

Association of Preoperative Depression and Anxiety With Long-term Opioid Use After Hysterectomy for Benign Indications

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OBJECTIVE: To assess whether preoperative depression or anxiety is associated with increased risk of long-term, postoperative opioid use after hysterectomy among women who are opioid-naïve.

METHODS: We conducted an observational cohort study of 289,233 opioid-naïve adult women (18 years or older) undergoing hysterectomy for benign indications

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from 2010 to 2017 using IBM MarketScan databases. Opioid use and refills in the 180 days after surgery and preoperative depression and anxiety were assessed. Secondary outcomes included 30-day incidence of emergency department visits, readmission, and 180-day incidence of opioid complications. The association of depression and anxiety were compared using inverse-probability of treatment weighted log-binomial and proportional Cox regression.

RESULTS: Twenty-one percent of women had preoperative depression or anxiety, and 82% of the entire cohort had a perioperative opioid fill (16% before surgery, 66% after surgery). Although perioperative opioid fills were relatively similar across the two groups (risk ratio [RR] 1.07, 95% CI 1.06–1.07), women with depression or anxiety were significantly more likely to have a postoperative opioid fill at every studied time period (RRs 1.44–1.50). Differences were greater when restricted to persistent use (RRs 1.49–2.61). Although opioid complications were rare, women with depression were substantially more likely to be diagnosed with opioid dependence (hazard ratio [HR] 5.54, 95% CI 4.12–7.44), and opioid use disorder (HR 4.20, 95% CI 1.97–8.96).

CONCLUSION: Perioperative opioid fills are common after hysterectomy. Women with preoperative anxiety and depression are more likely to experience persistent use and opioid-related complications.

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In the United States, opioid prescribing increased by a staggering 400% from 1999 to 2010.¹ Despite a decline in the prescribing rate since 2012, the amount of opioids in morphine milligram equivalents prescribed per person remains approximately three times higher than in 1999.² The opioid crisis, which is still considered a major health threat, is associated with an



average of 130 American deaths each day from opioid misuse or opioid use disorder.³

Perioperative opioid prescribing has been repeatedly found to be excessive and inconsistent among surgeons, regardless of the type of surgery performed.^{4–6} Moreover, in a national study of U.S. adults, approximately 6% of opioid-naïve patients went on to use opioids for more than 90 days after their surgical procedure.⁴ Opioid use after hysterectomy follows a similar pattern, and studies have found that surgeons overprescribe up to four times the needed amount of opioids postoperatively^{7,8} and opioid persistence rates range from 1.5% to 6%.^{4,9} As new-onset opioid dependence has been linked to opioid prescribing surrounding both minor and major surgical procedures, a focus on pre-existing patient comorbidities and preoperative pain rather than the surgery itself may offer insights to persistent use.⁴

There is a bidirectional relationship between depression, anxiety, and opioid use. Although several studies have shown that chronic opioid use is associated with the risk of new-onset depression,^{10–12} a few studies have now also found that individuals with a history of depression and anxiety are at a higher risk for initiation and continuation of opioid use overall¹³ and 1 month after major surgery.¹⁴ However, although hysterectomy is considered major surgery, technological advances have led to minimal discomfort after procedures and most procedures now occur in an outpatient setting¹⁵—both of which suggest that opioid prescribing and use may differ in this patient population. Additionally, depression and anxiety are common among women with endometriosis, pelvic inflammatory disease, and generally among women undergoing hysterectomy,^{16–18} which could make women at higher risk for long-term use, misuse, and use disorder. Despite this, the association of preoperative depression or anxiety and long-term opioid use after hysterectomy is currently unknown. The purpose of our study was to assess the association of depression and anxiety on perioperative and postoperative opioid use, opioid dependence, and postoperative outcomes among women undergoing hysterectomy in the United States.

METHODS

This study was conducted using the IBM Watson Health/Truven Health Analytics MarketScan Commercial Claims and Encounters database. This administrative database contains de-identified, individual-level health insurance claims across the continuum of care (eg, inpatient services, outpatient services, outpatient pharmacy) as well as enrollment data from

roughly 150 large employers and health plans across the United States who provide private health care coverage for employees, their spouses, and dependents (roughly 50 million individuals each year). Diagnoses and procedures were captured using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes and Current Procedural Terminology (CPT) codes.

All adult women (18–65 years old) who underwent total abdominal hysterectomy, total laparoscopic hysterectomy, laparoscopic supracervical hysterectomy, vaginal hysterectomy, or laparoscopic-assisted vaginal hysterectomy between January 1, 2010, and December 31, 2017, were eligible for inclusion. International Classification of Diseases, Ninth Revision, Clinical Modification and CPT procedure codes were identified using clinical review and prior studies; ICD-10-CM procedure codes were identified using forward and backward mapping with CMS Generalized Equivalence Mappings. If a woman had multiple billed encounters with hysterectomy codes, the first one was used for analysis. Surgery was classified as abdominal (total abdominal hysterectomy), laparoscopic (total laparoscopic hysterectomy, laparoscopic supracervical hysterectomy, laparoscopic-assisted vaginal hysterectomy), and vaginal (vaginal hysterectomy). Women with multiple surgical approaches (on the same day) were categorized using the most invasive surgical approach (most to least invasive: abdominal, laparoscopic, vaginal).

