Use and Misuse of Opioids After Endocrine Surgery Operations

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Objective: To examine the rate of new and persistent opioid use after endocrine surgery operations

Summary of Background Data: A global epidemic of opioid misuse and abuse has been evolving over the past 2 decades with opioid use among surgical patients being a particularly difficult problem. Minimal data exists regarding opioid misuse after endocrine surgical operations.

Methods: A retrospective cohort study using the MarketScan identified adult patients who underwent thyroidectomy, parathyroidectomy, neck dissections for thyroid malignancy, and adrenalectomy from 2008 to 2017. Persistent opioid use was defined as receipt of $\geq$1 opioid prescription 90–180 days postop with no intervening procedures or anesthesia. Multivariable models were used to examine associations between clinical characteristics and any use and new persistent use of opioids.

Results: A total of 259,115 patients were identified; 54.6% of opioid naïve patients received a perioperative opioid prescription. Fulfillment of this prescription was associated with malignant disease, greater extent of surgery, younger age, residence outside of the Northeast, and history of depression or substance abuse. The rate of new persistent opioid use was 7.4%. A lateral neck dissection conferred the highest risk for persistent opioid use ($P < 0.01$). Persistent opioid use was also associated with older age, Medicaid coverage, residency outside of the Northeast, increased medical co-morbidities, a history of depression, anxiety, substance use disorder, and chronic pain (all $P < 0.01$). Importantly, the risk for persistent opioid use increased with higher doses of total amount of opioids prescribed.

Conclusions: The rate of new, persistent opioid use after endocrine surgery operations is substantial but may be mitigated by decreasing the number of postoperative opioids prescribed.

Keywords: endocrine surgery, opioid misuse, opioid use

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A global epidemic of opioid misuse and abuse has been evolving over the past 2 decades with the use of prescription opioid analgesics quadrupling since 1999 with a parallel rise in the number of overdoses from the most commonly prescribed opioids.[1] Notably, the countries that have been most affected by this crisis are those located in North America, western and central Europe, and Oceana. A particularly difficult problem is the use of opioids among surgical patients.[2] Approximately 320 million people,[3] including 51 million Americans, undergo surgery annually, and opioids remain a primary modality for postoperative pain management.[1] Despite early claims that prescription opioids are not addictive if used as directed,[4,5] there is now growing literature demonstrating that patients who have had an operation are at increased risk for chronic opioid use.[2,6–8] Studies have also suggested that prescribing patterns may contribute to the differential impact of the opioid crises across countries. For example, studies have shown that surgical patients in the US are frequently prescribed opioids in excess of what is needed for pain control, and that many receive prescriptions for opioids that are not needed at all for adequate pain relief after minor procedures.[9–12] In fact, studies have shown that the total amount of opioids prescribed for low-risk outpatient operations has increased over time, with over 80% of patients prescribed opioids.[2] Growing awareness and concerns regarding overprescribing have led to a range of efforts to reexamine prescription patterns after low-risk outpatient operations.

The majority of operations performed for surgical endocrine disorders induce low amounts of postoperative pain[13,14] and include thyroidectomies, parathyroidectomies, adrenalectomies, and some neck dissections, with many of these performed in the outpatient setting. Although there is some data examining the use of opioids after thyroidectomy,[2,10,15] there is limited data available describing patterns of opioid use and misuse associated with other common endocrine operations. The objective of our study was to examine patterns of opioid use in the endocrine surgery patient population. The primary outcome was to measure persistent opioid use after endocrine operations whereas the secondary outcomes were to understand the factors associated with initial and persistent use of opioids after endocrine operations.

METHODS

Data Sources and Study Cohort

The Truven Health MarketScan database was used for analysis. MarketScan includes approximately 350 payers and captures claims from more than 50 million privately insured patients across the country and 6 million Medicaid beneficiaries from 12 U.S. states.[16] It collects medical claims for inpatient and outpatient services and pharmaceutical claims.[16] Data were de-identified and deemed exempt by the Columbia University Institutional Review Board.

MarketScan data from the years 2008–2017 were used to identify patients aged 18–65 years who underwent the following procedures: adrenalectomy, neck lymph node dissections associated with the diagnosis of thyroid cancer, substernal thyroidectomy, complete thyroidectomy, partial thyroidectomy, and parathyroidectomy. The cohort was restricted to patients who had continuous health insurance and drug benefit coverage from 12 months prior until 6 months after the surgical procedure. Patients who underwent anesthesia for another procedure or indication in the 6-month postoperative period were excluded to minimize the influence of necessary opioid use for other indications. The cohort was limited to opioid naïve patients, defined as those who did not fill a prescription for an opioid during the period from 12 months until 31 days before the index procedure (Fig. 1).

