

New and Persistent Controlled Substance Use Among Patients Undergoing Mastectomy and Reconstructive Surgery

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Abstract

Purpose

Prolonged use of controlled substances can place patients at increased risk of dependence and complications. Women who have mastectomy and reconstructive surgery (M+R) may be vulnerable to becoming new persistent users (NPU) of opioid and sedative-hypnotic medications.

Methods

Using the MarketScan health care claims database, we identified opioid- and sedative-hypnotic-naïve women who had M+R from 2008-2017. Women who filled ≥ 1 peri-operative prescription and ≥ 2 post-operative prescriptions within one year after surgery were classified as NPUs. Univariate and multivariable logistic regression analyses were used to estimate rates of new persistent use and predictive factors. Risk summary scores were created based on the sum of associated factors.

Results

We evaluated 25,270 opioid-naïve women and 27,651 sedative-hypnotic-naïve women.

We found that 18,931 opioid-naïve women filled a peri-operative opioid prescription, and of those, 3,315 (17.5%) became opioid NPUs post-operatively. Additionally, 10,781 sedative-hypnotic-naïve women filled a peri-operative sedative-hypnotic prescription, and of those, 1,837 (17.0%) became sedative-hypnotic NPUs. Development of new persistent sedative-hypnotic use was associated with age ≤ 49 (OR 1.79 [95% CI 1.43–2.25]) and age 50-64 (1.65 [1.31-2.07]) compared to age ≥ 65 ; Medicaid insurance (1.92 [1.23–2.98]); southern residence (1.38 [1.20–1.59]); breast cancer diagnosis (1.78 [1.09–2.91]); and chemotherapy (2.24 [2.02–2.49]). Risk of NPU increased with higher risk score. Women with ≥ 3 of these risk factors were three times more likely to become sedative-hypnotic NPUs than patients with 0 or 1 factors (3.03 [2.60–3.53]). Comparable findings were seen regarding new persistent opioid use.

Conclusion

Women who have M+R are at risk of developing both new persistent opioid and new persistent sedative-hypnotic use. A patient's risk of becoming an NPU increases as their number of risk factors increases. Non-pharmacologic strategies are needed to manage pain and anxiety following cancer-related surgery.

Introduction

Misuse of controlled substances is a major public health issue in the United States[1, 2]. In addition to the ongoing opioid epidemic, there is growing recognition of the prevalence of sedative-hypnotic misuse[3]. According to the 2019 National Survey on Drug Use and Health, 4.8 million people (1.8% of the population) reported misuse of benzodiazepine sedative-hypnotics in the prior year, in addition to 10.1 million people (3.7%) who misused opioids[4]. An additional 1.6 million people (0.5%) are estimated to annually misuse other common non-benzodiazepine sedative-hypnotics, such as zolpidem (Ambien)[5]. Prolonged use of opioids and sedative-hypnotics is prevalent in the cancer population[6–8]. Such persistent use puts patients at risk of overdose mortality and other harms from these medications, such as increased hospital admissions and healthcare-related spending[9–13].

Despite high rates of anxiety and insomnia among women with breast cancer, little is known about the rates of prolonged sedative-hypnotic use in this population[14]. Half of patients with early breast cancer have anxiety, depression or both in the year after diagnosis[15]. Depressive symptoms persist for at least two years after diagnosis in up to one in five patients[16]. Insomnia is present in 42–69% of patients up to 18 months after curative surgery for breast cancer, and breast cancer is associated with an odds ratio of 3.17 for a diagnosis of insomnia relative to other cancers[17–20]. Investigation into the prevalence of and risk factors for prolonged sedative hypnotic use is necessary in this population.

The post-operative period is one of high risk for patients undergoing breast cancer-related surgery to become new persistent users of opioids[21, 22]. Whether this is also a high-risk period for the development of new persistent sedative-hypnotic use is unknown. Some studies have shown 12.3% of patients become new persistent opioid users after a range of breast cancer-related procedures[21], and 10% become new users after mastectomy and immediate reconstruction surgery, however the definitions of persistent use vary from study to study[22]. Given the high levels of anxiety and insomnia that often surround surgical procedures, peri-operative patients may be at increased risk of exposure to sedative-hypnotics. Yet while these symptoms may only be transiently exacerbated, a large amount of preventable prolonged sedative-hypnotic use may occur after such prescriptions.

