Opioid Prescription and Consumption after Hospital Discharge following Laparoscopic Bariatric Surgery: A Prospective Cohort study

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ABSTRACT

Introduction: In the current opioid crisis, bariatric surgical patients are at increased risk of harms related to postoperative opioid overprescribing. This study aimed to assess the extent to which opioids prescribed at discharge after bariatric surgery are consumed by patients.
Methods: This multicenter prospective cohort study included adult patients (≥18yo) undergoing laparoscopic bariatric surgery. Preoperative assessments included demographics and patient-reported measures. Information regarding surgical and perioperative care interventions (including discharge prescriptions) was obtained from medical records. Self-reported opioid consumption was assessed weekly up to 30 days post-discharge. Number of opioid pills prescribed and consumed was compared using Wilcoxon signed-rank test. Zero-inflated negative binomial regression was used to identify predictors of post-discharge opioid consumption.
Results: We analyzed 351 patients (mean age 44±11 years, BMI 45±8.0 kg/m^2, 77% female, 71% sleeve gastrectomy, length of stay 1.6±0.6 days). The quantity of opioids prescribed at discharge (median 15 pills [IQR 15-16], 112.5 morphine milligram equivalents (MMEs) [IQR 80-112.5]) was significantly higher than patient-reported consumption (median 1 pill [IQR 0-5], 7.5 MMEs [IQR 0-37.5]) ($p<0.001$). Overall, 37% of patients did not take any opioids post-discharge and 78.5% of the opioid pills prescribed were unused. Increased post-discharge opioid consumption was associated with male sex (IRR 1.54 [95%CI 1.14 to 2.07]), higher BMI (1.03 [95%CI 1.01 to 1.05]), preoperative opioid use (1.48 [95%CI 1.04 to 2.10]), current smoking (2.32 [95%CI 1.44 to 3.72]), higher PROMIS-29 depression score (1.03 [95% CI 1.01 to 1.04]), anastomotic procedures (1.33 [95%CI 1.01 to 1.75]), and number of pills prescribed (1.04 [95%CI 1.01 to 1.06]).
Conclusion: This study supports that most opioid pills prescribed to bariatric surgery patients at discharge are not consumed. Patient and procedure-related factors may predict opioid consumption. Individualized post-discharge analgesia strategies with minimal or no opioids may be feasible and should be further investigated in future research.

RÉSUMÉ

Introduction: Dans le contexte actuel de la crise des opioïdes, les patients ayant subi une chirurgie bariatrique courent un risque accru de subir des préjudices liés à la prescription excessive d'opioïdes en période postopératoire. Cette étude visait à évaluer dans quelle mesure les opioïdes prescrits à la sortie de l'hôpital après une chirurgie bariatrique sont consommés par les patients.

Méthodes: Cette étude de cohorte prospective multicentrique a inclus des patients adultes (≥18ans subissant une chirurgie bariatrique laparoscopique. Les évaluations préopératoires incluaient des données démographiques et des mesures rapportées par les patients. Les informations concernant les interventions chirurgicales et les soins préopératoires (y compris les prescriptions de sortie) ont été obtenues à partir des dossiers médicaux. La consommation d'opioïdes déclarée par les patients a été évaluée chaque semaine jusqu'à 30 jours après la sortie de l'hôpital. Le nombre de comprimés d'opioïdes prescrits et consommés a été comparé à l'aide du test de rangs signés de Wilcoxon. Une régression binomiale négative avec excès de zéros a été utilisée pour identifier les facteurs prédictifs de la consommation d'opioïdes après la sortie.

Résultats: Nous avons analysé 351 patients (âge moyen 44±11 ans, IMC 45±8.0 kg/m2, 77% femmes, 71% sleeve gastrectomie, durée de séjour 1.6±0.6 jours). La quantité d'opioïdes prescrite à la sortie (médiane 15 pilules [IQR 15-16], 112,5 équivalents milligrammes de morphine (EMM) [IQR 80-112,5]) était significativement plus élevée que la consommation déclarée par les patients (médiane 1 pilule [IQR 0-5], 7,5 EMM [IQR 0-37,5]) ($p<0,001$). Dans l'ensemble, 37 % des patients n'ont pris aucun opioïde après leur sortie et 78,5 % des comprimés d'opioïdes prescrits n'ont pas été utilisés. La consommation accrue d'opioïdes après la sortie était associée au sexe masculin (IRR 1,54 [95%CI 1,14 à 2,07]), à un IMC plus élevé (1,03 [95%CI 1,01 à 1,05]), à l'utilisation préopératoire d'opioïdes (1,48 [95%CI 1,04 à 2,10]), au tabagisme actuel (2,32 [95 % IC 1,44 à 3,72]), un score de dépression PROMIS-29 plus élevé (1,03 [95 % IC 1,01 à 1,04]), des procédures anastomotiques (1,33 [95 % IC 1,01 à 1,75]) et le nombre de pilules prescrites (1,04 [95 % IC 1,01 à 1,06]).

Conclusion: Cette étude confirme que la plupart des pilules opioïdes prescrites aux patients ayant subi une chirurgie bariatrique à la sortie de l'hôpital ne sont pas consommées. Les facteurs liés au patient et à la procédure peuvent prédire la consommation d'opioïdes. Des stratégies

d'analgésie individualisées après la sortie de l'hôpital avec un minimum d'opioïdes ou sans opioïdes peuvent être réalisables et devraient être étudiées de manière plus approfondie dans le cadre de recherches futures.

STATEMENT OF ORIGINALITY

The work presented in this thesis represents original contributions to the body of knowledge on opioid prescription and consumption following bariatric surgery. While I have received support from my supervisor, study co-authors, and Research Advisory Committee members, the data presented in the following chapters represent my original work.

STATEMENT OF SUPPORT

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I would like to dedicate this work to my parents and my brother. Any achievement of mine is also theirs, as none of this would have been possible without their constant encouragement, support, and efforts in ensuring I have the opportunity to pursue any of my passions. Thank you.

AUTHOR CONTRIBUTIONS

Shrieda Jain (Primary author): Study design, project coordination, participant recruitment, data collection, analysis, preparation of manuscript and thesis.

Maxime Lapointe-Gagner: Study design, project coordination, participant recruitment, data collection, and review of manuscript.

Dr. Naser Alali: Study design, data collection, and review of manuscript.

Hiba Elhaj: Study design, participant recruitment, data collection, and review of manuscript.

Anne-Sophie Poirier: Data collection, participant recruitment, and review of manuscript.

Pepa Kaneva: Study design, coordination of ethics approval for study, review of manuscript.

Dr. Mohsen Alhashemi: Study design, supervision of recruitment and data collection, review of manuscript.

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Dr. Amin Andalib: Study design, supervision of recruitment and data collection, review of manuscript.

Dr. Julio F Fiore Jr (Primary supervisor): Study design, supervision of recruitment, data collection and analysis, preparation, and review of manuscript

PREFACE

The study reported in this manuscript-based thesis has been published in the journal Surgical Endoscopy:

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This study results have been reported as a podium presentation at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) annual conference in Montreal, Quebec, on March 29th, 2023.

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LIST OF ABBREVIATIONS

APS: American Pain Society

ASA: American Society of Anesthesiologists

BMI: Body Mass Index

BPD-DS: Biliopancreatic Diversion with Duodenal Switch

CDC: Centers for Disease Control and Prevention

CABPS: Canadian Association of Bariatric Physicians and Surgeons

ERAS: Enhanced Recovery After Surgery

GERD: Gastroesophageal Reflux Disease

IQR: Interquartile Range

IRR: Incidence Rates Ratio

IFSO: The International Federation for the Surgery of Obesity and Metabolic Disorders

LRYGB: Laparoscopic Roux-En-Y Gastric Bypass

LSG: Laparoscopic Sleeve Gastrectomy

MUHC: McGill University Health Center

MME: Morphine Milligram Equivalents

NSAID: Non-Steroidal Anti-Inflammatory Drug

NAFLD: Non-Alcoholic Fatty Liver Disease

OAGB: One Anastomosis Gastric Bypass

OSA: Obstructive Sleep Apnea

PACU: Post-Anesthesia Care Unit

PAM: Patient Activation Measure

POD: Postoperative Day

PONV: Postoperative Nausea and Vomiting

PRO: Patient-Reported Outcome

PROMIS-29: Patient-Reported Outcomes Measurement Instrument System 29

RCT: Randomized Controlled Trial

REB: Research Ethics Board

REDCap: Research Electronic Data Capture

SAGES: Society of American Gastrointestinal and Endoscopic Surgeons

SADI: Single-Anastomosis Duodeno-Ileal Bypass

SD: Standard Deviation

SG: Sleeve Gastrectomy

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TAP: Transversus Abdominis Plane

T2D: Type-2 Diabetes

CHAPTER 1- INTRODUCTION

1.1 Opioid crisis in North America

The opioid crisis is a public health emergency concerning opioid misuse, abuse, and addiction, leading to an increased rate of opioid-related deaths and hospitalizations. [1] North America is at the center of the opioid crisis, owing to increased access to prescription opioids in the United States (US) and Canada. [2] The reasons contributing to the widespread use of opioids in these countries are multifactorial but include industry promotion of opioids as highly effective and non-addictive, and the use of pain scores as a surrogate measure of 'good patient care'. [3,4] This opioid epidemic emerged in the mid-1990s when North American pharmaceutical companies started using deceptive marketing strategies to promote the prescription of opioids for the management of acute and chronic pain. [3] During the same period, the American Pain Society (APS) launched the 'pain as the fifth vital sign' campaign, which encouraged clinicians to adopt aggressive opioid-based pain management strategies to reduce patient-reported pain and ensure patient satisfaction. [4] Over 25 years later, the US and Canada remain the largest consumers of prescription opioids in the world. [5]

Currently, opioids are the leading cause of drug overdoses in the United States, causing 79,731 deaths in 2022. [6] The situation in Canada is equally alarming, with 7,328 opioid-related deaths occurring in the same year. [7] From 2016 to 2019, the estimated economic cost of opioid misuse in Canada when accounting for lost productivity and the resources required to mitigate the loss of life was at least $8.8 billion. [8] Furthermore, the Public Health Agency of Canada and the CDC (Centers for Disease Control and Prevention) in the US have both reported that the COVID-19 pandemic has exacerbated the opioid crisis, with substantially elevated rates of fatal overdoses in both countries since the onset of the pandemic. [4,7,9] These grim statistics support that, despite government and societal efforts to address this issue, the opioid epidemic in North America is far from being resolved.

Surgeons are considered to be important contributors to the opioid crisis as, in North America, opioids analgesics are widely prescribed for postoperative pain management after surgical discharge. [10] However, recent literature support that this practice is rare in many other parts of the world. In a recent cohort study by Kaafarani et al. (2020), opioids were prescribed to

95% of patients undergoing general surgery in the US compared to only 5% in European, Asian, South American, and Middle Eastern countries. [11] In a similar study by Ladha et al. (2019), surgical patients in the US and Canada receive opioid prescriptions at a rate 7 times higher than patients in Sweden. [12] Surgery often constitutes patients' first exposure to opioids, which can escalate into misuse and addiction. In fact, a study by Brummett et al (2017) including ~36,000 opioid-naïve patients undergoing general surgery, reported that 6-10% of patients continued using opioids >3 months after their procedure. [13] Among this cohort, patients undergoing bariatric surgery had the second highest incidence of persistent opioid use postoperatively (~8%). [13]

The diversion of opioids prescribed to surgical patients may be another important contributor to the opioid epidemic. [14,15] Existing literature supports that ~70% of all opioid pills obtained by surgical patients go unused – in other words, they are unnecessarily prescribed and become a readily available source for diversion. [14] In bariatric surgery, a recent systematic review of 481 patients reported that 87% of them had leftover opioid pills postoperatively. [15] To properly manage excess opioid medications, the Food and Drug Administration's (FDA) guidelines recommend the use of specific standards for drug disposal (e.g., take-back programs at pharmacies); however, these standards are rarely followed by surgical patients. [16,17] After bariatric surgery, it has been estimated that around 35% of patients do not properly dispose their excess opioids. [15] These undisposed leftover opioid pills are at risk of being either misused by the patient, or diverted for illicit use by friends, family, and other members of the community. [5] It is important to note that non-medical use of prescription opioids can serve as a gateway to the use of illicit 'street' opioids. For example, the literature supports that the use of prescription opioids is a risk factor for subsequent heroin use, with ~80% of heroin users reportedly transitioning to this drug after abusing prescription opioids. [18] Therefore, optimizing and reducing opioid prescribing after surgery is an important target to mitigate the opioid crisis.

1.2 Bariatric surgery as a treatment for obesity

Obesity (classified as BMI $\geq$ 30 kg/m^2) is a complex, chronic health condition that arises due to abnormal or excessive fat accumulation, leading to an increased risk of mortality and poor health outcomes. [19-21] Common obesity-related comorbidities that impact patients' quality of life and mortality risk include sleep apnea, Type-2 diabetes (T2D), dyslipidemia, hypertension,

non-alcoholic fatty liver disease (NAFLD), asthma, arthritis, chronic joint/back pain, and gastroesophageal reflux disease (GERD). [21,22] Unfortunately, the rate of severe obesity (BMI $\geq$ 35 kg/m^2), the fastest growing subgroup of obesity, has been increasing exponentially, affecting an estimated 1.9 million Canadian adults in 2016. [22] If this trend continues, it is estimated that obesity will affect more than one-third of adults in Canada by 2031. [23] This increasing prevalence of obesity has been attributed to multiple factors, including greater consumption of high-calorie processed foods, sedentary lifestyles, genetics, as well as social and environmental factors, such as individuals with a low socioeconomic status living in "food deserts" with limited access to healthy foods. [24,25]

Data from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) supports that 507,298 bariatric surgeries for obesity treatment were performed worldwide in 2021. [26] With common bariatric procedures (i.e., sleeve gastrectomy [SG] and Roux-en-Y gastric bypass [RYGB]) being less invasive and safer using laparoscopy techniques, bariatric surgery became the gold standard treatment for obesity when non-surgical options have been exhausted. [27] The latter include behavioural therapy (e.g., self-monitoring and relapse prevention), dietary/lifestyle interventions (e.g., reducing caloric intake and increasing physical activity), and pharmacotherapy (e.g., consumption of orlistat, liraglutide, semaglutide). [28,29] According to current guidelines by the Canadian Association of Bariatric Physicians and Surgeons (CABPS), patients with a BMI $\geq$ 40 kg/m^2, patients with a BMI $\geq$ 35 kg/m^2 and severe obesity-related comorbidities, or patients with a BMI 30-35 kg/m^2 with poorly controlled T2D, can all be considered eligible for a bariatric procedure. [30] A 2013 systematic review and meta-analysis supported that, compared to non-surgical options, bariatric surgery leads to higher rates of remission of T2D, improved cholesterol levels, greater rates of weight loss, and overall improvements in quality of life. [31]