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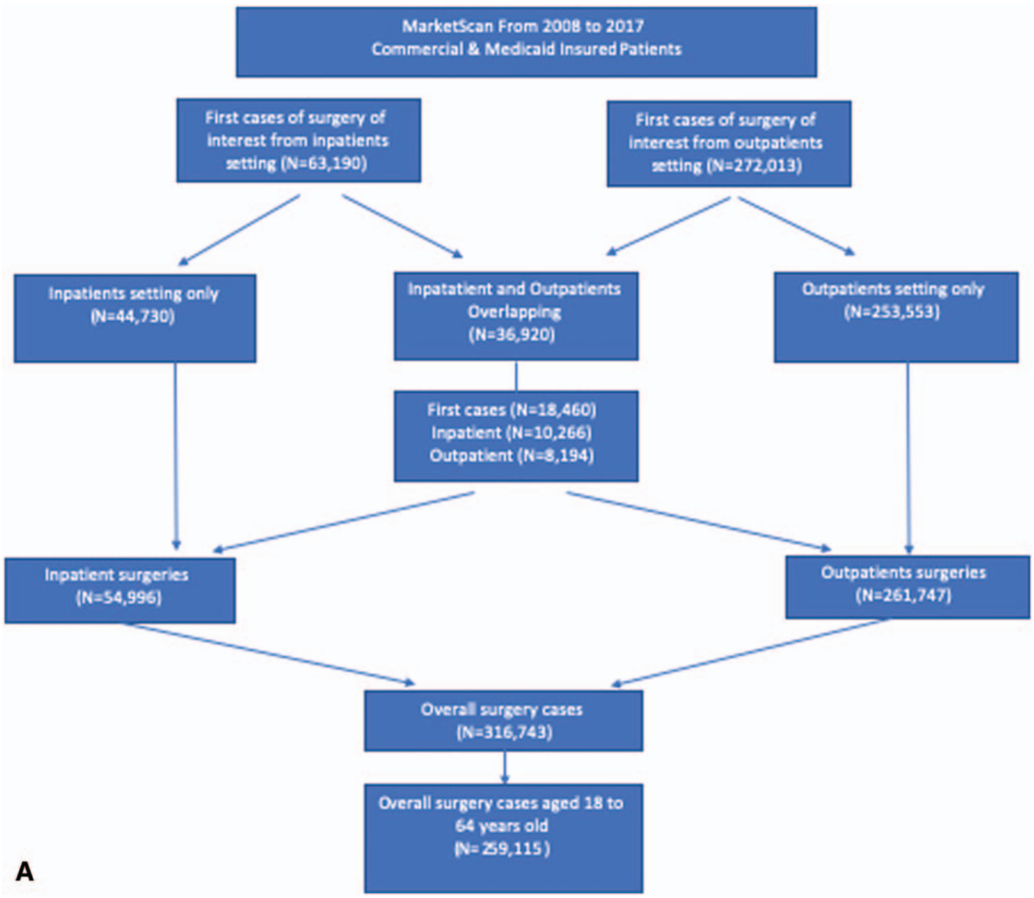

FIGURE 1. (A) MarketScan database case selection. (B) Pation cohort selection.

Opioid Exposure

Perioperative opioid exposure was defined as any prescription of an opioid filled from 30 days before surgery until 2 weeks after the procedure. We assessed pharmaceutical claims to determine initial opioid exposure, including days of opioid supplied, total dose and daily dosage of opioid. Opioids examined included codeine, morphine, oxycodone, hydromorphone, hydrocodone, meperidine, oxymorphone, methadone, and fentanyl. National Drug Codes were used to specify route of administration, drug dosing concentration (milligram per unit), and drug type. To compare opioid dosage, each prescription was converted into morphine milligram equivalents (MMEs) using a standard published conversion factor.[17] MMEs of all opioid prescriptions during the perioperative period were summed to obtain the total dose. We calculated the daily dosage by dividing total dose by total days supplied. Prescriptions filled within 30 days before the index procedure date were classified as preoperative prescriptions.

Outcomes

We examined opioid use and persistent opioid use. Opioid use was defined as the fill of at least 1 opioid prescription in the period from 30 days before 2 weeks after surgery. Persistent opioid use was defined as fill of at least 1 opioid prescription within the window of 90 to 180 days after surgery as previously described.[2]

Patient Factors

Demographic data included age (<30, 30–39, 40–49, 50–59, 60–64 years) at the time of surgery, sex (male, female), procedure year, hospital setting for surgery (inpatient or ambulatory visits), metropolitan statistical area (metropolitan statistical area [MSA], yes, no, unknown), region (northeast, north-central, south, west, unknown), and race (white, black, Hispanic, other). Information on MSA and region were available for commercially insured patients only, and race was available only for Medicaid beneficiaries only. Comorbid medical disease was estimated using the Elixhauser comorbidity index, and categorized as 0, 1, $\geq$2.[18] The occurrence of chronic pain and underlying psychiatric diagnoses including anxiety, depression, and substance use disorders (SUDs) during the 12 months before surgery were also noted. Chronic pain was defined as the occurrence of 2 claims, >30 days apart for a condition associated with chronic pain as previously reported.[19]

Statistical Analysis

Patients' characteristics and perioperative opioid exposures were presented descriptively and compared using Chi-square tests by the status of perioperative opioid use (Table 1). The pattern of perioperative opioid prescription was described by operation type, procedure years, presence of malignant disease, sex, and health insurance (Table 2). Patients' characteristics and perioperative opioid