The objective of this study was to evaluate rates of new persistent controlled substance use, specifically, opioid and sedative-hypnotic use, after mastectomy and reconstruction. We also sought to determine factors associated with the development of new persistent opioid and sedative-hypnotic use.

Methods

Database

We used data from the IBM MarketScan Research Database[23]. This database consists of medical and pharmaceutical claims (both inpatient and outpatient) for more than 50 million privately insured patients nationwide, including Medicare beneficiaries in commercial managed care plans, and 6 million Medicaid-insured patients from 12 US states. Data are de-identified, and multiple steps are taken to ensure data validity and quality control. We followed the STROBE (Strengthening Reporting of Observational Studies in Epidemiology) reporting guidelines for observational studies[24].

Cohort

We identified women age 18 or older who had at least one claim between 2008 and 2017 with an ICD or CPT code indicating a mastectomy and reconstructive surgery (Supplemental Table 1). We included women who had continuous health insurance and drug benefit coverage from 12 months before to 12 months after surgery, to ensure complete capture of all commercial, Medicaid and Medicare claims. Within this cohort, we defined three periods: 365 to 31 days prior to surgery (period 1); 31 days prior to 90 days after surgery (period 2); and 90 days to 365 days after surgery (period 3).

We identified opioid and sedative-hypnotic medications of interest from Lexicomp Online™. We then identified prescriptions for these medications during the three study periods, cross-referencing prescriptions against a pre-established list of generic drug names (Supplemental Table 2). Patients who filled at least one prescription for a given agent during period 1 were excluded from the analysis. Patients who had no use in period 1, but filled at least one prescription for a given agent during period 2 and at least two prescriptions for the same class of agent during period 3 were considered new persistent users. This definition of new persistent use is consistent with prior studies of new persistent opioid use after cancer-related surgery[21, 22]. However, we were more conservative in our definition, in that we required at least two prescriptions during period 3, rather than at least one prescription. Further, we followed patients for up to one year after surgery, rather than up to 180 days after surgery as in prior studies. This allowed for increased confidence that we were seeing truly persistent use. In terms of sedative-hypnotics, given the limited literature on new persistent sedative-hypnotic use, we felt it reasonable to apply the same definition as used for new persistent opioid use.

Patient-level factors of interest were captured from MarketScan, using ICD-9, ICD-10 and CPT codes. Demographic data included age at surgery and insurance status (Medicaid vs. commercial). Other categorical variables of interest included breast cancer diagnosis, receipt of chemotherapy and receipt of radiation at any point during the study period, as well as mental health diagnoses (anxiety or mood disorders) prior to surgery. A diagnosis of breast cancer was not required for inclusion in this study, as patients may receive mastectomy and reconstruction for other reasons, such as to prevent cancer in those at high risk of breast cancer, or as a gender-affirming procedure. As such, women in our cohort without a diagnosis of breast cancer were presumed to have received mastectomy and reconstruction for an alternative indication.

Statistical Analysis

Demographic and clinical characteristics were presented descriptively and the rate of new persistent substance use was estimated for each covariate among the substance-naïve cohorts. The unadjusted associations between risk factors and persistent opioid use were compared using chi-square tests. Multivariable logistic regression models were used to evaluate the association between risk factors and the development of new persistent substance use. We generated risk summary scores by summing statistically significant risk factors associated with persistent use of both drug classes, and risk scores were assigned based on a patient's cumulative number of risk factors. Logistic regression models were used to analyze the association between assigned risk scores and development of new persistent controlled substance use. All hypothesis tests were two-sided. All analyses were conducted using SAS Studio Version 3.71 (SAS Institute Inc., Cary, North Carolina).