1.3 Perioperative care and pain management after bariatric surgery

Enhanced Recovery After Surgery (ERAS) refers to the use of multidisciplinary, evidence-based, perioperative care interventions to enhance postoperative recovery, with optimal pain management being an integral part of this approach. [32] Given its potential benefits, there has been increasing interest in applying ERAS in bariatric surgery. [32, 33] For bariatric patients, preoperative ERAS interventions entail patient education, expectation setting, multimodal pre-

anesthesia medication, and preoperative weight-loss programs to reduce liver volume. [33] ERAS components in the intraoperative period include standardized anesthetic protocols, multimodal analgesia, and use of neuromuscular blocks (such as transversus abdominus plane [TAP] blocks). [33] Postoperatively, early oral nutrition (including increased supplementation of vitamins and minerals to reduce risk of deficiencies), early mobilization, thromboprophylaxis to prevent thromboembolic complications, and multimodal analgesia are recommended. Emerging evidence supports that the use of ERAS in bariatric surgery reduces hospital length stay without compromising morbidity rates. [34,35]

Pain management following surgery is a primary concern for patients and clinicians as inadequate pain control can contribute to a prolonged length of stay, increased psychological stress, higher readmission rates, and increased cost of care. [36] Importantly, poorly controlled acute pain is a relevant risk factor for the development of chronic postoperative pain. [37] To address these concerns, current ERAS guidelines for bariatric patients stress the importance of optimizing postoperative pain management using multimodal analgesia approaches. [33] This refers to the use opioid-sparing pain management interventions with different mechanisms of action (i.e., neuromuscular blocks, acetaminophen, non-steroidal inflammatory drugs [NSAIDs]) with the goal of improving analgesia while reducing individual drug side-effects. [38] The use of multimodal analgesia after bariatric surgery is considered crucial for reducing the need for opioid prescriptions and minimizing opioid-related harms. [39]

1.4 Opioid harms after bariatric surgery

The prescription of opioids after bariatric surgery is intended to reduce postoperative pain and patient discomfort; however, opioid consumption is associated with increased risk of experiencing symptoms such as postoperative nausea and vomiting (PONV), opioid-induced hyperalgesia, drowsiness, constipation, and opioid-induced respiratory complications, which may ultimately impair postoperative recovery. [40] In addition, given the current opioid crisis, there has been increasing attention to the risk of opioid misuse and dependence after bariatric surgery. [41] Bariatric patients are particularly susceptible to opioid-related harms due to multiple biological and psychosocial factors. For example, patients with severe obesity commonly have impulse control deficits and are consequently at a greater risk of substance abuse due to maladaptive coping strategies. [42] Additionally, anatomical changes to the gastrointestinal

system after bariatric surgery (i.e., gastric bypass) causes an increased rate of opioid absorption and exposure in the central nervous system. [43,44] These pharmacokinetic changes alter analgesic sensitivity and can increase the risk of postoperative opioid-related adverse events. [44] Furthermore, weight loss after bariatric surgery has been associated with significant changes to the neuronal activity in the mesolimbic dopamine reward pathway. [45] This pathway regulates motivation, reward-seeking behaviour, and promotes positive feelings with intake of natural substances, like food, but is also sensitive to illicit substances such as opioids, alcohol, cocaine, and nicotine. [46] Bariatric surgery may affect reward-driven behaviours related to craving toward addictive substances and increase the risk of postoperative opioid misuse and abuse (i.e., 'addiction transfer'). [47] Importantly, bariatric patients often experience obesity-related chronic pain, for which they may be already consuming opioids preoperatively. [41] In a retrospective cohort study comprising 11,719 bariatric surgery patients, it was observed that 36% patients used prescribed opioids in the year before surgery. [48] Preoperative use of opioids may be associated with increased sensitivity to pain, altered pain processing, and increased opioid tolerance, which potentially leads to increased postoperative consumption. [49]

Considering the contextual factors described above, using multimodal, opioid-sparing strategies to manage postoperative pain may be particularly beneficial for patients undergoing bariatric surgery. [34] However, despite the importance of multimodal analgesia, there are some barriers associated with the use of non-opioid analgesics for bariatric patients. For example, the use of NSAIDs after bariatric surgery has been discouraged by bariatric care guidelines given a potential risk for marginal ulcers, particularly after gastric bypass procedures. [50] This recommendation may limit the opioid-sparing interventions available and exacerbate the over-prescription of opioids to bariatric patients.

1.5 Research gap

Although previous studies have assessed patterns of opioid prescribing and consumption in other surgical populations, research focusing on bariatric surgery patients remains scarce. A 2023 meta-analysis reviewing opioid prescribing practices after bariatric surgery indicated that most of the studies in this field were retrospective in nature with lack of patient follow-ups and increased risk of selection and underreporting bias. [16] Moreover, the few prospective studies reported had small sample sizes and lacked the assessment of patient and care characteristics (i.e., prior

opioid use, mental health status, pre-existing chronic pain, use of multimodal analgesia) that may impact postoperative opioid consumption. [16] This research gap hinders the development of evidence-based initiatives aimed at mitigating opioid-related harms after bariatric surgery.

1.6 Thesis objectives

The primary objective of this thesis research was to assess the extent to which opioids prescribed at discharge after bariatric surgery are actually consumed by patients.

Secondarily, this research aimed to identify predictors of post-discharge opioid consumption and assess opioid storage/disposal practices by patients undergoing bariatric surgery.

CHAPTER 2- MANUSCRIPT

Prescription and Consumption of Opioids After Bariatric Surgery: A Multicenter Prospective Cohort Study

Short running head: Opioid use after Bariatric Surgery

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2.1 INTRODUCTION

North America is in the midst of a devastating opioid crisis which is exacerbated by the over-prescription of opioids by clinicians. [7, 51] As surgeons are the second largest subgroup of physicians involved in prescribing opioids [52], they are considered to be important contributors to this crisis. [10] Surgery often serves as the initial event for opioid-naïve patients to obtain a prescription for opioids and spiral into misuse and addiction. It has been estimated that 6-10% of patients continue using opioids for at least three months after undergoing a surgical procedure. [13,14] Furthermore, there is a troubling concern that up to 70% of postoperatively prescribed opioid pills go unused, increasing the risk of diversion to others in the community for non-medical use. [15,53,54]

Patients undergoing bariatric surgery may be at an increased risk of opioid-related harms in comparison to other surgical populations. The impulse control deficits commonly present in morbidly obese patients are believed to predispose these individuals to opioid misuse and substance use disorder. [41] Evidence supports that among opioid-naïve patients undergoing general surgery procedures, those undergoing bariatric surgery have the second highest incidence of persistent opioid use postoperatively (7.9%). [13] Moreover, a considerable proportion of bariatric surgery patients use opioids preoperatively to treat chronic pain and are at risk for increased opioid use postoperatively. [41] This can be partially attributed to procedure-related anatomical changes (i.e., gastric bypass) which can modify the pharmacokinetic properties of opioid analgesics leading to faster absorption and increased motivation to take opioids.[44, 55,56] Finally, the potential risk of side effects from non-steroidal anti-inflammatory drugs (NSAIDs) after gastric bypass (i.e., marginal ulcers) limits the available analgesic options and may further exacerbate surgeons' over-prescription of opioids postoperatively. [57]

Taken together, these challenges highlight a critical need to optimize opioid prescribing practices after bariatric surgery. While many previous studies have addressed patterns of opioid prescribing and consumption in other surgical populations [15,58], a recent meta-analysis indicated that opioid research focused on bariatric surgery has been scarce or retrospective in nature, with lack of patient follow-up and risk for selection and underreporting bias. [16] This important knowledge gap prevents the development of evidence-based initiatives to mitigate opioid harms after bariatric surgery. To address this issue, the objective of this study was to

evaluate the extent to which opioids prescribed at discharge after bariatric surgery are consumed by patients. We hypothesized that current prescribing practices poorly reflect the actual analgesic needs of patients undergoing bariatric surgery. Secondarily, we assessed predictors of post-discharge opioid consumption and opioid disposal practices by bariatric surgery patients.

2.2 METHODS

This multicentre, prospective cohort study was conducted and reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [59] (checklist available in Supplementary Material S1). Ethics approval was granted to conduct the study at the participating institutions (MUHC REB ref: 2021-7699; McGill University REB ref: A07-E36-21B (21-07-076) and all participants provided informed written consent.

2.2.1 Participants and Setting

We included consecutive patients (aged 18 years old and over) scheduled to undergo laparoscopic bariatric surgery (primary, second-stage, or revisional procedures) at two academic hospitals and a private surgical clinic in Montreal, Canada. Participants were excluded if they had: (1) a concomitant major (non-bariatric) surgical procedure other than cholecystectomy or hernia repair, (2) a second non-bariatric surgical procedure during the study's follow-up period, (3) conditions that could interfere with outcome assessment (e.g., cognitive impairment, inability to speak English or French), and (4) difficulty to be reached after discharge (e.g., limited access to a telephone or computer). All patients were treated within enhanced recovery pathways according to current guidelines. [34] The pathways included preoperative education (i.e., expectation setting), early oral intake (liquids on postoperative day [POD] 0, pureed/fluid diet on POD 1), early mobilization (out-of-bed on POD 0) and multimodal analgesia (generally with acetaminophen and opioids). When patients tolerated oral intake, they were transitioned to oral analgesia; epidurals were not used as part of the pathway. Transversus abdominis plane (TAP) blocks were used at the surgeons' and/or anaesthetists' discretion. At the academic study sites, hospital discharge was targeted for POD 1, with same-day discharge possible for selected cases. [60] At the private clinic, discharge was targeted for POD 2 after an overnight stay at the post-anaesthesia care unit (PACU) and a one-night stay at a hotel with around-the-clock monitoring by nursing staff.

2.2.2 Measurement strategy

Patient, surgical, and perioperative care characteristics

Patient (i.e., age, sex, Body Mass Index [BMI], American Society of Anesthesiologists [ASA] score), surgical (i.e., type of surgery, duration), and perioperative care characteristics (in-hospital analgesia interventions, discharge prescription) were obtained from medical records. Preoperatively, participants completed surveys focused on general health status using the Patient-Reported Outcomes Measurement Information System 29 Profile [PROMIS-29]; raw scores from 7 domains were converted to a standardized T-score, where a mean of 50 and standard deviation of 10 represents the average US population. [61] These domains include physical function [score range 22.9-56.9], anxiety [40.3-81.6], depression [41.0-79.4], sleep disturbance [32.0-73.3], pain interference [41.6-75.6], fatigue [33.7-75.8], and social participation [29.0-64.1]). Other measures assessed were pain intensity [0-10], pain catastrophizing (Pain Catastrophizing Scale [0-52]) [62], expected intensity of postoperative pain (0-10) [63], and engagement in own health care (Patient Activation Measure [dichotomized as low [$\leq$ 55.1] vs high [> 55.1] activation)]) [64]. Participants were also asked about chronic pain (defined as persistent or recurrent pain lasting $\geq$ 3 months before surgery, according to the International Pain Outcomes Questionnaire) [65] and any preoperative filling of an opioid prescription within 365 and 31 days prior to surgery. Participants who did not fill an opioid prescription within this period were deemed 'opioid-naïve'. [13,14] Characteristics of the patient-reported measures addressed in this study are described in Supplementary Material S2.

Postoperative outcomes

Our primary outcome of interest, number of opioid pills consumed within 30 days post-discharge, was assessed using a standardized weekly survey adapted from Thiels et al (Supplementary Material S3). [66] At Week 4, the survey included questions regarding the amount of remaining (unused) opioid pills, and if applicable, how these unused pills were stored and/or disposed. Prior to implementation, the survey was pilot tested with 5 patients and modified based on their feedback. The amount of opioids prescribed and consumed by participants was reported in number of pills and morphine milligram equivalents (MME), calculated using a standardized conversion table. [67] Information on hospital length of stay, 30-day postoperative complications (classified according to Clavien-Dindo [68]) and 30-day

unplanned healthcare utilization (emergency visits and readmissions) were obtained from medical records.

Data collection and follow-up procedures

All preoperative and postoperative patient-reported data were collected through self-administered electronic surveys administered through a secured REDCap platform (Research Electronic Data Capture, Vanderbilt University, Nashville, USA) accessed via a smartphone, tablet, or personal computer. Links to the electronic surveys were sent to patients via email or text messages in the morning of each assessment time point. Participants could also opt to respond to the surveys via telephone interviews according to their preference. Participants were asked to complete the questionnaires within a 24-hour window and reminded by phone or email up to 3 times in case of no response. Participants were contacted by e-mail or phone to clarify any unclear or missing responses. All study data was entered and stored in a secured RED Cap server.

2.2.3 Sample size

The sample size requirement for this study was estimated considering a margin of error of 5% and 95% confidence to detect a rate of unused opioids of 70%. [15] According to this estimate, a sample of 322 was considered sufficient for our primary analysis. A sample size of 350 participants was targeted to account for an attrition rate of ~10% and possible increase in data variance due to multiple imputation of missing data.

2.2.4 Statistical Analysis

Statistical analyses were performed using Stata® version 17 software (Stata Corp., College Station, TX, USA). Continuous variables were summarized using means and standard deviations (SDs) or medians and interquartile ranges (IQR), as appropriate. Categorical variables were summarized using frequencies and percentages. In our primary analysis, the total number of opioid pills prescribed and consumed at 30 days after discharge were compared using the Wilcoxon signed-rank test. Patterns of storage and disposal of unused pills were assessed using descriptive statistics. Predictors of 30-day consumption of opioid pills were identified using zero-inflated negative binomial regression with incidence rate ratios (IRR) and 95% confidence intervals (CI). Twenty-five potential predictors (patient, procedure, and perioperative care

characteristics) were considered based on findings from previous literature, and/or clinical plausibility (Table 1). [48, 69-79] Stepwise backward selection was performed for variable selection, retaining those with p-value < 0.10. [80] To minimize potential bias arising from missing data, multiple imputations were carried out using chained equations and predictive mean matching. Estimates from 50 simulations were combined using Rubin's rules. [81] To further assess the robustness of our regression model, we conducted *post hoc* sensitivity regression analyses by: (1) assessing opioid consumption in MMEs [82] (using a generalized linear model with negative binomial distribution), (2) with the exclusion of outliers (n=1, identified via box plots and standardized residual plots), and (3) including only opioid-naïve patients. [37] A p-value <0.05 was considered statistically significant.

Table 1 Patient and procedure/organizational characteristics assessed as potential predictors of post-discharge opioid consumption.

