2020

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PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology
ISPE

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Journal:	*Pharmacoepidemiology and Drug Safety*
Manuscript ID	PDS-18-0298.R2
Wiley - Manuscript type:	Original Report
Date Submitted by the Author:	n/a
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Keywords:	hysterectomy, predictors, chronic opioid use
Abstract:	Background: Most women are prescribed an opioid after hysterectomy. The objective of this study was to determine the association between initial opioid prescribing characteristics and chronic opioid use after hysterectomy. Methods: This study included women enrolled in a commercial health plan who had a hysterectomy between July 01, 2010 and March 31, 2015. We used trajectory models to define chronic opioid use as patients with the highest probability of having an opioid prescription filled during the 6 months post-surgery. We used multivariable logistic regression to examine the association between initial opioid dispensing (amount prescribed and duration of treatment) and chronic opioid use after adjusting for potential confounders. Results: A total of 693 of 50,127 (1.38%) opioid naïve women met the criteria for chronic opioid use following hysterectomy. The baseline variables and initial opioid prescription characteristics predicted the pattern of long-term opioid use with moderate discrimination (c statistic = 0.70). Significant predictors of chronic opioid use included initial opioid daily dose (≥60 MME vs < 40 MME, aOR: 1.43, 95%CI: 1.14-1.79), and days' supply 4-7 days vs 1-3 days, aOR: 1.28, 95%CI: 1.06-1.54; ≥8 days vs 1-3 days, aOR: 1.41, 95%CI: 1.05-1.89). Other significant baseline predictors included older age, abdominal or laparoscopic/robotic hysterectomy, tobacco use, psychiatric medication use, back pain, and headache. Conclusion: Initial opioid prescribing characteristics are associated with risk of chronic opioid use after hysterectomy. Prescribing lower daily doses and shorter days' supply of opioids to women after hysterectomy

	may result in lower risk of chronic opioid use.

Chronic Opioid Use in Women following Hysterectomy: Patterns and Predictors

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Abstract

Background: Most women are prescribed an opioid after hysterectomy. The objective of this study was to determine the association between initial opioid prescribing characteristics and chronic opioid use after hysterectomy.

Methods: This study included women enrolled in a commercial health plan who had a hysterectomy between July 01, 2010 and March 31, 2015. We used trajectory models to define chronic opioid use as patients with the highest probability of having an opioid prescription filled during the 6 months post-surgery. We used multivariable logistic regression to examine the association between initial opioid dispensing (amount prescribed and duration of treatment) and chronic opioid use after adjusting for potential confounders.

Results: A total of 693 of 50,127 (1.38%) opioid naïve women met the criteria for chronic opioid use following hysterectomy. The baseline variables and initial opioid prescription characteristics predicted the pattern of long-term opioid use with moderate discrimination (c statistic = 0.70). Significant predictors of chronic opioid use included initial opioid daily dose (≥60 MME vs < 40 MME, aOR: 1.43, 95%CI: 1.14-1.79), and days' supply 4-7 days vs 1-3 days, aOR: 1.28, 95%CI: 1.06-1.54; ≥8 days vs 1-3 days, aOR: 1.41, 95%CI: 1.05-1.89). Other significant baseline predictors included older age, abdominal or laparoscopic/robotic hysterectomy, tobacco use, psychiatric medication use, back pain, and headache.

Conclusion: Initial opioid prescribing characteristics are associated with risk of chronic opioid use after hysterectomy. Prescribing lower daily doses and shorter days' supply of opioids to women after hysterectomy may result in lower risk of chronic opioid use.

Introduction

The rapid increase in the incidence of opioid-related overdoses and deaths has become a major public health crisis in the United States. Overdose and death from prescription opioid overdose increased 400% in women between 1999 and 2013.[1-3] For many women, their first exposure to prescription opioids often occurs during the post-operative period, which makes this a potential target for strategies to reduce the risk of chronic opioid use.[4-6] Several observational studies suggest that surgery is a risk factor for chronic opioid use.[5-18] Two studies have examined the relationship between the initial opioid prescribing characteristics and chronic opioid use in the postoperative setting and arrived at contradictory conclusions.[6,12] One study reported that initial exposure to prescription opioids after minor surgery increases the risk of chronic opioid use by 44%,[12] while the other suggested that the initial opioid prescribing characteristics, including type of opioid dispensed, days' supply, or daily dose (in morphine milligram equivalents), were not associated with chronic opioid use after cesarean delivery.[6]

Hysterectomy, the most commonly performed non-obstetric surgery among women in the United States,[19-21] poses a potential risk for chronic opioid use because an estimated 82% of patients receive an opioid prescription after the hysterectomy surgery.[20,22] However, the relationship between the initial opioid prescribing characteristics and chronic opioid use after hysterectomy remains largely unknown. The objective of this study was to identify baseline risk factors for chronic opioid use after hysterectomy and examine the association between initial opioid prescribing characteristics after hysterectomy and subsequent chronic use of opioids among opioid naïve women.

Methods

Data Sources: Study data were derived from the national OptumInsight Clinformatics Data Mart™ (OptumInsight, Eden Prairie, MN). The Optum Clinformatics Data Mart is an administrative health claims database from a large national insurer which includes

approximately 35 million beneficiaries. The dataset contains transactional reimbursement data for health care utilization including outpatient pharmacy dispensing, and inpatient and outpatient medical claims.[23] The administrative enrollment file has eligibility information, the outpatient pharmacy file has the national drug code (NDC) for each drug dispensed, and the medical files have the Current Procedural Terminology (CPT) code for medical procedure, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for medical procedure and diagnosis. Patients included in the database had both medical and prescription coverage. The data was used under license agreement between the University of Rhode Island and OptumInsight Inc.

Study Population: This study included women (≥ 18 years) who had a hysterectomy between July 01, 2010 and March 30, 2015. Women were required to have at least 6 months of continuous enrollment prior to hysterectomy. To identify an opioid-naïve study cohort, we excluded women with a diagnosis of opioid use disorders or any opioids filled 6 months before the date of the hysterectomy (index date) (eTable 1). The hysterectomy procedures were identified using ICD-9-CM procedure and CPT codes from both the inpatient and outpatient claims (eTable 1).[21,24] We excluded patients who had a radical hysterectomy and patients for whom we could not rule-out a cancer diagnosis which was defined as ≥ 2 separate medical claims with a cancer diagnosis occurred ≥42 days apart or receipt of chemotherapy, radiation, or other cancer-related surgery (eTable 1).[25] Women who filled at least one opioid prescription at a retail pharmacy within 7 days of discharge were considered exposed to prescription opioids and included in the final study cohort. The 7-day window was based on the assumption that an opioid prescription filled by an opioid naïve individual during this period was likely used to treat acute pain after hysterectomy. This study was approved by the University of Rhode Island Institutional Review Board (IRB#957873-2).

Exposure to opioids: Opioid prescriptions were identified using national drug codes (NDC) from the outpatient pharmacy claims. Opioid prescriptions were classified as hydrocodone,

oxycodone and others (including codeine, fentanyl, hydromorphone, meperidine, morphine, pentazocine, tapentadol, and tramadol). Duration of the initial prescription was categorized as 1-3, 4-7, ≥ 8 days. We calculated the morphine milligram equivalent (MME) for the initial opioid prescription using the Center for Disease Control (CDC) conversion Tables (2016 version). The average daily MME dose was categorized into tertiles (≤40mg/day, 40.50-58.9mg/day, and ≥60mg/day).

Outcome Assessment: We used trajectory models to generate our dichotomous primary study outcome as chronic opioid use after hysterectomy present or absent.[11] The trajectory models allow the use of observed longitudinal data to determine distinct opioid prescription filling patterns in the study population during the six months period after hysterectomy. This approach classifies patients into groups with similar opioid prescription filling patterns during follow-up without relying on a prespecified cutoff value for the definition of chronic opioid use.[26,27] In order to classify the trajectory groups for opioid use during the defined follow-up window (6 months after hysterectomy), we first generated 6 dichotomous variables to indicate if a study participant filled a prescription of an opioid analgesic during each of 6 consecutive 30-day follow-up periods, e.g., month 1 is from 7 to 37 days, month 2 is from 37 to 67 days, and month 6 is from 157 to 187 days.[11] We then modeled these 6 binary indicators of opioid use in each 30-day follow-up period as a longitudinal response in a logistic group-based trajectory.[28,29] Using the trajectory model, we estimated the probability of membership of patients in each group, and the probability of filling an opioid prescription over time as a smooth function of time. The model was fitted using 2 to 5 opioid exposure groups and the number of groups was chosen based on the value of the Bayesian Information Criterion.[30] In each group, a third-order polynomial (including linear, squared, and cubic terms) of time were used to model the probability of filling a prescription for opioids. Patients were assigned to the trajectory group in which they had the highest probability of membership. Based on the model results, the trajectory group with the highest probability of filling any opioid prescription beyond the initial prescription was defined as

"chronic opioid users". All other trajectory groupings were classified as non-chronic opioid users. The percentage of patients who filled an opioid prescription was reported in each trajectory for every consecutive 30-day follow-up period.

Potential Predictors of Chronic Opioid Use: We collected data on potential confounding variables that may be related to both initial opioid prescribing characteristics and chronic opioid use after hysterectomy.[6-11,31] Previous studies demonstrated that age, certain pain conditions, and psychiatric disorders are associated with both postsurgical chronic pain and chronic prescription opioid use.[6,21,31-36] Covariates assessed in our analyses included age at hysterectomy, Charlson comorbidity index, hospital length of stay, smoking status, use of alcohol and illicit substances, psychiatric medication use, pre-operative pain conditions, types of hysterectomy procedure performed, US census region, type of insurance (Medicare or private insurance) and health plan (exclusive provider organization, health maintenance organization, point of service, and others including indemnity and preferred provider organization), year of surgery, and initial opioid prescribing characteristics (medication type, average daily dose, and number of days' supplied).

Statistical Analysis: Categorical variables were examined and compared using Chi-squared or Fisher exact tests. Continuous variables were compared using the student *t* test. Statistical tests and modeling were conducted to identify risk factors for chronic opioid use among women after hysterectomy. A multivariable logistic regression model was used to estimate the association between baseline demographic and clinical variables, initial opioid prescribing characteristics, and chronic opioid use after hysterectomy among opioid-naive patients who filled at least one opioid prescription within 7 days after hysterectomy.

Sensitivity studies were conducted using multivariate logistic regression models to examine if the significant association between initial prescribing pattern and subsequent chronic opioid use were upheld with a different definition of chronic opioid use post hysterectomy or a more restricted definition for opioid naivety after adjusting for other covariates.

A probability of type 1 error (alpha) = 0.05 was set as the threshold of statistical significance. The trajectory models were conducted using "Proc Traj". All statistical analyses were performed using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc, Cary, NC).

Results

Study cohort: A total of 157,934 women underwent hysterectomy between 07/01/2010 and 03/31/2015. Of these patients, 22,186 (14%) patients did not meet the continuous enrollment criteria, 14,696 (9%) had suspected cancer diagnoses or radical hysterectomy, 18,202 (12%) didn't fill an opioid prescription within 7 days of surgery, 3,918 (2%) were missing important demographic data, 48,778 (31%) used opioids in the 6 months prior to surgery and 232 (0.1%) were diagnosed with OUD within 6 months prior to hysterectomy, leaving 50,127 (32%) patients for the analysis. A total of 12,985 (26%) patients had an abdominal hysterectomy; 29,640 (59%) patients had a laparoscopic or robotic assisted laparoscopic hysterectomy; and 7,502 (15%) patients had a vaginal hysterectomy (Figure 1).

The trajectory model identified 4 distinct trajectories of prescription opioid use after hysterectomy, with total 39,677 (79.15%) patients in trajectory 1, 3,304 (6.59%) in trajectory 2, 6,453 (12.87%) in trajectory 3, and 693 (1.38%) in trajectory 4. (Figure 2). Among the patients in trajectory 4 (n=693, 1.38%), 57%, 55%, 57%, 55%, 48%, and 41% filled an opioid prescription at 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months following an initial prescription in the 7 days post-hysterectomy, respectively. Patients in trajectory 4 were classified as chronic opioid users. No patient in trajectory 1 (n=39,677, 79.15%) filled any opioid prescription (0%) from month 1 to 6. Among patients in trajectory 2 (n=3,304, 6.59%), 0.3% filled a prescription at month 1, which increased to 2.6% at month 2, 8% at month 3, and then followed by 10% with opioid fills for the subsequent 3 months. Thirty-five percent of patients in trajectory 3 (n=6,543, 12.87%) filled an opioid prescription at month 1, which decreased to 8%

at month 2, and then gradually decreased to 4% at month 3, and 3% at months 4, 5, and 6. A description of the demographic and clinical characteristics of the patients assigned to each of these 4 trajectories is included in eTable2.