Women were required to have at least 180 days of continuous coverage (with 8-day grace periods) before either their hysterectomy date (outpatient surgeries) or admission date (inpatient surgeries) and 30 or more days of coverage after their hysterectomy (outpatient) or discharge date (inpatient), Figure 1. The lookback window (days –180 to –1) was used to identify diagnoses of preoperative depression or anxiety, antidepressant use, gynecologic cancer, and comorbidities (Appendices 1 and 2, available online at <http://links.lww.com/AOG/C451>). The postoperative 30-day window (days 0–30) was used to identify undiagnosed preoperative gynecologic or peritoneal cancer. Women with gynecologic cancer were excluded ($n=26,980$ [6%] diagnosed before hysterectomy, $n=6,639$ [1%] diagnosed after hysterectomy), as were women with inpatient hospitalizations longer than 4 days ($n=6,840$ [5% of all inpatient hysterectomies]).

Women were also excluded if they had prevalent opioid use before hysterectomy. Prevalent use was



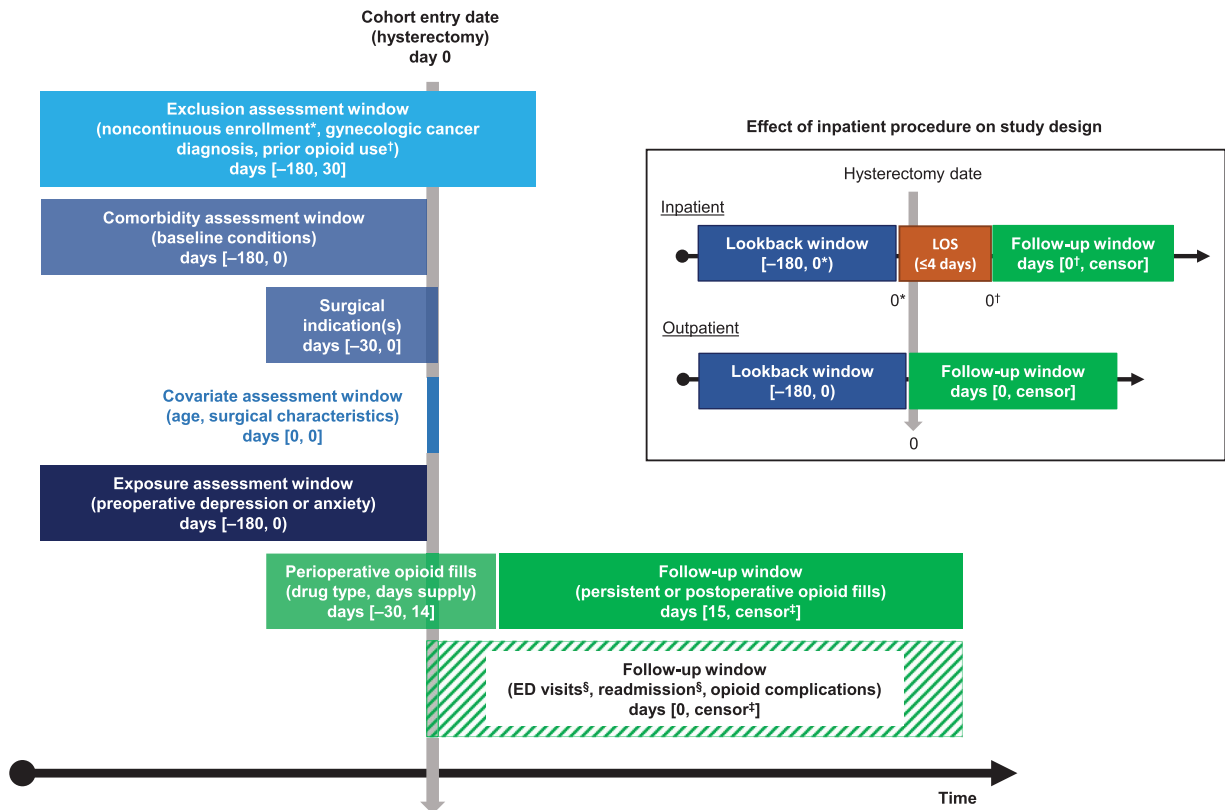


Fig. 1. Study timeline for privately insured women who underwent hysterectomy for benign indications between 2010 and 2017. *Up to 8-day gaps in insurance enrollment allowed; includes prescription coverage. †Prior opioid use was defined as any opioid fill between -180 and -31 days or more than one opioid fill between -30 and -1 day (to allow for perioperative fills before surgery). ‡Earliest of: insurance disenrollment, invasive surgery, end of follow-up (180 days after hysterectomy); postoperative opioid fills were assessed in time windows (15–30, 31–60, 61–90, and 91–180 days after surgery); only patients with complete follow-up during the time window were included for analyses. §Emergency department (ED) visits and readmission were assessed for only 30 days after surgery or discharge. LOS, length of stay.