Patient characteristics		**Procedure/ Organizational characteristics**
Demographics	**Patient-reported measures** [a]	
Age (years) [85]	PROMIS-29 anxiety scale [69-70]	Concomitant procedure [79]
Sex [85]	PROMIS-29 depression scale [69-70]	Type of surgery [79,48] [e]
High-risk alcohol use [72] [a]	PROMIS-29 sleep scale [71]	Revisional procedure [f]
Current smoker [72]	PROMIS-29 pain interference scale [69]	30-day postoperative complications [79]
Preoperative BMI (kg/m^2) [74]	PROMIS-29 pain intensity scale [69]	Length of stay (LOS) [69]
ASA score (≥3) [75]	Pain expectation [69]	Intraoperative TAP block [70,90,91]
	Pain catastrophizing scale [76]	In-patient opioid use (at POD 0-1) [92]
	Patient activation measure [77]	Opioids prescribed at discharge [94] (Number of pills/prescription size)
	Chronic pain [73] [b]	
	Race [69] [c]	
	Preoperative opioid use [78] [d]	

Patient-reported measures assessed preoperatively through questionnaires responded online, in-person, or by phone.
[a] High-risk alcohol use defined as >10 drinks a week for women; >15 drinks a week for men.

[b] Chronic pain defined as persistent or recurrent pain lasting longer than 3 months.
[c] Dichotomized as White/Non-white race for purpose of analysis.
[d] Preoperative opioid use defined as been prescribed opioids in the past year (excluding 30-days preceding the operation).
[e] Type of surgery dichotomized as sleeve gastrectomy or anastomotic (bypass-related) procedures for purpose of analysis.
[f] Dichotomous variable: primary vs revisional procedure.
ASA: American Society of Anesthesiologists, TAP: Transversus Abdominis Plane, MME: Morphine Milligram Equivalents, PROMIS-29: Patient-Reported Outcomes Measurement Information System, POD: Postoperative Day.

2.3 RESULTS

2.3.1 Patient and surgery characteristics

A total of 351 patients were recruited between September 2021 to April 2022 (Figure 1); 208 (59%) were recruited from the private surgical clinic and 143 patients (41%) from the two academic hospitals. During the 30-day follow up, 304 participants (87%) completed follow-up questionnaires regarding opioid use (13% missing data was addressed using multiple imputation). Participants demographic characteristics and baseline patient-reported measures are reported in Table 2. Among the participants, 77% were female, mean age was 44 ± 11 years, mean BMI was 45 ± 8.0 kg/m^2, and 44% had an ASA score ≥3. Most participants were opioid-naïve (85% did not fill an opioid prescription within one year before surgery) and 37% reported chronic pain before surgery. Mean preoperative PROMIS-29 T-scores were 56.2 ± 8.5 for anxiety, 50.8 ± 8.5 for depressive symptoms, 51.8 ± 9.4 for pain interference, and 50.3 ± 8.1 for sleep disturbance (all above the average of 50 in the US general population). [61] Patients had an average preoperative PROMIS-29 pain intensity score of 2.9 ± 2.7 (out of 10), pain catastrophizing score of 10.5 ± 10.5 (out of 52) and expected an average postoperative pain of 5.7 ± 2.4 (out of 10). Most patients (73.5%) were deemed as having high engagement with their own healthcare (PAM score ≥ 55.1). [83] All procedures were laparoscopically performed, with the most common being sleeve gastrectomy (71%) and Roux-en-Y Gastric bypass (21%). The average procedure duration was 94 ± 41 minutes. Concomitant procedures included hiatal hernia repair (20.2%), cholecystectomy (0.6%), and umbilical hernia repair (1.4%).

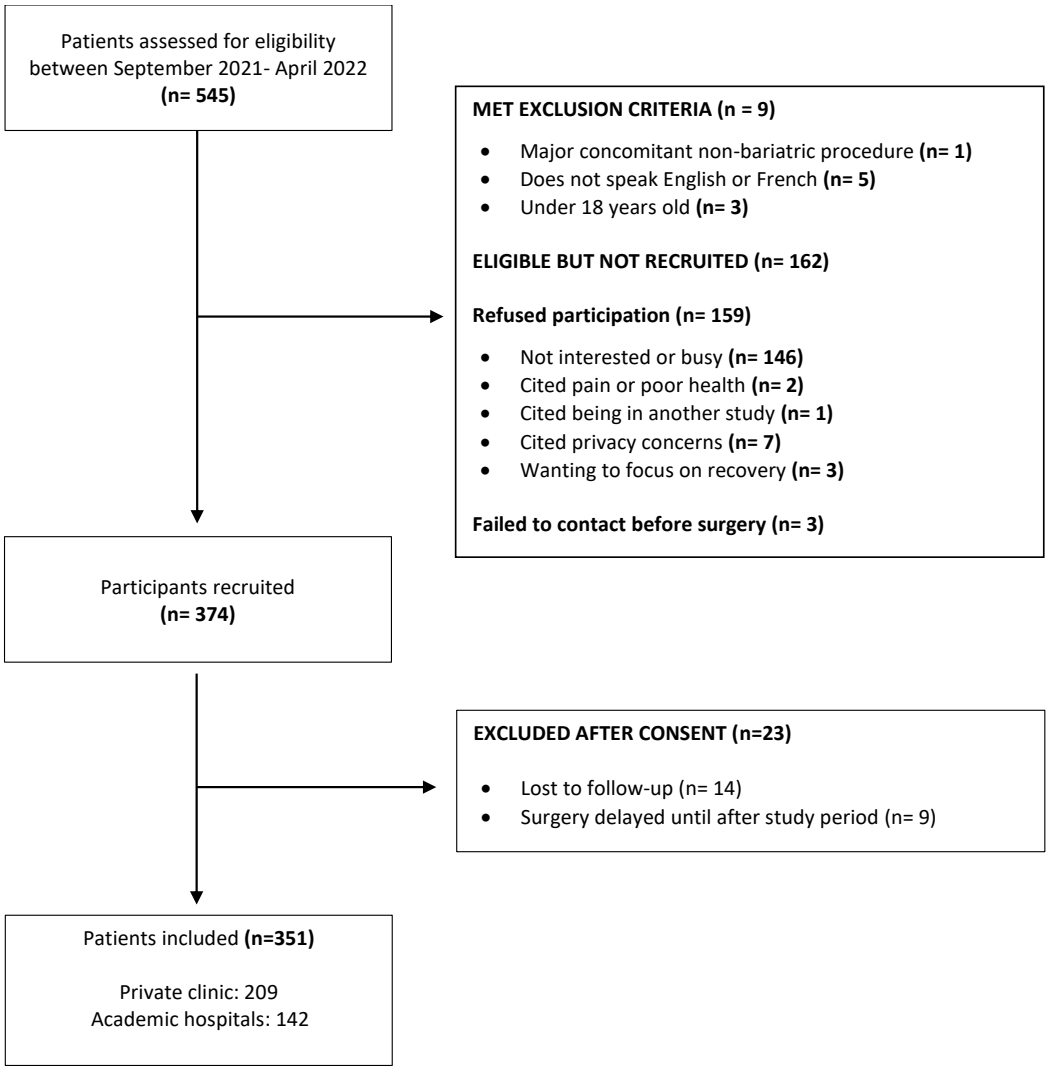

Figure 1. Participant flowchart.

Table 2 Patient and surgery characteristics (N=351).

Demographics	
Age (years)	44 ± 10.7
Sex (Female)	271 (77)
BMI (kg/m^2)	45 ± 8.0
ASA score (≥3)	154 (43.9)
Study site	
Academic hospitals	143 (40.7)
Private clinic	208 (59.3)
Preoperative patient-reported measures [a]	
High-risk alcohol use [b]	7 (2)
Current smoker [c]	20 (5.7)
Opioid naïve [d]	294 (85)
Race [e]	
White	266 (75.8)
Black	27 (7.7)
Middle Eastern	23 (6.5)
Latino	10 (2.8)
Asian	7 (2)
Indigenous	6 (1.7)
Missing	26 (7.4)
Chronic pain	127 (36.9)
Patient activation measure (Low) [f]	91 (26)
Pain catastrophizing score [0-52]	10.5 ± 10.5
Pain expectation [0-10]	5.7 ± 2.4
PROMIS-29 scores [g]	
PROMIS-29 physical function	45.5 [40.5-57.0]

PROMIS-29 social participation	50.0 [44.2-58.3]
PROMIS-29 anxiety	57.7 [51.2-61.4]
PROMIS-29 depression	51.8 [41.0-57.3]
PROMIS-29 sleep disturbance	50.5 [46.2-56.1]
PROMIS-29 pain interference	52 [41.6-58.5]
PROMIS-29 fatigue	53.1 [46.0-58.8]
PROMIS-29 pain intensity	2.0 [0.0-5.0]
Surgical characteristics	
Type of surgery (Laparoscopic) [h]	
Sleeve Gastrectomy [i]	249 (71.0)
Roux-en-Y Gastric bypass	75 (21.4)
Other (BPD-DS, SADI, OAGB)	27 (7.6)
Revisional procedure [n (%)] [j]	13 (3.7)
Concomitant procedure [n (%)] [k]	78 (22.2)
Surgery duration, mean (SD) (minutes) [c]	94.1 ± 40.6

Data are reported as frequency n (%), mean ± SD, or median [IQR]

[a] Missing baseline data for Chronic pain, Pain expectation and PROMIS-29 domains (n=7), Patient Activation Measure (n=8), Pain Catastrophizing score (n=6).

[b] High-risk alcohol use defined as >10 drinks a week for women; >15 drinks a week for men. Missing follow-up data: n=2.

[c] Missing follow-up data: n=1.

[d] Opioid naïve defined as not been prescribed opioids in the past year (excluding 30-days preceding the operation). Missing data: n=7.

[e] Dichotomized as White/Non-white race for purpose of analysis. Cumulative frequency of ethnicity exceeds 100% due to multiple choice.

[f] Patient Activation Measure dichotomized for purpose of analysis (Low: <55.5, High: ≥55.5).

[g] PROMIS-29 domains reported as their T-scores, except pain intensity. Higher scores on physical function and social participation domains, and lower scores on anxiety, depression, pain interference, sleep disturbance, and fatigue domain represent better outcomes.

[h] Type of surgery was dichotomized into sleeve gastrectomy procedures vs anastomotic procedures for purpose of analysis: Includes OAGB (n=4), SADI (one- or second-stage) (n=9), BPD-DS (one- or second-stage) (n=2), Conversion of SG to RYGB (n=9), Conversion of SADI to BPD-DS (n=1), and Re-do Gastro-jejunal anastomosis after RYGB (n=2).

[i] Includes one conversion of RYGB to SG (n = 1)

[j] Revisional procedures included Conversion of SG to RYGB (n=9), Re-do Gastro-jejunal anastomosis after RYGB (n=2), Conversion of RYGB to SG (n=1), Conversion of SADI to DS (n=1)

[k] Concomitant procedures included hiatal hernia repair (n=71), umbilical hernia repair (n=5), cholecystectomy (n=2)

ASA: American Society of Anesthesiologists (ASA) score, BMI: Body Mass Index, PROMIS-29: Patient-Reported Outcomes Measurement Information System, RYGB Roux-en-Y Gastric Bypass, SADI Single-Anastomosis

2.3.2 Analgesia management and postoperative outcomes

Most of the study participants received pre-emptive analgesia (acetaminophen 59%, gabapentinoids 52%, opioids 50%) and a TAP block intraoperatively (55% [40 mL 0.25% Bupivacaine, bilateral]) (Table 3). During in-patient stay (POD 0 to POD 1), participants consumed a median of 92.5 MMEs of opioids (IQR 55-142.5). All discharge prescriptions comprised multimodal analgesia, most commonly including opioids (100%) and acetaminophen (97.7%) 'as needed,' with a minority of patients receiving NSAIDs (3.7%, celecoxib 'around-the-clock'). The opioids most commonly prescribed at discharge were oxycodone (58.2% of patients) and hydromorphone (41.5%). The mean length of stay was 1.6 ± 0.6 days (in the hospitals 1.1 ± 0.6 days; in the private clinic 2.0 ± 0.1 days), and 22 patients (6.3%) were discharged on the same day of the procedure. A total of 20 participants (5.7%) experienced postoperative complications requiring medical intervention within 30 days after surgery. Rates and definitions of specific complications are reported in Supplementary Material S4. A total of 18 participants (5%) had an emergency department visit and 6 participants (0.3%) were re-admitted within 30 days (Table 4).

Table 3 Analgesia regimen characteristics.

Preoperative Analgesia Regimen	**n (%)**
Preoperative analgesia administered [a]	211 (60.1)
Acetaminophen (1000 mg)	207 (58.9)
Hydromorphone (1-2 mg)	166 (47.3)
Oxycodone (5-10 mg)	9 (2.5)
Pregabalin (75 mg) [b]	181 (51.5)
Gabapentin (300-600 mg)	3 (0.8)
In-patient Analgesia Regimen	
Use of TAP block	193 (55)
Inpatient opioid consumption at POD 0-1 in MME (Median [IQR]) [c]	92.5 [55-142.5]

Postoperative Regimen (Prescribed at Discharge)	
Non-Opioids	
Acetaminophen (Every 4-6 hrs, PRN)	343 (97.7)
500 mg	15 (4.3)
975 mg	13 (3.7)
1000 mg	315 (89.7)
Celecoxib (100 mg, Every 12 hrs, PRN)	13 (3.7)
Opioids	
Oxycodone (5 mg, Every 4 hrs, PRN)	199 (56.7)
Hydromorphone (1-2 mg, Every 4-6 hrs, PRN)	142 (40.4)
Morphine (30 mg, Every 8 hrs, PRN)	1 (0.2)
Codeine (30 mg, Every 4 hrs, PRN)	1 (0.2)
Tramacet (37.5 mg, Every 6 hrs, PRN)	8 (2.3)

Data are reported as frequency n (%), mean ± SD, or median [IQR]
[a] All were orally administered. Analgesia categories exceeds n=211 since the regimen given to patients included a combination of medicines listed. Most commonly, 142 patients (40.4%) received acetaminophen, hydromorphone, and pregabalin concurrently.
[b] 97% received 75 mg, 3% received varying dosage 2-200 mg.
[c] Acute in-hospital opioid consumption was measured up to the first day after surgery (POD 0-1), to account for the different lengths of stay. POD: Postoperative Day, POD-0: Day of Surgery, POD-1 first day after surgery.
PRN: pro re nata (as needed, TAP: Tranversus Abdominus Plane, MME: Morphine Milligram Equivalent.

Table 4 Postoperative outcomes.

30-day postoperative complications [a]	20 (5.7)
30-day postoperative complication score (Clavien-Dindo Classification) [b]	
I	5 (1.3)
II	8 (2.3)
IIIa	6 (1.7)
Length of stay (LOS, days)	2 [1-2]
Same-day discharge	22 (6.3)
30-day emergency department visit	18 (5.1)

30-day readmission	6 (0.3)

Data is reported as frequency n (%) or median [IQR].
[a] Supplementary Material S5 for rates and definitions of complications.
[b] Graded complications cumulatively does not sum 100% due to some patients experiencing more than 1 complication.

