05 along with 95% confidence intervals were used to assess the statistical significance of associations. We used multivariable linear regression, adjusted for surgical specialty as fixed effects, to analyze associations of sociodemographic data, as well as data about chronic pain and high-risk substance use with all outcomes. We calculated intraclass correlations to partition variance in each outcome attributable to surgical specialties.

RESULTS

Population and Demographics

We enrolled 181 participants in the study and analyzed data on the 149 participants who completed follow-up assessments (see Figure 1 for study enrollment schema). The participants were 54% female, 44% white, 34% black, and 22% “other” (i.e., mixed race/ethnicity). The mean age was 49 years, and 69% of participants had some postsecondary education (Table 1).

Participants’ Pain, Substance Use, and Mental Health

At baseline, 24% of participants had highly disabling and severely limiting pain; 18% had highly disabling and moderately limiting pain; 32% had low-disabling and highly intense pain; and 26% reported low-disabling and low-intensity pain or no pain. At baseline, 5% of participants indicated high-risk alcohol use including dependence (AUDIT), and 18% reported use of illegal drugs or prescribed drugs for nonmedical reasons (DUDIT) (Table 1).

Surgeon’s Postoperative Prescribing Practices

Surgeons prescribed opioids for postoperative pain to 95% of participants; 85% of these participants received either oxycodone or oxycodone with acetaminophen. Surgeons prescribed a mean of 242 total MED per patient during the postoperative period, the equivalent of 32 oxycodone (5 mg) pills. In total, surgeons prescribed 36,273 total MED, the equivalent of 4,836 oxycodone (5 mg) pills. Participants reported using a mean of 116 total MED (48%), or the equivalent of 18 oxycodone (5 mg) pills. We estimate about 145 mg oxycodone pills of leftover medication per patient (Table 2).

Effectiveness of Pain Management and Use of Prescribed Opioid Pain Medication

At follow up, using the Postoperative Pain Scale, 32% of participants rated the effectiveness of their pain relief as complete (10), 36% as high (7–9), 24% as moderate (4–6), 5% as low (1–3), and 3% as ineffective (0). Nearly one quarter (22%) of participants reported that they would have liked more pain treatment than received. For opioid medication taken postoperatively, 13% reported taking 0 total MED, 44% took 1–100 total MED, 24% took 101–200 total MED, and 13% took 201–300 total MED, and

6% took more than 300 total MED over the 10-day period (Figure 2). Of participants taking any opioid analgesic medication, 14% reported taking them more often than prescribed and 10% reported needing an early refill. Most participants (76%) reported that they had pain medication left over; 33% of these participants reported intentions to use a safe means of disposal (e.g., flushing down the toilet, giving to the police), while 48% planned to keep (33%) or continue taking (15%) their medications. The remaining participants with leftover medications reported plans to throw them away (6%) or did not know their plans (5%) (Figure 3).

Associations of Patient Factors with the Amount of Opioids Prescribed and Used

On average, a 10-year increase in patient age was associated with 12 total MED fewer prescribed opioids (p<0.01). Each one-point increase in the preoperative GCPS was associated, on average, with an increase in opioid consumption by 18 total MED (p<0.01), and 5% fewer unused opioids (p=0.03). Prior opioid prescription was associated with an increase in opioid consumption by 55 total MED (p=0.03), and 19% fewer unused opioids (p=0.03). High-risk drug use, on average, trended towards 9% fewer unused opioids (p=0.05) (Table 3).

The following factors were not associated with postoperative prescribing practices: pain severity in last three months (adjusted odds ratio [aOR] 5.49, 95% CI [-9.97, 20.95]); high-risk alcohol use (aOR -20.77, 95% CI [-68.99, 27.45]); high-risk drug use (aOR 15.88, 95% CI [-33.12, 64.89]); and prior opioid prescription (aOR 30.82, 95% CI [-14.25, 75.89]).

DISCUSSION

Principal Findings

In a convenience sample of patients receiving ambulatory surgery at an academic urban safety-net hospital, we found that participants reported well-controlled pain relief postoperatively and, on average, received twice as many opioid analgesics as they consumed postoperatively. Our study corroborates past studies documenting that patients use substantially fewer opioids than prescribed following surgery.[26–30] We extend those findings by prospectively identifying that surgeons do not vary the amount of opioids prescribed based on key baseline characteristics and that these characteristics are associated with postoperative opioid consumption.

Strengths and Limitations

Our study had several limitations. Firstly, the generalizability of this study may be limited because of its relatively small size at a single academic urban safety-net hospital. Secondly, our data about the amount of medication taken and its effectiveness were obtained by patient report; we did not conduct objective tests to ascertain accuracy of self-reported data. Third, we did not differentiate between preexisting pain and pain directly related to the indication for surgery.

Strengths and Weaknesses in Relation to Other Studies

The finding that the total amount of opioids consumed was unrelated to the total amount of opioids prescribed supports the argument that prescribing is directed more so by habitual practices than by patient circumstances. Individual physicians may have prescribing patterns that lead to higher or lower intensity prescribing, which Barnett and colleagues found to predict long-term opioid use.[60] Efforts by systems and groups of surgeons to target postoperative prescribing has markedly decreased prescriptions nationally.[61, 62] Whether this leads to optimized postoperative pain management is the subject of other research studies.

Important Differences and Meaning in the Results

Using analysis of variance (ANOVA) to calculate the variation of portioning of total MED attributable to the specialty level (both between and within specialty) versus the patient level, surgical specialty was found to explain a high proportion of variance of prescribing (data not reported here). The prescribing patterns of these surgeons likely reflect their typical approach to postoperative pain management, which is likely based on their experiences and perceptions of the pain that their patients typically experience postoperatively. Because of the small number of surgeons in each specialty in this study, the findings cannot be generalized to any specific specialty pattern on a large scale. However, it points to the likelihood that the culture in a local department or specialty influences prescribing patterns. In academic medical centers, residents often write the prescriptions and likely learn the types and amounts of medications to prescribe from more senior trainees, which then establishes unofficial but routine and standard prescription practices over time.[59]

Screening for individual patient factors to guide postoperative pain management may assist surgeons in determining appropriate postoperative pain management practices while minimizing the potential harm from opioid medications. These risks include: the development, unmasking, or worsening of substance use disorders; diversion; or overdose. We found that older participants were prescribed fewer opioid medications (lower total MED) compared with younger participants, perhaps reflecting surgeons' adjusted prescribing practices per the susceptibility of older patients to delirium, falls, or other age-related concerns. We observed that higher postoperative opioid consumption was positively correlated with patients' preoperative pain and prior therapeutic opioid use. Not surprisingly, the percentage of unused opioid medications was predicted by patient report of pain severity in the last three months, prior opioid prescriptions, and history of high-risk drug use as detected by the DUDIT. Although certain preoperative risks (e.g., pain severity in the last three months, prior opioid prescription, and high-risk alcohol or drug use) were not associated with postoperative prescribing practices, this may be due to small numbers and low statistical power. The process of identifying such risks could be incorporated into routine preoperative testing.

Participants reported a variety of strategies to handle their leftover medications; one-third reported intentions to dispose of them safely, and more than half indicated plans to keep their medications for potential future use. This latter behavior, while there were

minimal pills remaining for each patient, amounts to a large public health threat with risk for potential diversion or misuse or these leftover medications.[63]

Future Research Directions

Because postoperative opioid prescribing by surgeons remains incompletely studied, this represents an opportunity to test and refine optimal postoperative pain management strategies.[52] Additionally, effective methods to educate patients on safe disposal need to be studied. Patient education could be incorporated into preoperative planning for surgery, along with testing best approaches for possible future implementation. Despite recent policy efforts (i.e., regulations and guidelines) to establish appropriate levels of opioid prescribing, there remains an urgent need to expand surgeon training, establish a systematic preoperative patient screening mechanism for key risk factors, and educate patients and set realistic expectations for postoperative pain management. A comprehensive and systematic approach that employs a robust patient-centered postoperative pain management system to optimize the balance between pain control and opioid prescribing risk management is needed. Future areas for research include development, implementation, and testing of targeted educational materials for patients on appropriate postoperative pain management (i.e., consumption, dosage, storage, and disposal) as well as training and guidelines on postoperative prescribing of opioids and non-opioid alternatives for surgeons.

CONCLUSION

Participants with preoperative history of chronic pain, risky drug use, or prior opioid prescription are more likely to consume higher amounts of opioid medication postoperatively. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties along with targeted patient education and monitoring.

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Table 1: Participant Characteristics (N=149)

Characteristic	
	Mean (SD)
Age (years)	49 (14.8)
	Percent (%)
Female	53.5
Race and ethnicity⁺	
Non-Hispanic White	44.2
Non-Hispanic Black	34.0
Hispanic	15.0
Other	6.8
Education⁺	
High School or Less	31.5
Some College or More	68.5
Annual individual income ≤ $40,000⁺⁺	55.6
Public health insurance	63.3
Pain in last three months (GCPS)⁺	
Highly disabling, highly limiting	24.2
Highly disabling, moderately limiting	17.5
Low-disabling, High intensity	32.2
Low-disabling, Low intensity/No Pain	26.2
Believed surgery would relieve pain⁺	53.9
Surgical specialty	
General	30.7
Urology	18.7
Otolaryngology	13.3
Orthopedic	13.3
Podiatry	10.0
Maxillofacial Oral	8.0
Gynecology	6.0
Prior opioid prescription (< 3 months)	17.3
CAGE-AID-positive	26.7
High-risk alcohol use⁺ (AUDIT)	5.4
Illicit substance use (DUDIT)	18.0

+: ≤10% of data missing

++: >10% of data missing

GCPS: Graded Chronic Pain Scale

PHQ-8: Patient Health Questionnaire depression scale

AUDIT: Alcohol Use Disorders Identification Test

CAGE-AID: CAGE is the acronym of its 4 questions (**C**ut, **A**nnoyed, **G**uilty, **E**ye-opener)

DUDIT: Drug Use Disorders Identification Test

Table 2: Postoperative Opioid Medications Prescribed and Consumed, and Effectiveness of Pain Control (N=149)

Variable	
Opioid medication type prescribed *	**N (%)**
Oxycodone	128 (85.3)
Hydrocodone	7 (4.7)
Hydromorphone	5 (3.3)
Codeine	3 (2.7)
No prescription	8 (5.3)
Effectiveness of pain control, on scale of 0–10 +	
Complete (10)	48 (32.7)
High (7–9)	53 (36.1)
Moderate (4–6)	35 (23.8)
Low (1–3)	7 (4.8)
Ineffective (0)	4 (2.7)
	Mean (SD)**
Total MED prescribed	241.8 (128.1)
Total MED consumed	
Total MED consumed ±	104.2 (112.3)
Total MED unused ^	165.7 (111.8)
*Total MED unused (%)^*	64.2 (40.0)

*Accounts for multiple prescriptions (i.e., does not sum to 100%)

**Total MED: Morphine Equivalent Dose (dose per pill multiplied by total number of pills prescribed)

+: ≤10% of data missing

±: Excludes participants with missing opioid consumption information

^: Excludes participants with no leftover medications

Table 3: Patient Factors Associated with Prescribed, Consumed, and Unused Opioids (Adjusted^ Models)