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defined as 1) any opioid use between 180 and 30 days before hysterectomy or 2) more than one opioid prescription within the 30 days before surgery.⁹ Perioperative opioid use was defined as an opioid fill during the perioperative period (days -30 to 14), Figure 1.

All women were then followed after their hysterectomy date (outpatient surgeries) or date of discharge (inpatient surgeries) until insurance disenrollment, date of another invasive surgery,¹⁹ or 180 days, whichever came first. The primary outcome of interest was long-term, postoperative opioid use during the first 6 months after surgery. Postoperative time was categorized into the following periods: 15–30, 31–60, 61–90, and 91–180 days after hysterectomy. New, persistent opioid use was classified in two ways: 1) any fill during the postoperative time periods listed above and 2) consecutive fills during the postoperative time periods (high-risk persistent use). These def-

initions have been used previously for assessing posthysterectomy opioid use.⁹ Additional outcomes of interest included the 30-day incidence of emergency department (ED) visits and readmission and 180-day incidence of opioid dependence, use disorder, and poisoning. Emergency department visits were identified using CPT codes 99281–99285, revenue codes 0450–0459 and 0981, and place of service code 23.

Other variables of interest included other psychiatric disorders and comorbidities that may affect postoperative outcomes or are associated with opioid use. All comorbidities were captured using inpatient and outpatient service records in the 180 days before surgery or admission (Fig. 1). Charlson Comorbidity Index score was calculated using the methodology described in Deyo et al.²⁰ Surgical indications (benign neoplasm of uterus, inflammatory pelvic disease, endometriosis, prolapse, menstrual disorders) were



identified using records in the 30 days before and the date of surgery (or admission, days -30 to 0); women were allowed to have more than one indication for surgery.

Differences in patient demographics, comorbidities, and surgical characteristics were assessed using descriptive statistics. Trends in preoperative depression and anxiety—stratified into medically managed depression or anxiety (medication fill with or without diagnosis) and nonmedically managed depression or anxiety (diagnosis alone)—and perioperative opioid use (stratified into fills before and on or after surgery) were also described.

Differences in long-term, postoperative opioid use (any and persistent) among women with and without depression or anxiety were assessed using inverse-probability of treatment weighted log-binomial regression. Complete follow-up during the time period was required for each analysis (eg, a woman with 80 days follow-up would be included in perioperative [-30 to 14 days], 15–30, and 31–60 days analyses, but excluded for 61–90 and 91–180). Inverse-probability of treatment weighted Cox proportional hazards regression was used to estimate the association between preoperative depression or anxiety and the 30-day incidence of ED visits, readmission, and 180-day incidence of opioid complications (dependence, use disorder, and poisoning). Inverse-probability of treatment weighted for each patient were calculated using multivariable logistic regression, adjusting for age at surgery (treated as restricted quadratic spline), Charlson Comorbidity Index score (categorized as 0, 1, 2, and 3 or more), surgical indications, comorbidities (other psychiatric diagnoses, hypertension, obesity, pain), nonopioid analgesic medication use, procedure type (abdominal, laparoscopic, vaginal), inpatient procedure, and timing of surgery (treated as categorical by year and quarter).

We performed two sensitivity analyses. First, we assessed the association of depression or anxiety between women with medically managed and nonmedically managed depression or anxiety, compared with women without depression or anxiety. We re-calculated inverse-probability of treatment weights for each patient using generalized logistic regression (to allow for a three-level exposure). Wald χ^2 tests were used to compare the effect of medically managed and nonmedically managed depression or anxiety. Second, we restricted our definition of depression or anxiety to major depressive disorder (ICD-9-CM: 296.20–296.36; ICD-10-CM: F32.0-F33.9); women classified as having preoperative depression or anxiety,

but not major depressive disorder were excluded. We again re-calculated inverse-probability of treatment weights for each patient before analysis.

All analyses were performed using SAS 9.4. This study was classified as exempt by the University of North Carolina at Chapel Hill Institutional Review Board (IRB# 18–1890).