2.3.3 Comparison between opioids prescribed and consumed

The amount of opioid pills prescribed at discharge (median 15 pills [IQR 15-16]) was significantly higher than patient-reported consumption (median 1 pill [IQR 0-5]) ($p<0.001$). Similarly, the amount of MMEs prescribed (median 112.5 [IQR 80-112.5]) was significantly higher than the amount consumed (median 7.5 MMEs [IQR 0-37.5]) ($p<0.001$). Overall, out of 5535 opioid pills prescribed, 4343 pills were left unused (78.5%). A total of 130 participants (37%) reported not taking any opioids after discharge.

2.3.4 Predictors of postoperative opioid consumption

In multivariable regression, 30-day opioid consumption was significantly associated with male sex (IRR 1.54 [95%CI 1.14 to 2.07]), higher preoperative BMI (1.03 [95%CI 1.01 to 1.05]), preoperative opioid use (1.48 [95%CI 1.04 to 2.10]), current smoking (2.32 [95%CI 1.44 to 3.72]), higher PROMIS-29 depression score (1.03 [95% CI 1.01 to 1.04]), anastomotic procedure (vs. sleeve gastrectomy; 1.33 [95%CI 1.01 to 1.75]), and number of pills prescribed (1.04 [95%CI 1.01 to 1.06]) (Table 5). Sensitivity analyses focused on opioid consumption in MMEs (Supplementary Material S6-7), exclusion of outliers (Supplementary Material S8-9), and opioid-naïve patients (Supplementary Material S10-11) supported male sex, current smoking, depression, BMI, preoperative opioid use, and number of pills prescribed as significant predictors of post-discharge consumption. In all sensitivity analyses, in-patient opioid consumption (in MMEs) was a significant predictor of opioid consumption post-discharge.

Table 5 Predictors of 30-day post-discharge opioid consumption (in number of pills).

Predictor	Incidence Rate Ratio [95% CI]	p-value
Male sex (vs. Female)	1.54 [1.14 to 2.07]	**0.004**
Preoperative BMI (higher)	1.03 [1.01 to 1.05]	**0.028**
Preoperative opioid use (vs. opioid-naïve)	1.48 [1.04 to 2.10]	**0.028**

Current smoker (vs. non-smokers)	2.32 [1.44 to 3.72]	**0.001**
PROMIS-29 depression score (higher)	1.03 [1.01 to 1.04]	**0.001**
Anastomotic procedure (vs. sleeve gastrectomy)	1.33 [1.01 to 1.75]	**0.044**
Number of pills prescribed (higher)	1.04 [1.01 to 1.06]	**0.001**
In-patient MME consumed (higher)	1.002 [0.99 to 1.004]	0.065

Incidence Rate Ratios should be interpreted as between-group differences in rates of pill consumption (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), when all other variables are held constant.
BMI: Body Mass Index, MME: Morphine Milligram Equivalents, PROMIS-20: Patient Reported Outcomes Measurement Information System

2.3.5 Storage/Disposal Practices of unused pills

A total of 322 patients responded to the survey focused on opioid storage and disposal practices. A total of 15 participants (4.6%) reported not filling their opioid prescription at all. Among the participants who did, 284 (88.2%) reported having leftover pills at 4 weeks. Most of the participants (n=201, 62.4%) stored the leftover pills, 54 (16.7%) returned them to the pharmacy, 22 (6.8%) disposed them either in the trash or toilet, and 1 participant (0.3%) reported sharing their prescription with others (Table 6). Six participants (1.9%) were still using opioids at 4 weeks, and 23 (7.1%) participants used the entire prescription.

Table 6 Storage/Disposal practices for unused opioid pills (n=322).

Storage/Disposal Method for Unused Pills	n (%)
Prescription not obtained	15 (4.6)
No unused pills	23 (7.1)
Medication stored	201 (62.4)
Threw in trash	11 (3.4)
Flushed in toilet	11 (3.4)
Took back to pharmacy	54 (16.7)
Shared with others	1 (0.3)
Still taking	6 (1.9)

2.4 DISCUSSION

The findings from this multicenter cohort study support that the number of opioid pills prescribed after laparoscopic bariatric surgery largely exceeds the amount consumed by patients. The analgesia strategies offered to study participants varied, but were generally multimodal including pre-emptive analgesia, TAP blocks, oral acetaminophen, and opioids, with a minority of participants receiving NSAIDs. In this context of care, surgeons prescribed a median of 15 opioid pills at discharge [IQR 15-16] while patients reported a median consumption of only 1 pill [IQR 0-5]. Our results support that a significant shift in practice targeting multimodal post-discharge pain management with minimal or no opioids may be feasible to mitigate opioid-related harms after bariatric surgery.

A recent meta-analysis showed that previous research focused on opioid consumption after bariatric surgery has been limited to retrospective studies and small (n<120) single-center prospective studies. [16] Hence, major strengths of our research include its prospective multicenter design, sample size sufficient to address our research aims (n=351), and methodological rigor to minimize risk of bias. We used broad inclusion criteria with participants recruited from tertiary hospitals and a private surgical clinic, so our findings reflect a range of bariatric surgery settings. Other strengths include addressing comprehensive information about preoperative patient-reported health status and perioperative care characteristics, use of an elaborate statistical approach accounting for missing data, sensitivity analyses, and compliance with the STROBE guidelines to optimize reporting. [59] Given these design considerations, our study contributes important new knowledge to inform analgesia prescribing after bariatric surgery.

We identified patient, surgical, and care characteristics that may predict post-discharge opioid consumption after bariatric surgery. Previous research assessing the relationship between sex and postoperative opioid consumption reported conflicting findings. [84-87] In our study, the increased opioid consumption by males may reflect the fact that males (representing only 23% of our sample, in line with existing literature [88]) often present for bariatric surgery with more comorbidities that may be associated with increased opioid use. [89] Our primary analysis indicated that patients undergoing anastomotic procedures (i.e., gastric bypass) consume more opioids post-discharge than those undergoing sleeve gastrectomy. However, this association was

not sustained in sensitivity analyses and should be further investigated in future research. The benefit of TAP blocks in bariatric patients has inconsistent evidence [90,91] and was not found an independent predictor of opioid consumption in our cohort. Despite not reaching statistical significance in our primary analysis, our sensitivity analyses (Supplementary Material S6-S11) indicated that in-patient opioid consumption may potentially predict post-discharge consumption, which is in line with previous literature. [92] Importantly, our study corroborates previous research supporting that the quantity of opioids prescribed at discharge have a strong association with patient-reported consumption. [93] This finding is in line with the principle of cognitive anchoring adjustment, i.e., patients are believed to adjust their postoperative opioid consumption based on the number of pills available (the 'anchor'). [94,95] Our results also corroborate previous literature supporting that current smoking [96,97], higher BMI [74,98,99], depressive symptoms [100], and preoperative opioid use [49,101] are associated with increased postoperative opioid consumption. Taken together, these results may assist clinicians targeting specific patient groups for optimization of multimodal analgesia to reduce the reliance on opioids for post-discharge pain management.

The over-prescription of opioids to bariatric surgery patients is worrisome for several reasons. Considering the observed average of 14 pills (105 MMEs) prescribed in excess per patient and the volume of bariatric surgeries conducted in the United States and Canada every year (~250,000) [102,103], an estimated 3,500,000 opioid pills (26,250,000 MMEs) are leftover in these countries yearly due to bariatric surgery prescriptions alone. These excess opioid pills not only place bariatric patients at risk for misuse and prolonged opioid use but may also become a source of opioid diversion to the community. Approximately 88% of our study participants had leftover pills at 30 days after surgery and 62% kept their excess pills rather than disposing them according to current recommendations. [104,105] This is particularly concerning as over 60% of people who misuse opioids obtain the drug from friends or relatives with unused prescriptions. [106] Importantly, although the majority of opioid overdoses (~80%) currently involve illicit non-medical opioids (i.e., fentanyl and heroin) [7,107], most users (50-86%) transition to these drugs after abusing prescription opioids. [108] Given this alarming scenario, evidence-based strategies are required to support judicious opioid prescribing after bariatric surgery while ensuring effective postoperative pain management. [109]

Current guidelines focused on postoperative opioid prescribing suggest that patients undergoing common bariatric procedures should be prescribed from 0 to 15 opioid pills (5 mg oxycodone, or equivalent) at hospital discharge. [110-112] The current prescribing practices at our institutions are in accordance with these guidelines, as a median of 15 pills were prescribed to study participants; however, our finding suggests that, on average, patients consumed less than 10% of these pills. A common benchmark for opioid prescribing recommendations targets a quantity of opioids equivalent to the 75th percentile of patient-reported opioid consumption. [111] Based on the data from our study, this calculation supports that the prescription of 5 opioid pills is sufficient to address the needs of 75% of patients undergoing bariatric surgery in the context of enhanced recovery with multimodal analgesia. However, it is important to note that 37% of our study participants did not consume any opioids after discharge. This finding supports that opioid-free analgesia after bariatric surgery may be feasible and should be investigated in future comparative-effectiveness trials. [113]

Our study has many limitations. As with any observational study, our analysis has an inherent risk of confounding by unmeasured variables. Information regarding opioid consumption and disposal was patient-reported and may be subject to recall bias or inaccurate responses due to stigma regarding opioid use. This cohort study was conducted in Canada, so our findings may not be fully generalizable to other countries. Previous prospective studies from the United States (conducted between 2017-2018) reported an average of 27-30 pills dispensed and 15 pills consumed after common bariatric procedures [110, 114], but these figures may have changed in response to recent guidelines. [110-112] We were unable to obtain data from patients who declined participation in the study and their patterns of opioid use may be different from study participants. To facilitate the interpretation and clinical application of our study findings, our primary analysis focused on ‘numbers of pills’ prescribed and consumed, [110,112] but data were also reported and analyzed in MMEs to account for the relative potency of different drugs. [26] Due to safety concerns (i.e., risk for marginal ulcers [115,116]), NSAIDs were rarely prescribed as part of patients’ multimodal analgesia approach. However, current ERAS guidelines for bariatric surgery endorse the use of NSAIDs [34,117] and emerging evidence supports their safety and effectiveness. [118-120] Also, in our study, non-opioids drugs were generally prescribed for use ‘as needed’ while scheduled (‘around-the-clock’) use has been recommended to improve pain management. [121] Therefore, we cannot exclude that further

optimization of our multimodal analgesic approach could have further reduced post-discharge opioid consumption and increased rates of opioid-free analgesia.

CONCLUSIONS

In this multicenter cohort study, most of the opioid pills prescribed at discharge after bariatric surgery were not consumed by patients. We identified patient and procedure-related factors that may predict opioid consumption. Our findings support that individualized post-discharge analgesia strategies with minimal or no opioids may be feasible and should be further investigated in future research aimed at mitigating opioid-related harms after bariatric surgery.

DISCLOSURES

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CHAPTER 3- CONCLUSION AND FUTURE DIRECTIONS

Opioids remain a mainstay treatment for postoperative pain despite the risk of short-term side effects (i.e., nausea, vomiting, constipation) [33] and long-term persistent opioid use and addiction. [13] Bariatric surgery patients are particularly vulnerable to these opioid harms due to obesity-related biological and psychosocial factors. [41] In accordance with ERAS principles, it is important to implement evidence-based, opioid-sparing pain management strategies to ensure adequate pain control while reducing opioid-related harms to bariatric patients. [34] However, the findings of this thesis support that current prescribing practices poorly reflect the actual analgesic needs of patients undergoing bariatric surgery, with opioid being widely overprescribed. Patients in this study were prescribed a significantly higher number of pills than they consumed, and a considerable proportion of participants (37%) did not consume any opioids post-discharge. Our findings also indicated that many patient and procedural factors can predict increased post-discharge opioid consumption after bariatric surgery (i.e., male sex, higher preoperative BMI, current smokers, preoperative use of opioids, higher depressive scores, anastomotic procedures, and greater number of pills prescribed). These findings may assist clinicians targeting specific patient groups for optimization of multimodal analgesia. [39] The use of opioid-free pharmacological (i.e., acetaminophen, NSAIDs) and non-pharmacological pain interventions (e.g., expectation setting, cold packs, relaxation) [122,123] may be particularly relevant to bariatric patients given their increased risk of opioid-related harms.

Despite the large number of opioid pills left unused, most bariatric patients in this study (over 60%) did not adhere to recommended opioid disposal practices. [17] Opioids not appropriately disposed are a common source of opioid diversion to friends, family, and other community members. [5] The use of patient education interventions regarding proper opioid disposal, as well as reducing prescription sizes according to existing evidence, have a great potential to mitigate this issue. Traditional strategies to properly dispose unused opioids include returning them to a pharmacy and throwing them in the trash mixed with something that tastes bad (i.e., cat litter or coffee grounds). [124] Additional strategies that have been successfully implemented in other settings include opioid buy-back programs (offering small monetary incentives to motivate patients to return any unused opioids) [125] or returning unused pills during routine follow-ups with clinicians. [126] Postoperatively, bariatric patients are closely

followed-up in primary care settings for weight loss-based adjustments of long-term medications (e.g., dyslipidemia, anti-hypertensive, and diabetes drugs). [127] This provides a valuable opportunity for healthcare providers to monitor postoperative opioid use and retrieve unused opioids. [16,128]

Overall, the results from this thesis research suggest that using postoperative analgesia strategies with minimal or no opioids may be feasible after bariatric surgery. In fact, a recent systematic review of randomized controlled trials (RCTs) by our group supported that opioid prescribing at postoperative discharge does not significantly reduce pain intensity when compared with opioid-free analgesia but does increase adverse events. [129] However, the evidence identified only covered surgeries of minor (e.g., dental) to intermediate extent (e.g., cholecystectomies) and none of the trials addressed patients undergoing bariatric surgery. While this thesis results indicate that a considerable proportion of bariatric patients feasibly manage pain using only non-opioid interventions, the comparative effectiveness of post-discharge opioid versus opioid-free analgesia after bariatric surgery should be further investigated in future RCTs. In addition to supporting the feasibility of future research on opioid-free analgesia, this thesis provides relevant data to inform standardized, evidence-based opioid prescribing guidelines to optimize pain management after bariatric surgery while potentially reducing bariatric surgeons' contribution to the opioid crisis.