Results

We identified 107,725 women who had mastectomy and reconstruction from 2008 to 2017 (Fig. 1). We generated two study cohorts: 25,270 opioid-naïve women, and 27,651 sedative-hypnotic-naïve women (Table 1). The majority of these women (> 90%) were less than 65

years of age, had commercial insurance and had a diagnosis of breast cancer. Approximately 40% received chemotherapy, and 20% had a pre-existing mental health diagnosis.

Controlled Substances

The women in our cohorts filled 255,347 opioid prescriptions and 178,331 sedative-hypnotic prescriptions. Common opioid prescriptions included acetaminophen/hydrocodone (113,063 prescriptions, 44.3% of all opioid prescriptions), acetaminophen/oxycodone (61,753, 24.2%), tramadol (18,465, 7.2%) and oxycodone (19,151, 7.5%). Common sedative-hypnotic prescriptions included zolpidem (43,697 prescriptions, 24.5% of all sedative-hypnotic prescriptions), alprazolam (40,880, 22.9%), lorazepam (37,801, 21.2%), diazepam (26,478, 14.9%) and clonazepam (16,168, 9.7%).

Rates of New Persistent Use

In our cohort of 25,270 opioid-naïve women who had mastectomy and reconstructive surgery, 18,931 (74.9%) filled a peri-operative opioid prescription (Fig. 2A). Out of these women with a peri-operative exposure, we found that 3,315 women (17.5%) became new persistent opioid users (Fig. 2B). In other words, three out of four opioid-naïve women filled an opioid prescription related to surgery, and almost one in five of these women continued to fill opioid prescriptions up to one year later.

In the sedative-hypnotic-naïve cohort, a similar rate of new persistent use was seen despite less peri-operative exposure. Out of 27,651 sedative-hypnotic-naïve women, 10,781 (40.0%) filled a peri-operative sedative-hypnotic prescription. Subsequently, 1,837 (17.0%) became new persistent sedative-hypnotic users. Thus, while less than half of women were exposed to sedative-hypnotics peri-operatively, nearly one in five continued to fill sedative-hypnotic prescriptions up to one year post-operatively.

Risk Factors for New Persistent Use

Several variables were predictive of the development of both new persistent opioid and sedative-hypnotic use: age < 65, residence in the south, Medicaid insurance, breast cancer diagnosis and chemotherapy treatment (Table 2).

Younger patients were more likely to become new persistent controlled substance users. Both younger age groupings (49 or less and 50–64) were associated with new persistent use relative to patients aged 65 or greater. The association was more pronounced for sedative-hypnotic dependence than opioid dependence for both younger groupings (OR = 1.79 [95% CI 1.43–2.25] vs. 1.27 [1.09–1.49] for age 49 or less; 1.65 [1.31–2.07] vs. 1.29 [1.11–1.51] for age 50–64).

Higher odds of new persistent use were seen in almost all major region groupings relative to the northeast region. Residence in the south was most markedly associated with new persistent use relative to the northeast (1.67 [1.50–1.85] for opioid use; 1.38 [1.20–1.59] for sedative-hypnotic use). Residence in the north-central region and the western region were also generally associated with new persistent use.

Medicaid insurance coverage was associated with both categories of controlled substance use relative to commercial insurance, particularly for new persistent opioid use (2.26 [1.56–3.28] for opioids; 1.92 [1.23–2.98] for sedative hypnotics). Chemotherapy treatment, on the other hand, was more strongly associated with new persistent sedative-hypnotic use than with opioid use (2.24 [2.02–2.49] vs. 1.33 [1.23–1.44]).

Risk Summary Scores

To generate risk summary scores, we used five significant risk factors for the development of new persistent use of both drug categories: age 49 or less, residence in the south, Medicaid insurance, breast cancer diagnosis and chemotherapy treatment. Age 49 or less was chosen among the age categories to reflect a subset of patients; similar findings would be anticipated with the inclusion of age 50–64 instead. Southern region was chosen for inclusion as this region was the most significantly associated with new persistent use, relative to northeastern residence, across both drug groups. Scores were grouped into three categories: 0 or 1 risk factors, 2 risk factors and 3 or 4 risk factors. Among substance-naïve patients, no patients had all five risk factors.