Characteristics of patients and initial prescriptions: Among the total 50,127 opioid naïve patients who filled at least one opioid prescription within 7 days after hysterectomy, 693 (1.38%) patients were categorized as chronic opioid users and 48,434(98.62%) were categorized as non-chronic users. Baseline characteristics among chronic opioid users after hysterectomy were significantly different from non-chronic opioid users (Table 1). Compared to the women without chronic opioid use, women with chronic opioid use were older and more likely to have a history of tobacco use, and a history of alcohol use. Chronic opioid users also were also more likely to be taking psychiatric medications, including benzodiazepines, antidepressants, and stimulants. Back pain and headache syndromes were more prevalent in the chronic opioid use group. Compared to women with commercial insurance, women with Medicare insurance had higher rates of chronic opioid use. About 1.5 percent of Medicare patients who were chronic opioid users after hysterectomy were younger than 65.

In unadjusted analyses, the average daily MME/day and the type of the initial opioid prescription were similar between women categorized as having chronic use and not having chronic opioid use. The days' supplied of the initial opioid was marginally greater among chronic users than for non-chronic users (5.12 versus 4.85 days, respectively, p = 0.02) (Table 1). Overall, oxycodone was more frequently prescribed hydrocodone or other opioids.

Predictors of chronic opioid use among all patients in the study: The results of multivariable logistic regression analyses are shown in Table 2. A number of factors were significantly associated with chronic opioid use after hysterectomy including older age, abdominal or laparoscopic/robotic hysterectomy, Charlson comorbidity index, tobacco use, alcohol use, and prescribed psychotropic medications. Pain conditions, including headache syndromes and back pain at baseline, were also identified as significant risk factors for chronic

opioid use after hysterectomy. Health plan type, census region, surgical setting, fibromyalgia, and other substance use disorders were not included in the final multivariable analyses due to lack of significance.

The characteristics of the initial opioid prescription, including type of opioid dispensed, days' supply, and daily dose in MME, were fitted in the model. Among initial opioid prescribing characteristics, significant predictors of chronic opioid use were initial prescription of hydrocodone (compared to oxycodone, aOR: 1.31, 95%CI: 1.10-1.57), days' supply (4-7 days vs ≤3 days, aOR: 1.28, 95%CI: 1.06-1.54; ≥8 days vs ≤ 3 days, aOR: 1.41, 95%CI: 1.05-1.89), and daily dose in MME (≥60 mg/day vs ≤40 mg/day, aOR: 1.43, 95%CI: 1.14-1.79), The C-statistic for the fitted full model was 0.70, indicating moderate predictability (Table 2)

The frequencies of post-surgery complications and other conditions associated with pain during the 6-month follow-up were examined in the study cohort (Table 3). Compared with non-chronic opioid users, women who developed chronic opioid use after hysterectomy were more frequently diagnosed with chronic pancreatitis, headache syndrome, back pain, fibromyalgia, and underwent additional anesthetic procedures.

Sensitivity Studies

We redefined chronic opioid use as a total duration of opioid use (total days' supply) that exceeded 90 days during 6-month follow-up period, finding that the days supplied and MME of the initial opioid prescription were associated with chronic opioid use according to this definition. An initial days supply was associated with an adjusted 1.81 fold increase in chronic use as compared with a supply of less than 3 days (95%CI: 1.21-2.70); while an initial MME/day of 60 or greater was associated with an adjusted 1.37 fold increase in chronic use (95%CI: 1.00-1.87) as compared with an initial MME of ≤ 39.64 mg/day). These results are similar as the results which defined chronic use using trajectory models.

In another sensitivity analysis, we applied a more restricted definition of opioid naivety by only including patients having 12-month continuous eligibility and without any opioid dispensing or diagnosis of OUD during the 12 months prior to hysterectomy. In this analysis, the highest tertile of MME/day (exceeding 58.92 mg) for the initial opioid prescription remained predictive of subsequent chronic opioid use as compared with the lowest tertile of ≤ 39.64 mg/day (aOR: 1.38; 95%CI: 1.07-1.80); while the trend for days supplied also remained consistent, albeit failing to reach statistical significance. (aOR: 1.38, 95%CI: 1.0-1.90 for 8+ days' supply vs ≤3 days' supply)

Discussion

Hysterectomy is the most common surgical procedure among non-pregnant women. In our study, among the 50,127 opioid naïve women who had a hysterectomy and were dispensed at least one opioid prescription within 7 days after hysterectomy, 1.38% became chronic opioid users during the 6 months after surgery. Several demographic factors, such as age, mode of hysterectomy, tobacco use, alcohol use, and psychiatric use were associated with chronic opioid use after hysterectomy. More importantly, however, we found that characteristics of the initial opioid prescription, including type, dose, and duration affected the probability of chronic opioid use. An initial supply of 8 or more days, and an initial MME of at least 60 mg per day were each associated with a greater than 40% increase in the risk of subsequent chronic use of opioids (Table 2). Each year in the United States, there are approximately 430,000 inpatient hysterectomy cases.[37] The findings of this study suggest that lessening the duration and amount of opioids in the initial opioid prescription may decrease in the risk of chronic opioid use after hysterectomy.

Multiple demographic and clinical factors were associated with increased risk of chronic opioid use after hysterectomy, including older age, abdominal or laparoscopic/robotic hysterectomy, comorbidities, tobacco use, substance use disorders, certain pain conditions, and

use of prescription psychiatric medications use (Table 2). Our findings were similar to other studies that showed that these factors increase the risk of chronic opioid use after major cardiac, thoracic, abdominal and pelvic procedures, or specific surgeries, including cesarean delivery, hysterectomy, hip or knee arthroplasty, spine, or bariatric surgeries.[5-17, 38, 39] These findings underscore the importance of considering the individual patient's pain management needs,risk factors for opioid misuse at the time of opioid prescribing after hysterectomy and other surgical procedures, and importance of medical care, monitoring and follow-up post-operatively .

The literature describing the relationship between the initial opioid prescribing characteristics and the risk of chronic opioid use after hysterectomy among opioid naïve patients is limited. Prior observational studies have produced inconclusive results, which may be attributed to the study sample (inclusion of patients with minor surgical procedures) or small study sample size.[11,38] Our results showed that initial opioid prescribing characteristics, including opioid type, daily dose, and duration of days' supply were associated with chronic opioid use in the 6 months following hysterectomy among opioid naïve patients. The odds of chronic opioid use following initiation after hysterectomy were 31% higher among patients starting hydrocodone compared to patients who began therapy with oxycodone even though prior research has demonstrated that oxycodone is associated with risk of addiction, morbidity and mortality.[40-42] One explanation for this finding is that for many years hydrocodone was the most commonly prescribed opioid medication in the United States, in part because it was a schedule III drug during the study period and was considered to be lesser risk than schedule II opioids such as oxycodone, therefore, hydrocodone may have been prescribed more liberally, especially to patients with a higher tendency of opioid overuse, which is a possible confounding by contraindication. In August 21, 2014, the U.S. Drug Enforcement Administration (DEA) issued stricter prescribing requirements and moved hydrocodone-containing medications from a Schedule III to a Schedule II controlled substance.[43] Notably, the initial opioid prescribing

characteristics, such as longer days' supply and higher daily morphine milligram equivalent dose, that were associated with post-operative chronic opioid use after hysterectomy, are also risk factors for opioid misuse and opioid-related mortality.[44-47] By identifying modifiable risk factors for chronic opioid use after hysterectomy, such as pre-operative opioid prescribing, abdominal or laparoscopic/robotic hysterectomy, and characteristics of opioid prescribing after surgery, we may be able to develop strategies and interventions to decrease the likelihood of chronic opioid use.

There is no standard definition for chronic opioid use after surgery. We selected the trajectory modeling approach because of its advantages over other methods for describing longitudinal trajectories and identifying patients who used opioids consistently over a longer duration.[29,30] Traditional medication adherence measures, such as the proportion of days covered or the number of months of continuous medication use, may not distinguish between consistent users in follow-up periods or between patients who discontinue medication completely versus those who simply have a gap in use. The trajectory models repeatedly assess medication use throughout the entire follow-up period and summarize long-term medication adherence accounting for the time-varying nature of adherence.[29] We found that 1.38% of hysterectomy patients became chronic opioid users in the 6 months after surgery. Using Optum data from January 01, 2011 to December 31, 2014, Swenson et al. reported 0.5% (122 out of 24,331) of women who had a hysterectomy had new persistent opioid use following hysterectomy.[5] In Swenson's study, persistent opioid use in the 6 months post-hysterectomy was defined as a minimum of 2 opioid prescriptions in the 6 months post-surgery (one between 15-90 days and one at least 91-180 days) and top quartile use (amount and duration).[5] The difference in incidence of chronic use/new persistent use between these studies is attributable to the use of different definitions for chronic opioid use.

Our findings suggest that prescribing lower doses for shorter days' supply may reduce the risk of subsequent chronic opioid use, and is consistent with the strategies published in

guidelines advocated by multiple federal and state agencies, professional societies, and advocacy groups. Although specific guidelines differ in exact wording and specific recommendations, prescribing the lowest dose for the shortest amount of time and screening for substance use and opioid dependence are clearly defined themes across multiple guidelines.[48-50] However, practice change solely on the basis of guidelines can be slow, and current evidence suggests that physicians are prescribing excess opioids to patients to control acute pain post-surgery at hospital discharge. Studies from the surgical fields of urology, orthopedics, and obstetrics and gynecology have shown that physicians prescribe more than twice the amount of opioid medication patients actually consume post-discharge which adds up to millions of excess unused opioid tablets available for diversion and abuse.[51-54] A recent study showed that among obstetricians and gynecologists, only 62% reported tailoring prescriptions to the individual patient and only 22% reported they performed an opioid dependence screen prior to prescribing.[55] Improving adherence to best practices for opioid prescribing, including tailoring prescriptions to the individual patient's pain management needs and risks of future opioid misuse and abuse, could play a major role in reducing the magnitude of the opioid epidemic.

Limitations

First, the study subjects included in this study are commercially insured in the United States with 9% covered by Medicare Advantage (Table1). The demographic characteristics, clinical conditions, and opioid preoperative use patterns may differ from uninsured, Medicaid or Medicare covered populations. Thus, the study results might not be generalizable to patients enrolled in Medicaid or Medicare.

Our study is subject to several limitations due to the nature of observational studies using claims data. Some important medical indications, such as severity of pain, which may be related to the hysterectomy procedure or underlying conditions leading to hysterectomy, were

not captured in the data. Other unmeasured confounding factors included social and economic factors during follow up. The low prevalence of OUDs or methadone use excluded in figure 1, and other substance use disorders, tobacco use, and alcohol use presented in table 1 might be due to poor sensitivity of ICD-9 diagnosis codes or CPT codes. However, the impact may be non-differential if the unmeasured variables are similarly distributed in two comparison groups.

Opioid analgesics were assessed using pharmacy claims, which only captured opioid medications legally obtained and filled at outpatient pharmacies. Patients not filling the initial opioid prescription post-hysterectomy may be attributed to either not using opioids for post-surgical pain or to receiving their opioid prescription from an inpatient pharmacy. The actual patterns of opioid use (actual consumption) was not measured and, based on prior studies, differs substantially from the amount of opioid medication prescribed. Furthermore, the result that hydrocodone has a higher risk of chronic use after hysterectomy compared to oxycodone could be due to a possible confounding by contraindication.

The outcome assessed in this study was chronic opioid use during the first 6 months after hysterectomy. Although chronic opioid use within 6 months has been associated with opioid misuse and opioid-related death, it was not possible to differentiate whether patients persistently used opioids for 6 months as a treatment for pain control or because they became dependent upon opioids after their post-surgical pain had abated.[56] Additionally, it was not possible to determine if the women were continuing to receive their opioid for the pain related to their hysterectomy or for other pain; It is possible that the reason for filling opioid prescriptions in the 6 months following hysterectomy was not for personal use but for diversion.[57] Our findings that chronic opioid use post hysterectomy was significantly associated with initial opioid prescribing could be due to complex relationships between chronic pain post-surgery, acute pain post-surgery, and chronic pain pre-surgery.

Conclusions

In this study, approximately 3 in 200 opioid naïve women appear to become chronic opioid users after hysterectomy. Besides commonly recognized demographic and clinical risk factors, chronic opioid use after hysterectomy was associated with initial opioid prescribing characteristics, such as longer days' supply and higher daily opioid dose. Although prescription opioid medications provide effective analgesia after surgery, they must be used with caution given the potential risk for subsequent chronic opioid use that is associated with opioid misuse and overdose-related mortality. Our findings support the need to manage post-surgical pain with the least amount of opioid medication possible to effectively control a patient's symptoms, and close clinical post-op follow-up for those patients who prescribed opioids.

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Figure 1. Flow Chart of the Study Population.