REFERENCES

1. Fischer, B., Pang, M., Tyndall, M. (2019). The opioid death crisis in Canada: crucial lessons for public health. *The Lancet Public Health*, 4(2), e81–e82. https://doi.org/10.1016/S2468-2667(18)30232-9

2. The Lancet Public Health. (2022). Opioid overdose crisis: time for a radical rethink. *The Lancet Public Health*, 7(3), e195. https://doi.org/10.1016/S2468-2667(22)00043-3

3. The Lancet. (2022). Managing the opioid crisis in North America and beyond. *The Lancet,* 399(10324), 495. https://doi.org/10.1016/S0140-6736(22)00200-8

4. Levy, N., Sturgess, J., Mills, P. (2018). "Pain as the fifth vital sign" and dependence on the "numerical pain scale" is being abandoned in the US: Why?. *British Journal of Anaesthesia*, 120(3), 435–438. https://doi.org/10.1016/j.bja.2017.11.098

5. Belzak, L., Halverson, J. (2018). Evidence synthesis - the opioid crisis in Canada: A national perspective. *Health Promotion and Chronic Disease Prevention in Canada*, 38(6), 224–233. https://doi.org/10.24095/hpcdp.38.6.02

6. Centers for Disease Control and Prevention. (2023, July). *Products - vital statistics rapid release - provisional drug overdose data*. Retrieved from: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

7. Opioid- and Stimulant-related Harms in Canada. (2023, June). *Ottawa: Public Health Agency of Canada. Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses.* Retrieved from: https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/.

8. Cheung, A., Marchand, J., Mark, P. (2022). Loss of Life and Labor Productivity: The Canadian Opioid Crisis. *The ANNALS of the American Academy of Political and Social*

Science, 703(1), 303–323. https://doi.org/10.1177/00027162231155040

9. Centers for Disease Control and Prevention. (n.d.). *Understanding the Epidemic.* Retrieved from: https://www.cdc.gov/opioids/basics/epidemic.html.

10. Theisen, K., Jacobs, B., Macleod, L., Davies, B. (2018). The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. *BJU International*, 122(5), 754–759. https://doi.org/10.1111/bju.14446

11. Kaafarani, H. M. A., Han, K., El Moheb, M., Kongkaewpaisan, N., Jia, Z., El Hechi, M. W., van Wijck, S., Breen, K., Eid, A., Rodriguez, G., Kongwibulwut, M., Nordestgaard, A. T., Sakran, J. V., Ezzeddine, H., Joseph, B., Hamidi, M., Ortega, C., Flores, S. L., Gutierrez-Sougarret, B. J., Qin, H., Lillemoe, K. D. (2020). Opioids After Surgery in the United States Versus the Rest of the World: The International Patterns of Opioid Prescribing (iPOP) Multicenter Study. *Annals of Surgery*, 272(6), 879–886. https://doi.org/10.1097/SLA.0000000000004225

12. Ladha, K. S., Neuman, M. D., Broms, G., Bethell, J., Bateman, B. T., Wijeysundera, D. N., Bell, M., Hallqvist, L., Svensson, T., Newcomb, C. W., Brensinger, C. M., Gaskins, L. J., Wunsch, H. (2019). Opioid Prescribing After Surgery in the United States, Canada, and Sweden. *JAMA Network Open*, 2(9), e1910734. https://doi.org/10.1001/jamanetworkopen.2019.10734

13. Brummett, C. M., Waljee, J. F., Goesling, J., Moser, S., Lin, P., Englesbe, M. J., Bohnert, A. S. B., Kheterpal, S., Nallamothu, B. K. (2017). New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surgery,* 152(6), e170504. https://doi.org/10.1001/jamasurg.2017.0504

14. Bicket, M. C., Long, J. J., Pronovost, P. J., Alexander, G. C., Wu, C. L. (2017). Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. *JAMA Surgery,* 152(11), 1066–1071. https://doi.org/10.1001/jamasurg.2017.0831

15. Lin A, Verhoeff K, Mocanu V, Purich K, Nasser K, Kung JY, Birch DW, Karmali S, Switzer NJ. (2023). Opioid prescribing practices following bariatric surgery: a systematic review and pooled proportion meta-analysis. *Surgical Endoscopy,* 37, 62–74 https://doi.org/10.1007/s00464-022-09481-7

16. Ehrhart, A. L., Granek, E. F., Nielsen-Pincus, M., Horn, D. A. (2020). Leftover drug disposal: Customer behavior, pharmacist recommendations, and obstacles to drug take-back box implementation. *Waste management,* 118, 416–425. https://doi.org/10.1016/j.wasman.2020.08.038

17. Bartels, K., Mayes, L. M., Dingmann, C., Bullard, K. J., Hopfer, C. J., Binswanger, I. A. (2016). Opioid Use and Storage Patterns by Patients after Hospital Discharge following Surgery. *PloS one*, 11(1), e0147972. https://doi.org/10.1371/journal.pone.0147972

18. National Institute on Drug Abuse (NIDA). (2015, October). *Prescription opioid use is a risk factor for heroin use.* Retrieved from: https://nida.nih.gov/publications/research-reports/prescription-opioids-heroin/prescription-opioid-use-risk-factor-heroin-use.

19. Weir, C. B., & Jan, A. (2023, January). *BMI classification percentile and cut off points.* StatPearls. Treasure Island. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK541070/.

20. Xu, H., Cupples, L. A., Stokes, A., Liu, C. T. (2018). Association of Obesity With Mortality Over 24 Years of Weight History: Findings From the Framingham Heart Study. *JAMA Network Open*, 1(7), e184587. https://doi.org/10.1001/jamanetworkopen.2018.4587

21. Lin, X., Li, H. (2021). Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Frontiers in Endocrinology*, 12, 706978. https://doi.org/10.3389/fendo.2021.706978

22. Twells LK, Janssen I, Kuk JL. (2020, August). *Canadian Adult Obesity Clinical Practice Guidelines: Epidemiology of Adult Obesity.* Retrieved from:

https://obesitycanada.ca/guidelines/epidemiology.

23. Bancej, C., Jayabalasingham, B., Wall, R. W., Rao, D. P., Do, M. T., de Groh, M., Jayaraman, G. C. (2015). Evidence Brief--Trends and projections of obesity among Canadians. *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice*, 35(7), 109–112. https://doi.org/10.24095/hpcdp.35.7.02

24. Tiwari A, Balasundaram P. (2023, March). *Public Health Considerations Regarding Obesity.* StatPearls. Treasure Island. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK572122/.

25. Lee, A., Cardel, M., Donahoo, W. T. (2019, October). *Social and environmental factors influencing obesity.* Endotext [Internet]. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK278977/.

26. Brown WA, Kow L, Shikora S, Liem R, Welbourn R, Dixon J, Walton P, Kinsman R (2021, October). *Sixth IFSO Global Registry Report.* Retrieved from: https://www.ifso.com/pdf/ifso-6th-registry-report-2021.pdf.

27. Heymsfield, S. B., L. J. Aronne, I. Eneli, R. B. Kumar, M. Michalsky, E. Walker, B. M. Wolfe, S. J. Woolford, S. Yanovski. (2018). *Clinical perspectives on obesity treatment: Challenges, gaps, and promising opportunities.* NAM Perspectives. Discussion Paper, National Academy of Medicine. Retrieved from: https://doi.org/10.31478/201809b.

28. Chakhtoura, M., Haber, R., Ghezzawi, M., Rhayem, C., Tcheroyan, R., Mantzoros, C. S. (2023). Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. *EClinicalMedicine*, 58, 101882. https://doi.org/10.1016/j.eclinm.2023.101882

29. U.S. National Library of Medicine. (2014). Guidelines (2013) for managing overweight and obesity in adults. preface to the expert panel report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). *Obesity,* 22: S40 https://doi.org/10.1002/oby.20822

30. Garneau, P., Glazer, S., Jackson, T., Sampath, S., Reed, K., Christou, N., Shaban, J., Biertho, L. (2022). Guidelines for Canadian bariatric surgical and medical centres: a statement from the Canadian Association of Bariatric Physicians and Surgeons. *Canadian Journal of Surgery*, 65(2), E170–E177. https://doi.org/10.1503/cjs.020719

31. Gloy, V. L., Briel, M., Bhatt, D. L., Kashyap, S. R., Schauer, P. R., Mingrone, G., Bucher, H. C., Nordmann, A. J. (2013). Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ,* 347, f5934. https://doi.org/10.1136/bmj.f5934

32. Marinari, G., Foletto, M., Nagliati, C., Navarra, G., Borrelli, V., Bruni, V., Fantola, G., Moroni, R., Tritapepe, L., Monzani, R., Sanna, D., Carron, M., Cataldo, R. (2022). Enhanced recovery after bariatric surgery: an Italian consensus statement. *Surgical Endoscopy*, 36(10), 7171–7186. https://doi.org/10.1007/s00464-022-09498-y

33. Stenberg, E., Dos Reis Falcão, L. F., O'Kane, M., Liem, R., Pournaras, D. J., Salminen, P., Urman, R. D., Wadhwa, A., Gustafsson, U. O., Thorell, A. (2022). Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: A 2021 Update. *World Journal of Surgery*, 46(4), 729–751. https://doi.org/10.1007/s00268-021-06394-9

34. Zhou, J., Du, R., Wang, L., Wang, F., Li, D., Tong, G., Wang, W., Ding, X., Wang, D. (2021). The Application of Enhanced Recovery After Surgery (ERAS) for Patients Undergoing Bariatric Surgery: a Systematic Review and Meta-analysis. *Obesity Surgery*, 3*1*(3), 1321–1331. https://doi.org/10.1007/s11695-020-05209-5

35. Małczak, P., Pisarska, M., Piotr, M., Wysocki, M., Budzyński, A., Pędziwiatr, M. (2017). Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis. *Obesity Surgery*, 27(1), 226–235. https://doi.org/10.1007/s11695-016-2438-z

36. Chen, Q., Chen, E., Qian, X. (2021). A Narrative Review on Perioperative Pain Management Strategies in Enhanced Recovery Pathways-The Past, Present and Future. *Journal of Clinical Medicine*, 10(12), 2568. https://doi.org/10.3390/jcm10122568

37. Glare, P., Aubrey, K. R., Myles, P. S. (2019). Transition from acute to chronic pain after surgery. *The Lancet,* 393(10180), 1537–1546. https://doi.org/10.1016/S0140-6736(19)30352-6

38. Schwenk, E. S., Mariano, E. R. (2018). Designing the ideal perioperative pain management plan starts with multimodal analgesia. *Korean Journal of Anesthesiology*, 71(5), 345–352. https://doi.org/10.4097/kja.d.18.00217

39. Eipe, N., Budiansky, A. S. (2022). Perioperative Pain Management in Bariatric Anesthesia. *Saudi Journal of Anaesthesia*, 16(3), 339–346. https://doi.org/10.4103/sja.sja_236_22

40. Clarke, H. A., Manoo, V., Pearsall, E. A., Goel, A., Feinberg, A., Weinrib, A., Chiu, J. C., Shah, B., Ladak, S. S. J., Ward, S., Srikandarajah, S., Brar, S. S., McLeod, R. S. (2020). Consensus Statement for the Prescription of Pain Medication at Discharge after Elective Adult Surgery. *Canadian Journal of Pain*, 4(1), 67–85. https://doi.org/10.1080/24740527.2020.1724775

41. Heinberg, L. J., Pudalov, L., Alameddin, H., Steffen, K. (2019). Opioids and bariatric surgery: A review and suggested recommendations for assessment and risk reduction. *Surgery for Obesity and Related Diseases*, 15(2), 314–321. https://doi.org/10.1016/j.soard.2018.11.019

42. Bénard, M., Camilleri, G. M., Etilé, F., Méjean, C., Bellisle, F., Reach, G., Hercberg, S., Péneau, S. (2017). Association between Impulsivity and Weight Status in a General Population. *Nutrients*, 9(3), 217. https://doi.org/10.3390/nu9030217

43. Quercia, I., Dutia, R., Kotler, D. P., Belsley, S., Laferrère, B. (2014). Gastrointestinal changes after bariatric surgery. *Diabetes & Metabolism*, 40(2), 87–94. https://doi.org/10.1016/j.diabet.2013.11.003

44. Lloret-Linares, C., Hirt, D., Bardin, C., Bouillot, J. L., Oppert, J. M., Poitou, C., Chast, F., Mouly, S., Scherrmann, J. M., Bergmann, J. F., Declèves, X. (2014). Effect of a Roux-en-Y gastric bypass on the pharmacokinetics of oral morphine using a population approach. *Clinical Pharmacokinetics*, 53(10), 919–930. https://doi.org/10.1007/s40262-014-0163-0

45. Karlsson, H. K., Tuominen, L., Helin, S., Salminen, P., Nuutila, P., Nummenmaa, L. (2021). Mesolimbic opioid-dopamine interaction is disrupted in obesity but recovered by weight loss following bariatric surgery. *Translational Psychiatry*, 11(1), 259. https://doi.org/10.1038/s41398-021-01370-2

46. Orellana, E. R., Covasa, M., Hajnal, A. (2019). Neuro-hormonal mechanisms underlying changes in reward related behaviors following weight loss surgery: Potential pharmacological targets. *Biochemical Pharmacology*, 164, 106–114. https://doi.org/10.1016/j.bcp.2019.04.004

47. Brutman, J. N., Sirohi, S., Davis, J. F. (2019). Recent Advances in the Neurobiology of Altered Motivation Following Bariatric Surgery. *Current Psychiatry Reports*, 21(11), 117. https://doi.org/10.1007/s11920-019-1084-2

48. Raebel MA, Newcomer SR, Reifler LM, Boudreau D, Elliott TE, DeBar L, Ahmed A, Pawloski PA, Fisher D, Donahoo WT, Bayliss EA. (2013) Chronic use of opioid medications before and after bariatric surgery. *JAMA*, 310(13):1369-76. https://doi.org/10.1001/jama.2013.278344

49. Lee, M., Silverman, S. M., Hansen, H., Patel, V. B., Manchikanti, L. (2011). A comprehensive review of opioid-induced hyperalgesia. *Pain Physician,* 14(2), 145–161.

50. Mechanick, J. I., Apovian, C., Brethauer, S., Garvey, W. T., Joffe, A. M., Kim, J., Kushner, R. F., Lindquist, R., Pessah-Pollack, R., Seger, J., Urman, R. D., Adams, S., Cleek, J. B., Correa,

R., Figaro, M. K., Flanders, K., Grams, J., Hurley, D. L., Kothari, S., Seger, M. V., Still, C. D. (2020). Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Surgery for Obesity and Related Diseases*, 16(2), 175–247. https://doi.org/10.1016/j.soard.2019.10.025

51. National Center for Health Statistics. (2022, September*). Provisional Drug Overdose Deaths from 12 months ending in April 2022.* Retrieved from: https://nchstats.com/2022/09/14/provisional-drug-overdose-deaths-from-12-months-ending-in-april-2022/.