Table 3 shows the association between risk summary scores and new persistent substance use. In terms of opioids, as the number of risk factors possessed by a patient increased, their risk of becoming a new persistent substance user also increased. Out of 6,116 opioid-naïve patients with 0 or 1 risk factors, 611 (10%) became new persistent opioid users post-operatively. Rates of new persistent use increased linearly as the risk summary score increased (12.7% of 1,287 with 2 risk factors, 15.8% of 1,417 with 3 or 4 risk factors). Relative to those with 0 or 1 risk factors, those with 2 risk factors and 3 or 4 risk factors were significantly more likely to become new persistent users (1.31 [1.18–1.45] and 1.69 [1.42–1.86]).

The risk of new persistent sedative-hypnotic use was markedly more pronounced with increasing risk summary score. Out of 6,484 sedative-hypnotic-naïve patients with 0 or 1 risk factors, 3.3% became new persistent users post-operatively, increasing to 6.2% of 10,970 patients with 2 risk factors and 9.3% of 10,197 patients with 3 or 4 risk factors. Relative to those with 0 or 1 risk factors, patients with 2 risk factors were twice as likely to become new persistent sedative-hypnotic users (1.95 [1.67–2.28]), and patients with 3 or 4 risk factors were three times as likely to develop dependence (3.03 [2.60–3.53]).

Overlapping Controlled Substance Use

While both cohorts were naïve to the substance in question prior to surgery, some patients were exposed to the other substance during the study period. For instance, out of 3315 new persistent opioid users, 2350 (70.9%) filled a sedative-hypnotic prescription at some point during the study period. Of these, 537 (22.9%) filled at least one sedative-hypnotic prescription in each study period (presumably representing long-term sedative-hypnotic users), while 947 (40.3%) filled a peri-operative sedative-hypnotic prescription only. For the other cohort, out of 1837 new persistent sedative-hypnotic users, 1804 (98.2%) filled at least one opioid prescription during the study period. Of these, 375 (20.4%) filled opioid prescriptions throughout, while 724 (40.1%) filled only a peri-operative opioid prescription. Finally, there were 403 patients who became new persistent users of both opioid and sedative-hypnotic medications, representing 12% of the new persistent opioid users, and 22% of the new persistent sedative-hypnotic users.

Discussion

In this study, we found that a substantial number of women who had mastectomy and reconstructive surgery became new, persistent users of controlled substances post-operatively. In terms of opioids, three in four opioid-naïve women filled a peri-operative opioid prescription, and 17.5% of these women became new persistent opioid users. While a smaller percentage of sedative-hypnotic naïve women filled a peri-operative sedative-hypnotic prescription (40%), these women went on to become new persistent sedative-hypnotic users at a comparable rate (17%) to those in the opioid cohort. Several demographic, clinical and economic variables were highly associated with the development of both new persistent opioid and sedative-hypnotic use: age less than 65, residence in the south, Medicaid insurance, breast cancer diagnosis and chemotherapy treatment. As the number of these risk factors increased in an individual patient, their risk of becoming a new persistent user increased as well.

Our study is novel in demonstrating an association between mastectomy and reconstructive surgery and the development of new persistent sedative-hypnotic use in a large, heterogenous population of women. Anxiety and insomnia are common in the breast cancer population, with persistent symptoms seen up to 1.5 years after curative surgery[14, 20]. Our findings suggest that a substantial number of women receive sedative-hypnotics for what may have been worsening anxiety and insomnia around the time of surgery, and a significant proportion of these women go on to use these agents chronically. While some of this use may be psychiatrically indicated, the concern is that a large amount may be unnecessary and preventable. Sedative-hypnotic misuse is an underrecognized public health problem in the general population[3, 25]. Our study suggests that women who have mastectomy and reconstructive surgery are susceptible to prolonged use of these medications, placing them at risk of future dependence on and misuse of these agents.