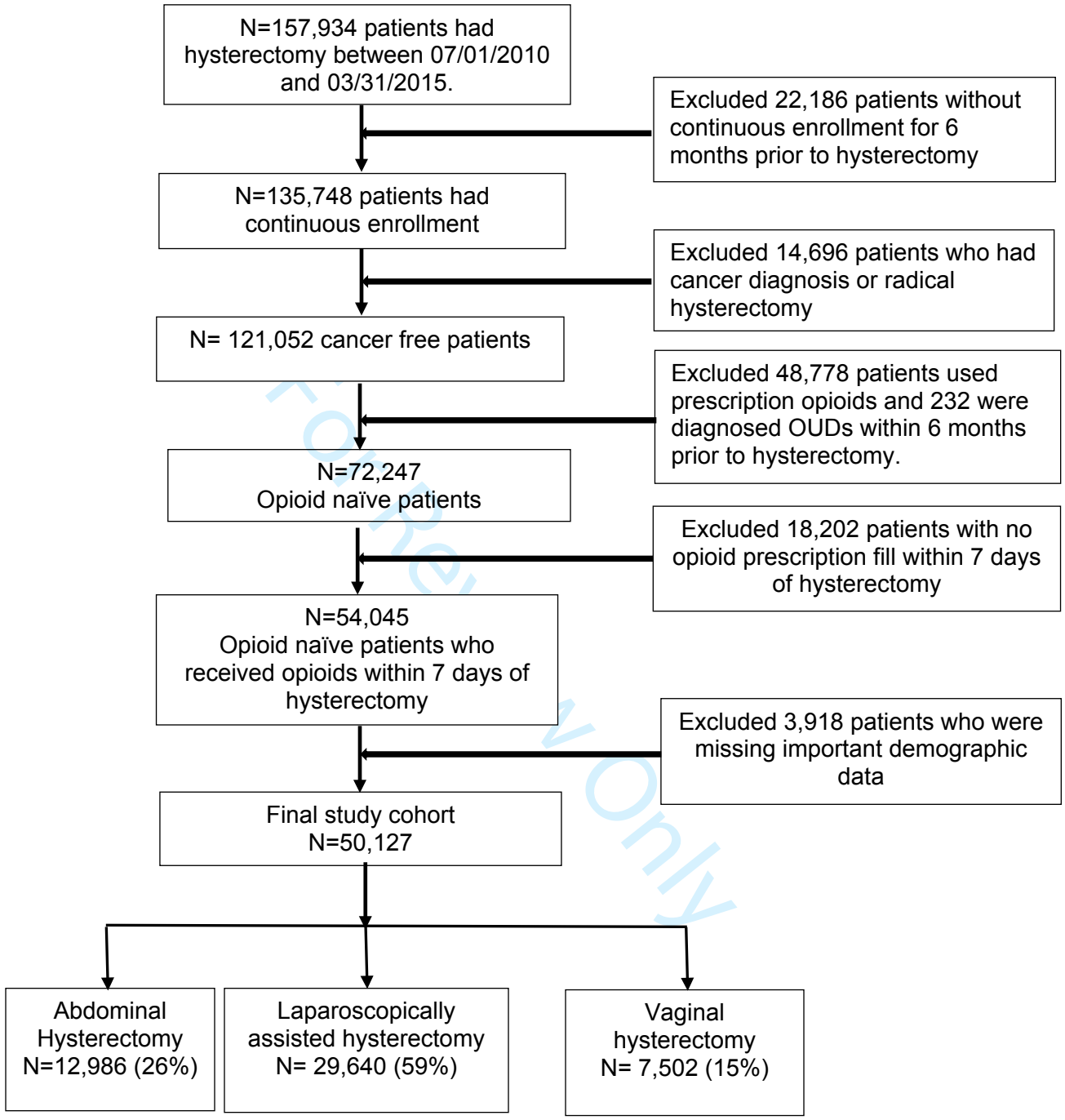
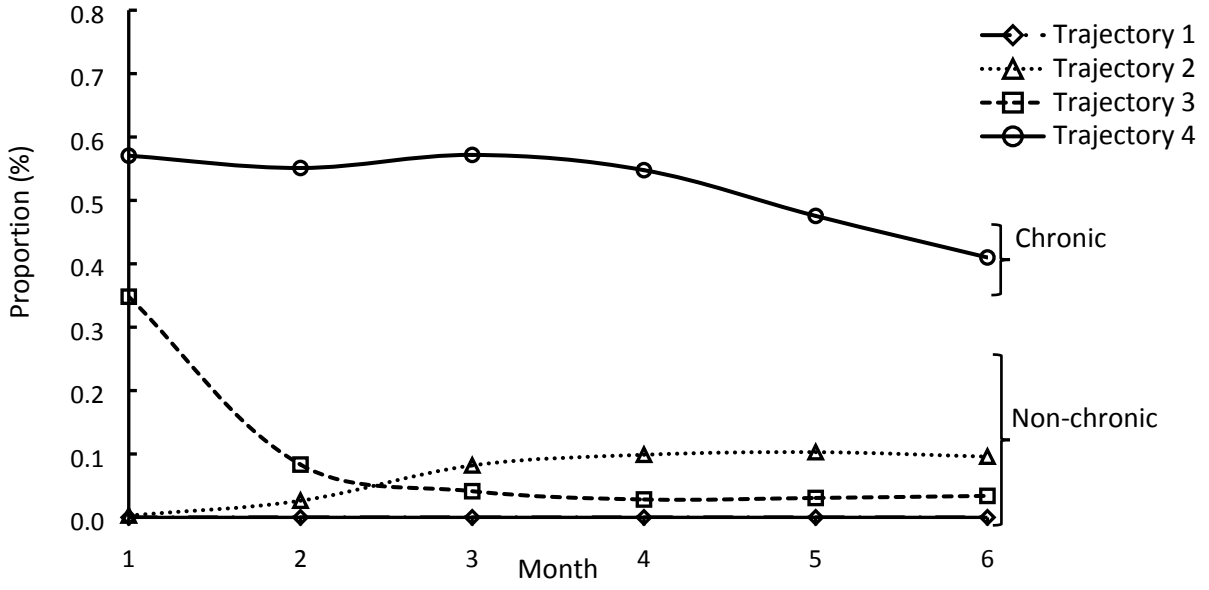


Figure 2. Trajectories of filling opioid prescriptions in 6 months post hysterectomy. The solid or dashed lines represent the distinct estimated opioid prescription filling trajectories. The dot symbols represent the mean estimated proportion in each trajectory group dispensed an opioid prescription at each month. These indicate the mean estimated probability of filling an opioid prescription for patients in each group at each time point. Overall counts and percentages of patients in each group are presented in the underneath table. Patients in trajectory 4 were classified as opioid chronic users. Patients in trajectories 1, 2, 3 were classified as opioid non-chronic users. The x-axis indicates each 30-day interval during the 6-month follow-up period, while the y-axis indicates the estimated proportion of patients filled a prescription opioid within each 30-day interval.



Trajectories	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4
N (%)	39,677 (79.15%)	3,304 (6.59%)	6,453 (12.87%)	693 (1.38%)

Table 1. Comparison of baseline patient characteristics among opioid-naïve patients who received prescription opioids within 7 days after hysterectomy, N=50,127

Patient characteristics	Non-chronic Users† (N=48,434)	Chronic Opioid Users‡ (N= 693)	P-value
Charlson Comorbidity Index, mean (95% CI)	1.60 (1.57, 1.64)	1.74 (1.45, 2.02)	0.3479
Length of stay in days, mean (95% CI)	2.32 (2.30, 2.35)	3.79 (3.39, 4.19)	<0.0001
Age, years, mean (95% CI)	48.1 (48.0, 48.2)	49.8 (48.9,50.7)	0.0004
Age at hysterectomy, years			
<40	9,100 (18.41)	126 (18.18)	<.0001
40-49	22,538 (45.59)	255 (36.80)	
50+	17,796 (36.00)	312 (45.02)	
Substance use and abuse, N (%)			
Tobacco	2,637 (5.33)	60 (8.66)	0.0001
Alcohol	177 (0.36)	9 (1.30)	<.0001
Other substance use disorders§	55 (0.11)	4 (0.58)	0.0004
Psychiatric medications, N (%)			
Benzodiazepines	4,201 (8.50)	125 (18.04)	<.0001
Antidepressants	9,984 (20.20)	233 (33.62)	< .0001
Stimulants	767 (1.55)	25 (3.61)	< .0001
Pain conditions, N (%)			
Fibromyalgia	1,530 (3.10)	30 (4.33)	0.0632
Headache syndromes	4,019 (8.13)	82 (11.83)	0 .0004
Back pain	4,659 (9.42)	110 (15.87)	< .0001
Type of hysterectomy, N (%)			
Abdominal hysterectomy	12,757 (25.81)	228 (32.90)	<.0001
Vaginal hysterectomy	7,428 (15.03	74 (10.68)	
Laparoscopic/Robotic	29,249 (59.17)	391 (56.42)	
Surgery setting, N (%)			
Inpatient	19,805 (40.06)	352 (50.79)	<.0001
Outpatient	29,629 (59.94)	341 (49.21)	
US census region, N (%)			
Midwest	13,705 (27.72)	186 (26.84)	0.6351
Northeast	5,075 (10.27)	66 (9.52)	
South	23,642 (47.83)	332 (47.91)	
West	7,012 (14.18)	109 (15.73)	
Insurance type, N (%)			
Commercial	45,107 (91.25)	586 (84.56)	< .0001
Medicare	4,327 (8.75)	107 (15.44)	
Type of health plan, N (%)			
Exclusive provider organization	5,990 (12.12)	70 (10.10)	0.0008
Health maintenance organization	4,913 (9.94)	89 (12.84)	
Point of service	34,004 (68.79)	449 (64.79)	
Others¶	4,527 (9.16)	85 (12.27)	
Year of hysterectomy			
2010-2013	21,949 (44.40)	287 (41.41)	0.1161
2014-2015	27,485 (55.60)	406 (58.59)	

Initial Opioid Prescription Characteristics			
Days' supply, days	4.85 (4.82, 4.87)	5.12 (4.89, 5.34)	0.0205
Average daily MME, mg/day	54.7 (54.3, 55.0)	58.4 (54.6, 62.2)	0.0571
Type of Opioid, N(%)			
Hydrocodone	17,555 (35.51)	266 (38.38)	0.0553
Oxycodone	27,434 (55.50)	354 (51.08)	
Other	4,445 (8.99)	73 (10.53)	
Tertile MME, mg/day			
<=40	16,154 (32.68)	219 (31.60)	0.2425
40.5-58.9	16,718 (33.82)	221 (31.89)	
60.0+	16,562 (33.50)	253 (36.51)	
Days' supply, days			
1-3	15,667 (31.69)	193 (27.85)	0.0566
4-7	29,098 (58.86)	423 (61.04)	
8+	4,669 (9.44)	77 (11.11)	

Abbreviation: MME=Morphine Milligram Equivalent

†Non-chronic users refer to patients in trajectory 1, 2, and 3 in Figure 2.

‡Chronic Opioid users refer to patients in trajectory 4 in Figure 2.

§Other substance use includes cocaine, marijuana, anxiolytic, stimulant, hallucinogenic drugs, or abuse of unspecified drugs/medications.

¶Others include Indemnity and Preferred provider organization.

Table 2. Baseline and initial opioid prescription characteristics that predict chronic opioid use following hysterectomy among opioid naive patients, 2010-2015; N=50, 127

Characteristics	Unadjusted OR (95% CI)	Adjusted OR[†] (95% CI)
Age group, years		
40-49	Ref.	Ref.
< 40	1.22 (0.99, 1.52)	1.20 (0.97, 1.49)
≥ 50	1.55 (1.31, 1.83)	1.37 (1.14 1.65)
Insurance type		
Commercial	Ref.	Ref.
Medicare	1.90 (1.55, 2.35)	1.98 (1.37, 2.87
Type of health plan, N (%)		
Exclusive provider organization	Ref.	Ref.
Health maintenance organization	1.55 (1.13, 2.13)	1.19 (0.84, 1.68)
Point of service	1.13 (0.88, 1.46)	1.10 (0.85, 1.42)
Others[‡]	1.61 (1.17, 2.21)	0.75 (0.48, 1.18)
Type of hysterectomy		
Vaginal hysterectomy	Ref.	Ref.
Laparoscopic/Robotic	1.79 (1.38, 2.34)	1.52 (1.16, 2.00)
Abdominal hysterectomy	1.34 (1.05, 1.72)	1.40 (1.09, 1.80)
Year (2010-2013 vs 2014-2015)	1.13 (0.97, 1.32)	1.24 (1.06, 1.46)
Length of stay (days)	1.14 (1.11, 1.16)	1.12 (1.10, 1.15)
Charlson comorbidity index	1.18 (1.06, 1.31)	1.16 (1.04, 1.30)
Pain conditions		
Headache (Yes vs. No)	1.52 (1.20, 1.91)	1.33 (1.04, 1.69)
Back pain (Yes vs. No)	1.81 (1.48, 2.23)	1.57 (1.27, 1.94)
Substance use		
Alcohol	3.66 (1.87, 7.18)	1.84 (0.91, 3.74)
Tobacco	1.68 (1.29, 2.20)	1.47 (1.12, 1.93)
Psychiatric medications		
Antidepressants	2.00 (1.71, 2.35)	1.71 (1.45, 2.03)
Benzodiazepines	2.37 (1.95, 2.88)	1.89 (1.54, 2.33)
Psychostimulants	2.38 (1.58, 3.56)	1.84 (1.21, 2.80)
Initial Opioid Prescription Characteristics		
Type of opioid		
Oxycodone	Ref.	Ref.
Hydrocodone	1.17 (1.00, 1.38)	1.31 (1.10, 1.57)
Other	1.27 (0.99, 1.64)	1.26 (0.96, 1.64)
Days' supply, days		
≤ 3	Ref.	Ref.
4-7	1.18 (0.99, 1.40)	1.28 (1.06, 1.54)
≥ 8	1.34 (1.03, 1.75)	1.41 (1.05, 1.89)
Tertile MME, mg/day		
< 40	Ref.	Ref.
40 -58.9	0.98 (0.81, 1.18)	1.14 (0.93, 1.40)
≥ 60.0	1.13 (0.94, 1.35)	1.43 (1.14, 1.79)

Abbreviation: MME=Morphine Milligram Equivalent

Adjusted model: c-statistic = 0.70; Hosmer-Lemeshow Goodness-of-fit Test: X^2 =19.30, df=8, p=0.0133

[†]Adjusted for baseline patient demographic and clinical characteristics listed in this table.
[‡]Others include Indemnity and Preferred provider organization.