RESULTS

Overall, 417,147 women underwent hysterectomy for benign indications; 121,914 (30%) were prevalent opioid users before surgery. Women with depression or anxiety were more likely to be prevalent users (41% vs 26%). After restricting to women who were opioid-naïve, 289,233 were included in the analyses; 21% of women (n=60,260) were classified as having preoperative depression or anxiety, and 83% (n=239,032) had complete follow-up (180 days). The prevalence of preoperative depression or anxiety slightly increased between 2010 and 2017 from 19% to 23% (Fig. 1A). Overall, women with and without depression had similar patient demographics (Table 1). Notable differences include women with depression having slightly higher prevalence of comorbidities (17% vs 13%), other psychiatric conditions (3% vs less than 1%), chronic pain conditions (20% vs 14%), and were less likely to have benign neoplasm as the indication for hysterectomy (61% vs 70%). Women with depression or anxiety were also less likely to undergo an abdominal hysterectomy (20% vs 26%) or have an inpatient surgery (31% vs 37%).

Perioperative opioid fills remained consistent during the study period, with 82% of women filling a prescription (16% before surgery, 66% after surgery; Fig. 2A). Women with depression or anxiety were slightly more likely to have a perioperative opioid fill (87% vs 81%), and the slight increase was seen both in fills before and after surgery (18% vs 16% and 69% vs 65%, respectively). The majority of opioid prescriptions were for either oxycodone or hydrocodone (51% and 38% of fills, respectively). There was no meaningful difference in the type of opioid drugs prescribed across women with and without depression or anxiety. Median days supplied was 5 days (interquartile range 3–5 days).

The 30-day ED visits and readmission rates were similar between women with and without depression or anxiety (8% and 8% vs 7% and 8%, respectively; Table 2). Additionally, only 15% of women who visited the ED (n=20,455) within 30 days of surgery were admitted the same day (14% depression or anxiety, 15% no depression or anxiety). Twelve percent of women with depression or anxiety and 8% of



Table 1. Patient Demographics and Surgical Characteristics, Stratified by Preoperative Depression

| | Preoperative Depression or Anxiety | | | SD [†] |
|---|------------------------------------|----------------------|--------------------------|------------------|
| | Medically Managed* | Nonmedically Managed | No Depression or Anxiety | |
| Total | 45,006 | 15,254 | 228,973 | — |
| Age (y) | 45 (40–50) | 44 (39–49) | 45 (41–50) | 0.07 |
| CCI score | | | | 0.17 |
| 0 | 37,085 (82) | 12,836 (84) | 198,071 (87) | — |
| 1 | 5,162 (11) | 1,599 (10) | 20,336 (9) | — |
| 2 | 2,208 (5) | 626 (4) | 8,558 (4) | — |
| 3 or higher | 551 (1) | 193 (1) | 2,008 (1) | — |
| Surgical indication [‡] | | | | |
| Benign neoplasm | 27,340 (61) | 9,695 (64) | 159,796 (70) | 0.18 |
| Inflammatory pelvic disease | 13,751 (31) | 4,668 (31) | 68,505 (30) | 0.01 |
| Endometriosis | 15,570 (35) | 5,264 (35) | 71,409 (31) | 0.07 |
| Prolapse | 6,979 (16) | 2,312 (15) | 36,719 (16) | 0.02 |
| Menstrual disorders | 29,231 (65) | 9,787 (64) | 142,886 (62) | 0.05 |
| Other or unknown | 1,468 (3) | 497 (3) | 6,300 (3) | — |
| Other comorbidities | | | | |
| Other psychiatric conditions [§] | 1,237 (3) | 364 (2) | 690 (<1) | 0.20 |
| Hypertension | 8,505 (19) | 2,763 (18) | 37,785 (17) | 0.06 |
| Obesity | 3,172 (7) | 1,214 (8) | 12,201 (5) | 0.08 |
| Chronic pain conditions | 9,197 (20) | 3,273 (21) | 32,680 (14) | 0.17 |
| Surgical approach | | | | 0.15 |
| Abdominal | 8,888 (20) | 3,227 (21) | 59,506 (26) | — |
| Laparoscopic | 29,991 (67) | 10,010 (66) | 138,221 (60) | — |
| Vaginal | 6,127 (14) | 2,017 (13) | 31,246 (14) | — |
| Inpatient procedure [¶] | 13,830 (31) | 4,815 (32) | 83,975 (37) | 0.12 |
| LOS (d) [*] | 2 (1–2) | 2 (1–2) | 2 (1–2) | 0.07 |
| Nonopioid analgesic use | 10,629 (24) | 3,110 (20) | 41,651 (18) | 0.11 |

[SD], absolute standardized difference; CCI, Charlson Comorbidity Index; LOS, length of stay.

Data are n, median (interquartile range), or n (%) unless otherwise specified.

* With or without a diagnosis of depression or anxiety.

[†] Absolute standardized difference between patients with and without preoperative depression or anxiety; a difference greater than 0.20 was considered meaningfully different.

[‡] Includes all diagnoses within 30 days of surgery, including day of surgery; patients could have multiple indications. “Other or unknown” includes patients who did not have a diagnosis for any of the surgical indications assessed (benign neoplasm, inflammatory pelvic disease, endometriosis, prolapse, menstrual disorders).