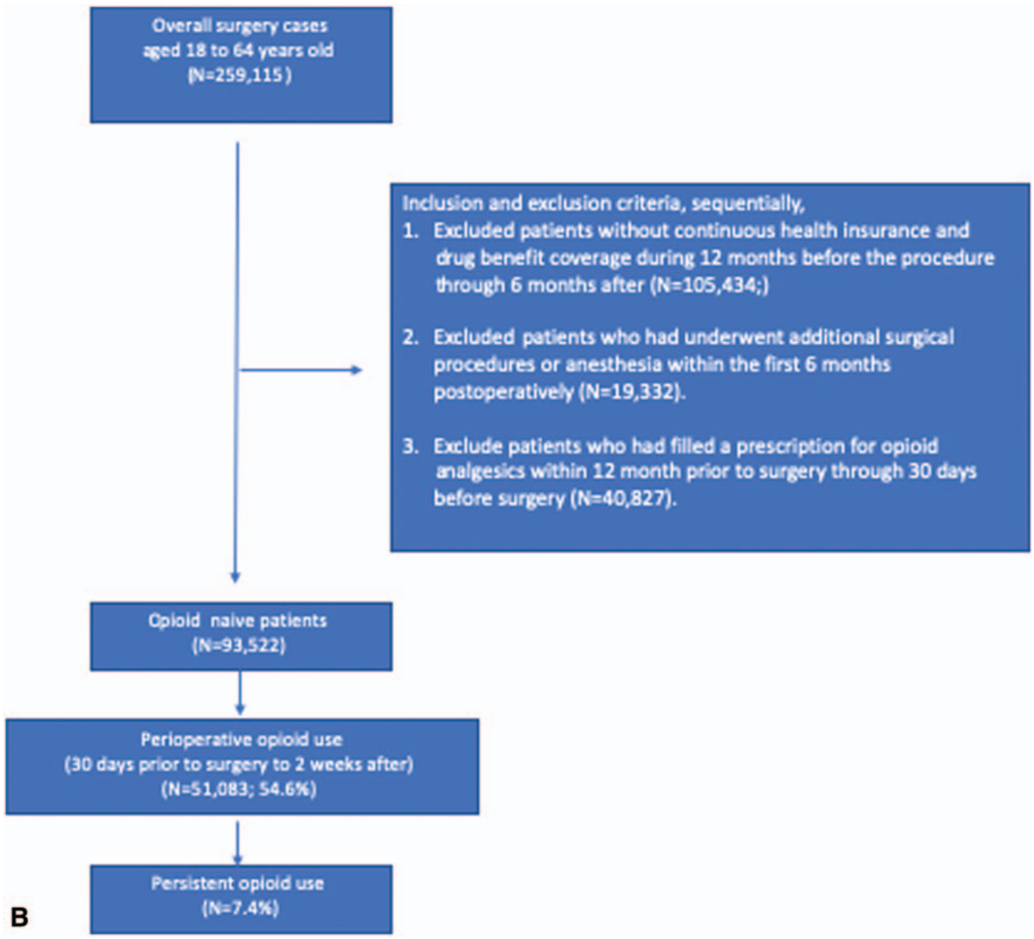

FIGURE 1. Continued

exposures were presented descriptively and compared using Chi-square tests by the status of persistent opioid use (Table 3). Multivariable log-linear regression models were developed to examine the factors associated with perioperative opioid use. Due to the correlation between total morphine equivalents (TMEs) dispensed and daily morphine equivalents (DMEs) dispensed (Pearson correlation coefficient $r = 0.49$), 2 separate models were developed to explore factors associated with new persistent opioid use among patients initiating opioid use in the perioperative period. One model included TMEs dispensed and supply days, and another model included DMEs dispensed. Both models included surgery, age, health insurance, metropolitan statistical area, region, Elixhauser comorbidity score, hospital setting, procedure year, past year mental health disorder, opioid prescription in 30 days before procedure. Estimates from multivariable log-linear regression models were reported as adjusted relative risks (RR) and 95% confidence interval (CI). Sensitivity analyses (1) excluding patients with a history of SUD or chronic pain and (2) evaluating adrenalectomies alone were also performed. Subset analysis of neck dissection patients comparing those undergoing neck dissection only versus those with concomitant thyroidectomy and open versus laparoscopic adrenalectomy were performed with Chi-square analysis.

All hypothesis tests were 2-sided. A P-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 259,115 patients between the ages of 18–65 years who underwent endocrine operations were identified (Fig. 1). Within this cohort, we ultimately identified 93,522 opioid naïve patients that were included in the analysis. The operations included 41,950 partial thyroidectomies (44.9%), 30,641 total thyroidectomies (32.8%), 13,198 parathyroidectomies (14.1%), 3008 substernal thyroidectomies (3.2%), 3139 lateral neck dissections for thyroid cancer (3.4%), and 1586 adrenalectomies (1.7%). The majority of these operations occurred in an outpatient setting (84.0%) and were performed for benign disease (95.1%). The patient cohort was mostly women (81.3%) with a median age of 50 years (interquartile range: 40–57) covered by commercial insurance (94.7%) (Table 1). The majority of patients had no significant underlying comorbidities (64.1%), but 7.9% of this cohort had a history of depression, 1.1% had anxiety, 7.2% had a substance abuse disorder, and 29.2% had chronic pain.

Overall, 54.6% of opioid naïve patients filled a perioperative opioid prescription after their endocrine operation (Table 1). The number of filled perioperative opioid prescriptions increased from 2009 (50.8%) to 2016 (57.2%), then decreased slightly in 2017 (55.6%). Patients who had their operation for malignant disease were 1.18 times (95% CI 1.16–1.21, $P < 0.0001$) more likely to fill a perioperative opioid prescription than those who had benign disease. Of the patients who had a total thyroidectomy, 70.2% filled a perioperative opioid prescription. Patients who underwent a partial

TABLE 1. Factors Associated With Perioperative Opioid Use Among Opioid Naïve Patients