Table 3. Distribution of possible indications for chronic opioid use during the 6-month follow-up period after hysterectomy: shown as N (%).

Possible indications	**All patients in cohort (N = 50,127)**	**Non-chronic Users (N = 49,434)**	**Chronic Opioid Users (N = 693)**	**P-value**
Chronic pancreatitis	70 (0.14)	63 (0.13)	7 (1.01)	<.0001
Headache syndromes	3,284 (6.55)	3,196 (6.47)	88 (12.70)	< .0001
Back pain	4,477 (8.93)	4,287 (8.67)	190 (27.42)	< .0001
Fibromyalgia	1,470 (2.93)	1,407 (2.85)	63 (9.09)	< .0001
Additional anesthetic procedures[†]				< .0001
0	46,132 (92.03)	45,768 (92.58)	364 (52.53)	
1	3,310 (6.60)	3,099 (6.27)	211 (30.45)	
2	525 (1.05)	459 (0.93)	66 (9.52)	
≥ 3	160 (0.32)	108 (0.22)	52 (7.50)	

[†]Number of additional procedures requiring anesthesia.

eTable 1. Operational definitions of essential baseline covariates

Patient characteristics	Operational definitions
Age	Age in years as of the date of the hysterectomy (index date). Age was categorized as <40, 40–49, and ≥50 years.
Charlson comorbidity index	The Charlson Comorbidity Index was to categorize comorbidities based on the presence of ICD-9 and ICD-10 diagnosis codes. A weighted sum provided in a single comorbidity score for a patient. We used a Quan's enhanced Charlson and Elixhauser comorbidity index.
Length of stay	Length of stay refers to the duration of hospitalization and clinical stay for the index hysterectomy procedure.
Year	The calendar year of the index date was divided into early (2010 to 2012) and late (2013 to 2015) and included in the model as a dichotomous variable.
Type of hysterectomy	Identified using ICD9 procedure codes and CPT codes
Opioid use disorder	ICD9 diagnosis codes for opioid use disorder and buprenorphine and methadone used for medication-assisted treatment.
Non-rule-out cancer diagnosis	Defined as ≥ 2 separate cancer diagnoses occurred ≥ 42 days apart or 1 cancer diagnosis with ≥ 1 procedures, including chemotherapy, radiation, or cancer-related surgery.[25]
Chronic opioid use	To identify chronic opioid use after hysterectomy group-based trajectory models were used to group together patients with similar patterns of medication filling during follow-up. The group with the highest filling probability was classified as chronic users.
Psychiatric medications	Psychotropic medication use during baseline identified using the American Hospital Formulary System (AHFS) Therapeutic codes and national drug codes
Pain conditions (fibromyalgia, headache syndromes, back pain)	Identified using ICD-9 diagnosis codes
Substance use and abuse (tobacco, alcohol, marijuana, cocaine, etc.)	Identified using ICD-9 diagnosis codes
US census region	US census region refers to the region where patient had the hysterectomy procedure as defined by the US Census Bureau
Insurance type	All patients in the database are insured. There were two types of insurance: commercial or Medicare.
Characteristics of initial opioid prescription	
Type of opioid	The first opioid prescriptions filled were classified as Oxycodone, Hydrocodone, or other (Codeine, Fentanyl, Hydromorphone, Meperidine, Morphine, Pentazocine, Tapentadol, and Tramadol).
Number of days' supply	Number of days' supply for the first opioid prescription after hysterectomy was divided into 3 categories (1-3 days, 4-7 days, and 8 or more days).
MME tertiles	The morphine milligram equivalent daily dose for the initial opioid prescription was determined, and the daily dose was

	divided into tertiles for the analysis (corresponding to thresholds of ≤40 mg, 40.50 mg to 57.86 mg and ≥58.33 mg of oral morphine equivalent).

eTable 2. Comparison of baseline patient characteristics among four trajectory-based model groups, N=50,127

Patient characteristics	TBM Group 1 (N=39,677)	TBM Group 2 (N= 3304)	TBM Group 3 (N= 6453)	TBM Group 4 (N=693)
LOS in days, mean (95% CI)	2.23 (2.20, 2.25)	2.46 (2.34, 2.58)	2.77 (2.68, 2.86)	3.79 (3.39, 4.19)
CCI, mean (95% CI)	1.59 (1.54, 1.63)	1.71 (1.57, 1.85)	1.63 (1.52, 1.75)	1.74 (1.45, 2.02)
Age (years), mean (95% CI)	48.27 (48.17, 48.38)	48.30 (47.92, 48.67)	47.17 (46.92, 47.42)	49.77 (48.87, 50.67)
Age at hysterectomy (years), N (%)				
< 40	7086 (17.86)	666 (20.16)	1348 (20.89)	126 (18.18)
40-49	18119 (45.67)	1411 (42.71)	3008 (46.61)	255 (36.80)
≥ 50	14472 (36.47)	1227 (37.14)	2097 (32.50)	312 (45.02)
Substance use and abuse, N (%)	1907 (4.81)	230 (6.96)	500 (7.75)	60 (8.66)
Tobacco use	117 (0.29)	12 (0.36)	48 (0.74)	9 (1.30)
Alcohol abuse	41 (0.10)	3 (0.09)	11 (0.17)	4 (0.58)
Other substance abuse†				
Psychiatric medications				
Benzodiazepines	3071 (7.74)	355 (10.74)	775 (12.01)	125 (18.04)
Antidepressants	7485 (18.86)	878 (26.57)	1621 (25.12)	233 (33.62)
Psychostimulants	556 (1.40)	86 (2.60)	125 (1.94)	25 (3.61)
Pain conditions, N (%)				
Fibromyalgia	1144 (2.88)	155 (4.69)	231 (3.58)	30 (4.33)
Headache syndromes	3012 (7.59)	356 (10.77)	651 (10.09)	82 (11.83)
Back pain	3624 (9.13)	363 (10.99)	672 (10.41)	110 (15.87)
Type of hysterectomy, N (%)	9779 (24.65)	773 (23.40)	2205 (34.17)	228 (32.90)
Vaginal hysterectomy	6113 (15.41)	499 (15.10)	816 (12.65)	74 (10.68)
Laparoscopic/Robotic	23785 (59.95)	2032 (61.50)	3432 (53.18)	391 (56.42)
Abdominal hysterectomy				
US census region, N (%)				
Midwest	11101 (27.98)	900 (27.24)	1704 (26.41)	186 (26.84)
Northeast	4232 (10.67)	313 99.47)	530 (8.21)	66 (9.52)
South	18700 (47.13)	1654 (50.06)	3288 (50.95)	332 (47.91)
West	5644 (14.22)	437 (13.23)	931 (14.43)	109 (15.73)
Insurance type, N (%)				
Commercial	36225 (91.30)	2964 (89.71)	5918 (91.71)	586 (84.56)
Medicare	3452 (8.70)	340 (10.29)	535 (8.29)	107 (15.44)
Type of health plan, N (%)				
Exclusive provider organization	4779 (12.04)	408 (12.35)	1,061 (12.54)	70 (10.10)
Health maintenance organization	3981 (10.03)	320 (9.69)	867 (10.24)	89 (12.84)
Others‡	3646 (9.19)	333 (10.08)	647 (7.65)	85 (12.27)
Point of service	27271 (68.73)	2243 (67.89)	5,888 (69.57)	449 (64.79)

Initial Opioid Prescription Characteristics				
Days' supply (days), mean (95% CI)	4.83 (4.81, 4.86)	4.86 (4.76, 4.95)	4.95 (4.88, 5.02)	5.12 (4.89, 5.34)
Avg. MME, mg/day (95% CI)	54.37 (53.99, 54.75)	55.93 (54.33, 57.54)	56.04 (54.96, 57.11)	58.39 (54.60, 62.18)
Type of Opioid, N (%)				
Hydrocodone	13697 (34.52)	1241 (37.56)	2617 (40.55)	266 (38.38)
Oxycodone	22431 (56.53)	1766 (53.45)	3237 (50.16)	354 (51.08)
Other	3549 (8.94)	297 (8.99)	599 (9.28)	73 (10.53)
Days' supply (days), N (%)				
1-3	12703 (32.02)	1048 (31.72)	1916 (29.69)	193 (27.85)
4-7	23273 (58.66)	1951 (59.05)	3874 (60.03)	423 (61.04)
≥ 8	3701 (9.33)	305 (9.23)	663 (10.27)	77 (11.11)
Tertile MME (mg/day), N (%)				
< 40	13034 (32.85)	1079 (32.66)	2041 (31.63)	219 (31.60)
40 – 58.93	13412 (33.80)	1102 (33.35)	2204 (34.15)	221 (31.89)
≥ 60	13231 (33.35)	1123 (33.99)	2208 (34.22)	253 (36.51)

Abbreviations: TBM=Trajectory based model; CCI= Charlson Comorbidity Index; LOS=Length of stay; MME=Morphine milligram equivalent;

[†]Other substance use includes marijuana, cocaine, anxiolytic, stimulant, hallucinogenic drugs, or abuse of unspecified drugs/medications.

[‡]Others include Preferred Provider Organization and Indemnity.

Chronic Opioid Use in Women following Hysterectomy: Patterns and Predictors

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Abstract

Background Most women are prescribed an opioid ~~at hospital discharge~~ after hysterectomy. The objective of this study was to determine the association between initial opioid prescribing characteristics and chronic opioid use after hysterectomy.

Methods: This study included women enrolled in a commercial health plan who had a hysterectomy between July 01, 2010 and March 31, 2015. We used trajectory models to define chronic opioid use as patients with the highest probability of having an opioid prescription filled during the 6 months post-surgery. We used multivariable logistic regression to examine the association between initial opioid dispensing (amount prescribed and duration of treatment) and chronic opioid use after adjusting for potential confounders.

Results: A total of ~~434~~ 693 of ~~49,844~~50,127 (~~0.9~~1.38%) opioid naïve women met the criteria for chronic opioid use following hysterectomy. The baseline variables and initial opioid prescription characteristics predicted the pattern of long-term opioid use with moderate discrimination (c statistic = ~~0.73~~0.70). Significant predictors of chronic opioid use included initial opioid daily dose (≥60 MME vs < 40 MME, aOR: ~~1.70~~1.43, 95%CI: ~~1.28~~1.14-~~2.26~~1.79), and days' supply 4-7 days vs 1-3 days, aOR: ~~1.41~~1.28, 95%CI: ~~1.11~~1.06-~~1.79~~1.54; ≥8 days vs 1-3 days, aOR: ~~2.04~~1.41, 95%CI: ~~1.43~~1.05-~~2.90~~1.89). Other significant baseline predictors included older age, abdominal or laparoscopic/robotic hysterectomy~~hysterectomy type~~, tobacco use, ~~co-morbidities~~psychiatric medication use, back pain, and ~~fibromyalgia~~headache.

Conclusion: Initial opioid prescribing characteristics are associated with risk of chronic opioid use after hysterectomy. Prescribing lower daily doses and shorter days' supply of opioids to women after hysterectomy may result in lower risk of chronic opioid use.