We found several factors to be particularly associated with the development of new persistent sedative-hypnotic use: age less than 65, chemotherapy treatment and Medicaid insurance. Sedative-hypnotic use and misuse is more common among those younger than 65 years of age in the general population[26–28], but to our knowledge this has not been well characterized in women undergoing breast cancer-related surgery[29]. Chemotherapy use generally reflects higher risk disease, and high rates of consequent anxiety and insomnia among these patients may render them particularly susceptible to sedative-hypnotic dependence. Additionally, sedative-hypnotics are frequently used to treat chemotherapy-related nausea[30]. Our findings suggest that a sedative-hypnotic prescription intended for the management of chemotherapy-related symptoms can put patients at risk of becoming persistent users. Finally, Medicaid insurance has previously been associated with persistent opioid use post-operatively[31]. Our study corroborates this finding in the mastectomy and reconstruction population, and additionally finds an association between Medicaid insurance and post-surgical sedative-hypnotic dependence.

We also found that a prior mental health diagnosis was not predictive of the development of new persistent sedative-hypnotic use. Women with pre-existing anxiety or mood disorders in our study cohorts were not previously managed with sedative-hypnotic medications, as patients filling prescriptions between 365 to 31 days prior to surgery were excluded from our analysis. It is possible that patients who were excluded increased use, however we were not able to study that in the current analysis.

Rates of sedative-hypnotic use and misuse in women with breast cancer have only been previously studied to a limited degree[7, 32]. One recent study assessed benzodiazepine use in elderly patients with breast cancer undergoing curative intent treatment using SEER-Medicare data[29]. The authors found that 111 of 955 benzodiazepine-naïve patients received and continued to fill prescriptions up to 3 months post-operatively. However, this study only assessed an older cohort of patients over a short duration of follow up. Our study defines mastectomy

and reconstructive surgery as a concrete, generalizable risk factor for the development of new persistent sedative-hypnotic use up to one year post-operatively.

The association between mastectomy and reconstructive surgery and new persistent opioid use has been demonstrated previously[21, 22]. Marcusa et al. (2017) found that among 4,113 opioid-naïve patients undergoing mastectomy and reconstruction over a four-year period, 10% continued to fill prescriptions for opioids up to 4 months post-operatively. Our study builds on these findings by examining a substantially larger cohort of opioid-naïve women (25,270 vs. 4,113) over a longer period of follow-up (12 months vs. 4 months). We were also more conservative in our definition of new persistent use, requiring patients to fill at least two prescriptions in the post-operative period in order to receive this designation.

An additional finding of note in our study is the high rate of overlap in controlled substance exposures. We found that 70.9% of new persistent opioid users filled a sedative-hypnotic prescription during the study period as well, while 98.2% of new persistent sedative-hypnotic users filled an opioid prescription. Sedative-hypnotics are known to potentiate the respiratory depressive effects of opioids[33], and concomitant opioid and sedative-hypnotic use has been associated with increased rates of long-term opioid use, opioid overdose and all-cause mortality[34–37]. In particular, pre-operative sedative-hypnotic use among opioid-naïve patients increases the risk of long-term opioid use post-operatively[38]. Patients prescribed both categories of controlled substances around the time of mastectomy and reconstruction should receive particular attention, as they may be at even high risk of long-term use and subsequent complications.

Our study has several limitations. We were only able to determine that prescriptions were filled by patients, not what the indication was for prescribing or whether patients actually took the medications. Additionally, we did not control for surgical complications or receipt of additional procedures after the index procedure. This could account for some of the opioid use seen during period 3, but is less likely to affect the sedative-hypnotic findings. Finally, we did not have information on potentially relevant sociodemographic characteristics, such as race and ethnicity, and certain medical details, such as cancer stage and chemotherapy regimen. As such, our risk summary scores are somewhat simplistic due to these limitations. While MarketScan is a rich database, there are limitations to the socioeconomic and medical variables that we can control for in building predictive models using this data.