	Perioperative Opioid Use			Log-linear Model
	Yes	No	*P*-value	
	N (Row%)	N (Row%)		aRR (95% CI)
Operation			<0.0001	
Adrenalectomy	1212 (76.4)	374 (23.6)		1.10 (1.03, 1.17)*
Neck lymph node dissections	2278 (72.6)	861 (27.4)		0.92 (0.88, 0.96)*
Substernal thyroidectomy	2155 (71.6)	853 (28.4)		1.09 (1.04, 1.14)*
Complete thyroidectomy	21,497 (70.2)	9144 (29.8)		Referent
Partial thyroidectomy	16,322 (38.9)	25,628 (61.1)		0.60 (0.59, 0.61)†
Parathyroidectomy	7619 (57.7)	5579 (42.3)		0.94 (0.91, 0.97)†
Procedure year			<0.0001	
2009	6268 (50.8)	6062 (49.2)		Referent
2010	6297 (52.4)	5717 (47.6)		0.99 (0.96, 1.03)
2011	7096 (53.7)	6121 (46.3)		1.02 (0.98, 1.05)
2012	6551 (53.7)	5657 (46.3)		1.00 (0.97, 1.04)
2013	5983 (56.2)	4656 (43.8)		1.04 (1.00, 1.07)
2014	5696 (56.9)	4315 (43.1)		1.05 (1.01, 1.08)*
2015	5311 (57.7)	3893 (42.3)		1.08 (1.04, 1.12)†
2016	5366 (57.2)	4012 (42.8)		1.09 (1.05, 1.14)†
2017	2515 (55.6)	2006 (44.4)		1.09 (1.05, 1.14)†
Hospital setting			<0.0001	
Inpatient	9417 (67.1)	4627 (32.9)		Referent
Outpatient	41,666 (52.4)	37,812 (47.6)		0.94 (0.92, 0.96)†
Age			<0.0001	
<=29	4133 (62.6)	2474 (37.4)		1.07 (1.04, 1.11)†
30–39	9067 (61.2)	5740 (38.8)		1.07 (1.04, 1.09)†
40–49	13,558 (56.7)	10,338 (43.3)		Referent
50–49	16,948 (51.6)	15,869 (48.4)		0.92 (0.90, 0.94)†
60–64	7377 (47.9)	8018 (52.1)		0.86 (0.83, 0.88)†
Sex			<0.0001	
Male	9982 (56.7)	7609 (43.3)		Referent
Female	41,101 (54.1)	34,830 (45.9)		0.98 (0.96, 1.00)
Health insurance			<0.0001	
Commercial or Medicare	48,157 (54.4)	40,366 (45.6)		Referent
Medicaid	2926 (58.5)	2073 (41.5)		1.05 (0.97, 1.15)
Metropolitan statistical area			<0.0001	
Non-MSA	6427 (52.7)	5764 (47.3)		Referent
MSA	40,827 (54.7)	33,871 (45.3)		1.01 (0.99, 1.04)
Unknown	3829 (57.7)	2804 (42.3)		1.18 (1.05, 1.33)*
Region			<0.0001	
Northeast	9452 (51.8)	8780 (48.2)		Referent
North-central	9889 (51.7)	9228 (48.3)		1.03 (1.00, 1.06)*
South	20,079 (55.6)	16,024 (44.4)		1.10 (1.08, 1.13)†
West	8100 (58.5)	5737 (41.5)		1.13 (1.10, 1.17)†
Unknown	3563 (57.2)	2670 (42.8)		0.88 (0.77, 1.01)
Elixhauser comorbidity score			0.0014	
0	32,510 (54.2)	27,460 (45.8)		Referent
1	11,907 (55.6)	9499 (44.4)		1.01 (0.99, 1.03)
>=2	6666 (54.9)	5480 (45.1)		0.99 (0.97, 1.02)
Depression			<0.0001	
No	46,656 (54.2)	39,447 (45.8)		Referent
Yes	4427 (59.7)	2992 (40.3)		1.05 (1.01, 1.08)*
Anxiety			<0.0001	
No	44,818 (54.0)	38,238 (46.0)		Referent
Yes	6265 (59.9)	4201 (40.1)		1.05 (1.02, 1.08)*
Substance use disorder			<0.0001	
No	46,707 (53.8)	40,086 (46.2)		Referent
Yes	4376 (65.0)	2353 (35.0)		1.15 (1.12, 1.19)†
Chronic pain			0.0001	
No	36,430 (55.0)	29,785 (45.0)		Referent
Yes	14,653 (53.7)	12,654 (46.3)		1.00 (0.98, 1.02)
Malignant disease associated with index procedures			<0.0001	
No	33,260 (49.4)	34,013 (50.6)	—	Referent
Yes	17,823 (67.9)	8426 (32.1)	—	1.18 (1.16, 1.21)†
Race/ethnicity			<0.0001	
Unknown (Commercial insurance)	48,566 (54.4)	40,699 (45.6)		
White	1353 (57.7)	993 (42.3)		
Black	1004 (62.1)	614 (37.9)		
Asian	71 (58.2)	51 (41.8)		
Other	89 (52.0)	82 (48.0)		

*$P < 0.01$.
†$P < 0.001$.
CI indicates confidence interval.

TABLE 2. Patterns of Perioperative Opioid Prescription Stratified by Surgery Type, Procedure Years, Malignant Disease, Sex, and Health Insurance