Introduction

The rapid increase in the incidence of opioid-related overdoses and deaths has become a major public health ~~issue~~ crisis in the United States. Overdose and death from prescription opioid overdose increased 400% in women between 1999 and 2013.[1-3] For many women, their first exposure to prescription opioids often occurs during the post-operative period, which makes this a potential target for strategies to reduce the risk of chronic opioid use.[4-6] Several observational studies suggest that surgery is a risk factor for chronic opioid use.[5-18] Two studies have examined the relationship between the initial opioid prescribing characteristics and chronic opioid use in the postoperative setting and arrived at contradictory conclusions.[6,12] One study reported that initial exposure to prescription opioids after minor surgery increases the risk of chronic opioid use by 44%,[12] while the other suggested that the initial opioid prescribing characteristics, including type of opioid dispensed, days' supply, or daily dose (in morphine milligram equivalents), were not associated with chronic opioid use after cesarean delivery.[6]

Hysterectomy, the most commonly performed non-obstetric surgery among women in the United States,[19-21] poses a potential risk for chronic opioid use because an estimated 82% of ~~hysterectomy~~ patients receive an opioid prescription ~~at hospital discharge~~after the hysterectomy surgery.[20,22] However, the relationship between the initial opioid prescribing characteristics and chronic opioid use after hysterectomy remains largely unknown. The objective of this study was to identify baseline risk factors for chronic opioid use after hysterectomy and examine the association between initial opioid prescribing characteristics after hysterectomy and subsequent chronic use of opioids among opioid naïve women.

Methods

Data Sources: Study data were derived from the national OptumInsight Clinformatics Data Mart™ (OptumInsight, Eden Prairie, MN). The Optum Clinformatics Data Mart is an

administrative health claims database from a large national insurer which includes approximately 35 million beneficiaries. The dataset contains transactional reimbursement data for health care utilization including outpatient pharmacy dispensing, and inpatient and outpatient medical claims.[23] The administrative enrollment file has eligibility information, the outpatient pharmacy file has the national drug code (NDC) for each drug dispensed, and the medical files have the Current Procedural Terminology (CPT) code for medical procedure, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for medical procedure and diagnosis. Patients included in the database had both medical and prescription coverage. The data was used under license agreement between the University of Rhode Island and OptumInsight Inc.

Study Population: This study included women (≥ 18 years) who had a hysterectomy between July 01, 2010 and March 30, 2015. Women were required to have at least 6 months of continuous enrollment prior to hysterectomy. To identify an opioid-naïve study cohort, we excluded women with a diagnosis of opioid use disorders or any opioids filled 6 months before the date of the hysterectomy (index date) (eTable 1). The hysterectomy procedures were identified using ICD-9-CM procedure and CPT codes from both the inpatient and outpatient claims (eTable 1).[21,24] We excluded patients who had a radical hysterectomy and patients for whom we could not rule-out a cancer diagnosis which was defined as ≥ 2 separate medical claims with a cancer diagnosis occurred ≥42 days apart or receipt of chemotherapy, radiation, or other cancer-related surgery (eTable 1).[25] Women who filled at least one opioid prescription at a retail pharmacy within 7 days of discharge were considered exposed to prescription opioids and included in the final study cohort. The 7-day window was based on the assumption that an opioid prescription filled by an opioid naïve individual during this period was likely used to treat acute pain after hysterectomy. This study was approved by the University of Rhode Island Institutional Review Board (IRB#957873-2).

Exposure to opioids: Opioid prescriptions were identified using national drug codes (NDC) from the outpatient pharmacy claims. Opioid prescriptions were classified as hydrocodone, oxycodone and others (including codeine, fentanyl, hydromorphone, meperidine, morphine, pentazocine, tapentadol, and tramadol). Duration of the initial prescription was categorized as 1-3, 4-7, ≥ 8 days. We calculated the morphine milligram equivalent (MME) for the initial opioid prescription using the Center for Disease Control (CDC) conversion Tables (2016 version). The average daily MME dose was categorized into tertiles (≤40mg/day, 40.50-58.9mg/day, and ≥60mg/day).

Outcome Assessment: We used trajectory models to generate our dichotomous primary study outcome as (chronic opioid use after hysterectomy present or absent).[11] The trajectory models allow the use of observed longitudinal data to determine distinct opioid prescription filling patterns in the study population during the six months period after hysterectomy. This approach classifies patients into groups with similar opioid prescription filling patterns during follow-up without relying on a ~~priori and often subjective~~ prespecified cutoff value for the definition of chronic opioid use.[26,27] In order to classify the trajectory groups for opioid use during the defined follow-up window (6 months after hysterectomy), we first generated 6 dichotomous variables to indicate if a study participant filled a prescription of an opioid analgesic during each of 6 consecutive 30-day follow-up periods, e.g., month 1 is from 7 to 37 days, month 2 is from 37 to 67 days, and month 6 is from 157 to 187 days.[11] We then modeled these 6 binary indicators of opioid use in each 30-day follow-up period as a longitudinal response in a logistic group-based trajectory.[28,29] Using the trajectory model, we estimated the probability of membership of patients in each group, and the probability of filling an opioid prescription over time as a smooth function of time. The model was fitted using 2 to ~~6~~ 5 opioid exposure groups and the number of groups was chosen based on the value of the Bayesian Information Criterion.[30] In each group, a third-order polynomial (including linear, squared, and cubic terms) of time were used to model the probability of filling a prescription for opioids. Patients were assigned to the trajectory group in

which they had the highest probability of membership. Based on the model results, the trajectory group with the highest probability of filling any opioid prescription beyond the initial prescription was defined as "chronic opioid users". All other trajectory groupings were classified as non-chronic opioid users. The percentage of patients who filled an opioid prescription was reported in each trajectory for every consecutive 30-day follow-up period.

Potential Predictors of Chronic Opioid Use: We collected data on potential confounding variables that may be related to both initial opioid prescribing characteristics and chronic opioid use after hysterectomy.[6-11,31] Previous studies demonstrated that age, certain pain conditions, and psychiatric disorders are associated with both postsurgical chronic pain and chronic prescription opioid use.[6,21,31-36] Covariates assessed in our analyses included age at hysterectomy, Charlson comorbidity index, hospital length of stay, smoking status, use of alcohol and illicit substances, psychiatric medication use, pre-operative pain conditions, types of hysterectomy procedure performed, US census region, type of insurance (Medicare or private insurance) and health plan (exclusive provider organization, health maintenance organization, point of service, and others including indemnity and preferred provider organization), year of surgery, and initial opioid prescribing characteristics (medication type, average daily dose, and number of days' supplied).

Statistical Analysis: Categorical variables were examined and compared using Chi-squared or Fisher exact tests. Continuous variables were compared using the student *t* test. Statistical tests and modeling were conducted to identify risk factors for chronic opioid use among women after hysterectomy. A multivariable logistic regression model was used to estimate the association between baseline demographic and clinical variables, initial opioid prescribing characteristics, and chronic opioid use after hysterectomy among opioid-naive patients who filled at least one opioid prescription within 7 days after hysterectomy.

Sensitivity studies were conducted using multivariate logistic regression models to examine if the significant association between initial prescribing pattern and subsequent chronic

opioid use were upheld with a different definition of chronic opioid use post hysterectomy or a more restricted definition for opioid naivety after adjusting for other covariates.

A probability of type 1 error (alpha) = 0.05 was set as the threshold of statistical significance. The trajectory models were conducted using "Proc Traj". All statistical analyses were performed using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc, Cary, NC).

Results

Study cohort: A total of 157,934 women underwent hysterectomy between 07/01/2010 and 03/31/2015. Of these patients, 22,186 (14%) patients did not meet the continuous enrollment criteria, 14,696 (9%) had suspected cancer diagnoses or radical hysterectomy, ~~23,707~~18,202 (12%) didn't fill an opioid prescription within 7 days of surgery, ~~3,810~~3,918 (2%) were missing important demographic data, ~~43,303~~48,778 (31%) used opioids in the 6 months prior to surgery and 232 (0.1%) were diagnosed with OUDs within 6 months prior to hysterectomy, leaving ~~49,844~~50,127 (32%) patients for the analysis. ~~In the final study cohort, only 3 patients lost eligibility and were censored during the 6-month follow-up period.~~ A total of 12,~~966~~ 985 (26%) patients had an abdominal hysterectomy; 29,~~409~~ 640 (59%) patients had a laparoscopic or robotic assisted laparoscopic hysterectomy; and 7,~~469~~ 502 (15%) patients had a vaginal hysterectomy (Figure 1).

The trajectory model identified 4 distinct trajectories of prescription opioid use after hysterectomy, with total 39,677 (79.15%) patients in trajectory 1, 3,304 (6.59%) in trajectory 2, 6,453 (12.87%) in trajectory 3, and 693 (1.38%) in trajectory 4. (Figure 2). Among the patients in trajectory 4 (n=~~434~~693, ~~0.87~~1.38%), ~~70~~57%, ~~60~~55%, ~~68~~57%, ~~76~~55%, ~~72~~48%, and ~~53~~41% filled an opioid prescription at 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months following an initial prescription in the 7 days post-hysterectomy, respectively. Patients in trajectory 4 were classified as chronic opioid users. No patient in trajectory 1 (n=39,677,

79.15%) filled any opioid prescription (0%) from month 1 to 6. Among patients in trajectory ~~1~~ 2 (n=~~2,808~~3,304, ~~5.66~~.59%), ~~50~~0.3% filled a prescription at month 1, which increased to 2.6% at month 2, 8% at month 3, and then followed by 10% with opioid fills for the subsequent 3 ~~months gradually decreased in each subsequent month to 0% with an opioid prescription fill at month 5~~. Thirty-~~two~~ five percent of patients in trajectory ~~2~~ 3 (n=~~2,543~~6,543, ~~5.1~~12.87%) filled an opioid prescription at month 1, which decreased to ~~5~~8% at month 2, and then gradually ~~increased~~ decreased to ~~from~~ 4% at month 3, and ~~to 29~~3% at months 4, 5, and 6. ~~Among patients seen in trajectory 3 (n=44,059, 88.4%), 24% filled an opioid prescription at month 1 followed by 0% with opioid fills for the subsequent 5 months.~~ A description of the demographic and clinical characteristics of the patients assigned to each of these 4 trajectories is included in eTable2.

Characteristics of patients and initial prescriptions: Among the total ~~49,844~~50,127 opioid naïve patients who filled at least one opioid prescription within 7 days after hysterectomy, ~~434~~ 693 (~~0.87~~1.38%) patients were categorized as chronic opioid users and ~~49,410~~48,434(~~99.13~~98.62%) were categorized as non-chronic users. Baseline characteristics among chronic opioid users after hysterectomy were significantly different from non-chronic opioid users (Table 1). Compared to the women without chronic opioid use, women with chronic opioid use were older and more likely to have ~~a higher Charlson comorbidity index,~~ a history of tobacco use, and a history of alcohol use. Chronic opioid users also were also more likely to be taking psychiatric medications, including benzodiazepines, antidepressants, and stimulants. Back pain and headache syndromes ~~fibromyalgia~~ were more prevalent in the chronic opioid use group. Compared to women with commercial insurance, women with Medicare insurance had higher rates of chronic opioid use. About 1.5 percent of Medicare patients who were chronic opioid users after hysterectomy were younger than 65.

In unadjusted analyses, the average daily MME/day and the type of the initial opioid prescription were similar between women categorized as having chronic use and not having

chronic opioid use. The days' supplied of the initial opioid was marginally greater among chronic users than for non-chronic users (5.12 versus 4.85 days, respectively, p = 0.0205) (Table 1). Overall, oxycodone was more frequently prescribed hydrocodone or other opioids.

Predictors of chronic opioid use among all patients in the study: The results of multivariable logistic regression analyses are shown in Table 2. A number of factors were significantly associated with chronic opioid use after hysterectomy including older age, geographic region, abdominal or laparoscopic/robotic hysterectomymode of hysterectomy, Charlson comorbidity index, tobacco use, alcohol use, and prescribed psychotropic medicationsother substance use, benzodiazepines use, antidepressants use, antipsychotics use, stimulants use. Pain conditions, including headache syndromes fibromyalgia and back pain at baseline, were also identified as significant risk factors for chronic opioid use after hysterectomy. Health plan type, census region, surgical setting, fibromyalgia, and other substance use disorders were not included in the final multivariable analyses due to lack of significance.

The characteristics of the initial opioid prescription, including type of opioid dispensed, days' supply, and daily dose in MME, were fitted in the model. Days' supply and daily dose in MME were divided into their tertiles. Among initial opioid prescribing characteristics, significant predictors of chronic opioid use were initial prescription of hydrocodone (compared to oxycodone, aOR: 1.3331, 95%CI: 1.1110-1.5957), days' supply (4-7 days vs ≤3 days, aOR: 1.3528, 95%CI: 1.1106-1.7954; ≥8 days vs ≤ 3 days, aOR: 2.041.41, 95%CI: 1.4305-2.901.89), and daily dose in MME (≥60 mg/day vs ≤40 mg/day, aOR: 1.7043, 95%CI: 1.2814-2.261.79), The C-statistic for the fitted full model was 0.7370, indicating moderate predictability (Table 2)

The frequencies of post-surgery complications and other conditions associated with pain during the 6-month follow-up were examined in the study cohort (Table 3). Compared with non-chronic opioid users, women who developed chronic opioid use after hysterectomy were more

frequently diagnosed with chronic pancreatitis, headache syndrome, back pain, fibromyalgia, and underwent additional anesthetic procedures.