	Total MED Prescribed (N=150)			Total MED Consumed (N=138)			% of Unused Opioids (N=121)		
Variable	β (se)	p-value	95% CI	β (se)	p-value	95% CI	β (se)	p-value	95% CI
Age (increment per year)	**-1.20 (0.43)**	**0.006****	**-2.05, -0.35**	0.09 (0.66)	0.87	-1.06, 1.25	-0.0004 (0.003)	0.88	-0.006, 0.005
Gender									
Male (ref)	REF	REF	REF	0.00 (0.00)	REF	REF	0.00 (0.00)	REF	REF
Female	-29.31 (16.06)	0.07	-60.79, 2.17	-20.39 (24.57)	0.41	-68.55, 27.77	-0.07 (0.06)	0.22	-0.19, 0.04
Race/Ethnicity									
Non-Hispanic white (ref)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Non-Hispanic black	26.80 (15.22)	0.08	-3.04, 56.63	1.30 (20.84)	0.95	-39.55, 42.15	0.02 (0.06)	0.77	-0.11, 0.14
Hispanic	-21.86 (21.15)	0.30	-63.32, 19.60	-16.00 (23.29)	0.49	-61.65, 29.65	0.01 (0.09)	0.91	-0.16, 0.18
Other	-37.91 (30.45)	0.22	-96.69, 22.67	-12.60 (23.29)	0.66	-68.01, 42.80	-0.20 (0.14)	0.15	-0.48, 0.07
Pain									
Pain severity (last 3 mos.)	5.49 (7.89)	0.49	-9.97, 20.95	**18.22 (5.81)**	**0.002****	**6.84, 29.60**	**-0.05 (0.02)**	**0.03***	**-0.09, -0.005**
Prior opioid prescription	30.82 (22.99)	0.18	-14.25, 75.89	**55.10 (25.37)**	**0.03***	**5.38, 104.82**	**-0.19 (0.08)**	**0.03***	**-0.35, -0.02**
Substance Use									
High-risk alcohol use (AUDIT)	-20.77 (24.60)	0.40	-68.99, 27.45	-17.60 (20.52)	0.39	-57.82, 22.63	-0.09 (0.10)	0.39	-0.20, 0.11
High-risk drug use (DUDIT)	15.88 (25.00)	0.52	-33.12, 64.89	23.84 (21.75)	0.27	-18.79, 66.48	**-0.09 (0.05)**	**0.05***	**-0.19, 0.002**

* significant at α = 0.05 ** significant at α = 0.01 **Bolded text** is significant at at-least α = 0.05

^ All models adjusted for surgical subspecialty

Figures

Figure 1. Study Enrollment and Schema

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

Contribution of Each Individual Author

Author contributions were as follows: 1. **CW Shanahan, MD MPH**: corresponding author, study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, final manuscript editing and preparation, submission to BMJ; 2. **O Reding, MPH**: data cleaning and analytic support, results and analytic review, manuscript editing and preparation; 3. **I Holmdahl, BA**: protocol development, subject recruitment, informed consent, data collection, and cleaning; 4. **J Keosaian, MPH**: protocol development, grant proposal, IRB authorization application and compliance; 5. **Z Xuan, PhD**: study design, biostatistical analytic support; 6. **DB McAneny, MD**: clinical content expert, 7. **M LaRochelle, MD MPH**: results and analytic review, paper preparation, editing; 8. **JM Liebschutz, MD MPH**: study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, paper preparation, final manuscript editing and preparation.

Data sharing statement

Technical appendix, statistical code, and dataset available from corresponding author upon request.

Conflict of Interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: No financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

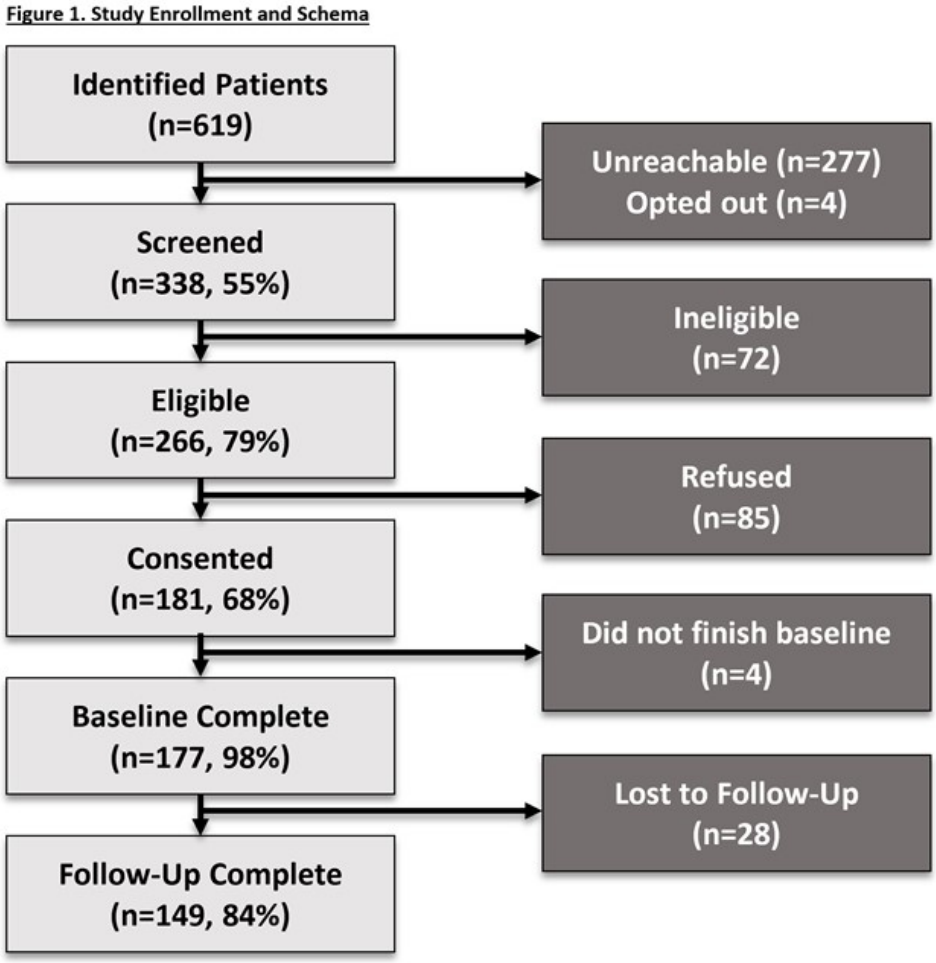

Figure 1. Study Enrollment and Schema

173x177mm (96 x 96 DPI)

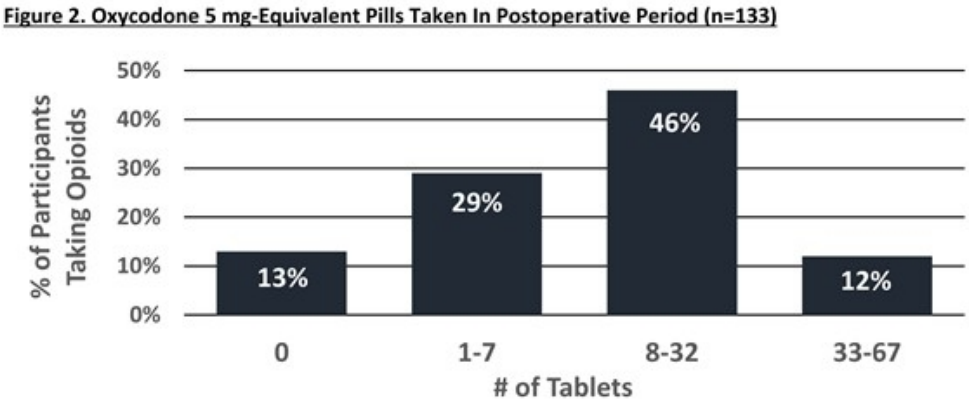

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

152x65mm (96 x 96 DPI)

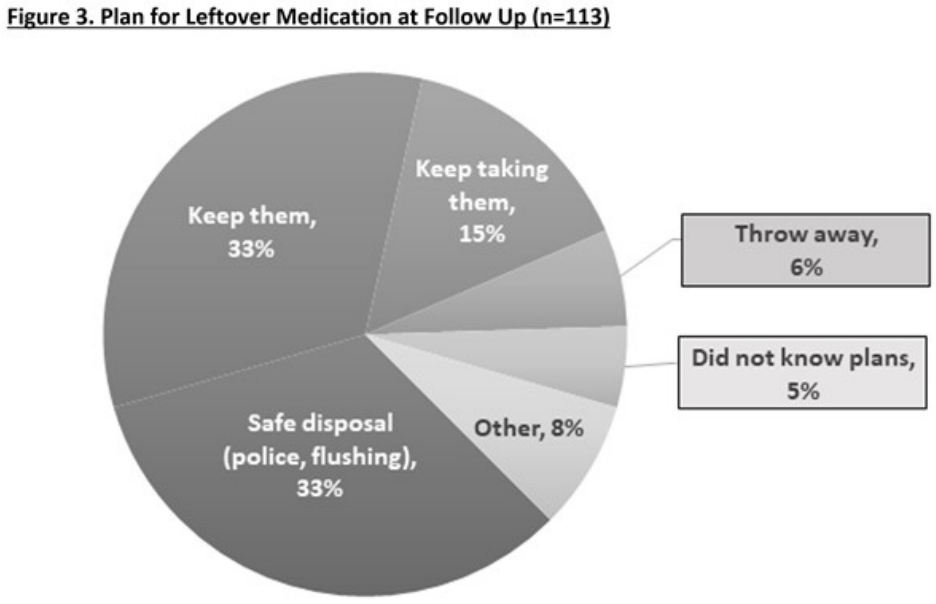

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods	6

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6, 7
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6, 7
Bias	#9	Describe any efforts to address potential sources of bias	4, 6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6, 7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
7			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	6, 7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	
na			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	8, 9

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	Fig. 1.
Participants	#13c	Consider use of a flow diagram	
Fig. 1.			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	17
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
6 , 17			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
6, 17			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
8, 18			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 19
Main results	#16b	Report category boundaries when continuous variables were categorized	19
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
8, 19			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 19

Discussion

Key results	#18	Summarise key results with reference to study objectives	9, 10, 11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	9, 10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10, 11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10, 11
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

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Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

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Primary Subject Heading:	Addiction
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Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

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Key words: Opioid analgesic, Substance Use, Postoperative Pain, Pain Management, Medication Misuse.

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ABSTRACT

Objectives: To prospectively characterize: (1) postoperative opioid analgesic prescribing practices; (2) experience of patients undergoing elective ambulatory surgeries; and (3) impact of patient risk for medication misuse on postoperative pain management.

Design: Longitudinal survey of patients seven days before and seven to 14 days after surgery.

Setting: Academic urban safety-net hospital.

Participants: 181 participants recruited, 18 surgeons, follow-up data from 149 participants (82% retention); 54% female; mean age: 49 years.

Interventions: None.

Primary and secondary outcome measures: Total morphine equivalent dose (MED) prescribed and consumed, percentage of unused opioids.

Results: Surgeons postoperatively prescribed a mean of 242 total MED per patient, equivalent to 32 oxycodone (5 mg) pills. Participants used a mean of 116 MEDs (48%), equivalent to 18 oxycodone (5 mg) pills (~145 mg of oxycodone remaining per patient). A 10-year increase in patient age was associated with 12 (95% CI [-2.05, -0.35]) total MED fewer prescribed opioids. Each one-point increase in the preoperative Graded Chronic Pain Scale was associated with an 18 (6.84, 29.60) total MED increase in opioid consumption, and 5% (-0.09, -0.005) fewer unused opioids. Prior opioid prescription was associated with a 55 (5.38, -104.82) total MED increase in opioid consumption, and 19% (-0.35, -0.02) fewer unused opioids. High-risk drug use was associated with 9% (-0.19, 0.002) fewer unused opioids. Pain severity in previous three months, high-risk alcohol use, and prior opioid prescription were not associated with postoperative prescribing practices.

Conclusions: Participants with preoperative history of chronic pain, prior opioid prescription, and high-risk drug use were more likely to consume higher amounts of opioid medications postoperatively. Additionally, surgeons did not incorporate key patient-level factors (e.g., substance use, preoperative pain) into opioid prescribing practices. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties, and patient education and monitoring.