	Number of Patients N (%)	Total Morphine Equivalents Dispensed Median (IQR) mg	Daily Morphine Equivalents Dispensed Median (IQR) mg	Initial Total Day Supply Median (IQR) d	Opioid Prescription Before Procedure N (%)
Surgery type					
Adrenalectomy	1212 (2.4)	250.0 (187.5, 414.3)	50.0 (37.5, 75.0)	5.0 (4.0, 8.0)	92 (7.8)
Neck lymph node dissection	2278 (4.5)	225.0 (150.0, 375.0)	45.0 (32.1, 68.8)	5.0 (4.0, 7.0)	318 (14.0)
Substernal thyroidectomy	2155 (4.2)	225.0 (150.0, 300.0)	45.0 (32.1, 66.7)	5.0 (3.0, 7.0)	285 (13.2)
Complete thyroidectomy	21,497 (42.1)	200.0 (150.0, 300.0)	45.0 (32.1, 67.5)	5.0 (3.0, 6.0)	2549 (11.9)
Partial thyroidectomy	16,322 (32.0)	225.0 (150.0, 300.0)	45.0 (31.3, 66.7)	5.0 (3.0, 6.0)	2606 (16.0)
Parathyroidectomy	7619 (14.9)	175.0 (135.0, 250.0)	45.0 (30.0, 60.0)	4.0 (3.0, 5.0)	759 (10.0)
P-value		<0.0001	<0.0001	<0.0001	<0.0001
Procedure year					
2009	6268 (12.3)	375.0 (954.9)	45.0 (33.3, 75.0)	5.0 (3.0, 6.0)	819 (13.1)
2010	6297 (12.3)	200.0 (150.0, 300.0)	45.0 (33.3, 75.0)	5.0 (3.0, 6.0)	860 (13.7)
2011	7096 (13.9)	200.0 (150.0, 300.0)	45.0 (33.3, 67.5)	5.0 (3.0, 6.0)	981 (13.8)
2012	6551 (12.8)	200.0 (150.0, 300.0)	45.0 (31.3, 66.7)	5.0 (3.0, 6.0)	869 (13.3)
2013	5983 (11.7)	225.0 (150.0, 300.0)	45.0 (32.1, 66.7)	5.0 (3.0, 6.0)	869 (14.5)
2014	5,696 (11.2)	225.0 (150.0, 300.0)	45.0 (30.7, 62.3)	5.0 (3.0, 6.0)	650 (11.4)
2015	5311 (10.4)	225.0 (150.0, 300.0)	45.0 (30.0, 60.0)	5.0 (3.0, 6.0)	594 (11.2)
2016	5366 (10.5)	200.0 (150.0, 300.0)	45.0 (30.0,60.0)	5.0 (3.0, 6.0)	692 (12.9)
2017	2515 (4.9)	200.0 (135.0, 262.5)	45.0 (30.0, 56.3)	5.0 (3.0, 6.0)	275 (10.9)
P-value		<0.0001	<0.0001	<0.0001	<0.0001
Malignant disease					
Non-cancer	33,260 (65.1)	200.0 (150.0, 300.0)	45.0 (31.3, 66.7)	5.0 (3.0, 6.0)	2195 (12.32)
Cancer	17,823 (34.9)	225.0 (150.0, 300.0)	45.0 (32.1, 67.5)	5.0 (3.0, 6.0)	4414 (13.27)
P-value		<0.0001	<0.0001	0.0259	0.0022
Sex					
Male	9982 (19.5)	225.0 (150.0, 300.0)	45.0 (32.1, 66.7)	5.0 (3.0, 6.0)	1276 (12.8)
Female	41,101 (80.5)	200.0 (150.0, 300.0)	45.0 (31.3, 66.7)	5.0 (3.0, 6.0)	5333 (13.0)
P-value		<0.0001	0.0039	0.0215	0.6075
Health insurance					
Commercial/Medicare	48,157 (94.3)	200.0 (150.0, 300.0)	45.0 (31.7, 66.7)	5.0 (3.0, 6.0)	6195 (12.9)
Medicaid	2926 (5.7)	225.0 (150.0, 375.0)	45.0 (30.0, 60.0)	5.0 (4.0, 8.0)	414 (14.2)
P-value		<0.0001	<0.0001	<0.0001	0.044

IQR indicates interquartile range.

thyroidectomy (38.9%), or a parathyroidectomy (57.7%) were less likely to fill a perioperative opioid prescription, but those that underwent a substernal thyroidectomy (71.6%), lateral neck dissection (72.6), or adrenalectomy (76.4%) had a higher rate of perioperative opioid use ($P < 0.0001$). Performing the operation in an outpatient setting decreased the risk of perioperative opioid use by 66% ($P < 0.001$). In a multivariable model, younger patients and those residing outside of the Northeast were more likely to fill an opioid prescription. A history of depression [adjusted relative risk (aRR) 1.05 (1.01–1.08)], and SUD [aRR 1.15 (1.12–1.19)] were associated with a higher risk of perioperative opioid use. A sensitivity analysis excluding patients with a history of SUD or chronic pain was performed and presented in Supplemental Table 1A, http://links.lww.com/SLA/B939. The significant risk factors for perioperative opioid use remained unchanged. A sensitivity analysis excluding the adrenalectomy patients also demonstrated no change in the significant risk factors associated with perioperative opioid use (Supplemental Table 1B, http://links.lww.com/SLA/B939). To further evaluate the association between type of operation and perioperative opioid use, a sub-analysis of patients who underwent a neck dissection and those that underwent an adrenalectomy (1114 laparoscopic, 472 open) were also performed. Although there was no difference noted between laparoscopic and open adrenalectomy (76.4% vs 76.5%, $P = 0.97$), a neck dissection and concomitant thyroidectomy (n = 2426) was associated with higher perioperative opioid use than neck dissection alone (n = 713; 74.5% vs 66.1%, $P < 0.0001$).

Patterns of perioperative opioid prescription are summarized in Table 2. Although there was no significant difference in calculated DME prescribed for the different operations, there was a trend for higher total morphine equivalent (TME) prescribed for operations with more extensive dissection, with the highest prescribed dosages for patients undergoing adrenalectomy. However, there also seems to be a trend for decreased TME prescribed over time, decreasing from 375 mg in 2009 to 200 mg in 2017. The median dosage prescribed was 9 tablets of 5 mg hydrocodone for a median supply of 5 days, for a total of 40–45 hydrocodone tablets (5 mg). Male patients, those with malignant disease, and Medicaid patients were prescribed higher doses (all 225 mg vs 200 mg, $P < 0.001$). A sensitivity analysis excluding patients with a history of SUD or chronic pain demonstrated no significant change in these prescription patterns (Supplemental Table 2, http://links.lww.com/SLA/B939).