Sensitivity Studies

We redefined chronic opioid use as a total duration of opioid use (total days' supply) that exceeded 90 days during 6-month follow-up period, finding that the days supplied and MME of the initial opioid prescription were associated with chronic opioid use according to this definition. An initial days supply was associated with an adjusted 1.81 fold increase in chronic use as compared with a supply of less than 3 days (95%CI: 1.21-2.70); while an initial MME/day of 60 or greater was associated with an adjusted 1.37 fold increase in chronic use (95%CI: 1.00-1.87) as compared with an initial MME of ≤ 39.64 mg/day). These results are similar as the results which defined chronic use using trajectory models.

In another sensitivity analysis, we applied a more restricted definition of opioid naivety by only including patients having 12-month continuous eligibility and without any opioid dispensing or diagnosis of OUD during the 12 months prior to hysterectomy. In this analysis, the highest tertile of MME/day (exceeding 58.92 mg) for the initial opioid prescription remained predictive of subsequent chronic opioid use as compared with the lowest tertile of ≤ 39.64 mg/day (aOR: 1.38; 95%CI: 1.07-1.80); while the trend for days supplied also remained consistent, albeit failing to reach statistical significance. (aOR: 1.38, 95%CI: 1.0-1.90 for 8+ days' supply vs ≤3 days' supply)

Discussion

Hysterectomy is the most common surgical procedure among non-pregnant women. In our study, among the ~~49,844~~50,127 opioid naïve women who had a hysterectomy and were dispensed at least one opioid prescription within 7 days after hysterectomy, ~~0.87~~1.38% became chronic opioid users during the ~~within~~ 6 months after surgery. Several demographic factors,

such as age, mode of hysterectomy, tobacco use, alcohol use, and psychiatric use were associated with chronic opioid use after hysterectomy. More importantly, however, we found that characteristics of the initial opioid prescription, including type, dose, and duration affected the probability of chronic opioid use. An initial supply of 8 or more days, and an initial MME of at least 60 mg per day were each associated with a greater than 40% increase in the risk of subsequent chronic use of opioids (Table 2). Each year in the United States, there are approximately 430,000 inpatient hysterectomy cases.[37] The findings of this study suggest that lessening the ~~intensity~~duration and amount of opioids in the initial ~~focusing on these easily modifiable~~ opioid prescription ~~characteristics~~ may ~~lead to~~ decrease in the risk ~~incidence of~~ chronic opioid use after hysterectomy. ~~this prevalent surgical procedure.~~The findings of this study suggest that we could focus on t~~hese easily modifiable opioid prescription characteristics to decrease the incidence of chronic opioid use after this prevalent surgical procedure.~~

Multiple demographic and clinical factors were associated with increased risk of chronic opioid use after hysterectomy, including older age, abdominal or laparoscopic/robotic hysterectomy~~mode of hysterectomy~~, comorbidities, tobacco use, substance ~~abuse~~use disorders, certain pain conditions, and use of prescription ~~any~~ psychiatric medications use (Table 2). Our findings were similar to other studies that showed that these factors increase the risk of chronic opioid use after major cardiac, thoracic, abdominal and pelvic procedures, or specific surgeries, including cesarean delivery, hysterectomy, hip or knee arthroplasty, spine, or bariatric surgeries.[5-17, 38, 39] ~~Previous studies have reported that residing in the South or Midwest regions of the U.S. was associated with prescription opioid abuse specifically among women. In our study, the risk of chronic opioid use after hysterectomy was also higher in the South, Midwest, and West compared with the Northeast.(Table 2)~~ These findings underscore the importance of considering the individual patient's pain management needs, ~~and~~ risk factors for opioid misuse at the time of opioid prescribing after hysterectomy and other surgical procedures, and importance of medical care, monitoring and follow-up post-operatively .

The literature describing the relationship between the initial opioid prescribing characteristics and the risk of chronic opioid use after hysterectomy among opioid naïve patients is limited. Prior observational studies have produced inconclusive results, which may be attributed to the study sample (inclusion of patients with minor surgical procedures) or small study sample size.[11,38] Our results showed that initial opioid prescribing characteristics, including opioid type, daily dose, and duration of days' supply were associated with chronic opioid use in the 6 months following hysterectomy among opioid naïve patients. The odds of chronic opioid use following initiation after hysterectomy were ~~35~~31% higher among patients starting hydrocodone compared to patients who began therapy with oxycodone even though prior research has demonstrated that oxycodone is associated with risk of addiction, morbidity and mortality.[40-42] One explanation for this finding is that for many years hydrocodone was the most commonly prescribed opioid medication in the United States, in part because it was a schedule III drug during the study period and was considered to be lesser risk than schedule II opioids such as oxycodone, therefore, hydrocodone may have been prescribed more liberally, especially to patients with a higher tendency of opioid overuse, which is a possible confounding by contraindication. In August 21, 2014, the U.S. Drug Enforcement Administration (DEA) issued stricter prescribing requirements and moved hydrocodone-containing medications from a Schedule III to a Schedule II controlled substance.[43] Notably, the initial opioid prescribing characteristics, such as longer days' supply and higher daily morphine milligram equivalent dose, that were associated with post-operative chronic opioid use after hysterectomy, are also risk factors for opioid misuse and opioid-related mortality.[44-47] By identifying modifiable risk factors for chronic opioid use after hysterectomy, such as pre-operative opioid prescribing, abdominal or laparoscopic/robotic hysterectomy~~mode of hysterectomy~~, and characteristics of opioid prescribing after surgery, we may be able to develop strategies and interventions to decrease the likelihood of chronic opioid use.

There is no standard definition for chronic opioid use after surgery. We selected the trajectory modeling approach because of its advantages over other methods for describing longitudinal trajectories and identifying patients who used opioids consistently over a longer duration.[29,30] Traditional medication adherence measures, such as the proportion of days covered or the number of months of continuous medication use, may not distinguish between consistent users in follow-up periods or between patients who discontinue medication completely versus those who simply have a gap in use. The trajectory models repeatedly assess medication use throughout the entire follow-up period and summarize long-term medication adherence accounting for the time-varying nature of adherence.[29] We found that ~~0.9~~1.38% of hysterectomy patients became chronic opioid users in the 6 months after surgery. Using Optum data from January 01, 2011 to December 31, 2014, Swenson et al. reported 0.5% (122 out of 24,331) of women who had a hysterectomy had new persistent opioid use following hysterectomy.[5] In Swenson's study, persistent opioid use in the 6 months post-hysterectomy was defined as a minimum of 2 opioid prescriptions in the 6 months post-surgery (one between 15-90 days and one at least 91-180 days) and top quartile use (amount and duration).[5] The difference in incidence of chronic use/new persistent use between these studies is attributable to the use of different definitions for chronic opioid use.

Our findings suggest that prescribing lower doses for shorter days' supply may reduce the risk of subsequent chronic opioid use~~, be a better strategy for post-surgical pain management~~, and~~which~~ is consistent with the strategies published in guidelines advocated by multiple federal and state agencies, professional societies, and advocacy groups. Although specific guidelines differ in exact wording and specific recommendations, prescribing the lowest dose for the shortest amount of time and screening for substance use and opioid dependence are clearly defined themes across multiple guidelines.[48-50] However, practice change solely on the basis of guidelines can be slow, and current evidence suggests that physicians are prescribing excess opioids to patients to control acute pain post-surgery at hospital discharge. Studies from the

surgical fields of urology, orthopedics, and obstetrics and gynecology have shown that physicians prescribe more than twice the amount of opioid medication patients actually consume post-discharge which adds up to millions of excess unused opioid tablets available for diversion and abuse.[51-54] A recent study showed that among obstetricians and gynecologists, only 62% reported tailoring prescriptions to the individual patient and only 22% reported they performed an opioid dependence screen prior to prescribing.[55] Improving adherence to best practices for opioid prescribing, including tailoring prescriptions to the individual patient's pain management needs and risks of future opioid misuse and abuse, could play a major role in reducing the magnitude of the opioid epidemic.

Limitations

First, the study subjects included in this study are commercially insured in the United States with ~~10~~9% covered by Medicare Advantage (Table1). The demographic characteristics, clinical conditions, and opioid preoperative use patterns may differ from uninsured, Medicaid or Medicare covered populations. Thus, the study results might not be generalizable to patients enrolled in Medicaid or Medicare. ~~with government covered insurances.~~

Our study is subject to several limitations due to the nature of observational studies using claims data. Some important medical indications, such as severity of pain, which may be related to the hysterectomy procedure or underlying conditions leading to hysterectomy, were not captured in the data. Other unmeasured confounding factors included social and economic factors during follow up. The low prevalence of OUDs or methadone use excluded in figure 1, and other substance ~~abuse~~use disorders, tobacco use, and alcohol ~~ab~~use presented in table 1 might be due to poor sensitivity of ICD-9 diagnosis codes or CPT codes. However, the impact may be non-differential if the unmeasured variables are similarly distributed in two comparison groups.

Opioid analgesics were assessed using pharmacy claims, which only captured opioid medications legally obtained and filled at outpatient pharmacies. ~~The 69% prevalence of~~ Patients not filling the initial opioid prescription post-hysterectomy may be attributed to either ~~some patients~~ not using opioids for post-surgical pain or to ~~patients~~ receiving their opioid prescription from an inpatient pharmacy. The actual patterns of opioid use (actual consumption) was not measured and, based on prior studies, differs substantially from the amount of opioid medication prescribed. Furthermore, the result that hydrocodone has a higher risk of chronic use after hysterectomy compared to oxycodone could be due to a possible confounding by contraindication.

The outcome assessed in this study was chronic opioid use during the first 6 months after hysterectomy. Although chronic opioid use within 6 months has been associated with opioid misuse and opioid-related death, it was not possible to differentiate whether patients persistently used opioids for 6 months as a ~~legitimate~~ treatment for pain control or because they became dependent upon opioids after their post-surgical pain had abated.~~use of the medications to treat acute pain~~.[56] Additionally, it was not possible ~~is impossible~~ to determine ~~know~~ if the women were continuing to receive their opioid for the pain related to their hysterectomy or for other pain; ~~the reason for the opioid prescription fills during this time periods;~~ It is possible that the reason for filling opioid prescriptions in the 6 months following hysterectomy was not for personal use but for diversion.[57] Our findings that chronic opioid use post hysterectomy was significantly associated with ~~preoperative opioid use and~~ initial opioid prescribing could be due to complex relationships between chronic pain post-surgery, acute pain post-surgery, and chronic pain pre-surgery.

Conclusions

In this study, ~~About 0.87% of~~approximately 3 in 200 opioid naïve women appear to become chronic opioid users after hysterectomy. Besides commonly recognized demographic and clinical risk factors, chronic opioid use after hysterectomy was associated with initial opioid prescribing characteristics, such as longer days' supply and higher daily opioid dose. Although prescription opioid medications provide effective analgesia after surgery, they must be used with caution given the potential risk for subsequent chronic opioid use that is associated with opioid misuse and overdose-related mortality. Our findings support the need to manage post-surgical pain with the least amount of opioid medication possible to effectively control a patient's symptoms, and close clinical post-op follow-up for those patients who prescribed opioids.

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Figure 1. Flow Chart of the Study Population.