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ARTICLE SUMMARY (Strengths and limitations of this study)

The strengths of this study included:

1. We executed the study in a real-life setting and gave no guidance to prescribing surgeons about the study objectives.
2. We studied the postoperative pain management strategies across a variety of surgical subspecialties, surgeons, and procedures.

The limitations of this study included:

1. Generalizability of this study may be limited because of the study's small size at a single academic urban safety-net hospital.
2. We did not validate accuracy of self-reported data on preexisting and postoperative pain and medication taken.
3. We did not collect data on long-term outcomes (e.g., continuation of opioid-based pain treatment, opioid medication misuse, diagnosis or recurrence of opioid use disorder).

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INTRODUCTION

Prescription opioid misuse is a major public health problem. Therapeutically prescribed opioid analgesics constitute the single largest source of misused opioids, and opioid prescribing by physicians increased dramatically from the late 1990s until the mid-2010s when it began to level off.[1–4] Opioid analgesics prescribed for postoperative and acute pain management can lead to patients' long-term opioid use,[5–12] which may be associated with development of opioid use disorder and other opioid medication adverse events.[12–23]

In addition to inducing long-term use and potential addiction, unused opioid pills prescribed for surgical procedures are available for misuse by the patient, friends, or family. In fact, most individuals who misuse opioids obtain them from friends or family.[24, 25] Numerous studies have found that a majority of patients report having unused or unfilled prescriptions postoperatively.[26–30] Wide variations in opioid prescribing for the same procedure also support the concept that postoperative opioid prescribing is not evidence-based and may result in excess opioid prescribing with unknown benefits in pain outcomes.[31]

In a national survey of adults prescribed opioids, nearly half reported having no recollection of receiving information on safe medication storage or disposal.[32] Among those with leftover medications, 62% reported keeping them for future use.[33–35] Bicket and colleagues (2017) performed a systematic review of unused opioid analgesics postoperatively and found that 67–97% of patients report unused opioids, with 42–71% of prescribed opioid tablets remaining unused.[26] Furthermore, two prior studies that examine storage of excess medications found that a minority of patients stored the medications in safe manner, and even fewer planned to dispose of unused medications using U.S. Food and Drug Administration (FDA)-recommended methods.[23, 24]

Patient-associated factors may potentially impact surgeons' postoperative prescribing practices, as well as patients' opioid medication-taking behaviors. A history of chronic pain is associated with more opioid medication use postoperatively.[36–39] There is also evidence of racial and ethnic disparities in opioid prescribing (e.g., black race has been shown to be associated with fewer opioids prescribed compared to white race).[40] A history of chronic opioid use is associated with greater postoperative opioid use.[41, 42] Opioid-tolerant patients require longer durations of higher dosage of postoperative opioid use to achieve the same level of pain relief as non-opioid-tolerant patients taking opioids postoperatively.[43, 44] Patients reporting depression are more likely to use opioids postoperatively in an non-prescribed manner,[45, 46] and anxiety is associated with prolonged postoperative opioid usage.[44] Moreover, little is known about if, what, and to what degree patient-associated factors impact surgeons' postoperative prescribing practices.

Using data collected prospectively from patients undergoing elective ambulatory surgery, we analyzed the associations between participants' sociodemographic factors, high-risk substance use, and chronic pain on (1) surgeons' opioid prescribing patterns, (2) participants' plans for postoperative opioid use, and (3) plans for remaining opioid

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disposal. To assess potential risk factors for postoperative medication misuse and look for correlations with surgeons' postoperative pain prescribing practices, we collected preoperative data on participants' baseline mental health status, prior prescription opioid use, and high-risk substance use.

METHODS

Study Design

This was a one-year, prospective study of surgeons' postoperative opioid prescribing practices for participants undergoing elective ambulatory surgery in Spring 2015. A study research assistant (RA) assessed participants over the phone or in person in the seven days leading up to the scheduled surgery. Follow-up assessment occurred between seven and 14 days postoperatively via telephone.

Ethical Approval Statement

The Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB) approved Study (Optimizing Opioid Prescribing in Ambulatory Surgery) Protocol Number: H-33147.

Patient and Public Involvement Statement

Patients were first involved in the research when recruited and informed verbally about the details of the study. Research questions and outcome measures were developed by several members of the research team (CWS, JML, OR, IH, DM). These questions and measures were informed by team members' priorities, experience, and preferences. Patients and the public were indirectly involved in the design of this study through careful monitoring of the issues and challenges associated with their recent surgeries and, when appropriate, specific questions were fashioned to optimally characterize their concerns. Patients were contacted and introduced to the study research assistant by the recruiting physician during their medical visits. Patients were provided a brief overview of the study; if they were interested in participating, they were referred to the study research assistant to receive more verbal information about the study. If interested, the patients underwent a formal informed consent process as previously approved by the Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB). Once consented, patients were enrolled into the study. As part of the study, participants were informed about the degree of burden of the intervention and time required to participate in the research. Participants were not involved in our wider plan to disseminate the study results to participants and relevant wider patient communities.

The purpose of this study was to pilot a procedure intended to recruit a larger number of subjects for use in a larger program of research. Simultaneously, we used other data gathered from this investigation to establish power calculations for a later and larger full-scale study. We have also used this work to evaluate the financial, technical, administrative, and logistic feasibility of a full-scale study, including issues of data collection, protocol adherence, and questionnaire design. The sample size was based

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on and justified by these results. This article will inform the probable impact that the pilot study will have on future research decisions.

Sample

The recruitment process began with identifying ambulatory procedures that were most likely to generate at least moderate postoperative pain (identified by D. McAneny) to increase the likelihood that patients would likely be considered for receipt of postoperative opioid medication treatment. We excluded cancer-related procedures and those not expected to generate significant postoperative pain (e.g., endoscopy). Next, we identified and recruited 18 surgeons among nine selected surgical specialties (colorectal surgery, general surgery, gynecology, oral surgery, orthopedic surgery, otolaryngology, podiatry, trauma, and urology) from a single academic urban safety-net hospital (see Table 1) because they typically performed these moderate to severely painful procedures. All surgeons agreed to participate in the study. To reduce selection bias, surgeons only received a broad background of the study (i.e., that participants would be interviewed about their pre- and postoperative pain management).

We then identified potential participants via their electronic health records (EHRs). An RA generated a list of patients who were scheduled to have elective surgery in predesignated categories between 14 and 23 days in the future; thus, this was a convenience sample of patients who planned to undergo ambulatory procedures expected to generate at least moderate postoperative pain. Eligibility criteria were: age 18 to 89 years, English comprehension, an active telephone line in the EHR, and availability to complete a follow-up telephone interview two weeks after surgery. We generated a personalized study introduction letter for each patient. Each surgeon was asked to remove patients from potential study participation that they judged would not be able to comply with the study procedures due to cognitive or language abilities (i.e., understanding of English). The surgeon signed the letter for each approved patient before the study team mailed it to the patient. This process and surgeons' limited information about the study enabled them to efficiently remove any patients they did not feel would be appropriate for the study without bias.

The letter patients' received included a high-level description of the study, indicating that each participant would be interviewed as to his or her pre-and postoperative pain management for the identified surgery. The letter also included an "opt-out" choice that required the participant to call the study team one week before the planned surgery to avoid undesired contact. To capture postoperative pain management practices, the letter included a study brochure and a "pain diary," which the participant was advised to use to record pain, prescription medicine use, and over-the-counter medicine use during the 10 days after the surgery if he or she was eventually enrolled in the study.

Starting seven days before planned surgical procedures, the RA contacted patients to obtain their consent to participate in the study and administer the baseline assessment. The consent form also included a brief description of the study's purpose; specifically, "The goal of this study is to learn how surgeons prescribe pain medications and how patients use them after surgery." The RA reminded participants to fill out the pain diary

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to improve recall and accuracy at the follow-up assessment. The RA collected follow-up data over the phone between seven and 14 days postoperatively using an interviewer-administered questionnaire.

Data Collection

Preoperative baseline patient-reported data included: demographics (age, gender, race/ethnicity); chronic pain severity and function in the past three months per the Graded Chronic Pain Scale's (GCPS's) standard categories of disability, intensity, and functional limitations; and high-risk alcohol and drug use (Alcohol Use Disorders Identification Test [AUDIT] and Drug Use Disorders Identification Test [DUDIT], respectively).[47–49] Postoperative patient reported data included: postoperative pain via a postoperative pain scale with a 0 (no pain relief) to 10 (complete pain relief) scale, adapted from Albi-Feldzer, et al (2013);[50–53] Timeline-Follow-Back (TLFB) of total opioids consumed and pain rating on each day; prescription opioid misuse via the Prescription Opioid Misuse Index (POMI)[54] and Prescription Misuse Questionnaire (PMQ);[55] substance use since surgery; and intentions for leftover medication storage and disposal (concepts based on Winstock et al, 2007).[56] In addition, participants verified pain medication data extracted from the EHR.

EHR data included date of surgery, surgery type, and detailed opioid prescriptions, as well as any history of opioid prescription prior to surgery. To determine the total amount of opioid medications prescribed at the time of surgery, we calculated a total morphine equivalent dose (total MED) for all prescribed opioid medications as the number of pills multiplied by the MED of the opioid.[57]

Dependent Variable

The dependent variables for this analysis included: (1) amount of opioid analgesic medications prescribed for postoperative pain management as calculated by total MED (source: EHR); (2) opioids consumed over the 10-day postoperative period (total MED) (source: TLFB); and (3) percent of unused opioids after the 10-day postoperative period (sources: EHR and TLFB). We obtained the percent of unused opioids by subtracting reported total MED consumed from total MED prescribed for each participant, then divided by total MED prescribed. We converted opioid amounts from total MED back to oxycodone-equivalent 5 mg pills to make the data more clinically accessible. We used the highest possible dose interpretable when surgeons prescribed a dosing range for these analyses.

Independent Variable

Independent variables included age, gender, race/ethnicity (white, black, and "other" [i.e., mixed race/ethnicity]), and high-risk alcohol and drug use in the past month (AUDIT score greater than 15, DUDIT score greater than 9).

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Analysis

We included only participants for whom we had follow-up data in this analysis. The available number of patients recruited from 18 surgeons during the study period determined the size of this convenience sample. Two-sided type-I error rates of 0.05 along with 95% confidence intervals were used to assess the statistical significance of associations. We used multivariable linear regression, adjusted for surgical specialty as fixed effects, to analyze associations of sociodemographics, chronic pain, and high-risk substance use with all outcomes. We calculated intraclass correlations to partition variance in each outcome attributable to surgical specialties.

RESULTS

Population and Demographics

We enrolled 181 participants in the study and analyzed data on the 149 participants who completed follow-up assessments (see Figure 1 for study enrollment schema). The participants were 54% female, 44% white, 34% black, and 22% “other” (i.e., mixed race/ethnicity). The mean age was 49 years, and 69% of participants had some postsecondary education (Table 1).

Participants’ Pain, Substance Use, and Mental Health

At baseline, 24% of participants had highly disabling and severely limiting pain; 18% had highly disabling and moderately limiting pain; 32% had low-disabling and highly intense pain; and 26% reported low-disabling and low-intensity pain or no pain. At baseline, 5% of participants indicated high-risk alcohol use including dependence (AUDIT), and 18% reported use of illegal drugs or prescribed drugs for nonmedical reasons (DUDIT) (Table 1).

Surgeon’s Postoperative Prescribing Practices

Surgeons prescribed opioids for postoperative pain to 95% of participants; 85% of these participants received either oxycodone or oxycodone with acetaminophen. Surgeons prescribed a mean of 242 total MED per patient during the postoperative period, the equivalent of 32 oxycodone (5 mg) pills. In total, surgeons prescribed 36,273 total MED, the equivalent of 4,836 oxycodone (5 mg) pills. Participants reported using a mean of 116 total MED (48%), or the equivalent of 18 oxycodone (5 mg) pills. We estimate about 145 mg oxycodone pills of leftover medication per patient (Table 2). Non-opioid medication prescription and use were not the focus of this study; therefore, we did not analyze this domain as part of this pilot study.