[§] Includes diagnoses of bipolar disorder, manic disorder, drug-induced psychiatric disorder, and “other” mood disorders.

^{||} Includes diagnoses of migraine, irritable bowel syndrome (IBS), joint disorders, back pain, myositis, fibromyalgia, interstitial cystitis, endometriosis, and vulvodynia.

[¶] Includes patients with both inpatient and outpatient service records (n=5,470).

#Among inpatient hospitalizations only (n=107,049).

women without depression or anxiety had at least one opioid fill 91–180 days after surgery; however, after restricting to new high-risk persistent use (ie, requiring consecutive fills in every time period prior), this dropped to 0.2% and 0.1%, respectively. Opioid complications were also very rare.

After accounting for age at surgery, comorbidities, nonopioid analgesic medication use, procedure type, inpatient procedure, and date of surgery through weighting, women with depression or anxiety were significantly more likely to have an ED visit (hazard ratio [HR] 1.17, 95% CI 1.13–1.21), but there was a similar incidence of 30-day readmission across groups (HR 0.99, 95% CI 0.96–1.03; Table 2). Additionally, although perioperative opioid fills were relatively sim-

ilar across the two groups (risk ratio [RR] 1.07, 95% CI 1.06–1.07), women with depression or anxiety were significantly more likely to have an opioid fill at every postoperative time period (RR 1.44–1.50). After restricting to new high-risk persistent use, the association of depression or anxiety increased (RR 1.49–2.61). Finally, although opioid complications were rare, women with depression or anxiety were substantially more likely to be diagnosed with opioid dependence (HR 5.54, 95% CI 4.12–7.44) and opioid use disorder (HR 4.20, 95% CI 1.97–8.96). Unweighted results are presented in Appendix 3, available online at <http://links.lww.com/AOG/C451>.

Women taking antidepressants, compared with nonmedically managed depression or anxiety, were



