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Study Protocol: The Association of Preoperative Opioid Use and Patient Outcomes

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The objective of this retrospective cohort study is to investigate the differences in clinical and patient-reported outcomes among patients after surgery based on the exposure of opioids in the year before surgery. Patients from the Michigan Surgical Quality Collaborative (MSQC) registry are included if they underwent one of nine procedural categories between January 1, 2017, and October 31, 2019. The primary exposure of interest is whether or not patients were prescribed opioids from day 365 to day 31 before admission to surgery as recorded in a state prescription drug monitoring program. The primary outcome of our study is postoperative pain as reported from the MSQC survey given between postoperative days 30 and 90. Secondary outcomes include the incidences of emergency department visits, hospital readmissions, and hospital reoperations in the 30 days after surgery as well as patient-reported outcomes of regret undergoing surgery, quality of life after surgery, and overall satisfaction after surgery. Multivariable ordered logistic regression models will be used to adjust for certain explanatory variables that pose differences between study groups.

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Brief Rationale and Hypothesis

1 This study examines the question of how outcomes reported by patients after surgery for pain, satisfaction, regret of undergoing surgery, and quality of life as well as clinical outcomes differ among patients based on the exposure of opioids in the year before surgery.

In general, we hypothesize that patients who are exposed to opioids in the year before surgery, compared to those who have no exposure in the year before surgery, will have worse patient and clinical reported outcomes after surgery. Specifically, our hypotheses that are driving this work include the following:

- Patients who have been exposed to opioids in the year before surgery, compared to those who have not, will experience higher ratings in *postoperative pain intensity* in the week after surgery.
- Patients with preoperative opioid exposure will be more likely to have lower *satisfaction* after surgery.
- Patients with preoperative opioid exposure will be more likely to have lower *quality of life* after surgery.
- Patients with preoperative opioid exposure will be more likely to have *regret of undergoing surgery*.
- Patients with preoperative opioid exposure will be more likely to utilize the *emergency department* within 30 days after their operation.
- Patients with preoperative opioid exposure will be more likely to have a *hospital readmission* to the hospital within 30 days after their operation.
- Patients with preoperative opioid exposure will be more likely to have a *reoperation* within 30 days after their operation.

Study Design

2 Retrospective cross-sectional study using a clinical registry linked to a prescription drug monitoring program.

Data Sources

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3 Data sources for this study will include:

1. **Michigan Surgical Quality Collaborative (MSQC) Clinical Registry**: The MSQC maintains a clinical registry that collects patient demographics, perioperative processes, and 30-day outcomes for patients undergoing surgery in Michigan. Specifically, the MSQC captures patient reported outcomes by surveying patients between 30 and 90 days after the surgery. Participating hospitals receive funding from Blue Cross Blue Shield of Michigan to fund trained data abstractors that use standardized methods to obtain data for patients. Cases are audited annually for accuracy and reviewed using a sampling algorithm designed to minimize selection bias.
2. **Michigan Automated Prescription System (MAPS)**: The MAPS database is Michigan's prescription drug monitoring program (PDMP) which tracks all controlled substance fills (schedules 2-5) for residents of Michigan. Within this database, all controlled substance prescription fills are uniquely linked to individuals. The purpose of MAPS is to allow prescribers to monitor whether patients have existing controlled substance prescriptions or prescriptions from multiple sources and assess the associated risk prior to providing a new prescription.

Data linkage between MSQC and MAPS is performed by an independent third party data broker who then provides encrypted, de-identified data.

Inclusion Criteria

4 Inclusion criteria for this study will consist of the following elements:

1. Adult patients 18 years of age or older who undergo surgery captured in the MSQC clinical registry
2. Time frame patients undergo surgery will span from January 1, 2017, to October 31, 2019.
3. Data available on preoperative opioid exposure for 365 days before surgery
4. Patients will undergo surgery from one of the following MSQC surgery categories:
   - Laparoscopic Cholecystectomy
   - Laparoscopic Appendectomy
   - Open/Laparoscopic Inguinal/Femoral/Umbilical/Epigastric Hernia Repair
   - Open/Laparoscopic Ventral/Incisional Hernia Repair
   - Open/Laparoscopic Colectomy
   - Open/Laparoscopic Hysterectomy
   - Vaginal Hysterectomy

Exclusion Criteria

5 Exclusion criteria for this study will consist of the following elements:

1. Patients who have more than one match in MAPS. We anticipate a low proportion of patients to have multiple matches, which will not be possible to reconcile based on the use of the third party broker.
2. Non-Michigan residents. Out of state-controlled substance fills are not captured by MAPS, and thus an understanding of opioid use via prescription fills would not be complete.
3. Patients who have had surgery recorded within 90 days after discharge.

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4. Patients who die within 30 days of surgery.
5. Patients with a length of stay greater than 14 days.
6. Patients who are discharged not to home. While we anticipate most patients being discharged home, opioid use and other characteristics are likely to differ for persons not discharged home.
7. Patients with invalid surgeon data. We anticipate controlling for the surgeon in statistical models.
8. Patients with missing or unknown covariates.