Effectiveness of Pain Management and Use of Prescribed Opioid Pain Medication

At follow up, using the Postoperative Pain Scale, 32% of participants rated the effectiveness of their pain relief as complete (10), 36% as high (7–9), 24% as moderate (4–6), 5% as low (1–3), and 3% as ineffective (0). Nearly one quarter (22%) of participants reported that they would have liked more pain treatment than received. For

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opioid medication taken postoperatively, 13% reported taking 0 total MED, 44% took 1–100 total MED, 24% took 101–200 total MED, and 13% took 201–300 total MED, and 6% took more than 300 total MED over the 10-day period (Figure 2). Of participants taking any opioid analgesic medication, 14% reported taking them more often than prescribed and 10% reported needing an early refill. Most participants (76%) reported that they had pain medication left over; 33% of these participants reported intentions to use a safe means of disposal (e.g., flushing down the toilet, giving to the police), while 48% planned to keep (33%) or continue taking (15%) their medications. The remaining participants with leftover medications reported plans to throw them away (6%) or did not know their plans (5%) (Figure 3).

Associations of Patient Factors with Amount of Opioids Prescribed and Used

On average, a 10-year increase in patient age was associated with 12 total MED fewer prescribed opioids ($p<0.01$). Each one-point increase in the preoperative GCPS was associated, on average, with an increase in opioid consumption by 18 total MED ($p<0.01$), and 5% fewer unused opioids ($p=0.03$). Prior opioid prescription was associated with an increase in opioid consumption by 55 total MED ($p=0.03$), and 19% fewer unused opioids ($p=0.03$). High-risk drug use, on average, was associated with 9% fewer unused opioids ($p=0.05$) (Table 3).

The following factors were not associated with postoperative prescribing practices: pain severity in last three months (adjusted odds ratio [aOR] 5.49, 95% CI [-9.97, 20.95]); high-risk alcohol use (aOR -20.77, 95% CI [-68.99, 27.45]); high-risk drug use (aOR 15.88, 95% CI [-33.12, 64.89]); and prior opioid prescription (aOR 30.82, 95% CI [-14.25, 75.89]).

DISCUSSION

Principal Findings

In a convenience sample of patients receiving ambulatory surgery at an academic urban safety-net hospital, we found that participants reported well-controlled pain relief postoperatively and, on average, received twice as many opioid analgesics as they consumed postoperatively. Our study corroborates past studies documenting that patients use substantially fewer opioids than prescribed following surgery.[26–30] We extend those findings by prospectively identifying that surgeons do not vary the amount of opioids prescribed on the basis of key baseline characteristics and that these characteristics are associated with postoperative opioid consumption.

Limitations and Strengths

Our pilot study had several limitations. First, the generalizability of this study may be limited because of (1) its relatively small size at a single academic urban safety-net hospital, (2) the small proportion of individuals that completed follow-up assessments (see Figure 1), and (3) the high proportion of participants who reported chronic pain prior to the surgery. Second, our data about the amount of medication taken and its

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effectiveness were obtained by patient report; we did not conduct objective tests to ascertain accuracy of self-reported data. Third, we did not differentiate between preexisting pain and pain directly related to the indication for surgery. Last, we have no long-term data to determine what percentage of patients continued to receive long-term opioid-based pain treatment (either new or part of a continuation of preoperative chronic pain management with opioid medications), exhibited opioid medication misuse, or developed a diagnosis or reoccurrence of opioid use disorder.

Using analysis of variance (ANOVA) to calculate the variation of portioning of total MED attributable to the specialty level (both between and within specialty) versus the patient level, surgical specialty was found to explain a high proportion of variance of prescribing (data not reported here). The prescribing patterns of these surgeons likely reflect their typical approach to postoperative pain management, which is likely based on their experiences and perceptions of the pain that their patients typically experience postoperatively. Because of the small number of surgeons in each specialty in this study, the findings cannot be generalized to any specific specialty pattern on a large scale. However, it points to the likelihood that the culture in a local department or specialty influences prescribing patterns. In academic medical centers, residents often write the prescriptions and likely learn the types and amounts of medications to prescribe from more senior trainees, which then establishes unofficial but routine and standard prescription practices over time.[5]

Strengths and Weaknesses in Relation to Other Studies

The finding that the total amount of opioids consumed was unrelated to the total amount of opioids prescribed supports the argument that prescribing is directed more so by habitual practices than by patient circumstances. Individual physicians may have prescribing patterns that lead to higher or lower intensity prescribing, which Barnett and colleagues found to predict long-term opioid use.[58] Efforts by systems and groups of surgeons to target postoperative prescribing has markedly decreased prescriptions nationally.[59, 60] Whether this leads to optimized postoperative pain management is the subject of other research studies.

Important Differences and Meaning in the Results

Screening for individual patient factors to guide postoperative pain management may assist surgeons in determining appropriate postoperative pain management practices while minimizing the potential harm from opioid medications. These risks include; the development, unmasking, or worsening of substance use disorders; diversion; or overdose. We found that older participants were prescribed fewer opioid medications (lower total MED) compared with younger participants, perhaps reflecting surgeons' adjusted prescribing practices per the susceptibility of older patients to delirium, falls, or other age-related concerns. We observed that higher postoperative opioid consumption was positively correlated with patients' preoperative pain and prior therapeutic opioid use. Not surprisingly, the percentage of unused opioid medications was predicted by patient report of pain severity in the last three months, prior opioid prescriptions, and history of high-risk drug use as detected by the DUDIT. Although certain preoperative

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risks (e.g., pain severity in the last three months, prior opioid prescription, and high-risk alcohol or drug use) were not associated with postoperative prescribing practices, this may be due to small numbers, low statistical power, and the heterogeneity of the sample. The process of identifying such risks could be incorporated into routine preoperative testing.

Participants reported a variety of strategies to handle their leftover medications; one-third reported intentions to dispose of them safely, and more than half indicated plans to keep their medications for potential future use. This latter behavior, while there were minimal pills remaining for each patient, amounts to a large public health threat with risk for potential diversion or misuse or these leftover medications.[61]

Future Research Directions

As the aim of this pilot study was to generate hypotheses, we envision the results from this convenience sample as informative of future research endeavors. Because postoperative opioid prescribing by surgeons remains incompletely studied, this pilot study represents an opportunity to test and refine optimal postoperative pain management strategies.[52] Additionally, effective methods to educate patients on safe disposal need to be studied. Patient education could be incorporated into preoperative planning for surgery, along with testing best approaches for possible future implementation. Despite recent policy efforts (i.e., regulations and guidelines) to establish appropriate levels of opioid prescribing, there remains an urgent need to expand surgeon training, establish a systematic preoperative patient screening mechanism for key risk factors, and educate patients and set realistic expectations for postoperative pain management. A comprehensive and systematic approach that employs a robust patient-centered pre- and postoperative pain management system to optimize the balance between pain control and opioid prescribing risk management is needed. Future areas for research include further investigation into the associations between preoperative behavioral health factors (e.g., anxiety, depression, substance use disorder, other social determinants of health); development, implementation, and testing of targeted educational materials for patients on appropriate postoperative pain management (i.e., consumption, dosage, storage, and disposal); and training, guidelines, and screening tools for comprehensive preoperative risk evaluation and preparation and postoperative prescribing of opioids and non-opioid alternatives for surgeons. Use of EHR-based clinical decision support tools for determining pain management approaches is another area of interest for future research. For example, surgeons and anesthesiologists use frailty assessments (e.g., Clinical Frailty Scale) to preoperatively assess elderly patients and develop appropriate postoperative pain management plans.[62] Given the increased use of such tools with corresponding technological advances (e.g., machine learning, artificial intelligence), it is important to understand the value of these tools in effectively guiding surgeons' prescribing and pain management practices.

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CONCLUSION

Participants with preoperative history of chronic pain, prior opioid prescription, or history of high-risk drug use were more likely to consume higher amounts of opioid medications postoperatively. Additionally, surgeons did not appear to incorporate key patient-level factors (e.g., substance use, preoperative pain) into opioid prescribing practices. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties along with targeted patient education and monitoring.

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Table 1: Participant Characteristics (N=149)

Characteristic	
	Mean (SD)
Age (years)	49 (14.8)
	Percent (%)
Female	53.5
Race and ethnicity⁺	
Non-Hispanic White	44.2
Non-Hispanic Black	34.0
Hispanic	15.0
Other	6.8
Education⁺	
High School or Less	31.5
Some College or More	68.5
Annual individual income ≤ $40,000⁺⁺	55.6
Public health insurance	63.3
Pain in last three months (GCPS)⁺	
Highly disabling, highly limiting	24.2
Highly disabling, moderately limiting	17.5
Low-disabling, High intensity	32.2
Low-disabling, Low intensity/No Pain	26.2
Believed surgery would relieve pain⁺	53.9
Surgical specialty	
General	30.7
Urology	18.7
Otolaryngology	13.3
Orthopedic	13.3
Podiatry	10.0
Maxillofacial Oral	8.0
Gynecology	6.0
Prior opioid prescription (< 3 months)	17.3
CAGE-AID-positive	26.7
High-risk alcohol use⁺ (AUDIT)	5.4
Illicit substance use (DUDIT)	18.0

+: ≤10% of data missing

++: >10% of data missing

GCPS: Graded Chronic Pain Scale

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PHQ-8: Patient Health Questionnaire depression scale

AUDIT: Alcohol Use Disorders Identification Test

CAGE-AID: CAGE is the acronym of its 4 questions (**C**ut, **A**nnoyed, **G**uilty, **E**ye-opener)

DUDIT: Drug Use Disorders Identification Test

Table 2: Postoperative Opioid Medications Prescribed and Consumed, and Effectiveness of Pain Control (N=149)

Variable	
Opioid medication type prescribed *	**N (%)**
Oxycodone	128 (85.3)
Hydrocodone	7 (4.7)
Hydromorphone	5 (3.3)
Codeine	3 (2.7)
No prescription	8 (5.3)
Effectiveness of pain control, on scale of 0–10 +	
Complete (10)	48 (32.7)
High (7–9)	53 (36.1)
Moderate (4–6)	35 (23.8)
Low (1–3)	7 (4.8)
Ineffective (0)	4 (2.7)
	Mean (SD)**
Total MED prescribed	241.8 (128.1)
Total MED consumed	
Total MED consumed ±	104.2 (112.3)
Total MED unused ^	165.7 (111.8)
*Total MED unused (%)^*	64.2 (40.0)

*Accounts for multiple prescriptions (i.e., does not sum to 100%)

**Total MED: Morphine Equivalent Dose (dose per pill multiplied by total number of pills prescribed)

+: ≤10% of data missing

±: Excludes participants with missing opioid consumption information

^: Excludes participants with no leftover medications

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Table 3: Patient Factors Associated with Prescribed, Consumed, and Unused Opioids (Adjusted^ Models)