Persistent opioid use was identified in 7.4% of patients prescribed an opioid during the perioperative period. A multivariable model examining factors associated with new persistent opioid use after perioperative opioid use is presented in Table 3. There was a decline in persistent opioid use from 8.6% in 2009 to 5.9% in 2017 ($P < 0.0001$). When compared to a total thyroidectomy, the only type of operation associated with a significantly higher risk for persistent opioid use was a lateral neck dissection [aRR 1.21 (1.03, 1.42), $P < 0.01$]. The risk for persistent opioid use was associated with older age, Medicaid coverage, residency outside of the Northeast, and increased medical co-morbidities. A history of depression, anxiety,

TABLE 3. Factors Associated With New Persistent Opioid Use Among Patients Initiating Opioid at Surgery

	Persistent Opioid Use		*P*-value	Log-linear Model
	Yes	No		aRR (95% CI)
Operation			0.053	
Adrenalectomy	90 (7.4)	1122 (92.6)		0.89 (0.71, 1.11)
Neck lymph node dissections	184 (8.1)	2094 (91.9)		1.21 (1.03, 1.42)*
Substernal Thyroidectomy	142 (6.6)	2013 (93.4)		0.84 (0.71, 1.00)
Complete Thyroidectomy	1553 (7.2)	19,944 (92.8)		Referent
Partial Thyroidectomy	1289 (7.9)	15,033 (92.1)		1.04 (0.96, 1.12)
Parathyroidectomy	545 (7.2)	7074 (92.8)		1.00 (0.90, 1.11)
Procedure year			<0.0001	
2009	539 (8.6)	5729 (91.4)		Referent
2010	534 (8.5)	5763 (91.5)		1.03 (0.92, 1.17)
2011	545 (7.7)	6551 (92.3)		0.91 (0.81, 1.02)
2012	512 (7.8)	6039 (92.2)		0.88 (0.78, 1.00)*
2013	423 (7.1)	5560 (92.9)		0.80 (0.70, 0.91)*
2014	415 (7.3)	5281 (92.7)		0.80 (0.70, 0.91)*
2015	396 (7.5)	4915 (92.5)		0.78 (0.68, 0.88)*
2016	291 (5.4)	5075 (94.6)		0.56 (0.49, 0.65)†
2017	148 (5.9)	2367 (94.1)		0.56 (0.49, 0.65)†
Hospital setting			0.8304	
Inpatient	706 (7.5)	8711 (92.5)		Referent
Outpatient	3097 (7.4)	38,569 (92.6)		0.99 (0.90, 1.08)
Age			0.0001	
<=29	252 (6.1)	3881 (93.9)		Referent
30–39	649 (7.2)	8418 (92.8)		1.15 (0.99, 1.33)
40–49	1043 (7.7)	12,515 (92.3)		1.29 (1.12, 1.48)*
50–49	1240 (7.3)	15,708 (92.7)		1.24 (1.08, 1.43)*
60–64	619 (8.4)	6758 (91.6)		1.43 (1.23, 1.67)†
Sex			0.0667	
Male	700 (7.0)	9282 (93.0)		Referent
Female	3103 (7.5)	37,998 (92.5)		1.04 (0.95, 1.13)
Health insurance			<0.0001	
Commercial/ Medicare	3367 (7.0)	44,790 (93.0)		Referent
Medicaid	436 (14.9)	2490 (85.1)		2.05 (1.48, 2.84)†
Metropolitan statistical area			<0.0001	
Non-MSA	540 (8.4)	5887 (91.6)		Referent
MSA	2778 (6.8)	38,049 (93.2)		0.87 (0.79, 0.95)*
Unknown	485 (12.7)	3344 (87.3)		0.51 (0.26, 0.98)*
Region			<0.0001	
Northeast	500 (5.3)	8952 (94.7)		Referent
North-central	667 (6.7)	9222 (93.3)		1.25 (1.11, 1.41)*
South	1577 (7.9)	18,502 (92.1)		1.41 (1.27, 1.56)†
West	582 (7.2)	7518 (92.8)		1.29 (1.14, 1.45) †
Unknown	477 (13.4)	3086 (86.6)		1.98 (0.96, 4.07)
Elixhauser comorbidity score			<0.0001	
0	2215 (6.8)	30,295 (93.2)		Referent
1	937 (7.9)	10,970 (92.1)		1.09 (1.01, 1.18)*
>=2	651 (9.8)	6015 (90.2)		1.22 (1.11, 1.34)†
Depression			<0.0001	
No	3351 (7.2)	43,305 (92.8)		Referent
Yes	452 (10.2)	3975 (89.8)		1.12 (1.00, 1.24)*
Anxiety			<0.0001	
No	3198 (7.1)	41,620 (92.9)		Referent
Yes	605 (9.7)	5660 (90.3)		1.20 (1.09, 1.32)*
Substance use disorder			<0.0001	
No	3269 (7.0)	43,438 (93.0)		Referent
Yes	534 (12.2)	3842 (87.8)		1.40 (1.27, 1.54)†
Chronic pain			<0.0001	
No	2517 (6.9)	33,913 (93.1)		Referent
Yes	1286 (8.8)	13,367 (91.2)		1.16 (1.08, 1.24)†
Malignant disease			<0.0001	
No	2588 (7.8)	30,672 (92.2)		Referent
Yes	1215 (6.8)	16,608 (93.2)		0.93 (0.86, 1.00)
Total OME perioperatively			<0.0001	
<150	585 (5.8)	9449 (94.2)		Referent
150–199	773 (6.3)	11,495 (93.7)		1.06 (0.95, 1.18)
200–299	951 (6.9)	12,774 (93.1)		1.14 (1.02, 1.26)*
>=300	1494 (9.9)	13,562 (90.1)		1.25 (1.12, 1.40)†

TABLE 3. (*Continued*)

	Persistent Opioid Use		*P*-value	Log-linear Model
	Yes	No		aRR (95% CI)
Supply days perioperatively			<0.0001	
1–3 d	982 (6.1)	15,184 (93.9)		Referent
4–5 d	1332 (6.5)	19,120 (93.5)		1.01 (0.93, 1.10)
6–7 d	494 (7.8)	5880 (92.2)		1.10 (0.98, 1.23)
8–13 d	583 (10.0)	5273 (90.0)		1.28 (1.14, 1.44)†
>=14 d	412 (18.4)	1823 (81.6)		2.00 (1.75, 2.29)†
Opioid prescription 30 d before surgery			<0.0001	
No	3030 (6.8)	41,444 (93.2)		Referent
Yes	773 (11.7)	5836 (88.3)		1.39 (1.28, 1.51)†
Daily OME perioperatively‡			0.1238	
<30	589 (7.6)	7168 (92.4)		Referent
30–49	1469 (7.2)	19,007 (92.8)		0.98 (0.89, 1.08)
50-89	1177 (7.5)	14,585 (92.5)		1.05 (0.95, 1.16)
>=90	568 (8.0)	6520 (92.0)		1.08 (0.96, 1.22)