Explanatory Variables

6 Our analysis will include the following explanatory variables:

1. Demographics: age in years, sex, race/ethnicity
2. Patient Characteristics:
   - American Society of Anesthesiologists (ASA) classification status
   - Obesity (body mass index >30 kg/m2)
   - Cancer
   - Congestive heart failure
   - Diabetes
   - Chronic obstructive pulmonary disease
   - Tobacco use within 1 year before surgery
3. Procedure and clinical characteristics
   - Procedure type - categorized as the MSQC surgery categories
   - Admission status - categorized as inpatient vs. outpatient
   - Surgical priority - categorized as elective vs. urgent/emergent
   - Length of stay in days
4. Primary exposure/**key explanatory variable**: filling vs. not filling a pre-operative opioid medication in the 365 days to 31 days prior to surgery as recorded in MAPS (yes/no)
5. Complications: The Agency of Healthcare Research and Quality Clinical Classification System was used to assign the International Classification of Disease 10th Edition (ICD-10-CM) diagnosis codes. MSQC recorded the first ICD code for an ER visit or readmission in the 30 days after surgery. The various common complications are as follows:
   - GI (obstruction, ileus, hernia, nausea/vomiting, diarrhea, ulcer disease, pancreaticobiliary complication, etc.)
   - Infectious (infection of any organ system)
   - Hematologic (hemorrhage, hematoma, anemia)
   - Other (diagnoses of cardiovascular, cerebrovascular, respiratory, gynecologic, musculoskeletal, ophthalmologic, and skin/soft tissue organ systems, traumatic injury)
   - Pain

Primary Outcome

7 The primary outcome of our study will be postoperative pain as reported from the MSQC survey given between postoperative days 30 and 90 on the first seven days after surgery. The survey asks patients to respond to the following question: "Thinking back, how would you rate your pain in the first week after your surgery." Responses on a 4-point Likert Scale are as follows:

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- No pain ("1")
- Mild pain ("2")
- Moderate pain ("3")
- Severe pain ("4")

Secondary Outcomes

8 Secondary outcomes for this study will include the following:

1. The incidence of emergency department visits in the 30 days after surgery from MSQC.
2. The incidence of hospital readmissions in the 30 days after surgery from MSQC.
3. The incidence of hospital reoperations in the 30 days after surgery from MSQC.
4. Regret undergoing surgery as reported from a survey given between postoperative days 30 and 90 which uses the 5 point Likert Scale Regret Rating. The survey asked patients to respond to the following question: do you regret your decision to undergo surgery? The options on the Likert Scale Regret Rating are as follows: 1= extremely regret surgery to 5= absolutely no regret.
5. Quality of Life (QOL) as reported from a survey given between postoperative days 30 and 90 which uses the 5 point Likert QOL Rating. The survey asked patients to respond to the following question: In general, what do you say your quality of life is. The options on the Likert Scale QOL Rating are as follows: 1= worst possible to 5= best possible
6. Satisfaction as reported from a survey given between postoperative days 30 and 90 using the 10 point Likert Satisfaction Rating. The survey asked patients to respond to the following question: Overall, how would you rate your satisfaction with your experience after surgery. The options on the Likert Scale Satisfaction Rating are as follows: 0= extremely dissatisfied to 10= extremely satisfied.

Statistical Analysis

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1. Descriptive analysis of patients who fill a prescription vs. patients who do not fill a prescription for opioids in the 365 days before surgery
2. Multilevel ordered logistic regression analysis using the key independent variable of opioid exposure in the year before surgery with other explanatory variables as additional independent variables, on the dependent variable of postoperative pain scores (primary). This will be used to estimate the predicted probability of having pain after surgery
3. Multilevel logistic regression of opioid exposure in the year before surgery with other patient-reported outcomes (dichotomized as highly satisfied vs. not highly satisfied, best possible quality of life vs. less than best possible quality of life, no regret vs. some regret), which will be used to estimate the predicted probabilities of patient-reported outcomes between the two study groups by procedure.
4. Multilevel logistic regression of clinical outcomes 30 days after surgery (emergency department visits, hospital readmissions, hospital operations) due to the five categories of complications (pain, GI, infectious, hematologic, and other), which will be used to estimate the predicted probabilities between the two study groups within each complication category
5. Sensitivity analysis excluding complications

Limitation of the Study

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10 1. MSQC limitations - retrospective, sampling algorithm, may not be applicable to other types of surgeries
2. We may miss prescriptions in some unusual cases or in instances in which opioid prescriptions are filled at pharmacies that don't participate in the state PDMP, though this is anticipated to be unlikely.
3. Decision to prescribe/ not prescribe is influenced by factors not analyzed such as diagnosis, patient age
4. Survey limitations-self-selection, recall bias

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