	Total MED Prescribed (N=150)			Total MED Consumed (N=138)			% of Unused Opioids (N=121)		
Variable	β (se)	p-value	95% CI	β (se)	p-value	95% CI	β (se)	p-value	95% CI
Age (increment per year)	**-1.20 (0.43)**	**0.006****	**-2.05, -0.35**	0.09 (0.66)	0.87	-1.06, 1.25	-0.0004 (0.003)	0.88	-0.006, 0.005
Gender									
Male (ref)	REF	REF	REF	0.00 (0.00)	REF	REF	0.00 (0.00)	REF	REF
Female	-29.31 (16.06)	0.07	-60.79, 2.17	-20.39 (24.57)	0.41	-68.55, 27.77	-0.07 (0.06)	0.22	-0.19, 0.04
Race/Ethnicity									
Non-Hispanic white (ref)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Non-Hispanic black	26.80 (15.22)	0.08	-3.04, 56.63	1.30 (20.84)	0.95	-39.55, 42.15	0.02 (0.06)	0.77	-0.11, 0.14
Hispanic	-21.86 (21.15)	0.30	-63.32, 19.60	-16.00 (23.29)	0.49	-61.65, 29.65	0.01 (0.09)	0.91	-0.16, 0.18
Other	-37.91 (30.45)	0.22	-96.69, 22.67	-12.60 (23.29)	0.66	-68.01, 42.80	-0.21 (0.14)	0.15	-0.48, 0.07
Pain									
Pain severity (last 3 mos.)	5.49 (7.89)	0.49	-9.97, 20.95	**18.22 (5.81)**	**0.002****	**6.84, 29.60**	**-0.05 (0.02)**	**0.03***	**-0.09, -0.005**
Prior opioid prescription	30.82 (22.99)	0.18	-14.25, 75.89	**55.10 (25.37)**	**0.03***	**5.38, 104.82**	**-0.19 (0.08)**	**0.03***	**-0.35, -0.02**
Substance Use									
High-risk alcohol use (AUDIT)	-20.77 (24.60)	0.40	-68.99, 27.45	-17.60 (20.52)	0.39	-57.82, 22.63	-0.09 (0.10)	0.39	-0.20, 0.11
High-risk drug use (DUDIT)	15.88 (25.00)	0.52	-33.12, 64.89	23.84 (21.75)	0.27	-18.79, 66.48	**-0.09 (0.05)**	**0.05***	**-0.19, 0.002**

* significant at α = 0.05 ** significant at α = 0.01 **Bolded text** is significant at at least α = 0.05

^ All models adjusted for surgical subspecialty

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Contribution of Each Individual Author

Author contributions were as follows: 1. **CW Shanahan, MD MPH**: corresponding author, study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, final manuscript editing and preparation, submission to BMJ; 2. **O Reding, MPH**: data cleaning and analytic support, results and analytic review, manuscript editing and preparation; 3. **I Holmdahl, BA**: protocol development, subject recruitment, informed consent, data collection, and cleaning; 4. **J Keosaian, MPH**: protocol development, grant proposal, IRB authorization application and compliance; 5. **Z Xuan, PhD**: study design, biostatistical analytic support; 6. **DB McAneny, MD**: clinical content expert, 7. **M LaRochelle, MD MPH**: results and analytic review, paper preparation, editing; 8. **JM Liebschutz, MD MPH**: study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, paper preparation, final manuscript editing and preparation.

Data sharing statement

Technical appendix, statistical code, and dataset available from corresponding author upon request.

Figure captions

Figure 1. Study Enrollment and Schema

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

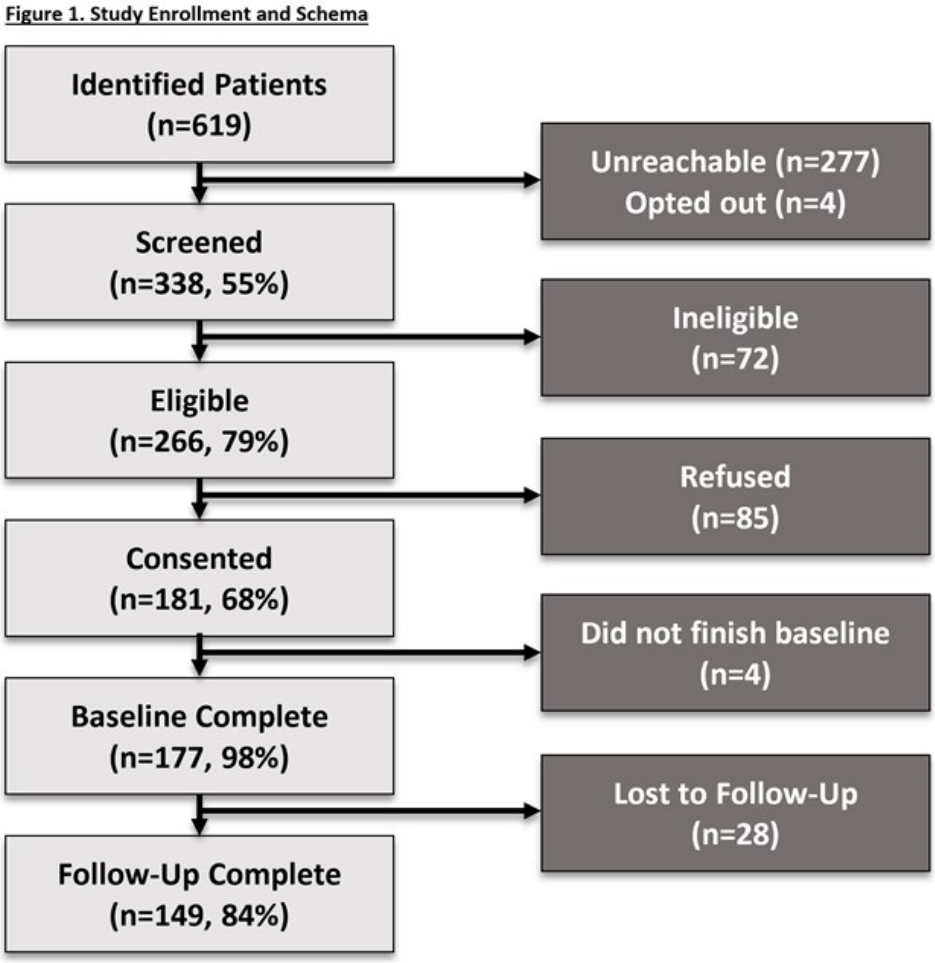

Figure 1. Study Enrollment and Schema

173x177mm (96 x 96 DPI)

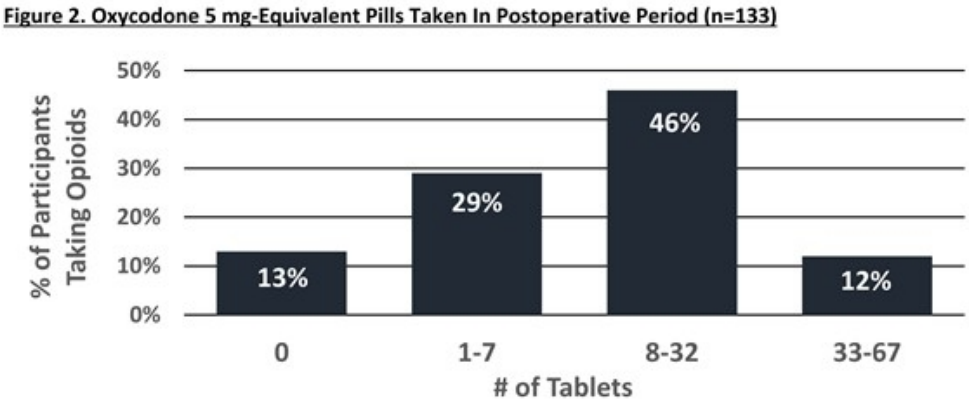

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

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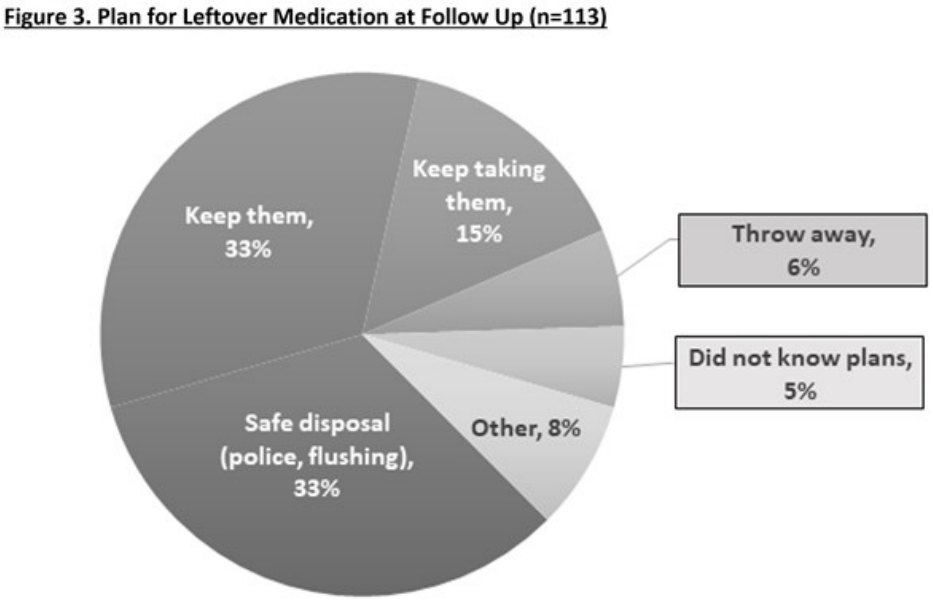

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

166x108mm (96 x 96 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P. 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P. 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	PP. 4–5
Methods			
Study design	4	Present key elements of study design early in the paper	P. 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	PP. 5–7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	PP. 5–7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P. 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P. 7
Bias	9	Describe any efforts to address potential sources of bias	P. 6
Study size	10	Explain how the study size was arrived at	PP. 6, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	PP. 7–8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P. 8
		(*b*) Describe any methods used to examine subgroups and interactions	PP. 8–9
		(*c*) Explain how missing data were addressed	P. 8

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P. 8
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P. 8
		(b) Give reasons for non-participation at each stage	P. 6; Figure 1, P. TBD
		(c) Consider use of a flow diagram	Figure 1, P. TBD
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, P.18
		(b) Indicate number of participants with missing data for each variable of interest	P. 8; Table 1, P. 18
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	PP. 6–7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	PP. 8–9; Table 1, P. 18
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	PP. 8–9; Table 2, P. 19
		(*b*) Report category boundaries when continuous variables were categorized	PP. 8–9; Table 3, P. 20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3, P. 20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P. 9; Table 3, P. 20
Discussion			
Key results	18	Summarise key results with reference to study objectives	P. 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	PP. 9–10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	PP. 9–11
Generalisability	21	Discuss the generalisability (external validity) of the study results	PP. 10–11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P. 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Surgery
Keywords:	GENERAL MEDICINE (see Internal Medicine), PUBLIC HEALTH, Substance misuse < PSYCHIATRY, SURGERY, PAIN MANAGEMENT

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Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

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Key words: Opioid analgesic, Substance Use, Postoperative Pain, Pain Management, Medication Misuse.

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ABSTRACT

Objectives: To prospectively characterize: (1) postoperative opioid analgesic prescribing practices; (2) experience of patients undergoing elective ambulatory surgeries; and (3) impact of patient risk for medication misuse on postoperative pain management.

Design: Longitudinal survey of patients seven days before and seven to 14 days after surgery.

Setting: Academic urban safety-net hospital.

Participants: 181 participants recruited, 18 surgeons, follow-up data from 149 participants (82% retention); 54% female; mean age: 49 years.

Interventions: None.

Primary and secondary outcome measures: Total morphine equivalent dose (MED) prescribed and consumed, percentage of unused opioids.