Our results suggest that women are susceptible to becoming new persistent users of both opioid and sedative-hypnotic medications after mastectomy and reconstructive surgery, with certain variables significantly and additively increasing their risk. Patients and providers should be aware of this important potential complication and attempt to limit use when appropriate. Providers should pay particular attention to patients receiving prescriptions for both opioid and sedative-hypnotics, as this overlap may render patients at increased risk for long-term use of one or both medication classes. Pharmacologic and non-pharmacologic strategies may help patients manage pain and anxiety after cancer-related surgery, and specific interventions may help patients use controlled substances safely and effectively[39].

Declarations

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Conflicts of interest/Competing interests: None

Availability of Data and Material: The data that support the findings of this study are available from IBM MarketScan, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of IBM MarketScan.

Code Availability: The codes utilized during the current study are available from the corresponding author on reasonable request.

Authors' Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jacob Cogan, Rohit Raghunathan and Dawn Hershman. The first draft of the manuscript was written by Jacob Cogan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

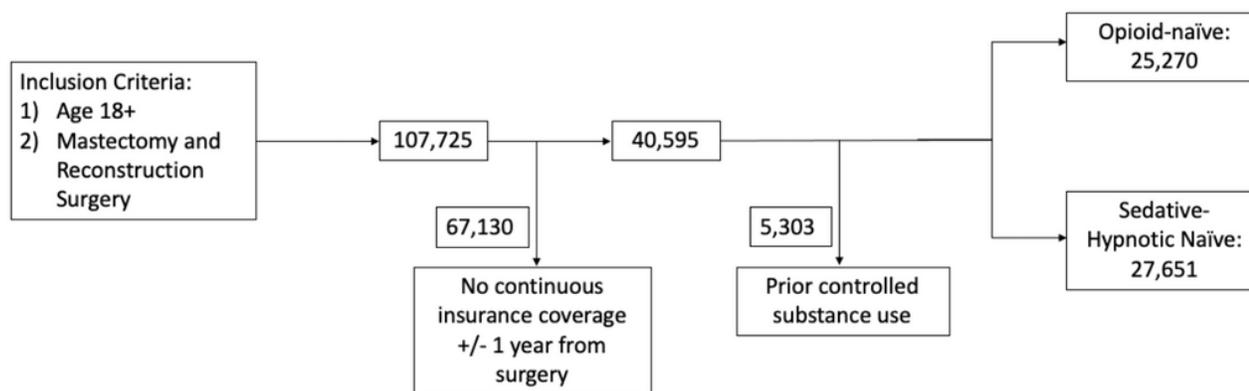


Figure 1

Study Cohort and Sample Criteria. Women age 18 or older who underwent mastectomy and reconstructive surgery between 2008 and 2017 were included unless they did not have continuous insurance coverage from one year prior to one year after surgery, and/or if they filled at least one prescription for a given controlled substance anytime from 365 to 31 days prior to surgery (period 1). Opioid-naïve women filled no opioid prescriptions in period 1; sedative-hypnotic-naïve women filled no sedative-hypnotic prescriptions during period 1.