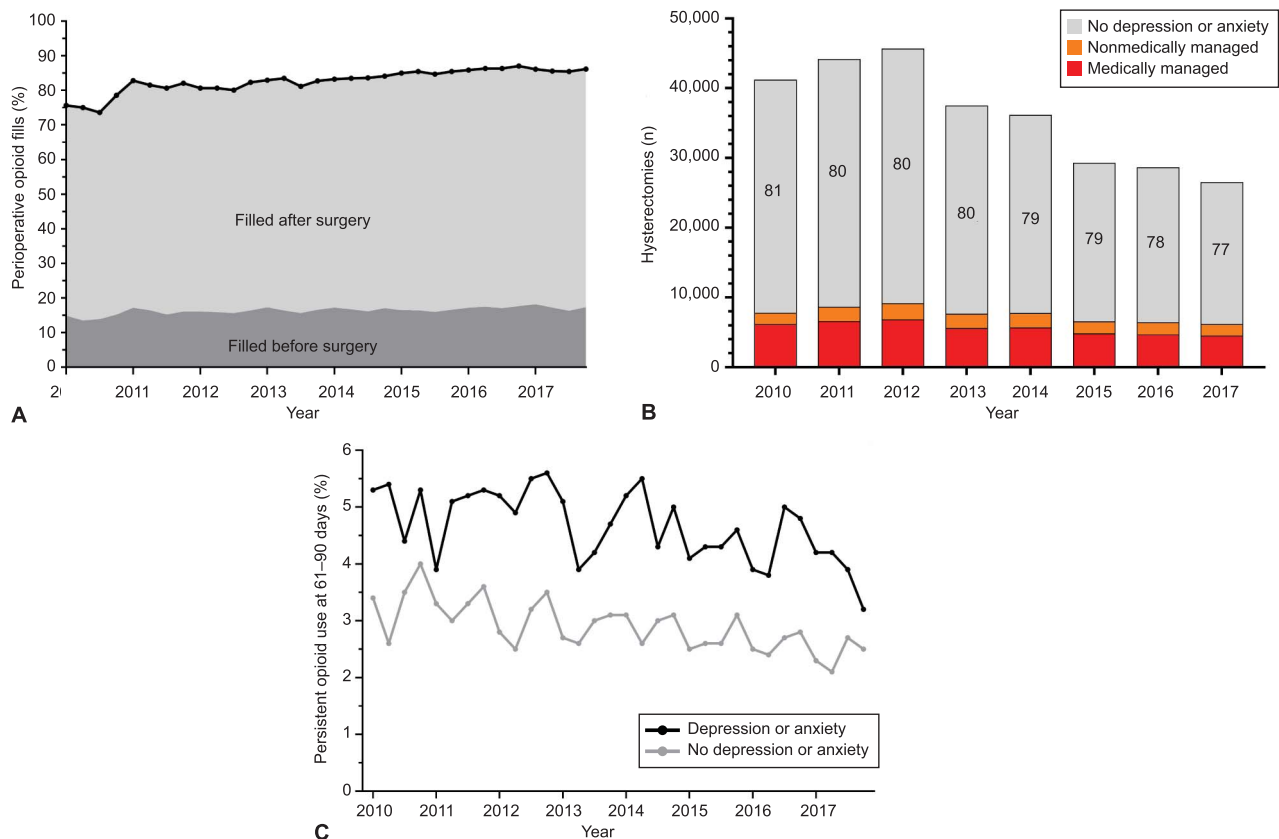


Fig. 2. Trends in prevalence of preoperative depression or anxiety (A), perioperative opioid use (B), and postoperative persistent opioid use at 61–90 days (C) among adult women (18–65 years of age) undergoing hysterectomy for benign indications. The percentages in A represent the proportion of women without a preoperative diagnosis of depression or anxiety. Perioperative fills in B were stratified into before (–30 to –1 day) and after (0–14 days) hysterectomy. Persistent postoperative opioid use in C was defined as having at least one opioid fill during the perioperative period, 15–30 days after surgery, and 31–60 days after surgery.

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significantly more likely to have a perioperative fill (90% vs 80%, RR 1.13, 95% CI 1.12–1.14) and overall long-term use, although both groups had a higher risk of long-term use compared with women without depression or anxiety (Table 3). When looking at new high-risk persistent postoperative use only, no differences were seen between groups. Similar incidences of opioid-related complications were seen between groups.

Fifteen percent of women (n=8,865) with depression or anxiety were diagnosed with major depressive disorder. When analyses were restricted to women with major depressive disorder, similar results were seen. See Appendix 4, available online at <http://links.lww.com/AOG/C451>.

DISCUSSION

In a national cohort of 289,233 women who are opioid-naïve who underwent hysterectomy for benign indica-

tions, we found that one in five were diagnosed with depression or anxiety before surgery. Additionally, despite perioperative opioid fills being relatively equal between women with and without depression or anxiety (87% and 81%, respectively), women with depression or anxiety were substantially more likely to continue to use opioids in every postoperative time period, become new high-risk persistent users, and be diagnosed with opioid dependence and opioid use disorder within 6 months.

Amidst the opioid epidemic, perioperative opioid prescribing after hysterectomy has been challenged. With the transition to minimally invasive hysterectomy and the implementation of enhanced recovery protocols, postoperative pain scores and opioid consumption has decreased.^{21,22} Interestingly, despite the implementation of protocols shown to reduce postoperative pain^{21,23} and the transition of minimally invasive hysterectomy to primarily an outpatient procedure, we



Table 2. Continued Opioid Use and Postoperative Outcomes After Hysterectomy for Benign Indications in Adult Women, Stratified by Preoperative Depression

| | Incidence | | Unweighted HR or RR (95% CI) | Weighted HR or RR (95% CI) * |
|---|-----------------------|--------------------------|------------------------------|------------------------------|
| | Depression or Anxiety | No Depression or Anxiety | | |
| Total | 60,260 | 228,973 | — | — |
| 30-d ED visit | 4,982 (8.3) | 15,473 (6.8) | 1.23 (1.19–1.27) | 1.17 (1.13–1.21) |
| 30-d readmission | 4,574 (7.6) | 17,633 (7.7) | 0.99 (0.95–1.02) | 0.99 (0.96–1.03) |
| Outpatient opioid fills | | | | |
| Perioperative [†] | 52,434 (87.0) | 185,582 (81.1) | 1.07 (1.07–1.08) | 1.07 (1.06–1.07) |
| Any postoperative (d) [‡] | | | | |
| 15–30 | 3,856 (6.6) | 10,063 (4.5) | 1.46 (1.41–1.51) | 1.44 (1.39–1.49) |
| 31–60 | 3,035 (5.4) | 7,677 (3.6) | 1.51 (1.45–1.58) | 1.46 (1.40–1.52) |
| 61–90 | 2,556 (4.7) | 6,184 (3.0) | 1.59 (1.52–1.66) | 1.50 (1.43–1.57) |
| 91–180 | 6,023 (12.3) | 15,157 (8.0) | 1.53 (1.49–1.58) | 1.45 (1.41–1.49) |
| Persistent postoperative (d) [§] | | | | |
| 15–30 | 3,615 (6.2) | 9,133 (4.1) | 1.51 (1.45–1.57) | 1.49 (1.43–1.55) |
| 31–60 | 701 (1.3) | 1,373 (0.6) | 1.95 (1.78–2.14) | 1.92 (1.75–2.11) |
| 61–90 | 198 (0.4) | 318 (0.2) | 2.39 (2.00–2.85) | 2.25 (1.87–2.70) |
| 91–180 | 112 (0.2) | 153 (0.1) | 2.83 (2.22–3.61) | 2.61 (2.03–3.37) |
| Opioid complications | | | | |
| Opioid dependence | 135 (0.2) | 73 (<0.1) | 7.06 (5.31–9.38) | 5.54 (4.12–7.44) |
| Opioid use disorder | 18 (<0.1) | 12 (<0.1) | 5.72 (2.75–11.88) | 4.20 (1.97–8.96) |
| Opioid poisoning | 18 (<0.1) | 47 (<0.1) | 1.46 (0.85–2.51) | 1.22 (0.68–2.16) |

HR, hazard ratio; RR, risk ratio; ED, emergency department. Data are n or n (%) unless otherwise specified.