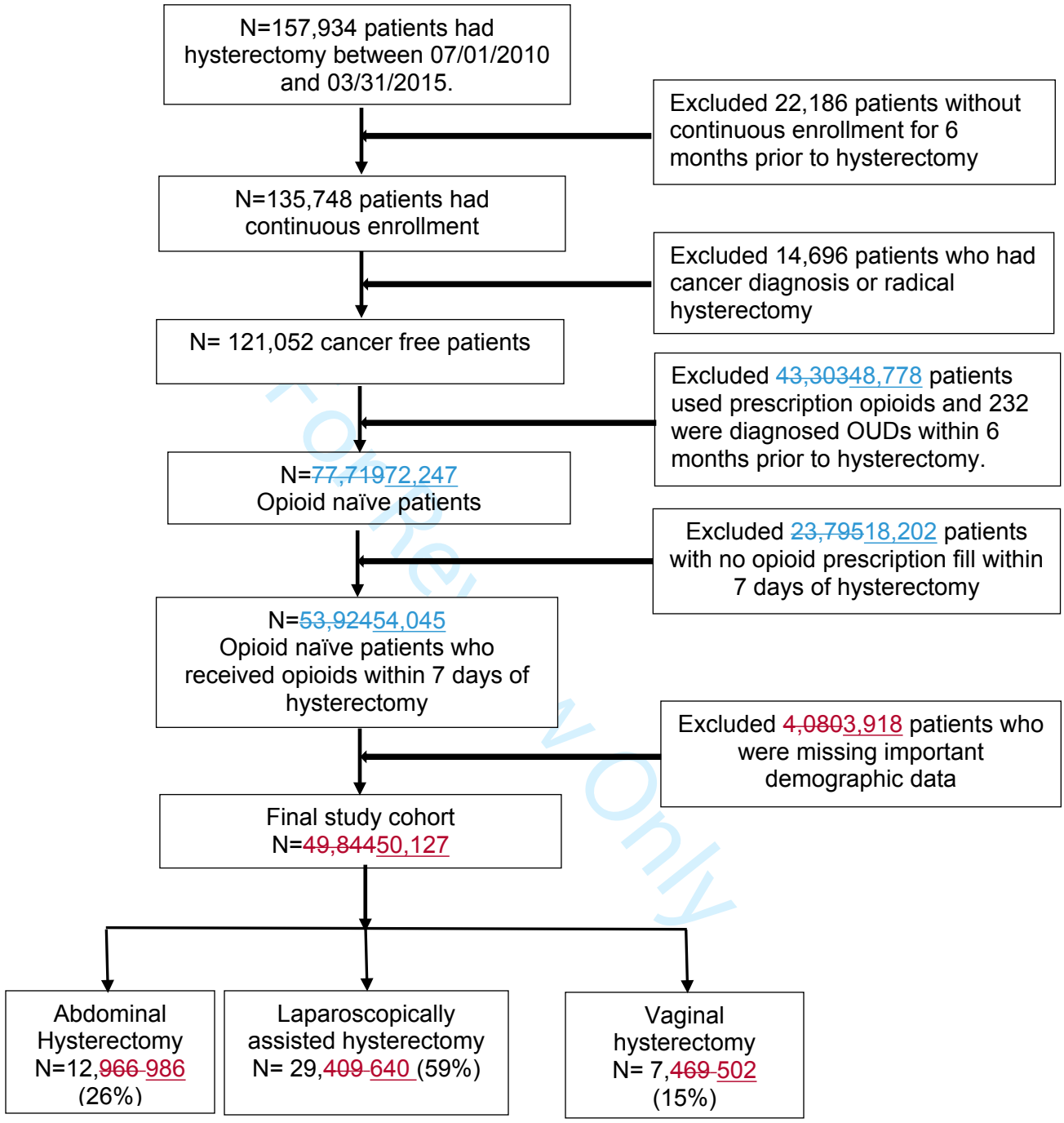
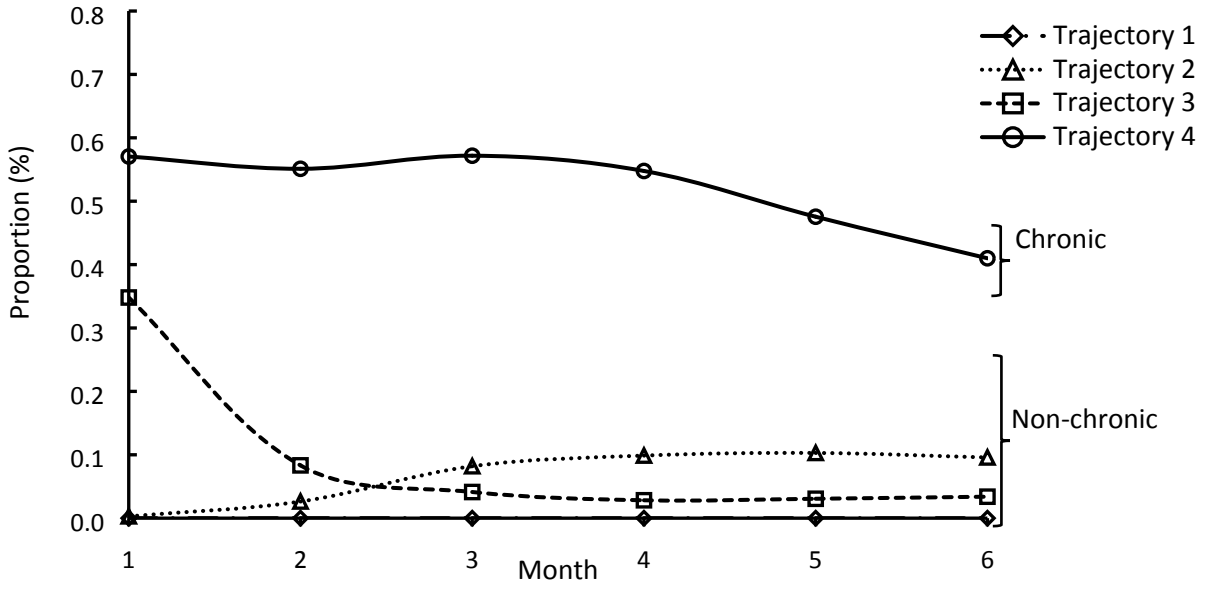
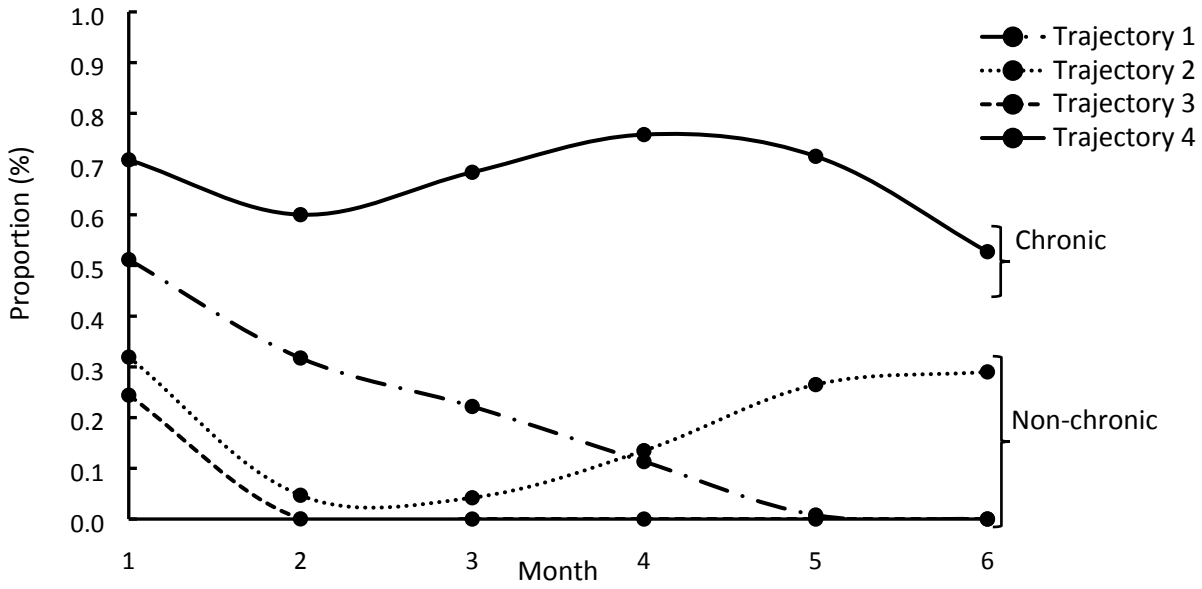


Figure 2. Trajectories of filling opioid prescriptions in 6 months post hysterectomy. The solid or dashed lines represent the distinct estimated opioid prescription filling trajectories. The dot symbols represent the mean estimated proportion in each trajectory group dispensed an opioid prescription at each month. These indicate the mean estimated probability of filling an opioid prescription for patients in each group at each time point. Overall counts and percentages of patients in each group are presented in the underneath table. Patients in trajectory 4 were classified as opioid chronic users. Patients in trajectories 1, 2, 3 were classified as opioid non-chronic users. The x-axis indicates each 30-day interval during the 6-month follow-up period, while the y-axis indicates the estimated proportion of patients filled a prescription opioid within each 30-day interval.



Trajectories	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4
N (%)	39,677 (79.15%)	3,304 (6.59%)	6,453 (12.87%)	693 (1.38%)

~~Figure 2. Proportion in each trajectory group dispensed an opioid prescription in each month.~~



~~Trajectories~~	~~1~~	~~2~~	~~3~~	~~4~~
~~N (%)~~	~~2,808 (5.63%)~~	~~2,543(5.10%)~~	~~44,059 (88.39%)~~	~~434 (0.87%)~~

Table 1. Comparison of baseline patient characteristics among opioid-naïve patients who received prescription opioids within 7 days after hysterectomy, N=50,127

Patient characteristics	Non-chronic Users† (N=48,434)	Chronic Opioid Users‡ (N= 693)	P-value
Charlson Comorbidity Index, mean (95% CI)	1.60 (1.57, 1.64)	1.74 (1.45, 2.02)	0.3479
Length of stay in days, mean (95% CI)	2.32 (2.30, 2.35)	3.79 (3.39, 4.19)	<0.0001
Age, years, mean (95% CI)	48.1 (48.0, 48.2)	49.8 (48.9,50.7)	0.0004
Age at hysterectomy, years			
<40	9,100 (18.41)	126 (18.18)	<.0001
40-49	22,538 (45.59)	255 (36.80)	
50+	17,796 (36.00)	312 (45.02)	
Substance use and abuse, N (%)			
Tobacco	2,637 (5.33)	60 (8.66)	0.0001
Alcohol	177 (0.36)	9 (1.30)	<.0001
Other substance use disorders§	55 (0.11)	4 (0.58)	0.0004
Psychiatric medications, N (%)			
Benzodiazepines	4,201 (8.50)	125 (18.04)	<.0001
Antidepressants	9,984 (20.20)	233 (33.62)	< .0001
Stimulants	767 (1.55)	25 (3.61)	< .0001
Pain conditions, N (%)			
Fibromyalgia	1,530 (3.10)	30 (4.33)	0.0632
Headache syndromes	4,019 (8.13)	82 (11.83)	0 .0004
Back pain	4,659 (9.42)	110 (15.87)	< .0001
Type of hysterectomy, N (%)			
Abdominal hysterectomy	12,757 (25.81)	228 (32.90)	<.0001
Vaginal hysterectomy	7,428 (15.03	74 (10.68)	
Laparoscopic/Robotic	29,249 (59.17)	391 (56.42)	
Surgery setting, N (%)			
Inpatient	19,805 (40.06)	352 (50.79)	<.0001
Outpatient	29,629 (59.94)	341 (49.21)	
US census region, N (%)			
Midwest	13,705 (27.72)	186 (26.84)	0.6351
Northeast	5,075 (10.27)	66 (9.52)	
South	23,642 (47.83)	332 (47.91)	
West	7,012 (14.18)	109 (15.73)	
Insurance type, N (%)			
Commercial	45,107 (91.25)	586 (84.56)	< .0001
Medicare	4,327 (8.75)	107 (15.44)	
Type of health plan, N (%)			
Exclusive provider organization	5,990 (12.12)	70 (10.10)	0.0008
Health maintenance organization	4,913 (9.94)	89 (12.84)	
Point of service	34,004 (68.79)	449 (64.79)	
Others¶	4,527 (9.16)	85 (12.27)	
Year of hysterectomy			
2010-2013	21,949 (44.40)	287 (41.41)	0.1161
2014-2015	27,485 (55.60)	406 (58.59)	
Initial Opioid Prescription Characteristics			

Days' supply, days	4.85 (4.82, 4.87)	5.12 (4.89, 5.34)	0.0205
Average daily MME, mg/day	54.7 (54.3, 55.0)	58.4 (54.6, 62.2)	0.0571
Type of Opioid, N(%)			
Hydrocodone	17,555 (35.51)	266 (38.38)	0.0553
Oxycodone	27,434 (55.50)	354 (51.08)	
Other	4,445 (8.99)	73 (10.53)	
Tertile MME, mg/day			
<=40	16,154 (32.68)	219 (31.60)	0.2425
40.5-58.9	16,718 (33.82)	221 (31.89)	
60.0+	16,562 (33.50)	253 (36.51)	
Days' supply, days			
1-3	15,667 (31.69)	193 (27.85)	0.0566
4-7	29,098 (58.86)	423 (61.04)	
8+	4,669 (9.44)	77 (11.11)	

Abbreviation: MME=Morphine Milligram Equivalent

†Non-chronic users refer to patients in trajectory 1, 2, and 3 in Figure 2.

‡Chronic Opioid users refer to patients in trajectory 4 in Figure 2.

§Other substance use includes cocaine, marijuana, anxiolytic, stimulant, hallucinogenic drugs, or abuse of unspecified drugs/medications.

¶Others include Indemnity and Preferred provider organization.