Results: Surgeons postoperatively prescribed a mean of 242 total MED per patient, equivalent to 32 oxycodone (5 mg) pills. Participants used a mean of 116 MEDs (48%), equivalent to 18 oxycodone (5 mg) pills (~145 mg of oxycodone remaining per patient). A 10-year increase in patient age was associated with 12 (95% CI [-2.05, -0.35]) total MED fewer prescribed opioids. Each one-point increase in the preoperative Graded Chronic Pain Scale was associated with an 18 (6.84, 29.60) total MED increase in opioid consumption, and 5% (-0.09, -0.005) fewer unused opioids. Prior opioid prescription was associated with a 55 (5.38, -104.82) total MED increase in opioid consumption, and 19% (-0.35, -0.02) fewer unused opioids. High-risk drug use was associated with 9% (-0.19, 0.002) fewer unused opioids. Pain severity in previous three months, high-risk alcohol use, and prior opioid prescription were not associated with postoperative prescribing practices.

Conclusions: Participants with preoperative history of chronic pain, prior opioid prescription, and high-risk drug use were more likely to consume higher amounts of opioid medications postoperatively. Additionally, surgeons did not incorporate key patient-level factors (e.g., substance use, preoperative pain) into opioid prescribing practices. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties, and patient education and monitoring.

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ARTICLE SUMMARY (Strengths and limitations of this study)

1. We executed the study in a real-life setting and gave no guidance to prescribing surgeons about the study objectives.
2. We studied the postoperative pain management strategies across a variety of surgical subspecialties, surgeons, and procedures.
3. Generalizability of this study may be limited because of the study's small size at a single academic urban safety-net hospital.
4. We did not validate accuracy of self-reported data on preexisting and postoperative pain and medication taken.
5. We did not collect data on long-term outcomes (e.g., continuation of opioid-based pain treatment, opioid medication misuse, diagnosis or recurrence of opioid use disorder).

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INTRODUCTION

Prescription opioid misuse is a major public health problem. Therapeutically prescribed opioid analgesics constitute the single largest source of misused opioids, and opioid prescribing by physicians increased dramatically from the late 1990s until the mid-2010s when it began to level off.[1–4] Opioid analgesics prescribed for postoperative and acute pain management can lead to patients' long-term opioid use,[5–12] which may be associated with development of opioid use disorder and other opioid medication adverse events.[12–23]

In addition to inducing long-term use and potential addiction, unused opioid pills prescribed for surgical procedures are available for misuse by the patient, friends, or family. In fact, most individuals who misuse opioids obtain them from friends or family.[24, 25] Numerous studies have found that a majority of patients report having unused or unfilled prescriptions postoperatively.[26–30] Wide variations in opioid prescribing for the same procedure also support the concept that postoperative opioid prescribing is not evidence-based and may result in excess opioid prescribing with unknown benefits in pain outcomes.[31]

In a national survey of adults prescribed opioids, nearly half reported having no recollection of receiving information on safe medication storage or disposal.[32] Among those with leftover medications, 62% reported keeping them for future use.[33–35] Bicket and colleagues (2017) performed a systematic review of unused opioid analgesics postoperatively and found that 67–97% of patients report unused opioids, with 42–71% of prescribed opioid tablets remaining unused.[26] Furthermore, two prior studies that examine storage of excess medications found that a minority of patients stored the medications in safe manner, and even fewer planned to dispose of unused medications using U.S. Food and Drug Administration (FDA)-recommended methods.[23, 24]

Patient-associated factors may potentially impact surgeons' postoperative prescribing practices, as well as patients' opioid medication-taking behaviors. A history of chronic pain is associated with more opioid medication use postoperatively.[36–39] There is also evidence of racial and ethnic disparities in opioid prescribing (e.g., black race has been shown to be associated with fewer opioids prescribed compared to white race).[40] A history of chronic opioid use is associated with greater postoperative opioid use.[41, 42] Opioid-tolerant patients require longer durations of higher dosage of postoperative opioid use to achieve the same level of pain relief as non-opioid-tolerant patients taking opioids postoperatively.[43, 44] Patients reporting depression are more likely to use opioids postoperatively in an non-prescribed manner,[45, 46] and anxiety is associated with prolonged postoperative opioid usage.[44] Moreover, little is known about if, what, and to what degree patient-associated factors impact surgeons' postoperative prescribing practices.

Using data collected prospectively from patients undergoing elective ambulatory surgery, we analyzed the associations between participants' sociodemographic factors, high-risk substance use, and chronic pain on (1) surgeons' opioid prescribing patterns, (2) participants' plans for postoperative opioid use, and (3) plans for remaining opioid

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disposal. To assess potential risk factors for postoperative medication misuse and look for correlations with surgeons' postoperative pain prescribing practices, we collected preoperative data on participants' baseline mental health status, prior prescription opioid use, and high-risk substance use.

METHODS

Study Design

This was a one-year, prospective study of surgeons' postoperative opioid prescribing practices for participants undergoing elective ambulatory surgery in Spring 2015. A study research assistant (RA) assessed participants over the phone or in person in the seven days leading up to the scheduled surgery. Follow-up assessment occurred between seven and 14 days postoperatively via telephone.

Ethical Approval Statement

The Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB) approved Study (Optimizing Opioid Prescribing in Ambulatory Surgery) Protocol Number: H-33147.

Patient and Public Involvement Statement

Patients were first involved in the research when recruited and informed verbally about the details of the study. Research questions and outcome measures were developed by several members of the research team (CWS, JML, OR, IH, DM). These questions and measures were informed by team members' priorities, experience, and preferences. Patients and the public were indirectly involved in the design of this study through careful monitoring of the issues and challenges associated with their recent surgeries and, when appropriate, specific questions were fashioned to optimally characterize their concerns. Patients were contacted and introduced to the study research assistant by the recruiting physician during their medical visits. Patients were provided a brief overview of the study; if they were interested in participating, they were referred to the study research assistant to receive more verbal information about the study. If interested, the patients underwent a formal informed consent process as previously approved by the Boston University Medical Center (BUMC)/Boston Medical Center (BMC) Institutional Review Board (IRB). Once consented, patients were enrolled into the study. As part of the study, participants were informed about the degree of burden of the intervention and time required to participate in the research. Participants were not involved in our wider plan to disseminate the study results to participants and relevant wider patient communities.

The purpose of this study was to pilot a procedure intended to recruit a larger number of subjects for use in a larger program of research. Simultaneously, we used other data gathered from this investigation to establish power calculations for a later and larger full-scale study. We have also used this work to evaluate the financial, technical, administrative, and logistic feasibility of a full-scale study, including issues of data collection, protocol adherence, and questionnaire design. The sample size was based

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on and justified by these results. This article will inform the probable impact that the pilot study will have on future research decisions.

Sample

The recruitment process began with identifying ambulatory procedures that were most likely to generate at least moderate postoperative pain (identified by D. McAneny) to increase the likelihood that patients would likely be considered for receipt of postoperative opioid medication treatment. We excluded cancer-related procedures and those not expected to generate significant postoperative pain (e.g., endoscopy). Next, we identified and recruited 18 surgeons among nine selected surgical specialties (colorectal surgery, general surgery, gynecology, oral surgery, orthopedic surgery, otolaryngology, podiatry, trauma, and urology) from a single academic urban safety-net hospital (see Table 1) because they typically performed these moderate to severely painful procedures. All surgeons agreed to participate in the study. To reduce selection bias, surgeons only received a broad background of the study (i.e., that participants would be interviewed about their pre- and postoperative pain management).

We then identified potential participants via their electronic health records (EHRs). An RA generated a list of patients who were scheduled to have elective surgery in predesignated categories between 14 and 23 days in the future; thus, this was a convenience sample of patients who planned to undergo ambulatory procedures expected to generate at least moderate postoperative pain. Eligibility criteria were: age 18 to 89 years, English comprehension, an active telephone line in the EHR, and availability to complete a follow-up telephone interview two weeks after surgery. We generated a personalized study introduction letter for each patient. Each surgeon was asked to remove patients from potential study participation that they judged would not be able to comply with the study procedures due to cognitive or language abilities (i.e., understanding of English). The surgeon signed the letter for each approved patient before the study team mailed it to the patient. This process and surgeons' limited information about the study enabled them to efficiently remove any patients they did not feel would be appropriate for the study without bias.

The letter patients' received included a high-level description of the study, indicating that each participant would be interviewed as to his or her pre-and postoperative pain management for the identified surgery. The letter also included an "opt-out" choice that required the participant to call the study team one week before the planned surgery to avoid undesired contact. To capture postoperative pain management practices, the letter included a study brochure and a "pain diary," which the participant was advised to use to record pain, prescription medicine use, and over-the-counter medicine use during the 10 days after the surgery if he or she was eventually enrolled in the study.

Starting seven days before planned surgical procedures, the RA contacted patients to obtain their consent to participate in the study and administer the baseline assessment. The consent form also included a brief description of the study's purpose; specifically, "The goal of this study is to learn how surgeons prescribe pain medications and how patients use them after surgery." The RA reminded participants to fill out the pain diary

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to improve recall and accuracy at the follow-up assessment. The RA collected follow-up data over the phone between seven and 14 days postoperatively using an interviewer-administered questionnaire.

Data Collection

Preoperative baseline patient-reported data included: demographics (age, gender, race/ethnicity); chronic pain severity and function in the past three months per the Graded Chronic Pain Scale's (GCPS's) standard categories of disability, intensity, and functional limitations; and high-risk alcohol and drug use (Alcohol Use Disorders Identification Test [AUDIT] and Drug Use Disorders Identification Test [DUDIT], respectively).[47–49] Postoperative patient reported data included: postoperative pain via a postoperative pain scale with a 0 (no pain relief) to 10 (complete pain relief) scale, adapted from Albi-Feldzer, et al (2013);[50–53] Timeline-Follow-Back (TLFB) of total opioids consumed and pain rating on each day; prescription opioid misuse via the Prescription Opioid Misuse Index (POMI)[54] and Prescription Misuse Questionnaire (PMQ);[55] substance use since surgery; and intentions for leftover medication storage and disposal (concepts based on Winstock et al, 2007).[56] In addition, participants verified pain medication data extracted from the EHR.

EHR data included date of surgery, surgery type, and detailed opioid prescriptions, as well as any history of opioid prescription prior to surgery. To determine the total amount of opioid medications prescribed at the time of surgery, we calculated a total morphine equivalent dose (total MED) for all prescribed opioid medications as the number of pills multiplied by the MED of the opioid.[57]

Outcomes

The primary and secondary outcome measures for this analysis included: (1) amount of opioid analgesic medications prescribed for postoperative pain management as calculated by total MED (source: EHR); (2) opioids consumed over the 10-day postoperative period (total MED) (source: TLFB); and (3) percent of unused opioids after the 10-day postoperative period (sources: EHR and TLFB). We obtained the percent of unused opioids by subtracting reported total MED consumed from total MED prescribed for each participant, then divided by total MED prescribed. We converted opioid amounts from total MED back to oxycodone-equivalent 5 mg pills to make the data more clinically accessible. We used the highest possible dose interpretable when surgeons prescribed a dosing range for these analyses.

Additional outcome measures included age, gender, race/ethnicity (white, black, and "other" [i.e., mixed race/ethnicity]), and high-risk alcohol and drug use in the past month (AUDIT score greater than 15, DUDIT score greater than 9).

Analysis

We included only participants for whom we had follow-up data in this analysis. The available number of patients recruited from 18 surgeons during the study period determined the size of this convenience sample. Two-sided type-I error rates of 0.05

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along with 95% confidence intervals were used to assess the statistical significance of associations. We used multivariable linear regression, adjusted for surgical specialty as fixed effects, to analyze associations of sociodemographics, chronic pain, and high-risk substance use with all outcomes. We calculated intraclass correlations to partition variance in each outcome attributable to surgical specialties.

RESULTS

Population and Demographics

We enrolled 181 participants in the study and analyzed data on the 149 participants who completed follow-up assessments (see Figure 1 for study enrollment schema). The participants were 54% female, 44% white, 34% black, and 22% “other” (i.e., mixed race/ethnicity). The mean age was 49 years, and 69% of participants had some postsecondary education (Table 1).