*$P < 0.01$.
†$P < 0.001$.
‡The calculation of daily opioid dose was based on the total dose and supply days. Accordingly, there is correlation between total morphine equivalents dispensed and daily morphine equivalents dispensed (Pearson correlation coefficient $r = 0.49$). Two separate models were developed. One included total morphine equivalents dispensed and supplied days, and another one included daily morphine equivalents dispensed. Both modes included surgery, age, health insurance, metropolitan statistical area, region, Elixhauser comorbidity score, hospital setting, procedure year, past year mental health disorder, opioid prescription in 30 d before procedure.
Estimates of demographics and clinical factors were generated from the model with total morphine equivalents dispensed and supplied days.
Initial total morphine equivalents dispensed cut-off: 25th percentile (150 mg), 50th (200 mg), 75th (300 mg).
Initial daily morphine equivalents dispensed cut-off: 25th percentile (30 mg), 50 mg, and 90 mg were chosen based on literature for clinical relevance.
Initial total day supply cut-off: 25th percentile (3 d), 5, 7, 14 d were chosen based on literature.
CI indicates confidence interval; OME = opioid morphine equivalent; MSA = metropolitan statistical area.

SUD, and chronic pain are also associated with persistent opioid use. A higher total MME and a longer day supply of opioid were associated with persistent opioid use. For example, compared to patients prescribed <150 MME, those prescribed >300 MME were 25% more likely to have persistent opioid use (RR = 1.25; 95% CI, 1.12–1.40). Morphine equivalent. Fill of an opioid prescription before the procedure was associated with a 39% increased risk of persistent opioid use (RR = 1.39; 95% CI, 1.28–1.51). A sensitivity analysis excluding patients with a history of SUD or chronic pain was performed and presented in Supplemental Table 3A, http://links.lww.com/SLA/B939. The significant risk factors for persistent opioid use remained unchanged. A sensitivity analysis excluding the adrenalectomy patients also demonstrated no change in the significant risk factors associated with persistent opioid use (Supplemental Table 3B, http://links.lww.com/SLA/B939). To further evaluate the association between type of operation and persistent opioid use, a sub-analysis of patients who underwent a neck dissection and those that underwent an adrenalectomy were also performed. Although there was no difference noted between laparoscopic and open adrenalectomy (7.8% vs 6.7%, $P = 0.50$), a neck dissection alone was associated with higher persistent opioid use than neck dissection and concomitant thyroidectomy (11.0% vs 7.3%, $P = 0.008$).

DISCUSSION

Our results from this cross-sectional study of a large national database provides a comprehensive overview of the patterns of opioid use and misuse after endocrine surgery. The study demonstrates that over half of all opioid naïve patients who undergo an endocrine operation fill a perioperative opioid prescription, and this number increased over the time frame of the study with a small decrease noted in 2017. Perioperative opioid use was associated with the extent of surgery, with a lower likelihood of filling a prescription among those patients undergoing less invasive operations such as partial thyroidectomy or parathyroidectomy. However, greater than 70% of patients undergoing a total thyroidectomy or more extensive operations such as adrenalectomy or lateral neck dissection, filled a new opioid prescription during the perioperative period.

Although studies have shown that only 5.9% of patients undergoing minor operations fill a perioperative opioid prescription,[2] our results are more in line with endocrine specific studies that found 57%–93% patients who undergo endocrine operations fill a perioperative opioid prescription.[15,20] Because the postoperative pain experienced after most endocrine operations is minimal,[13,14] this difference in the rate of filling prescriptions between these cohorts undergoing minor operations and those that undergo endocrine operations suggests that perioperative opioid use among endocrine surgery patients may be much higher than necessary. Our results are also similar to other studies that have demonstrated that younger age and a history of depression, SUD, and chronic pain are all associated with a higher risk of perioperative opioid use[1]; however, our sensitivity analyses also demonstrate that this risk is also independent of SUD and chronic pain.

Our examination of prescription patterns found that the total dosage of opioids prescribed is associated with the extent of the operation, with patients undergoing adrenalectomy receiving the highest prescribed doses. Interestingly, we found that even after adjusting for the type of procedure, operations performed in the outpatient setting significantly decreased the risk of perioperative opioid use, suggesting that the setting of surgery may bias the perceived need for opioids. We also found that there was significant geographic variation in opioid use patterns within the United States, with a higher risk of perioperative opioid use outside of the Northeast. This finding adds to the growing literature that there is significant variation in prescription patterns, not only at the country level, but also the state level, that contributes to the over prescribing of opioids in the perioperative period.[21] We also found that the median dosage prescribed was a total of 40–45 hydrocodone tablets (5 mg) for a 5-day supply. This is more than double the recommended 5–20 tablet count that has been endorsed by recent studies for patients undergoing thyroidectomy,[15,21] or similar procedures to laparoscopic adrenalectomies such as laparoscopic cholecystectomy or appendectomy (10 tablets).[15,21] This finding is even more concerning in light of recent evidence that greater than 95% of patients undergoing cervical endocrine operations can be successfully managed with acetaminophen alone.[13]