52. Levy B, Paulozzi L, Mack KA, Jones CM. (2015). Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *American Journal of Preventative Medicine, 49*(3):409-413. https://doi.org/10.1016/j.amepre.2015.02.020

53. Center for Behavioral Health Statistics and Quality. (2020, September*). 2019 National survey on drug use and health: Detailed tables. Rockville, MD: Substance abuse and mental health services administration.* Retrieved from: https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables.

54. Jones CM, Logan J, Gladden RM, Bohm MK. (2015). Vital signs: demographic and substance use trends among heroin users—United States, 2002-2013. *MMWR. Morbidity and Mortality Weekly Report,* 64(26):719–725.

55. Bae, S., Oh, J., Song, I., Yu, K. S., Lee, S. (2022). Considerations for clinical evaluation of the effects of bariatric surgery on the pharmacokinetics of orally administered drugs. *Translational and Clinical Pharmacology,* 30(3), 145–154. https://doi.org/10.12793/tcp.2022.30.e15

56. Biegler, J. M., Freet, C. S., Horvath, N., Rogers, A. M., Hajnal, A. (2016). Increased intravenous morphine self-administration following Roux-en-Y gastric bypass in dietary obese rats. *Brain Research Bulletin,* 123, 47–52. https://doi.org/10.1016/j.brainresbull.2015.08.003

57. Wallén, S., Szabo, E., Palmetun-Ekbäck, M., Näslund, I. (2018). Use of Opioid Analgesics Before and After Gastric Bypass Surgery in Sweden: a Population-Based Study. *Obesity Surgery*, 28(11), 3518–3523. https://doi.org/10.1007/s11695-018-3377-7

58. Feinberg, A. E., Chesney, T. R., Srikandarajah, S., Acuna, S. A., McLeod, R. S. (2018). Opioid Use After Discharge in Postoperative Patients: A Systematic Review. *Annals of Surgery*, 267(6), 1056–1062. https://doi.org/10.1097/SLA.0000000000002591

59. Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet,* 370(9596), 1453-1457.

60. Al-Masrouri, S., Alnumay, A., Vourtzoumis, P., Court, O., Demyttenaere, S., Feldman, L. S., Andalib, A. (2022). Ambulatory sleeve gastrectomy: a prospective feasibility and comparative study of early postoperative morbidity. *Surgical Endoscopy,* 1–8. https://doi.org/10.1007/s00464-022-09721-w

61. Hays, R. D., Spritzer, K. L., Schalet, B. D., Cella, D. (2018). PROMIS®-29 v2.0 profile physical and mental health summary scores. *Quality of Life Research*, 27(7), 1885–1891. https://doi.org/10.1007/s11136-018-1842-3

62. Sullivan, M. J. L., Bishop, S. R., Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment,* 7(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

63. Sipilä, R. M., Haasio, L., Meretoja, T. J., Ripatti, S., Estlander, A. M., Kalso, E. A. (2017). Does expecting more pain make it more intense? Factors associated with the first week pain

trajectories after breast cancer surgery. *Pain*, 158(5), 922–930. https://doi.org/10.1097/j.pain.0000000000000859

64. Hibbard, J. H., Mahoney, E. R., Stockard, J., Tusler, M. (2005). Development and testing of a short form of the patient activation measure. *Health Services Research*, *40*(6 Pt 1), 1918–1930. https://doi.org/10.1111/j.1475-6773.2005.00438.x

65. Rothaug J, Zaslansky R, Schwenkglenks M, Komann M, Allvin R, Backström R, Brill S, Buchholz I, Engel C, Fletcher D, Fodor L, Funk P, Gerbershagen HJ, Gordon DB, Konrad C, Kopf A, Leykin Y, Pogatzki-Zahn E, Puig M, Rawal N, Taylor RS, Ullrich K, Volk T, Yahiaoui-Doktor M, Meissner W. (2013). Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire. *The Journal of Pain,* 14(11):1361-1370. https://doi.org/10.1016/j.jpain.2013.05.016

66. Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, Cima RR, Habermann EB. (2018). Results of a Prospective, Multicenter Initiative Aimed at Developing Opioid-prescribing Guidelines After Surgery. *Annals of Surgery,* 268(3):457-468. https://doi.org/10.1097/SLA.0000000000002919

67. Agency Medical Directors' Group. (2015, June). *Opioid Dose Calculator v2.01*. Retrieved from: https://amdg.wa.gov/calculator/DoseCalculator.

68. Dindo D, Demartines N, Clavien PA. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery,* 240(2):205-213. DOI: 10.1097/01.sla.0000133083.54934.ae

69. Pagé MG, Kudrina I, Zomahoun HTV, Croteau J, Ziegler D, Ngangue P, Martin E, Fortier M, Boisvert EE, Beaulieu P, Charbonneau C, Cogan J, Daoust R, Martel MO, Néron A, Richebé P, Clarke H. (2020). A Systematic Review of the Relative Frequency and Risk Factors for Prolonged Opioid Prescription Following Surgery and Trauma Among Adults. *Annals of Surgery,* 271(5):845-854. https://doi.org/10.1097/SLA.0000000000003403

70. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. (2017). Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. *Anesthesia and Analgesia,* 125(5):1733-1740. https://doi.org/10.1213/ANE.0000000000002458

71. Fathi, H. R., Yoonessi, A., Khatibi, A., Rezaeitalab, F., Rezaei-Ardani, A. (2020). Crosstalk between Sleep Disturbance and Opioid Use Disorder: A Narrative Review. *Addiction & Health,* 12(2), 140–158. https://doi.org/10.22122/ahj.v12i2.249

72. Shipp, M. M., Sanghavi, K. K., Kolm, P., Zhang, G., Miller, K. E., Giladi, A. M. (2022). Preoperative Patient-Reported Data Indicate the Risk of Prolonged Opioid Use After Hand and Upper Extremity Surgeries. *The Journal of Hand Surgery,* 47(11), 1068–1075. https://doi.org/10.1016/j.jhsa.2022.06.026

73. Olds, C., Spataro, E., Li, K., Kandathil, C., Most, S. P. (2019). Assessment of Persistent and Prolonged Postoperative Opioid Use Among Patients Undergoing Plastic and Reconstructive Surgery. *JAMA Facial Plastic Surgery*, 21(4), 286–291. https://doi.org/10.1001/jamafacial.2018.2035

74. Stokes A, Berry KM, Collins JM, Hsiao CW, Waggoner JR, Johnston SS, Ammann EM, Scamuffa RF, Lee S, Lundberg DJ, Solomon DH, Felson DT, Neogi T, Manson JE. (2019). The contribution of obesity to prescription opioid use in the United States. *Pain,* (10):2255-2262. https://doi.org/10.1097/j.pain.0000000000001612. PMID: 31149978; PMCID: PMC6756256.

75. Gwam, C. U., Mistry, J. B., Mohamed, N. S., George, N. E., Etcheson, J. I., Virani, S., Scalsky, R., Singh, S., Piuzzi, N. S., Delanois, R. E. (2017). The Effect of Preoperative Physical Status on Pain Management in Total Knee Arthroplasty Patients Receiving Adductor Canal Blockade. *Surgical Technology International*, 31, 237–242.

76. Sharifzadeh, Y., Kao, M. C., Sturgeon, J. A., Rico, T. J., Mackey, S., Darnall, B. D. (2017). Pain Catastrophizing Moderates Relationships between Pain Intensity and Opioid Prescription: Nonlinear Sex Differences Revealed Using a Learning Health System. *Anesthesiology*, 127(1), 136–146. https://doi.org/10.1097/ALN.0000000000001656

77. Keen, A., Lu, Y., Oruche, U. M., Mazurenko, O., Burke Draucker, C. (2022). Patient Activation of Persons With Opioid Use Disorder in Intensive Outpatient Treatment. *Journal of the American Psychiatric Nurses Association,* 10783903221096473. https://doi.org/10.1177/10783903221096473

78. Sun, E. C., Darnall, B. D., Baker, L. C., Mackey, S. (2016). Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Internal Medicine,* 176(9), 1286–1293. https://doi.org/10.1001/jamainternmed.2016.3298

79. Simoni, A., Ladebo, L., Christrup, L., Drewes, A., Johnsen, S., Olesen, A. (2020). Chronic abdominal pain and persistent opioid use after bariatric surgery. *Scandinavian Journal of Pain,* 20(2), 239-251. https://doi.org/10.1515/sjpain-2019-0092

80. Chowdhury, M. Z. I., Turin, T. C. (2020). Variable selection strategies and its importance in clinical prediction modelling. *Family Medicine and Community Health*, 8(1), e000262. https://doi.org/10.1136/fmch-2019-000262

81. Li P., Stuart EA., Allison DB. (2015). Multiple imputation: a flexible tool for handling missing data. *JAMA,* 314:1966–1967. https://doi.org/10.1001/jama.2015.15281

82. Guy, G. P., Jr, Zhang, K., Bohm, M. K., Losby, J., Lewis, B., Young, R., Murphy, L. B., Dowell, D. (2017). Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. *MMWR. Morbidity and Mortality Weekly Report,* 66(26), 697–704. https://doi.org/10.15585/mmwr.mm6626a4

83. Mosen, David M., Schmittdiel, Julie., Hibbard, Judith Sobel., David MD., Remmers. Carol., Bellows, Jim. (2007). Is Patient Activation Associated With Outcomes of Care for Adults With Chronic Conditions? *Journal of Ambulatory Care Management,* 30(1):21-29. https://doi.org/10.1097/00004479-200701000-00005

84. Hrebinko, K. A., Myers, S. P., Tsang, W. L., Doney, L., Lazar, S., Teng, C., Subramaniam, K., Holder-Murray, J. (2020). Sex Comparisons in Opioid Use and Pain After Colorectal Surgery using Enhanced Recovery Protocols. *The Journal of Surgical Research,* 253, 105–114. https://doi.org/10.1016/j.jss.2020.03.040

85. Periasamy, S., Poovathai, R., Pondiyadanar, S. (2014). Influences of gender on postoperative morphine consumption. *Journal of Clinical and Diagnostic Research: JCDR,* 8(12), GC04–GC7. https://doi.org/10.7860/JCDR/2014/10770.5319

86. Hussain, A. M., Khan, F. A., Ahmed, A., Chawla, T., Azam, S. I. (2013). Effect of gender on pain perception and analgesic consumption in laparoscopic cholecystectomy: An observational study. *Journal of Anaesthesiology, Clinical Pharmacology, 29*(3), 337–341. https://doi.org/10.4103/0970-9185.117095

87. Karlsdottir, B. R., Zhou, P. P., Wahba, J., Mott, S. L., Goffredo, P., Hrabe, J., Hassan, I., Kapadia, M. R., Gribovskaja-Rupp, I. (2022). Male gender, smoking, younger age, and preoperative pain found to increase postoperative opioid requirements in 592 elective colorectal resections. *International Journal of Colorectal Disease,* 37(8), 1799–1806. https://doi.org/10.1007/s00384-022-04208-5

88. Aly, Sherif, Krista Hachey, Luise I. M. Pernar. (2020). Gender disparities in weight loss surgery. *Mini-invasive Surgery,* 4: 21. http://dx.doi.org/10.20517/2574-1225.2019.57

89. Dugan, N., Thompson, K. J., Barbat, S., Prasad, T., McKillop, I. H., Maloney, S. R., Roberts, A., Gersin, K. S., Kuwada, T. S., Nimeri, A. (2020). Male gender is an independent risk factor for patients undergoing laparoscopic sleeve gastrectomy or Roux-en-Y gastric bypass: an MBSAQIP® database analysis. *Surgical Endoscopy,* 34(8), 3574–3583. https://doi.org/10.1007/s00464-019-07106-0

90. Tian, C., Lee, Y., Oparin, Y., Hong, D., Shanthanna, H. (2021). Benefits of Transversus Abdominis Plane Block on Postoperative Analgesia after Bariatric Surgery: A Systematic Review and Meta-Analysis. *Pain Physician*, 24(5), 345–358.

91. Aamir, M. A., Sahebally, S. M., Heneghan, H. (2021). Transversus Abdominis Plane Block in Laparoscopic Bariatric Surgery-a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Obesity Surgery*, 31(1), 133–142. https://doi.org/10.1007/s11695-020-04898-2

92. Diaz, S. E., Dandalides, A. M., Carlin, A. M. (2022). Hospital opioid use predicts the need for discharge opioid prescriptions following laparoscopic bariatric surgery. *Surgical Endoscopy*, 36(8), 6312–6318. https://doi.org/10.1007/s00464-022-09035-x

93. Phillips JK, Ford MA, Bonnie RJ, editors; National Academies of Sciences, Engineering, and Medicine. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. *The National Academies Press.* https://doi.org/10.17226/24781.

94. Howard, R., Fry, B., Gunaseelan, V., Lee, J., Waljee, J., Brummett, C., Campbell, D., Jr, Seese, E., Englesbe, M., Vu, J. (2019). Association of Opioid Prescribing With Opioid Consumption After Surgery in Michigan. *JAMA Surgery*, 154(1), e184234. https://doi.org/10.1001/jamasurg.2018.4234

95. Epley, N., Gilovich, T. (2006). The anchoring-and-adjustment heuristic: why the adjustments are insufficient. *Psychological Science*, 17(4), 311–318. https://doi.org/10.1111/j.1467-9280.2006.01704.x

96. Weingarten, T. N., Sprung, J., Flores, A., Baena, A. M., Schroeder, D. R., Warner, D. O. (2011). Opioid requirements after laparoscopic bariatric surgery. *Obesity Surgery,* 21(9), 1407–1412. https://doi.org/10.1007/s11695-010-0217-9

97. Vega Palma, M. I., Klivinyi, C., Lampl, T., Lang-Illievich, K., Bornemann-Cimenti, H., Szilagyi, I. S. (2023). The Effect of Smoking Cessation on Acute Pain: A Systematic Review. *Pain and Therapy,* 12(1), 67–79. https://doi.org/10.1007/s40122-022-00462-1

98. Moon, A. M., Watkins, S. E., Lok, A. S., Firpi-Morell, R. J., Trinh, H. N., Kupec, J. T., Schoen, C., Neuschwander-Tetri, B. A., Barritt, A. S. (2021). Opioid Use Is More Common in Nonalcoholic Fatty Liver Disease Patients with Cirrhosis, Higher BMI, and Psychiatric Disease. *Digestive Diseases,* 39(3), 247–257. https://doi.org/10.1159/000511074

99. Stefanik, J. J., Felson, D. T., Apovian, C. M., Niu, J., Margaret Clancy, M., LaValley, M. P., Neogi, T. (2018). Changes in Pain Sensitization After Bariatric Surgery. *Arthritis Care & Research*, 70(10), 1525–1528. https://doi.org/10.1002/acr.23513

100. Zhao, S., Chen, F., Feng, A., Han, W., Zhang, Y. (2019). Risk Factors and Prevention Strategies for Postoperative Opioid Abuse. *Pain Research & Management,* 2019, 7490801. https://doi.org/10.1155/2019/7490801

101. Armaghani, S. J., Lee, D. S., Bible, J. E., Archer, K. R., Shau, D. N., Kay, H., Zhang, C., McGirt, M. J., Devin, C. J. (2014). Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery. *Spine,* 39(25), E1524–E1530. https://doi.org/10.1097/BRS.0000000000000622

102. Anvari, M., Lemus, R., Breau, R. (2018). A Landscape of Bariatric Surgery in Canada: For the Treatment of Obesity, Type 2 Diabetes and Other Comorbidities in Adults. *Canadian Journal of Diabetes*, 42(5), 560–567. https://doi.org/10.1016/j.jcjd.2017.12.007

103. American Society for Metabolic and Bariatric Surgery. (2022, June). *Estimate of Bariatric Surgery Numbers, 2011-2020*. Retrieved from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers.