Participants’ Pain, Substance Use, and Mental Health

At baseline, 24% of participants had highly disabling and severely limiting pain; 18% had highly disabling and moderately limiting pain; 32% had low-disabling and highly intense pain; and 26% reported low-disabling and low-intensity pain or no pain. At baseline, 5% of participants indicated high-risk alcohol use including dependence (AUDIT), and 18% reported use of illegal drugs or prescribed drugs for nonmedical reasons (DUDIT) (Table 1).

Surgeon’s Postoperative Prescribing Practices

Surgeons prescribed opioids for postoperative pain to 95% of participants; 85% of these participants received either oxycodone or oxycodone with acetaminophen. Surgeons prescribed a mean of 242 total MED per patient during the postoperative period, the equivalent of 32 oxycodone (5 mg) pills. In total, surgeons prescribed 36,273 total MED, the equivalent of 4,836 oxycodone (5 mg) pills. Participants reported using a mean of 116 total MED (48%), or the equivalent of 18 oxycodone (5 mg) pills. We estimate about 145 mg oxycodone pills of leftover medication per patient (Table 2). Non-opioid medication prescription and use were not the focus of this study; therefore, we did not analyze this domain as part of this pilot study.

Effectiveness of Pain Management and Use of Prescribed Opioid Pain Medication

At follow up, using the Postoperative Pain Scale, 32% of participants rated the effectiveness of their pain relief as complete (10), 36% as high (7–9), 24% as moderate (4–6), 5% as low (1–3), and 3% as ineffective (0). Nearly one quarter (22%) of participants reported that they would have liked more pain treatment than received. For opioid medication taken postoperatively, 13% reported taking 0 total MED, 44% took 1–100 total MED, 24% took 101–200 total MED, and 13% took 201–300 total MED, and 6% took more than 300 total MED over the 10-day period (Figure 2). Of participants taking any opioid analgesic medication, 14% reported taking them more often than prescribed and 10% reported needing an early refill. Most participants (76%) reported

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that they had pain medication left over; 33% of these participants reported intentions to use a safe means of disposal (e.g., flushing down the toilet, giving to the police), while 48% planned to keep (33%) or continue taking (15%) their medications. The remaining participants with leftover medications reported plans to throw them away (6%) or did not know their plans (5%) (Figure 3).

Associations of Patient Factors with Amount of Opioids Prescribed and Used

On average, a 10-year increase in patient age was associated with 12 total MED fewer prescribed opioids (p<0.01). Each one-point increase in the preoperative GCPS was associated, on average, with an increase in opioid consumption by 18 total MED (p<0.01), and 5% fewer unused opioids (p=0.03). Prior opioid prescription was associated with an increase in opioid consumption by 55 total MED (p=0.03), and 19% fewer unused opioids (p=0.03). High-risk drug use, on average, was associated with 9% fewer unused opioids (p=0.05) (Table 3). The term “fewer unused opioids” indicates that the population in question consumed more opioids when compared with the reference group.

The following factors were not associated with postoperative prescribing practices: pain severity in last three months (adjusted odds ratio [aOR] 5.49, 95% CI [-9.97, 20.95]); high-risk alcohol use (aOR -20.77, 95% CI [-68.99, 27.45]); high-risk drug use (aOR 15.88, 95% CI [-33.12, 64.89]); and prior opioid prescription (aOR 30.82, 95% CI [-14.25, 75.89]).

DISCUSSION

Principal Findings

In a convenience sample of patients receiving ambulatory surgery at an academic urban safety-net hospital, we found that participants reported well-controlled pain relief postoperatively and, on average, received twice as many opioid analgesics as they consumed postoperatively. Our study corroborates past studies documenting that patients use substantially fewer opioids than prescribed following surgery.[26–30] We extend those findings by prospectively identifying that surgeons do not vary the amount of opioids prescribed on the basis of key baseline characteristics and that these characteristics are associated with postoperative opioid consumption.

Limitations and Strengths

Our pilot study had several limitations. First, the generalizability of this study may be limited because of (1) its relatively small size at a single academic urban safety-net hospital, (2) the small proportion of individuals that completed follow-up assessments (see Figure 1), (3) the high proportion of participants who reported chronic pain prior to the surgery, and (4) the study did not include non-English speakers. Second, our data about the amount of medication taken and its effectiveness were obtained by patient report; we did not conduct objective tests to ascertain accuracy of self-reported data. Third, we did not differentiate between preexisting pain and pain directly related to the

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indication for surgery. Last, we have no long-term data to determine what percentage of patients continued to receive long-term opioid-based pain treatment (either new or part of a continuation of preoperative chronic pain management with opioid medications), exhibited opioid medication misuse, or developed a diagnosis or reoccurrence of opioid use disorder.

Using analysis of variance (ANOVA) to calculate the variation of portioning of total MED attributable to the specialty level (both between and within specialty) versus the patient level, surgical specialty was found to explain a high proportion of variance of prescribing (data not reported here). The prescribing patterns of these surgeons likely reflect their typical approach to postoperative pain management, which is likely based on their experiences and perceptions of the pain that their patients typically experience postoperatively. Because of the small number of surgeons in each specialty in this study, the findings cannot be generalized to any specific specialty pattern on a large scale. However, it points to the likelihood that the culture in a local department or specialty influences prescribing patterns. In academic medical centers, residents often write the prescriptions and likely learn the types and amounts of medications to prescribe from more senior trainees, which then establishes unofficial but routine and standard prescription practices over time.[5]

Strengths and Weaknesses in Relation to Other Studies

The finding that the total amount of opioids consumed was unrelated to the total amount of opioids prescribed supports the argument that prescribing is directed more so by habitual practices than by patient circumstances. Individual physicians may have prescribing patterns that lead to higher or lower intensity prescribing, which Barnett and colleagues found to predict long-term opioid use.[58] Efforts by systems and groups of surgeons to target postoperative prescribing has markedly decreased prescriptions nationally.[59, 60] Whether this leads to optimized postoperative pain management is the subject of other research studies.

Important Differences and Meaning in the Results

Screening for individual patient factors to guide postoperative pain management may assist surgeons in determining appropriate postoperative pain management practices while minimizing the potential harm from opioid medications. These risks include; the development, unmasking, or worsening of substance use disorders; diversion; or overdose. We found that older participants were prescribed fewer opioid medications (lower total MED) compared with younger participants, perhaps reflecting surgeons' adjusted prescribing practices per the susceptibility of older patients to delirium, falls, or other age-related concerns. We observed that higher postoperative opioid consumption was positively correlated with patients' preoperative pain and prior therapeutic opioid use. Not surprisingly, the percentage of unused opioid medications was predicted by patient report of pain severity in the last three months, prior opioid prescriptions, and history of high-risk drug use as detected by the DUDIT. Although certain preoperative risks (e.g., pain severity in the last three months, prior opioid prescription, and high-risk alcohol or drug use) were not associated with postoperative prescribing practices, this

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may be due to small numbers, low statistical power, and the heterogeneity of the sample. The process of identifying such risks could be incorporated into routine preoperative testing.

Participants reported a variety of strategies to handle their leftover medications; one-third reported intentions to dispose of them safely, and more than half indicated plans to keep their medications for potential future use. This latter behavior, while there were minimal pills remaining for each patient, amounts to a large public health threat with risk for potential diversion or misuse or these leftover medications.[61]

Future Research Directions

As the aim of this pilot study was to generate hypotheses, we envision the results from this convenience sample as informative of future research endeavors. Because postoperative opioid prescribing by surgeons remains incompletely studied, this pilot study represents an opportunity to test and refine optimal postoperative pain management strategies.[52] Additionally, effective methods to educate patients on safe disposal need to be studied. Patient education could be incorporated into preoperative planning for surgery, along with testing best approaches for possible future implementation. Despite recent policy efforts (i.e., regulations and guidelines) to establish appropriate levels of opioid prescribing, there remains an urgent need to expand surgeon training, establish a systematic preoperative patient screening mechanism for key risk factors, and educate patients and set realistic expectations for postoperative pain management. A comprehensive and systematic approach that employs a robust patient-centered pre- and postoperative pain management system to optimize the balance between pain control and opioid prescribing risk management is needed. Future areas for research include further investigation into the associations between preoperative behavioral health factors (e.g., anxiety, depression, substance use disorder, other social determinants of health); development, implementation, and testing of targeted educational materials for patients on appropriate postoperative pain management (i.e., consumption, dosage, storage, and disposal); and training, guidelines, and screening tools for comprehensive preoperative risk evaluation and preparation and postoperative prescribing of opioids and non-opioid alternatives for surgeons. Use of EHR-based clinical decision support tools for determining pain management approaches is another area of interest for future research. For example, surgeons and anesthesiologists use frailty assessments (e.g., Clinical Frailty Scale) to preoperatively assess elderly patients and develop appropriate postoperative pain management plans.[62] Given the increased use of such tools with corresponding technological advances (e.g., machine learning, artificial intelligence), it is important to understand the value of these tools in effectively guiding surgeons' prescribing and pain management practices.

CONCLUSION

Participants with preoperative history of chronic pain, prior opioid prescription, or history of high-risk drug use were more likely to consume higher amounts of opioid medications postoperatively. Additionally, surgeons did not appear to incorporate key patient-level

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factors (e.g., substance use, preoperative pain) into opioid prescribing practices. Opportunities to improve postoperative opioid prescribing include system changes among surgical specialties along with targeted patient education and monitoring.

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Table 1: Participant Characteristics (N=149)

Characteristic	
	Mean (SD)
Age (years)	49 (14.8)
	Percent (%)
Female	53.5
Race and ethnicity⁺	
Non-Hispanic White	44.2
Non-Hispanic Black	34.0
Hispanic	15.0
Other	6.8
Education⁺	
High School or Less	31.5
Some College or More	68.5
Annual individual income ≤ $40,000⁺⁺	55.6
Public health insurance	63.3
Pain in last three months (GCPS)⁺	
Highly disabling, highly limiting	24.2
Highly disabling, moderately limiting	17.5
Low-disabling, High intensity	32.2
Low-disabling, Low intensity/No Pain	26.2
Believed surgery would relieve pain⁺	53.9
Surgical specialty	
General	30.7
Urology	18.7
Otolaryngology	13.3
Orthopedic	13.3
Podiatry	10.0
Maxillofacial Oral	8.0
Gynecology	6.0
Prior opioid prescription (< 3 months)	17.3
CAGE-AID-positive	26.7
High-risk alcohol use⁺ (AUDIT)	5.4
Illicit substance use (DUDIT)	18.0

+: ≤10% of data missing

++: >10% of data missing

GCPS: Graded Chronic Pain Scale

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PHQ-8: Patient Health Questionnaire depression scale

AUDIT: Alcohol Use Disorders Identification Test

CAGE-AID: CAGE is the acronym of its 4 questions (**C**ut, **A**nnoyed, **G**uilty, **E**ye-opener)

DUDIT: Drug Use Disorders Identification Test

Table 2: Postoperative Opioid Medications Prescribed and Consumed, and Effectiveness of Pain Control (N=149)

Variable	
Opioid medication type prescribed *	**N (%)**
Oxycodone	128 (85.3)
Hydrocodone	7 (4.7)
Hydromorphone	5 (3.3)
Codeine	3 (2.7)
No prescription	8 (5.3)
Effectiveness of pain control, on scale of 0–10 +	
Complete (10)	48 (32.7)
High (7–9)	53 (36.1)
Moderate (4–6)	35 (23.8)
Low (1–3)	7 (4.8)
Ineffective (0)	4 (2.7)
	Mean (SD)**
Total MED prescribed	241.8 (128.1)
Total MED consumed	
Total MED consumed ±	104.2 (112.3)
Total MED unused ^	165.7 (111.8)
*Total MED unused (%)^*	64.2 (40.0)