* Inverse-probability of treatment weighted; weights included age (treated as restricted quadratic spline), Charlson Comorbidity Index score, surgical indications, comorbidities (other psychiatric diagnoses, hypertension, obesity, pain), nonopioid analgesic medication use, procedure type, inpatient procedure, and quarter and year of surgery.

[†] Perioperative period included an opioid fill 30 days before surgery until 14 days after surgery.

[‡] Among patients with complete follow-up through the time period; did not require patients to have a postoperative opioid fill in the time period(s) prior.

[§] Patients were required to have an opioid fill in the time period(s) prior in addition to complete follow-up through the time period; for example, patients classified as having persistent use 31–60 days after hysterectomy also had fills during the perioperative and 15–30 days postoperative time periods.

found no decrease in outpatient perioperative opioid fills over time in our cohort. These findings match other recent studies that have found that gynecologists prescribe between two and four times more opioids than patients need after hysterectomy for benign indications.^{7,8}

We also found that among women who filled a prescription, a median of 5 days of medication was prescribed, which is approximately twice the number of days most women need opioids after hysterectomy.⁸ Additionally, almost two in every 10 women undergoing hysterectomy filled their perioperative prescription before their actual date of surgery. Although writing prescriptions during preoperative visits may be convenient for some surgeons, it can also result in unneeded opioids in the home and potential misuse by the patient or others.

Depression and anxiety are the two most common psychological comorbidities in those dealing

with chronic pain.²⁴ These conditions are known moderators of pain perception and have strong, bidirectional and comorbid relationships with chronic pain; patients with depression or anxiety are more likely to report chronic pain, and conversely, developing chronic pain increases the risk of depression or anxiety.^{25,26} We found that 20% of women undergoing hysterectomy had preoperative depression or anxiety (75% medically managed), which is twice as high as the prevalence among women in the general population (10.4%).¹⁵ A similar relationship has also been identified with opioid use and misuse. Women with depression and anxiety have been found to be more likely to use and misuse opioids for both acute and chronic pain conditions.^{27,28} Additionally, prolonged opioid use, regardless of dose, has been associated with an increased risk of new-onset depression.²⁹

In our study, women with depression or anxiety were more than 50% more likely to not be opioid naïve



Table 3. Effect of Preoperative Depression (Medication or Diagnosis Only), Compared With No Depression, on Opioid Use and Postoperative Outcomes After Hysterectomy for Benign Indications in Adult Women

| | Preoperative Depression or Anxiety | | | | P* |
|---|------------------------------------|--------------------------------|----------------------|--------------------------------|-------|
| | Medically Managed [†] | | Nonmedically Managed | | |
| | n (%) | HR or RR (95% CI) [‡] | n (%) | HR or RR (95% CI) [‡] | |
| 30-d ED visit | 3,597 (8.0) | 1.12 (1.08–1.17) | 1,385 (9.1) | 1.28 (1.21–1.36) | <.001 |
| 30-d readmission | 3,392 (7.5) | 0.98 (0.95–1.02) | 1,182 (7.8) | 1.03 (0.97–1.09) | .19 |
| Outpatient opioid fills | | | | | |
| Perioperative [§] | 40,271 (89.5) | 1.10 (1.09–1.11) | 12,163 (79.7) | 0.98 (0.97–0.98) | <.001 |
| Any postoperative (d) | | | | | |
| 15–30 | 2,982 (6.9) | 1.49 (1.43–1.55) | 874 (5.9) | 1.29 (1.20–1.39) | <.001 |
| 31–60 | 2,358 (5.6) | 1.51 (1.44–1.58) | 677 (4.8) | 1.31 (1.21–1.42) | .002 |
| 61–90 | 2,008 (4.9) | 1.58 (1.50–1.66) | 548 (4.0) | 1.26 (1.15–1.38) | <.001 |
| 91–180 | 4,773 (12.9) | 1.52 (1.48–1.57) | 1,250 (10.3) | 1.22 (1.15–1.29) | <.001 |
| Persistent postoperative (d) [¶] | | | | | |
| 15–30 | 2,811 (6.5) | 1.55 (1.49–1.62) | 804 (5.5) | 1.32 (1.22–1.42) | <.001 |
| 31–60 | 538 (1.3) | 1.96 (1.78–2.18) | 163 (1.2) | 1.78 (1.50–2.11) | .29 |
| 61–90 | 148 (0.4) | 2.28 (1.86–2.79) | 50 (0.4) | 2.16 (1.58–2.95) | .76 |
| 91–180 | 82 (0.2) | 2.57 (1.94–3.40) | 30 (0.3) | 2.66 (1.76–4.02) | .88 |
| Opioid complications | | | | | |
| Opioid dependence | 101 (0.2) | 5.59 (4.09–7.65) | 34 (0.2) | 5.36 (3.49–8.24) | .84 |
| Opioid use disorder | 13 (<0.1) | 3.93 (1.73–8.94) | <11 | 4.84 (1.61–14.52) | .71 |
| Opioid poisoning | 14 (<0.1) | 1.26 (0.66–2.40) | <11 | 1.07 (0.37–3.13) | .80 |

HR, hazard ratio; RR, risk ratio; ED, emergency department.