104. Food and Drug Administration (FDA). (2020, October). *Disposal of Unused Medicines: What You Should Know.* Retrieved from: https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know#:~:text=The%20best%20way%20to%20dispose,%2C%20location%2C%20or%20program%20immediately.

105. Government of Canada, Health Canada. (2014, May). *Safe disposal of prescription drugs*. Retrieved from: https://www.canada.ca/en/health-canada/services/safe-disposal-prescription-drugs.html.

106. National Institute on Drug Abuse. (2023, June). *Drug Overdose Death Rates*. Retrieved from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates#:~:text=Overall%2C%20drug%20overdose%20deaths%20rose,overdose%20deaths%20reported%20in%202021.

107. Tuminello, S., Alpert, N., Flores, R., Taioli, E. (2019). Physician prescribing practices and opioid misuse in the USA. *The Lancet Psychiatry,* 6(3), e7. https://doi.org/10.1016/S2215-0366(19)30029-X

108. Compton, W. M., Jones, C. M., Baldwin, G. T. (2016). Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *The New England Journal of Medicine,* 374(2), 154–163. https://doi.org/10.1056/NEJMra1508490

109. Fiore JF Jr, Olleik G, El-Kefraoui C, Verdolin B, Kouyoumdjian A, Alldrit A, Figueiredo AG, Valanci S, Marquez-GdeV JA, Schulz M, Moldoveanu D, Nguyen-Powanda P, Best G, Banks A, Landry T, Pecorelli N, Baldini G, Feldman LS. (2019). Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia*. British Journal of Anaesthesia,* 123(5):627-636. https://doi.org/10.1016/j.bja.2019.08.014

110. Friedman, D. T., Ghiassi, S., Hubbard, M. O., & Duffy, A. J. (2019). Postoperative Opioid Prescribing Practices and Evidence-Based Guidelines in Bariatric Surgery. *Obesity Surgery*, 29(7), 2030–2036. https://doi.org/10.1007/s11695-019-03821-8

111. OPEN: Opioid Prescribing Engagement Network. (2023). *OPEN Prescribing Recommendations*. Retrieved from: https://doi.org/10.56137/OPEN.000054.

112. Hill, M. V., Stucke, R. S., Billmeier, S. E., Kelly, J. L., Barth, R. J., Jr. (2018). Guideline for Discharge Opioid Prescriptions after Inpatient General Surgical Procedures. *Journal of the American College of Surgeons*, 226(6), 996–1003. https://doi.org/10.1016/j.jamcollsurg.2017.10.012

113. Hoehn, R. S., Seitz, A. P., Singer, K. E., Thompson, J. R., Watkins, B. M. (2019). Enhanced Recovery Protocol for Laparoscopic Sleeve Gastrectomy: Are Narcotics Necessary?. *Journal of Gastrointestinal Surgery*, 23(8), 1541–1546. https://doi.org/10.1007/s11605-018-04091-y

114. Ehlers, A. P., Sullivan, K. M., Stadeli, K. M., Monu, J. I., Chen-Meekin, J. Y., Khandelwal, S. (2020). Opioid Use Following Bariatric Surgery: Results of a Prospective Survey. *Obesity Surgery,* 30(3), 1032–1037. https://doi.org/10.1007/s11695-019-04301-9

115. Wilson, J. A., Romagnuolo, J., Byrne, T. K., Morgan, K., Wilson, F. A. (2006). Predictors of endoscopic findings after Roux-en-Y gastric bypass. *The American Journal of Gastroenterology,* 101(10), 2194–2199. https://doi.org/10.1111/j.1572-0241.2006.00770.x

116. Coblijn, U. K., Goucham, A. B., Lagarde, S. M., Kuiken, S. D., van Wagensveld, B. A. (2014). Development of ulcer disease after Roux-en-Y gastric bypass, incidence, risk factors, and patient presentation: a systematic review. *Obesity Surgery*, 24(2), 299–309. https://doi.org/10.1007/s11695-013-1118-5

117. Thorell, A., MacCormick, A. D., Awad, S., Reynolds, N., Roulin, D., Demartines, N., Vignaud, M., Alvarez, A., Singh, P. M., Lobo, D. N. (2016). Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World Journal of Surgery*, 40(9), 2065–2083. https://doi.org/10.1007/s00268-016-3492-3

118. Erdogan Kayhan, G., Sanli, M., Ozgul, U., Kirteke, R., Yologlu, S. (2018). Comparison of intravenous ibuprofen and acetaminophen for postoperative multimodal pain management in bariatric surgery: A randomized controlled trial. *Journal of Clinical Anesthesia,* 50, 5–11. https://doi.org/10.1016/j.jclinane.2018.06.030

119. Abou Zeid H, Kallab R, Najm MA, Jabbour H, Noun R, Sleilati F, Chucri S, Dagher C, Sleilaty G, Naccache N. (2019). Safety and Efficacy of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Used for Analgesia After Bariatric Surgery: A Retrospective Case-Control Study. *Obesity Surgery,* 29(3):911-916. https://doi.org/10.1007/s11695-018-3608-y

120. Jung, J. J., Park, A. K., Witkowski, E. R., Hutter, M. M. (2022). Comparison of Short-term Safety of One Anastomosis Gastric Bypass to Roux-en-Y Gastric Bypass and Sleeve Gastrectomy in the United States: 341 cases from MBSAQIP-accredited Centers. *Surgery for Obesity and Related Diseases,* 18(3), 326–334. https://doi.org/10.1016/j.soard.2021.11.009

121. Scott, M. J., McEvoy, M. D., Gordon, D. B., Grant, S. A., Thacker, J. K. M., Wu, C. L., Gan, T. J., Mythen, M. G., Shaw, A. D., Miller, T. E. (2017). American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 2-From PACU to the Transition Home. *Perioperative Medicine,* 6, 7. https://doi.org/10.1186/s13741-017-0063-6

122. Barnett, T., Denke, L. (2020). Managing postoperative pain with opioid-sparing therapies. *Nursing*, 50(12), 60–63. https://doi.org/10.1097/01.NURSE.0000694772.54730.b8

123. Sabesan, V. J., Chatha, K., Koen, S., Dawoud, M., Gilot, G. (2020). Innovative patient education and pain management protocols to achieve opioid-free shoulder arthroplasty. *JSES International*, 4(2), 362–365. https://doi.org/10.1016/j.jseint.2020.01.005

124. U.S Food and Drug Administration (FDA). (2021, March). *Safe opioid disposal–Remove the Risk Outreach Toolkit*. Retrieved from: https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit.

125. Liu, J. Y., Franklin, J. S., Gesek, F. A., Anderson, J. C. (2020). Buyback Program of Unused Prescription Opioids in US Rural Communities, 2017-2018. *American Journal of Public Health*, 110(9), 1318–1324. https://doi.org/10.2105/AJPH.2020.305730

126. Lewis, P. R., Pelzl, C., Benzer, E., Szad, S., Judge, C., Wang, A., Van Gent, M. (2023). Bringing Opiates Off the Streets and Undertaking Excess Scripts: A novel opiate reclamation and prescription reduction program. *Surgery*, S0039-6060(23)00329-X. Advance online publication. https://doi.org/10.1016/j.surg.2023.05.034

127. Shiau J, Biertho L. (2020, August). *Canadian Adult Obesity Clinical Practice Guidelines: Bariatric Surgery: Postoperative Management.* Retrieved from: https://obesitycanada.ca/wp-content/uploads/2020/08/Bariatric-Surgery-PostOperativeMgmt.pdf.

128. Lorico, S., Colton, B. (2020). Medication management and pharmacokinetic changes after bariatric surgery. *Canadian Family Physician,* 66(6), 409–416.

129. Fiore, J. F., Jr, El-Kefraoui, C., Chay, M. A., Nguyen-Powanda, P., Do, U., Olleik, G., Rajabiyazdi, F., Kouyoumdjian, A., Derksen, A., Landry, T., Amar-Zifkin, A., Bergeron, A., Ramanakumar, A. V., Martel, M., Lee, L., Baldini, G., & Feldman, L. S. (2022). Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *The Lancet,* 399(10343), 2280–2293. https://doi.org/10.1016/S0140-6736(22)00582-7

APPENDIX

Table S1. Strobe Statement Checklist

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	21
Objectives	3	State specific objectives, including any prespecified hypotheses	21-22
Methods			
Study design	4	Present key elements of study design early in the paper	22-23
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	22-23
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	26-27, Figure 1 N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	22-24
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	22-23
Bias	9	Describe any efforts to address potential sources of bias	24-25
Study size	10	Explain how the study size was arrived at	24
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	23 (Table 2)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	24-25

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	25, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (e.g., average, and total amount)	25-30 (Tables 2-3)
Outcome data	15*	Report numbers of outcome events or summary measures over time	31-33
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	32-34
		(*b*) Report category boundaries when continuous variables were categorized	22-23 (Tables 2-3)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	32
Discussion			
Key results	18	Summarise key results with reference to study objectives	34
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	36-37
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	34-37
Generalisability	21	Discuss the generalisability (external validity) of the study results	34-35
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	20

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org

Table S2. Main Characteristics of Patient-Reported Measures

Measure	Subdomains [a]	Time of assessment	Recall Period	Scale rating	Score range
Pain Catastrophizing Scale [1]	-	Preoperatively	Present	13 questions, 5-point Likert scale	Total score: 0-52, (best - worse)
Patient Activation Measure (Shortened version) [2]	-	Preoperatively	Present	13 items, 5-point Likert scale	Total score: 100 (≤55.1 low activation, >55.1 high activation)
Chronic pain adapted from International Pain Outcomes Questionnaire [3]	-	Preoperatively	Past 3 months	1 Item, Dichotomous scale (Yes/No)	Total score: 0-1 (No/Yes)
Pain Expectation [b]	-	Preoperatively	Present	1 item, 10-point ordinal scale	Total score: 0-10 (Low expectation -High expectation)
Preoperative use of opioids [b]	-	Preoperatively	Past year up to 30 days prior to surgery	1 item, Dichotomous scale (Yes/No)	Total score: 0-1 (No/Yes)
PROMIS-29 [4,5]	Physical Function Anxiety Depression Fatigue Sleep disturbance Social roles and activities Pain intensity Pain interference	Preoperatively, POW [c] Weeks 1,2,3,4	1 week	29 items, 4 items per domain. 5-point scale (type varies with domain) Single item for Pain intensity, 11-point ordinal scale	T-scores: Physical function (22.9-56.9) Anxiety (40.3-81.6) Depression (41-79.4) Fatigue (33.7-75.8) Sleep disturbance (32-73.3) Social Roles (29-64.1) Pain Interference (41.6-75.6)
Modified Opioid Use Survey [6]	-	POW [c] Weeks 1,2,3,4	1 week	8 items, multiple choice questions based on analgesic consumption	Not applicable

[1] Sullivan MJL, Bishop SR, Pivik J. (1995) The Pain Catastrophizing Scale: Development and validation. Psychological Assessment. *Psychological Assessment*, 7(4):524-532.
[2] Hibbard JH, Mahoney ER, Stockard J, Tusler M. (2005) Development and testing of a short form of the patient activation measure. *Health Services Research,* 40(6 Pt 1):1918-1930.
[3] Rothaug J, Zaslansky R, Schwenkglenks M, Komann M, Allvin R, Backström R, Brill S, Buchholz I, Engel C, Fletcher D, Fodor L, Funk P, Gerbershagen HJ, Gordon DB, Konrad C, Kopf A, Leykin Y, Pogatzki-Zahn E, Puig M, Rawal N, Taylor RS, Ullrich K, Volk T, Yahiaoui-Doktor M, Meissner W. (2013) Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire. *The journal of pain,* 14(11):1361-1370.
[4] Van der Meij E, Anema JR, Huirne JAF, Terwee CB. (2018) Using PROMIS for measuring recovery after abdominal surgery: a pilot study. *BMC Health Services Research,* 18:128.
[5] Rothrock, N. E., Amtmann, D., & Cook, K. F. (2020). Development and validation of an interpretive guide for PROMIS scores. *Journal of patient-reported outcomes*, 4(1), 16. https://doi.org/10.1186/s41687-020-0181-7
[6] Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, Cima RR, Habermann EB. (2018) Results of a Prospective, Multicenter Initiative Aimed at Developing Opioid-prescribing Guidelines After Surgery. *Annals of Surgery,* 268(3):457-468.

[a] Domains of health scored separately within the same patient-reported measure; [b] Author-generated questions [c] POW: Postoperative Week

Table S3. Opioid Use Survey

[Adapted from: Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, Cima RR, Habermann EB. (2018) Results of a Prospective, Multicenter Initiative Aimed at Developing Opioid-prescribing Guidelines After Surgery. *Annals of Surgery,* 268(3):457-468.]

A. Our records indicate that you received a prescription for _____ when you were discharged from the hospital after your surgery.	1) Have you taken any of these pain medications in the past 7 days? ☐ Yes (answer 1.a, 1.b, and 1.c) ☐ No (answer 1.d)
	1.a) Please select the pain medications you have taken in the past 7 days: ☐ Acetaminophen (Tylenol) ☐ Ibuprofen (Advil) ☐ Naproxen (Aleve) ☐ Celecoxib (Celebrex) ☐ Ketoprofen (Orudis) ☐ Oxycodone (Supeudol) ☐ Morphine (e.g. MS Contin, Statex, Kadian, etc.) ☐ Hydromorphone (Dilaudid) ☐ Other (please specify _____)
	1.b) How many pills of _____ did you take in the past 7 days (after leaving the hospital)? Number of pills taken: _____
	1.c) Did you take your medications as instructed? ☐ Yes ☐ No (please explain why not _____)
	1.d) When did you stop taking any of these pain medications? ___ days ago ☐ I never took these pain medications
	2) Did you take any pain medications that were not included in your discharge prescription (e.g. over-the-counter or prescribed by another doctor) after leaving the hospital? ☐ Yes (please list the other medications _____) ☐ No
	3) Did you use any additional pain control strategies? If so, please select the strategies you used: ☐ Meditation ☐ Deep breathing ☐ Acupuncture ☐ Cold pack ☐ Talking to medical staff ☐ Walking ☐ Massage ☐ Talking to friends or relatives ☐ Relaxation ☐ TENS (Transcutaneous Electrical Nerve Stimulation) ☐ Distraction (like watching TV, listening to music, reading)

	☐ Other ☐ I did not use additional pain control strategies

B. If opioids were prescribed (POW 4 ONLY) Our records indicate that when you left the hospital after your surgery, you received a prescription of the following opioid medication to relieve your pain: _____	1) What did you do with your leftover prescription pain medication? ☐ I did not obtain this medication from the pharmacy ☐ Still taking the medication ☐ No unused pills (I took all the pills) ☐ Stored the medication ☐ Threw it in the trash ☐ Flushed it down the toilet ☐ Took it back to the pharmacy, hospital, or government office ☐ Shared it with others ☐ Other: _____

Comments, if any:

Thank you for your participation.