*Accounts for multiple prescriptions (i.e., does not sum to 100%)

**Total MED: Morphine Equivalent Dose (dose per pill multiplied by total number of pills prescribed)

+: ≤10% of data missing

±: Excludes participants with missing opioid consumption information

^: Excludes participants with no leftover medications

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Table 3: Patient Factors Associated with Prescribed, Consumed, and Unused Opioids (Adjusted^ Models)

	Total MED Prescribed (N=150)			Total MED Consumed (N=138)			% of Unused Opioids (N=121)		
Variable	β (se)	p-value	95% CI	β (se)	p-value	95% CI	β (se)	p-value	95% CI
Age (increment per year)	**-1.20 (0.43)**	**0.006****	**-2.05, -0.35**	0.09 (0.66)	0.87	-1.06, 1.25	-0.0004 (0.003)	0.88	-0.006, 0.005
Gender									
Male (ref)	REF	REF	REF	0.00 (0.00)	REF	REF	0.00 (0.00)	REF	REF
Female	-29.31 (16.06)	0.07	-60.79, 2.17	-20.39 (24.57)	0.41	-68.55, 27.77	-0.07 (0.06)	0.22	-0.19, 0.04
Race/Ethnicity									
Non-Hispanic white (ref)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Non-Hispanic black	26.80 (15.22)	0.08	-3.04, 56.63	1.30 (20.84)	0.95	-39.55, 42.15	0.02 (0.06)	0.77	-0.11, 0.14
Hispanic	-21.86 (21.15)	0.30	-63.32, 19.60	-16.00 (23.29)	0.49	-61.65, 29.65	0.01 (0.09)	0.91	-0.16, 0.18
Other	-37.91 (30.45)	0.22	-96.69, 22.67	-12.60 (23.29)	0.66	-68.01, 42.80	-0.21 (0.14)	0.15	-0.48, 0.07
Pain									
Pain severity (last 3 mos.)	5.49 (7.89)	0.49	-9.97, 20.95	**18.22 (5.81)**	**0.002****	**6.84, 29.60**	**-0.05 (0.02)**	**0.03***	**-0.09, -0.005**
Prior opioid prescription	30.82 (22.99)	0.18	-14.25, 75.89	**55.10 (25.37)**	**0.03***	**5.38, 104.82**	**-0.19 (0.08)**	**0.03***	**-0.35, -0.02**
Substance Use									
High-risk alcohol use (AUDIT)	-20.77 (24.60)	0.40	-68.99, 27.45	-17.60 (20.52)	0.39	-57.82, 22.63	-0.09 (0.10)	0.39	-0.20, 0.11
High-risk drug use (DUDIT)	15.88 (25.00)	0.52	-33.12, 64.89	23.84 (21.75)	0.27	-18.79, 66.48	**-0.09 (0.05)**	**0.05***	**-0.19, 0.002**

* significant at α = 0.05 ** significant at α = 0.01 **Bolded text** is significant at at least α = 0.05

^ All models adjusted for surgical subspecialty

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Contribution of Each Individual Author

Author contributions were as follows: 1. **CW Shanahan, MD MPH**: corresponding author, study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, final manuscript editing and preparation, submission to BMJ; 2. **O Reding, MPH**: data cleaning and analytic support, results and analytic review, manuscript editing and preparation; 3. **I Holmdahl, BA**: protocol development, subject recruitment, informed consent, data collection, and cleaning; 4. **J Keosaian, MPH**: protocol development, grant proposal, IRB authorization application and compliance; 5. **Z Xuan, PhD**: study design, biostatistical analytic support; 6. **DB McAneny, MD**: clinical content expert, 7. **M LaRochelle, MD MPH**: results and analytic review, paper preparation, editing; 8. **JM Liebschutz, MD MPH**: study conception and design, grant proposal, IRB authorization application, and compliance, results and analytic review, paper preparation, final manuscript editing and preparation.

Data sharing statement

Technical appendix, statistical code, and dataset available from corresponding author upon request.

Competing interests

None declared.

Figure captions

Figure 1. Study Enrollment and Schema

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

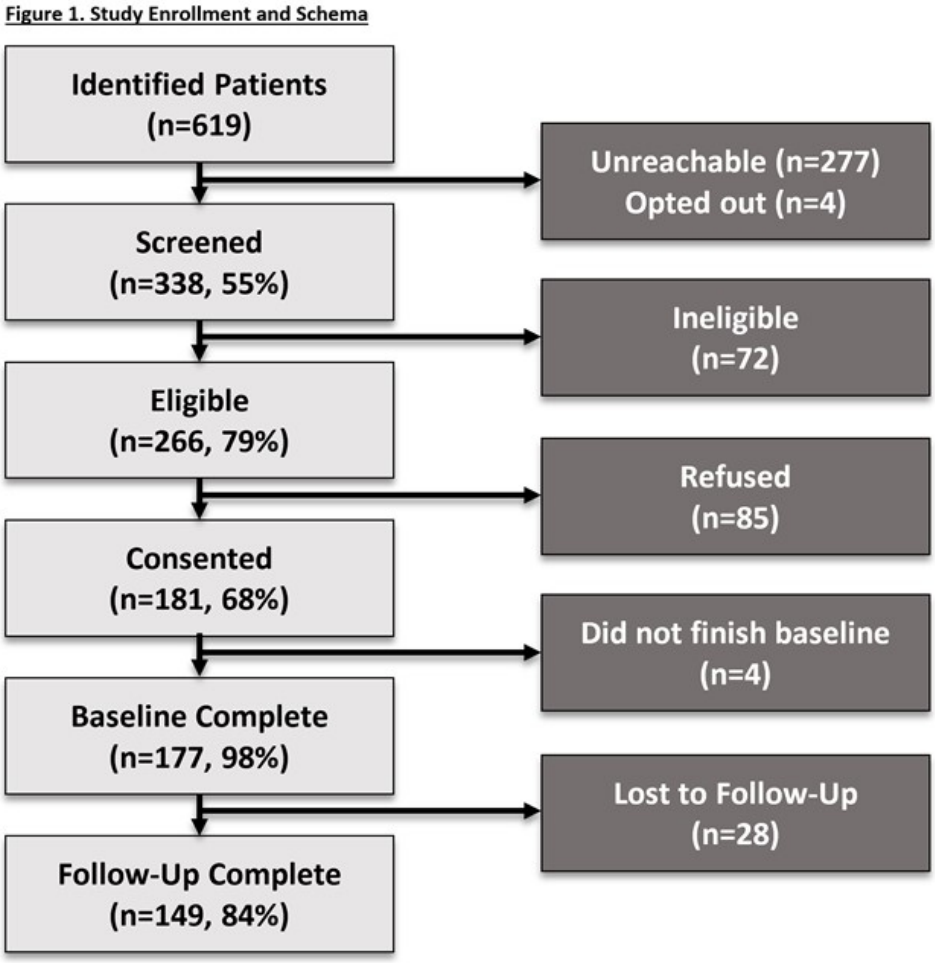

Figure 1. Study Enrollment and Schema

173x177mm (96 x 96 DPI)

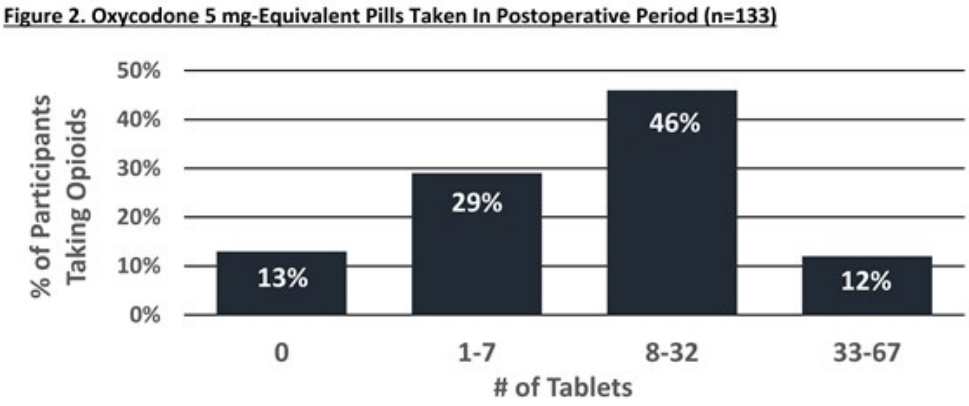

Figure 2. Oxycodone 5 mg-Equivalent Pills Taken In Postoperative Period (n=133)

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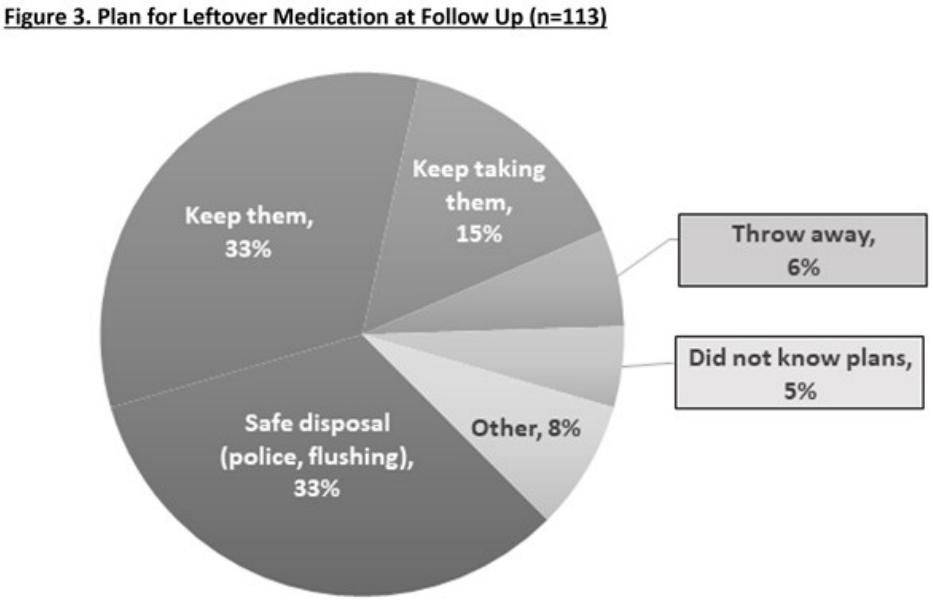

Figure 3. Plan for Leftover Medication at Follow Up (n=113)

166x108mm (96 x 96 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Opioid analgesic use after ambulatory surgery: A descriptive prospective cohort study of factors associated with quantities prescribed and consumed

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P. 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P. 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	PP. 4–5
Methods			
Study design	4	Present key elements of study design early in the paper	P. 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	PP. 5–7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	PP. 5–7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P. 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P. 7
Bias	9	Describe any efforts to address potential sources of bias	P. 6
Study size	10	Explain how the study size was arrived at	PP. 6, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	PP. 7–8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P. 8
		(*b*) Describe any methods used to examine subgroups and interactions	PP. 8–9
		(*c*) Explain how missing data were addressed	P. 8

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P. 8
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P. 8
		(b) Give reasons for non-participation at each stage	P. 6; Figure 1, P. TBD
		(c) Consider use of a flow diagram	Figure 1, P. TBD
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, P.18
		(b) Indicate number of participants with missing data for each variable of interest	P. 8; Table 1, P. 18
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	PP. 6–7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	PP. 8–9; Table 1, P. 18
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	PP. 8–9; Table 2, P. 19
		(*b*) Report category boundaries when continuous variables were categorized	PP. 8–9; Table 3, P. 20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3, P. 20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P. 9; Table 3, P. 20
Discussion			
Key results	18	Summarise key results with reference to study objectives	P. 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	PP. 9–10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	PP. 9–11
Generalisability	21	Discuss the generalisability (external validity) of the study results	PP. 10–11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P. 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.