* Wald χ^2 test comparing effect of medically managed depression and diagnosis only on outcomes.

[†] With or without a diagnosis of depression or anxiety.

[‡] Inverse-probability of treatment weighted; weights included age (treated as restricted quadratic spline), CCI score, surgical indications, comorbidities (other psychiatric diagnoses, hypertension, obesity, pain), nonopioid analgesic medication use, procedure type, inpatient procedure, and quarter and year of surgery; unweighted results are reported in Appendix 3 (<http://links.lww.com/AOG/C451>).

[§] Perioperative period included an opioid fill 30 days before surgery until 14 days after surgery.

^{||} Among patients with complete follow-up through the time period; did not require patients to have a postoperative opioid fill in the time period(s) prior.

[¶] Patients were required to have an opioid fill in time period(s) prior in addition to complete follow-up through the time period; for example, patients classified as having persistent use 31–60 days after hysterectomy also had fills during the perioperative and 15–30 days postoperative time periods.

at surgery (41% vs 26%) and among those that were opioid naïve, more likely to have a chronic pain condition (21% vs 14%). We also found that women with depression or anxiety were more likely to visit the ED, despite 30-day readmission rates being the same between groups. Increased ED use among women with preoperative depression or anxiety has been reported in at least one other study focused on gynecologic surgery.³⁰ Women with preoperative depression or anxiety are more likely to proceed to new high-risk opioid use after surgery. Targeted interventions focused on optimizing preoperative depression and anxiety and measuring the utilization of postoperative opioids and emergency services are needed.

This study has several important strengths. We used a national database of health care claims, which means results are highly generalizable to women aged 18–65 who are privately insured and not biased by individual institution practices or trends. We mea-

sured opioid fills, as opposed to opioid prescriptions, which would overestimate opioids available to women after surgery (because some likely do not fill their prescriptions). We also captured depression and anxiety using both diagnoses and outpatient medications and performed several analyses to assess whether treated and untreated depression or anxiety had different effects on opioid use.

This study has a few limitations. First, we were able to capture only those outpatient opioid fills that were reimbursed through insurance; opioids paid for out-of-pocket or obtained through other means (including inpatient opioid use) cannot be captured. However, we expect this to be relatively rare in an opioid-naïve patient population with private insurance and prescription drug coverage. Second, we were unable to determine the indication for the opioid prescription and attributed each prescription to postoperative pain. We restricted our study to women



who were opioid naïve in the 6 months before surgery to make this attribution more clinically reasonable, but it is likely that some opioids were prescribed for other causes. Third, we used diagnosis codes and outpatient medication fills to capture depression, anxiety, comorbidities, and opioid-related complications. This likely led to an underestimation of the prevalence of these factors, as undiagnosed conditions or conditions not related to any health care billing during the study period would be missed. Opioid-related dependence and use disorder are particularly under-estimated in claims data, and results should be interpreted with caution.³¹ The transition from ICD-9-CM to ICD-10-CM codes in October 2015 could also affect our results, although we saw consistent trends over time. We were also unable to capture several relevant clinical covariates in this data set, such as uterine weight, operative time, or postoperative complications, and residual confounding may exist in our analyses. Additionally, although hysterectomy is a major surgical intervention, most cases are performed using minimally invasive techniques in the outpatient setting, therefore the findings of this study may not be generalizable to other major surgery patients. Finally, our analyses were restricted to commercially insured individuals, and results may not generalize to women with public insurance (eg, Medicare, Medicaid) or those who are uninsured.

In summary, perioperative opioid fills remain very common among women who are opioid naïve undergoing hysterectomy for benign indications, with four out of five women filling a perioperative prescription (1 month before to 14 days after surgery). Women with depression or anxiety were more likely to have continued opioid fills 15–180 days after hysterectomy compared with those without depression or anxiety. Although relatively rare in this population, depression or anxiety substantially increases the risk of new high-risk persistent opioid use, opioid use disorder, and opioid dependence. Given the relatively high prevalence of depression and anxiety among women undergoing hysterectomy, clinicians and prescribers should be aware of the effects of these conditions and follow opioid-prescribing guidelines to reduce the incidence of long-term and inappropriate opioid use in their patients.

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