Table S4. Rates and Definitions of Postoperative 30-day Complications

Complication	Definition	Frequency n (%)
Intraoperative serosal burn	Serosal injury requiring primary repair and closure.	1 (0.3%)
Dehydration	Serum/plasma osmolality (pOsm) >300 or need for IV fluids.	1 (0.3%)
Incisional hernia	Palpable, reducible lump in the treated area, with or without symptoms.	1 (0.3%)
Anastomotic stricture	Narrowing of the gastric lumen associated with symptoms of upper gastrointestinal tract obstruction.	1 (0.3%)
Dysphagia	Not being able to swallow solids or/and liquids, requiring further endoscopic or surgical intervention.	1 (0.3%)
Myocardial infarction	Increase in cardiac biomarker values or characteristic ECG changes or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.	1 (0.3%)
Postoperative pain	Uncontrolled pain requiring emergency visit for assessment and pain management optimization.	1 (0.3%)
Surgical site infection	Visible pus and/or cellulitis without pus requiring debridement, drainage and/or antibiotics.	2 (0.6%)
Gastroesophageal reflux disease	New-onset reflux with need for treatment with acid-reducing medication.	2 (0.6%)
Urinary tract infection	Presence and growth of microbial pathogens in the urinary tract	2 (0.6%)
Diabetic Ketoacidosis	Hyperglycemia and metabolic acidosis with low serum bicarbonate level, high serum ketones level, or urinary ketones.	2 (0.6%)
Postoperative bleeding	Bleeding with need for revisional surgery and/or blood transfusions.	2 (0.6%)
Postoperative nausea/vomiting	Postoperative nausea and/or vomiting occurring in-hospital or post-discharge requiring an anti-emetic.	3 (0.8%)

Table S5. Complete Regression Model (Primary analysis- Number of pills outcome)- Before Stepwise Selection. n=351

Predictor	Incidence Rate Ratio [95% CI]	p-value
Age	1.01 [0.99 to 1.03]	0.072
Female sex	0.65 [0.48 to 0.88]	**0.006**
High alcohol use	0.88 [0.42 to 1.81]	0.730
Current smoker	2.17 [1.32 to 3.55]	**0.002**
Preoperative opioid use	1.56 [1.06 to 2.30]	**0.023**
Preoperative BMI	1.03 [1.01 to 1.05]	**0.001**
ASA (≥3)	0.84 [0.62 to 1.13]	0.241
Race (White)	0.86 [0.59 to 1.24]	0.424
PROMIS-29 anxiety score	0.99 [0.97 to 1.02]	0.835
PROMIS-29 depression score	1.02 [1.002 to 1.04]	**0.031**
Pain catastrophizing	0.99 [0.98 to 1.01]	0.794
Patient activation (high)	0.93 [0.67 to 1.29]	0.674
Concomitant procedure	0.96 [0.67 to 1.31]	0.824
Chronic pain	0.91 [0.65 to 1.27]	0.578
Type of surgery (sleeve vs anastomotic procedures)	0.78 [0.58 to 1.04]	0.095
Revisional procedure (vs primary procedure)	1.43 [0.74 to 2.76]	0.286
30-day complications	1.30 [0.73 to 2.32]	0.374
Pain expectation	1.00 [0.94 to 1.07]	0.847
PROMIS-29 pain intensity	0.96 [0.86 to 1.06]	0.385
PROMIS-29 pain interference score	1.01 [0.98 to 1.04]	0.416
TAP block	0.95 [0.67 to 1.35]	0.799
Number of pills prescribed	1.03 [1.01 to 1.06]	**0.005**
Length of stay	0.81 [0.61 to 1.08]	0.151

PROMIS-29 sleep disturbance score	1.01 [0.99 to 1.03]	0.276
In-patient opioids consumed (MME)	1.004 [1.0009 to 1.006]	**0.008**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Incidence Rate Ratios should be interpreted as difference in rates of pill consumption between groups (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), with all other variables held constant.
CI: Confidence Interval, PROMIS-29: Patient-Reported Outcomes Measurement Information System 29, MME: Morphine Milligram Equivalent, TAP: Transversus Abdominus Plane, ASA: American Society of Anesthesiologists

Table S6. Complete Regression Model (Sensitivity Analysis I- Outcome measured in MME)-Before Stepwise Selection. n=351

Predictor	Beta-coefficient [95% CI]	p-value
Age	+0.01 [-0.003 to +0.03]	0.129
Female sex	-0.53 [-0.83 to -0.23]	**0.001**
High alcohol use	-0.57 [-1.37 to +0.21]	0.152
Current smoker	+0.82 [+0.29 to +1.35]	**0.002**
Preoperative opioid use	+0.48 [+0.11 to +0.85]	**0.012**
Preoperative BMI	+0.03 [+0.01 to +0.05]	**0.001**
ASA (≥3)	-0.32 [-0.61 to -0.03]	**0.029**
Race (White)	-0.11 [-0.48 to +0.26]	0.564
PROMIS-29 anxiety score	-0.00 [-0.02 to +0.02]	0.946
PROMIS-29 depression score	+0.02 [+0.00007 to +0.04]	**0.049**
Pain catastrophizing	-0.00 [-0.02 to +0.11]	0.695
Patient activation (high)	-0.12 [-0.43 to +0.19]	0.465
Concomitant procedure	+0.03 [-0.28 to +0.34]	0.850
Chronic pain	-0.07[-0.40 to 0.26]	0.667
Type of surgery (sleeve vs anastomotic procedures)	-0.20 [-0.49 to +0.08]	0.167
Revisional procedure (vs primary procedure)	0.46 [-0.21 to +1.14]	0.175
30-day complications	+0.42 [-0.18 to +1.02]	0.166
Pain expectation	+0.02 [-0.04 to +0.08]	0.443
PROMIS-29 pain intensity	-0.04 [-0.13 to +0.06]	0.4445
PROMIS-29 pain interference score	+0.01 [-0.02 to +0.03]	0.6191
TAP block	-0.24 [-0.55 to +0.07]	0.136
Number of pills prescribed	+0.08 [+0.02 to +0.14]	**0.007**
Length of stay	-0.31 [-0.57 to -0.05]	**0.021**

PROMIS-29 sleep disturbance score	+0.02 [+0.001 to +0.04]	**0.036**
In-patient opioids consumed (MME)	+0.006 [+0.003 to +0.009]	**<0.001**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Coefficients should be interpreted as between-group differences in pill consumption (dichotomous predictors) or increase/decrease in pill consumption per unit increase (of continuous predictors), with all other variables held constant.

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Table S7. Final Regression Model (Sensitivity Analysis I- Outcome measured in MME)- After Stepwise Selection. n=351

Predictor	Beta-coefficient [95% CI]	p-value
Female sex	-0.55 [-0.84 to -0.26]	**<0.001**
Current smoker	+0.79 [+0.29 to +1.29]	**0.002**
Preoperative BMI	+0.03 [+0.01 to +0.05]	**0.001**
PROMIS-29 depression score	+0.02 [+0.007 to +0.04]	**0.005**
Number of pills prescribed	+0.08 [+0.03 to +0.13]	**0.002**
Preoperative opioid use	+0.41 [+0.07 to +0.74]	**0.017**
PROMIS-29 sleep disturbance score	+0.02 [+0.001 to +0.03]	**0.036**
ASA (≥3)	-0.24 [-0.51 to +0.02]	0.072
In-patient opioids consumed (MME)	+0.005 [+0.003 to +0.007]	**<0.001**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Coefficients should be interpreted as between-group differences in pill consumption (dichotomous predictors) or increase/decrease in pill consumption per unit increase (of continuous predictors), with all other variables held constant.

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Table S8. Complete Regression Model (Sensitivity Analysis II- Outlier removed)-Before Stepwise Selection. n=350

Predictor	Incidence Rate Ratio [95% CI]	p-value
Age	1.01 [0.99 to 1.03]	0.065
Female sex	0.64 [0.48 to 0.87]	**0.004**
High alcohol use	0.87 [0.43 to 1.78]	0.714
Current smoker	2.16 [1.33 to 3.50]	**0.002**
Preoperative opioid use	1.57 [1.07 to 2.29]	**0.019**
Preoperative BMI	1.03 [1.01 to 1.05]	**0.005**
ASA (≥3)	0.85 [0.63 to 1.14]	0.292
Race (White)	0.87 [0.61 to 1.25]	0.472
PROMIS-29 anxiety score	0.99 [0.97 to 1.02]	0.762
PROMIS-29 depression score	1.02 [1.002 to 1.04]	**0.029**
Pain catastrophizing	0.99 [0.98 to 1.01]	0.877
Patient activation (high)	0.94 [0.68 to 1.29]	0.702
Concomitant procedure	1.05 [0.75 to 1.46]	0.783
Chronic pain	0.91 [0.65 to 1.27]	0.581
Type of surgery (sleeve vs anastomotic procedures)	0.87 [0.64 to 1.17]	0.368
Revisional procedure (vs primary procedure)	1.52 [0.79 to 2.91]	0.204
30-day complications	1.44 [0.81 to 2.56]	0.213
Pain expectation	1.01 [0.95 to 1.07]	0.751
PROMIS-29 pain intensity	0.96 [0.87 to 1.06]	0.486
PROMIS-29 pain interference score	1.01 [0.98 to 1.04]	0.459
TAP block	0.91 [0.65 to 1.29]	0.619
Number of pills prescribed	1.23 [1.04 to 1.47]	**0.014**
Length of stay	0.83 [0.62 to 1.09]	0.194

PROMIS-29 sleep disturbance score	1.01 [0.99 to 1.03]	0.275
In-patient opioids consumed (MME)	1.004 [1.001 to 1.006]	**0.004**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Incidence Rate Ratios should be interpreted as difference in rates of pill consumption between groups (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), with all other variables held constant.
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Table S9. Final Regression Model (Sensitivity Analysis II- Outlier removed)- After Stepwise Selection. n=350

Predictor	Incidence Rate Ratio [95% CI]	p-value
Age	1.01 [0.99 to 1.02]	0.090
Female sex	0.66 [0.49 to 0.89]	**0.007**
Current smoker	2.15 [1.37 to 3.38]	**0.001**
Number of prescribed pills	1.26 [1.06 to 1.49]	**0.008**
Preoperative BMI	1.03 [1.01 to 1.05]	**0.002**
PROMIS-29 depression score	1.03 [1.01 to 1.04]	**0.000**
In-patient opioids consumed (MME)	1.003 [1.0008 to 1.005]	**0.008**
Preoperative opioid use [Opioid-naïve]	1.56 [1.11 to 2.21]	**0.011**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Incidence Rate Ratios should be interpreted as difference in rates of pill consumption between groups (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), with all other variables held constant.

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Table S10. Complete Regression Model (Sensitivity Analysis III- Opioid-naïve patients only)-Before Stepwise Selection. n=301

Predictor	Incidence Rate Ratio [95% CI]	p-value
Age	1.02 [1.003 to 1.04]	**0.021**
Female sex	0.59 [0.43 to 0.84]	**0.003**
High alcohol use	1.04 [0.45 to 2.41]	0.921
Current smoker	2.25 [1.36 to 3.73]	**0.002**
Preoperative BMI	1.03 [1.01 to 1.06]	**0.008**
ASA (≥3)	0.81 [0.57 to 1.14]	0.255
Race (White)	0.76 [0.51 to 1.14]	0.183
PROMIS-29 anxiety score	0.99 [0.97 to 1.02]	0.933
PROMIS-29 depression score	1.02 [1.005 to 1.06]	**0.019**
Pain catastrophizing	0.99 [0.98 to 1.01]	0.535
Patient activation (high)	0.85 [0.59 to 1.23]	0.400
Concomitant procedure	1.15 [0.77 to 1.71]	0.487
Chronic pain	0.88 [0.61 to 1.28]	0.513
Type of surgery (sleeve vs anastomotic procedures)	0.86 [0.61 to 1.22]	0.405
Revisional procedure (vs primary procedure)	1.36 [0.62 to 2.96]	0.438
30-day complications	1.45 [0.69 to 3.02]	0.320
Pain expectation	1.02 [0.95 to 1.09]	0.556
PROMIS-29 pain intensity	0.97 [0.86 to 1.08]	0.556
PROMIS-29 pain interference score	1.00 [0.97 to 1.04]	0.724
TAP block	0.96 [0.63 to 1.45]	0.850
Number of pills prescribed	1.27 [1.04 to 1.54]	**0.016**
Length of stay	0.76 [0.54 to 1.07]	0.117
PROMIS-29 sleep disturbance score	1.00 [0.98 to 1.03]	0.567

In-patient opioids consumed (MME)	1.005 [1.002 to 1.008]	**0.002**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Incidence Rate Ratios should be interpreted as difference in rates of pill consumption between groups (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), with all other variables held constant.

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Table S11. Final Regression Model (Sensitivity Analysis III- Opioid-naïve patients only)- After Stepwise Selection. n=301

Predictor	Incidence Rate Ratio [95% CI]	p-value
Female sex	0.61 [0.44 to 0.85]	**0.004**
Current smoker	2.12 [1.31 to 3.43]	**0.002**
Number of prescribed pills	1.31 [1.06 to 1.61]	**0.012**
Preoperative BMI	1.02 [1.004 to 1.05]	**0.019**
PROMIS-29 depression score	1.03 [1.01 to 1.04]	**0.002**
In-patient opioids consumed (MME)	1.003 [1.0002 to 1.005]	**0.032**

The predictor with the largest p-value is removed from the model in a backward stepwise fashion until all final predictor variables have p-value of <0.1. Incidence Rate Ratios should be interpreted as difference in rates of pill consumption between groups (dichotomous predictors) or difference in rates per unit increase (of continuous predictors), with all other variables held constant.

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