Table 2. Baseline and initial opioid prescription characteristics that predict chronic opioid use following hysterectomy among opioid naive patients, 2010-2015; N=50, 127

Characteristics	Unadjusted OR (95% CI)	Adjusted OR[†] (95% CI)
Age group, years		
40-49	Ref.	Ref.
< 40	1.22 (0.99, 1.52)	1.20 (0.97, 1.49)
≥ 50	1.55 (1.31, 1.83)	1.37 (1.14 1.65)
Insurance type		
Commercial	Ref.	Ref.
Medicare	1.90 (1.55, 2.35)	1.98 (1.37, 2.87
Type of health plan, N (%)		
Exclusive provider organization	Ref.	Ref.
Health maintenance organization	1.55 (1.13, 2.13)	1.19 (0.84, 1.68)
Point of service	1.13 (0.88, 1.46)	1.10 (0.85, 1.42)
Others[‡]	1.61 (1.17, 2.21)	0.75 (0.48, 1.18)
Type of hysterectomy		
Vaginal hysterectomy	Ref.	Ref.
Laparoscopic/Robotic	1.79 (1.38, 2.34)	1.52 (1.16, 2.00)
Abdominal hysterectomy	1.34 (1.05, 1.72)	1.40 (1.09, 1.80)
Year (2010-2013 vs 2014-2015)	1.13 (0.97, 1.32)	1.24 (1.06, 1.46)
Length of stay (days)	1.14 (1.11, 1.16)	1.12 (1.10, 1.15)
Charlson comorbidity index	1.18 (1.06, 1.31)	1.16 (1.04, 1.30)
Pain conditions		
Headache (Yes vs. No)	1.52 (1.20, 1.91)	1.33 (1.04, 1.69)
Back pain (Yes vs. No)	1.81 (1.48, 2.23)	1.57 (1.27, 1.94)
Substance use		
Alcohol	3.66 (1.87, 7.18)	1.84 (0.91, 3.74)
Tobacco	1.68 (1.29, 2.20)	1.47 (1.12, 1.93)
Psychiatric medications		
Antidepressants	2.00 (1.71, 2.35)	1.71 (1.45, 2.03)
Benzodiazepines	2.37 (1.95, 2.88)	1.89 (1.54, 2.33)
Psychostimulants	2.38 (1.58, 3.56)	1.84 (1.21, 2.80)
Initial Opioid Prescription Characteristics		
Type of opioid		
Oxycodone	Ref.	Ref.
Hydrocodone	1.17 (1.00, 1.38)	1.31 (1.10, 1.57)
Other	1.27 (0.99, 1.64)	1.26 (0.96, 1.64)
Days' supply, days		
≤ 3	Ref.	Ref.
4-7	1.18 (0.99, 1.40)	1.28 (1.06, 1.54)
≥ 8	1.34 (1.03, 1.75)	1.41 (1.05, 1.89)
Tertile MME, mg/day		
< 40	Ref.	Ref.
40 -58.9	0.98 (0.81, 1.18)	1.14 (0.93, 1.40)
≥ 60.0	1.13 (0.94, 1.35)	1.43 (1.14, 1.79)

Abbreviation: MME=Morphine Milligram Equivalent

Adjusted model: c-statistic = 0.70; Hosmer-Lemeshow Goodness-of-fit Test: X^2 =19.30, df=8, p=0.0133

[†]Adjusted for baseline patient demographic and clinical characteristics listed in this table.
[‡]Others include Indemnity and Preferred provider organization.

Table 3. Distribution of possible indications for chronic opioid use during the 6-month follow-up period after hysterectomy: shown as N (%).

Possible indications	All patients in cohort (N = 50,127)	Non-chronic Users (N = 49,434)	Chronic Opioid Users (N = 693)	P-value
Chronic pancreatitis	70 (0.14)	63 (0.13)	7 (1.01)	<.0001
Headache syndromes	3,284 (6.55)	3,196 (6.47)	88 (12.70)	< .0001
Back pain	4,477 (8.93)	4,287 (8.67)	190 (27.42)	< .0001
Fibromyalgia	1,470 (2.93)	1,407 (2.85)	63 (9.09)	< .0001
Additional anesthetic procedures[†]				< .0001
0	46,132 (92.03)	45,768 (92.58)	364 (52.53)	
1	3,310 (6.60)	3,099 (6.27)	211 (30.45)	
2	525 (1.05)	459 (0.93)	66 (9.52)	
≥ 3	160 (0.32)	108 (0.22)	52 (7.50)	

[†]Number of additional procedures requiring anesthesia.

Table 1. Comparison of baseline patient characteristics among opioid-naïve patients who received prescription opioids within 7 days after hysterectomy, N=49,844

Patient characteristics	Non-chronic Users** (N=49,410)	Chronic Opioid Users* (N= 434)	P-value
Charlson Comorbidity Index, mean (95% CI)	0.4 (0.4, 0.4)	0.8 (0.7, 0.9)	<.0001
Length of stay in days, mean (95% CI)	1.00 (1.00, 1.02)	2.19 (1.86, 2.51)	<.0001
Age, years, mean (95% CI)	48.1 (48.0, 48.2)	50.5 (49.3, 51.7)	<.0001
Age at hysterectomy, years			
<40	9,245 (18.71)	84 (19.35)	<.0001
40-49	22,461 (45.46)	141 (32.49)	
50+	17,704 (35.83)	209 (48.16)	
Substance use and abuse, N (%)			
Tobacco	2,714 (5.49)	49 (11.29)	<.0001
Alcohol	181 (0.37)	8 (1.84)	.0003
Marijuana	5 (0.01)	0 (0.00)	NA
Cocaine	8 (0.02)	1 (0.23)	0.08
Other substance abuse***	35 (0.07)	0 (0.0)	NA
Psychiatric medications, N(%)			
Benzodiazepines	4,403 (8.91)	87 (20.05)	<.0001
Antidepressants	10,331 (20.91)	159 (36.64)	<.0001
Stimulants	766 (1.55)	18 (4.15)	<.0001
Pain conditions, N (%)			
Fibromyalgia	1,692 (3.42)	32 (7.37)	<.0001
Headache syndromes	4,212 (8.52	41 (9.45)	0.49
Back pain	5,053 (10.23)	85 (19.59)	<.0001
Type of hysterectomy, N (%)			
Abdominal hysterectomy	12,814 (25.93)	152 (35.02)	<.0001
Vaginal hysterectomy	7,412 (15.00)	57 (13.13)	
Laparoscopic/Robotic	29,184 (59.06)	225 (51.84)	
US census region, N (%)			
Midwest	13,907 (28.15)	118 (27.19)	0.07
Northeast	5,041 (10.20)	36 (8.29)	
South	23,609 (47.78)	202 (46.54)	
West	6,853 (13.87)	78 (17.97)	
Insurance type, N (%)			
Commercial	44,966 (91.01)	354 (81.57)	<.0001
Medicare	4,444 (8.99)	80 (18.43)	
Type of health plan, N (%)			
Exclusive provider organization	5,905 (11.95)	43 (9.91)	0.0004
Health maintenance organization	4,899 (9.91)	55 (12.67)	
Point of service	33,992 (68.80)	274 (63.13)	
Others****	4,614 (9.31)	62 (14.29)	
Year of hysterectomy			
2010-2013	21,952 (44.43)	180 (41.47)	0.22
2014-2015	27,458 (55.57)	254 (58.53)	
Initial Opioid Prescription Characteristics			
Days' supply, days	4.81 (4.78, 4.83)	5.44 (5.07, 5.80)	< 0.0001
Average daily MME*****, mg/day	55.0 (54.7, 55.4)	61.1 (55.5, 66.8)	0.03
Type of Opioid, N(%)			
Hydrocodone	18,738 (37.92)	176 (40.55)	0.16

Oxycodone	27,332 (55.32)	222 (51.15)	
Other	3,340 (6.76)	36 (8.29)	
Tertile MME*****, mg/day			
<=40	16,964 (34.33)	140 (32.26)	0.05
40.5-58.9	15,794 (31.97)	124 (28.57)	
60.0+	16,652 (33.70)	170 (39.17)	
Days' supply, days			
1-3	15,838 (32.05)	116 (26.73)	0.001
4-7	29,097 (58.89)	259 (59.68)	
8+	4,475 (9.06)	59 (13.59)	

Note:

* Chronic Opioid users refer to patients in trajectory 4 in Figure 2.

** Non-chronic users refer to patients in trajectory 1, 2, and 3 in Figure 2.

*** Other substance use includes anxiolytic, stimulant, hallucinogenic drugs, or abuse of unspecified drugs/medications.

**** Others including Indemnity and Preferred provider organization.

***** MME=Morphine Milligram Equivalent

Table 2. Baseline and initial opioid prescription characteristics that predict chronic opioid use following hysterectomy among opioid naive patients, 2010-2015; N=49,844

Characteristics	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age group, years		
40-49	Ref.	Ref.
< 40	1.45 (1.10, 1.90)	1.42 (1.08, 1.87)
50+	1.88 (1.52, 2.33)	1.54 (1.22, 1.95)
US census region		
Northeast	Ref.	Ref.
Midwest	1.19 (0.82, 1.73)	1.33 (0.91, 1.96)
South	1.20 (0.84, 1.71)	1.31 (0.91, 1.88)
West	1.59 (1.07, 2.37)	1.77 (1.18, 2.66)
Insurance type		
Commercial	Ref.	Ref.
Medicare	2.29 (1.79, 2.92)	1.58 (1.19, 2.11)
Type of hysterectomy		
Vaginal hysterectomy	Ref.	Ref.
Laparoscopic/Robotic	1.00 (0.75, 1.34)	1.03 (0.77, 1.39)
Abdominal hysterectomy	1.54 (1.14, 2.09)	1.35 (0.98, 1.87)
Year (2010-2013 vs 2014-2015)	1.13 (0.93, 1.37)	1.27 (1.05, 1.56)
Length of stay (days)	1.13 (1.11, 1.16)	1.10 (1.07, 1.13)
Charlson comorbidity index	1.34 (1.26, 1.42)	1.18 (1.10, 1.26)
Pain conditions		
Fibromyalgia (Yes vs. No)	2.25 (1.56, 3.23)	1.58 (1.08, 2.31)
Back pain (Yes vs. No)	2.14 (1.69, 2.72)	1.70 (1.32, 2.18)
Substance use		
Alcohol	5.11 (2.50, 10.44)	2.28 (1.06, 4.87)
Tobacco	2.19 (1.62, 2.96)	1.81 (1.33, 2.46)
Psychiatric medications		
Antidepressants	2.19 (1.80, 2.66)	1.78 (1.44, 2.19)
Benzodiazepines	2.56 (2.02, 3.25)	1.94 (1.51, 2.49)
Psychostimulants	2.75 (1.71, 4.43)	2.07 (1.26, 3.41)
Initial Opioid Prescription Characteristics		
Type of opioid		
Oxycodone	Ref.	Ref.
Hydrocodone	1.15 (0.95, 1.41)	1.35 (1.07, 1.70)
Other	1.33 (0.93, 1.89)	1.37 (0.95, 1.97)
Days' supply, days		
<=3	Ref.	Ref.
4-7	1.22 (0.96, 1.51)	1.41 (1.11, 1.79)
8+	1.80 (1.31, 2.47)	2.04 (1.43, 2.90)
Tertile MME, mg/day		
<=40	Ref.	Ref.
40.5-58.9	0.95 (0.75, 1.21)	1.24 (0.95, 1.62)
60.0+	1.24 (0.99, 1.55)	1.70 (1.28, 2.26)

Adjusted model: c-statistic = 0.73; Hosmer-Lemeshow Goodness-of-fit Test: X^2 =9.32, df=8, p=0.32

*: Adjusted for baseline patient demographic and clinical characteristics listed in this table.

Table 3. Distribution of possible indications for chronic opioid use during the 6-month follow-up period after hysterectomy: shown as N (%).

Possible indications	All patients in cohort (N = 49,844)	Non-chronic Users (N = 49,410)	Chronic Opioid Users (N = 414)	P-value
Rheumatoid arthritis	6 (0.01)	6 (0.01)	0 (0.00)	NA
Chronic pancreatitis	73 (0.15)	67 (0.14)	6 (1.38)	<.0001
Sickle cell disease	7 (0.01)	7 (0.01)	0 (0.00)	NA
Headache syndromes	3,373 (6.77)	3,311 (6.70)	62 (14.29)	< 0.0001
Back pain	4,652 (9.33)	4,511 (9.13)	141 (32.49)	< 0.0001
Fibromyalgia	1,588 (3.19)	1,548 (3.13)	40 (9.22)	< 0.0001
Additional anesthetic procedures*				< 0.0001
0	45,840 (91.97)	45,621 (92.33)	219 (50.46)	
1	3,316 (6.65)	3,177 (6.43)	139 (32.03)	
2	524 (1.05)	479 (0.97)	45 (10.37)	
3+	164 (0.33)	133 (0.27)	31 (7.14)	

Note:
*: Number of additional procedures requiring anesthesia.

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N/A

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8. Manuscript title (first six words are sufficient)

Chronic Opioid Use in Women following Hysterectomy

9. Author's full name (a separate form must be submitted for each author)

Xuerong Wen

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