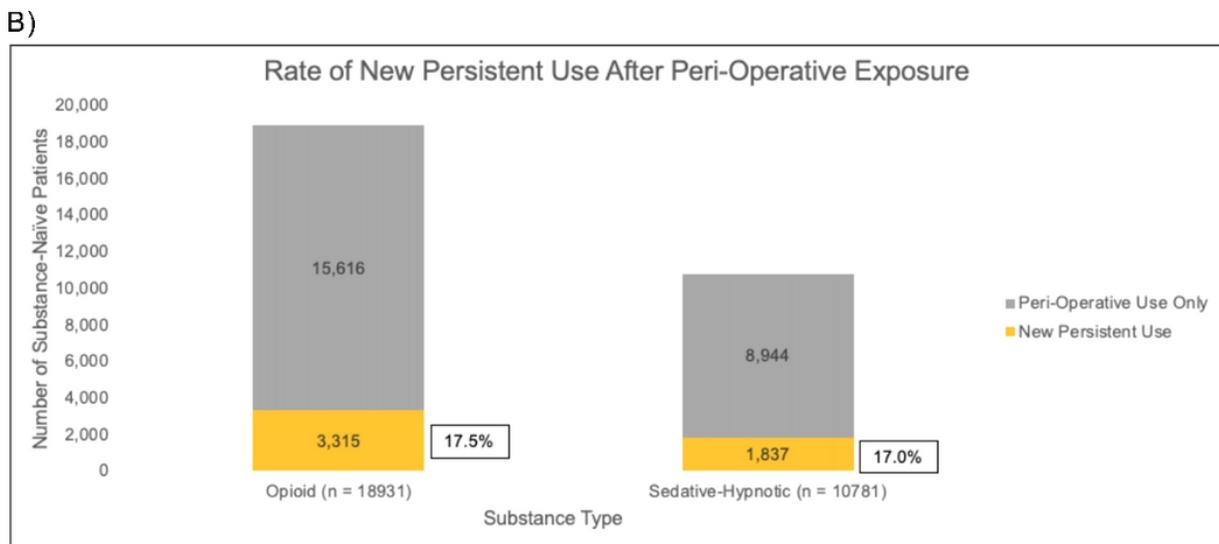
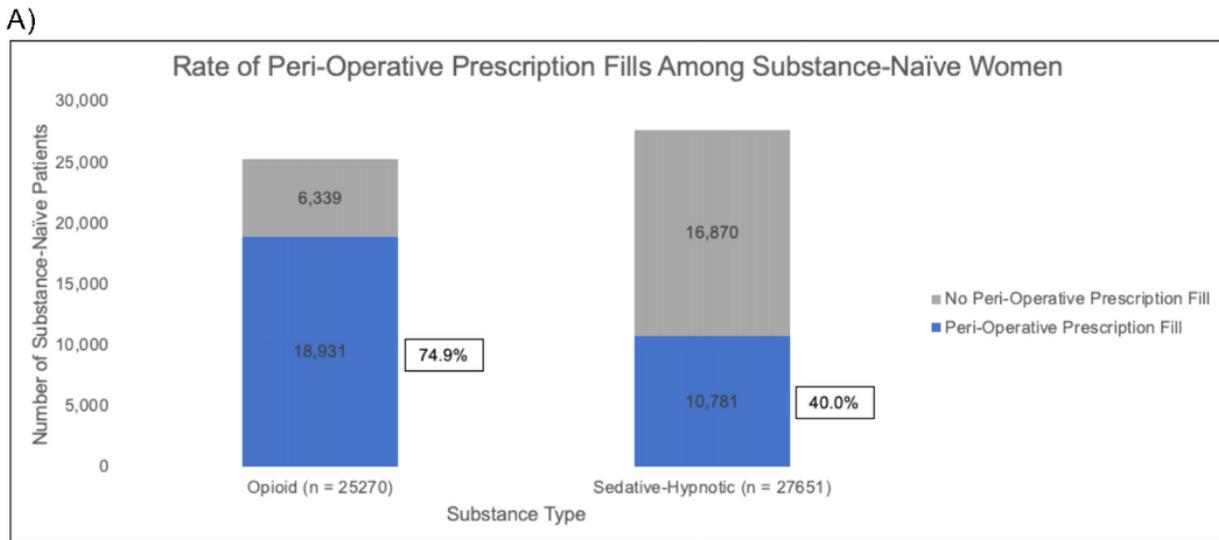


Figure 2

Rates of New Persistent Controlled Substance Use. A) Proportion of opioid- (left) and sedative-hypnotic- (right) naïve women who filled a peri-operative prescription for an opioid or sedative-hypnotic medication, respectively. A larger proportion of opioid-naïve women filled a peri-operative opioid prescription (74.9%) compared to sedative-hypnotic-naïve women who filled a peri-operative sedative-hypnotic prescription (40.0%). B) Proportion of previously substance-naïve women who went on to become new persistent opioid (left) or sedativehypnotic (right) users after filling a peri-operative opioid or sedative-hypnotic prescription, respectively. Comparable proportions became new persistent users (17.5% for opioids, 17.0% for sedative-hypnotics) after a peri-operative exposure to said agent.

Supplementary Files

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- [CoganControlledSubstancesTable1.pdf](#)
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