We found that 5.9% of opioid naïve patients undergoing endocrine operations developed persistent opioid use consistent with rates reported in the literature for other types of operations.[2] Similar to previous studies we found that older age and other medical comorbidities were predictive of persistent opioid use. However, we also found that a lateral neck lymph node dissection was associated with a 21% higher risk of persistent opioid use as compared to patients undergoing total thyroidectomy, this is in contrast to previous studies that found that the extent of the operation is a not a strong determinant of chronic postsurgical pain.[22–24] Interestingly, although neck dissection with concomitant thyroidectomy was associated with a higher risk of perioperative opioid use, it was neck dissection alone that was associated with a higher risk for persistent opioid use. Specifically, neck dissection alone, and not a neck dissection with concomitant thyroidectomy, was associated with a higher risk for persistent opioid use. Of note, adrenalectomy was not associated with a higher risk of persistent opioid use, and there was no difference between laparoscopic and open adrenalectomy. Although the reasons for this discrepancy is unclear, it may be explained by 2 different factors. First, dissection of lateral level IV lymph nodes can lead to manipulation, traction, skeletonization, and devascularization of the cervical nerve that cause significant neuropathic pain postoperatively.[25] Therefore, it may not be the physical extent of the operation but more specifically the necessary manipulation of nerves that is associated with persistent opioid use after a lateral neck dissection. Although the data points in MarketScan are not granular enough for us to be sure, patients who undergo neck dissection with concomitant thyroidectomy may have less disease burden than those undergoing neck dissection alone. The later cohort may reflect patients undergoing staged operations or treatment for recurrent disease. In addition, we may be noting a difference in different types of postoperative pain. Perioperative opioid use may be associated with acute inflammatory discomfort (intubation and tracheal manipulation during thyroidectomy) whereas persistent opioid use may be associated with less postoperative inflammation and caused by other types of pain like neuropathic pain. Second, although we found that approximately 70% of our adrenalectomies were coded as laparoscopic, it was unclear if the coding of laparoscopic versus open adrenalectomy was reliable in the database. Additionally, because both the neck dissection and adrenalectomy cohorts were relatively small, it is possible that despite use of a large national database, the analyses were underpowered. Importantly, we found a dose-response relationship between total dose of opioids prescribed and persistent opioid use after endocrine operations. The identification of this modifiable factor associated with persistent opioid use is a crucial first step in our efforts to decrease the risk of opioid misuse and abuse.

There is growing evidence that endocrine surgical patients require very little, if any, postoperative opioids.[13,14] In a recent prospective study of 216 patients undergoing cervical endocrine operations, Ruffolo et al[13] demonstrated that only 4% of patients actually requested opioids at discharge when given the choice between receiving a prescription automatically or receiving a prescription only after nonopioid medications failed to control their pain. Importantly, none of the patients that opted out of opioids upon discharge required any opioids for management of their postoperative pain. There is also evidence that educating endocrine surgeons regarding the minimal need for perioperative opioid use will help to lower discharge opioid recommendations.[26] Although the 5.9% risk of persistent opioid use after endocrine operations is relatively low compared to the 10% of all surgical patients who develop chronic pain syndrome,[1] this small percentage is still extremely high given that the endocrine surgery patient cohort likely requires no opioids at all to manage their postoperative pain. Given the emerging data regarding postoperative opioid use and the results of this study, we have modified our own practice. Whereas we were routinely discharging patients with 40 tablets of Norco 5 mg, we completely stopped prescribing opioids for our cervical neck operations and only prescribe a maximum of 5 tablets for our adrenalectomy patients. In concordance with Ruffolo et al, we have not noted an increase in patient calls or complaints because this practice modification was initiated. We plan to re-examine the perioperative opioid use for our adrenalectomy patients and if the data supports it, plan to cease routine opioid prescriptions for our adrenalectomy patients as well. We encourage similar re-examination and practice modifications for our colleagues in their practices.

We recognize that the conclusions drawn from our study need to be interpreted in consideration of a number of important limitations. As with all administrative data, coding errors and the inability to capture some underlying disease characteristics, patient factors, and use of nonopioid over the counter analgesics or other potential confounders of opioid use could have affected the results of our study. We are also unable to reliably capture use of adjunct treatment such as physical or occupational therapy that could affect our analysis as well. Furthermore, the MarketScan Database contains predominately commercially insured patients with some Medicaid patients and may not be generalizable to other populations. Although we excluded patients who underwent additional procedures or interventions that required anesthesia in the postoperative period, it is possible that a small number of patients classified as persistent opioid users may have received opioids for other indications we could not capture. Finally, although we report the rate of filling an opioid prescription, we cannot actually capture the rate of opioid consumption and; therefore, capturing a prescription filled for 40 tablets would not be able to differentiate consumption of 1 versus 10 tablets. Despite these limitations, we believe that the results of our study do provide a good overview of the use and misuse of perioperative opioids in the endocrine surgery population. Importantly, we also demonstrate that the use and misuse of opioids is prevalent across a variety of endocrine operations, and that with the exception of neck dissections, is largely independent of the type of operation performed (consistent with conclusions drawn from other studies).

These findings have important clinical implications for endocrine surgeons. Although generally considered operations with low postoperative pain, there is still a significant risk for new and persistent opioid use among patients who undergo endocrine operations. Opioid abuse may, in fact, be the highest risk complication for these operations where the risk for surgical complications is $<5\%$. The median total dose of opioids prescribed after endocrine operations is more than double the dose recommended for adequate postoperative pain management, and is predictive of persistent opioid use. Older patients, men, and patients with underlying medical comorbidities or psychosocial disorders are at particular risk. Our analysis supports the emerging data that suggests that perioperative and persistent opioid use after surgical procedures is less about inherent pain associated with operations, but more about misperceptions and biases that both physicians and patients may have about postoperative pain and required management. Continued efforts to educate and promote alternative pain management protocols and judicious use of perioperative opioid analgesia after endocrine operations may reduce the inappropriate prescribing of postoperative opioids and help combat the global opioid abuse epidemic.

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