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Comparison of Opioid Utilization Patterns After Major Head and Neck Procedures Between Hong Kong and the United States

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IMPORTANCE The current opioid abuse epidemic in the United States requires evaluation of prescribing practices within all medical specialties. This examination includes a review of postoperative pain management for patients undergoing major head and neck procedures.

OBJECTIVE To report differences in postoperative pain regimens between an international and domestic head and neck surgical program.

DESIGN, SETTING, AND PARTICIPANTS Pain management patterns after head and neck surgery in the programs at Chinese University of Hong Kong (CUHK) and Oregon Health and Science University (OHSU) were compared with a focus on opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen or paracetamol, and anxiolytics. Cases from July 1, 2013, through August 31, 2017, were reviewed. Standing medication orders the day before surgery (PRE1), postoperative day 6 (POD6), and postoperative day 14 (POD14) were compared between institutions.

EXPOSURES Head and neck surgery.

RESULTS A total of 253 cases from CUHK and 567 cases from OHSU were analyzed (mean [SD] age, 59.4 [14.3] and 60.1 [16.4] years, respectively). Patients from OHSU had a significantly higher frequency of opioid orders on PRE1 (15.3% vs 1.6%; odds ratio [OR], 11.3; 95% CI, 4.09-31.10), POD6 (86.8% vs 0.4%; OR, 1653.12; 95% CI, 228.51-11 959.01), and POD14 (71.4% vs 0.8%; OR, 313.75; 95% CI, 77.12-1276.52). There were no significant differences in acetaminophen or paracetamol, NSAID, or anxiolytic orders between institutions. Institution was the most significant indicator for the presence of opioid orders on POD6 (OR, 4271.10; 95% CI, 380.04-47 999.70) and POD14 (OR, 330.35; 95% CI, 79.67-1369.82). In addition to treating institution, multivariate analysis showed that PRE1 opioid orders indicated a significant increase in likelihood of opioid orders on POD6 (OR, 4.77; 95% CI, 1.23-18.57) but not POD14. POD6 anxiolytic orders remained a significant indicator of opioid orders for POD6 (95% CI, 1.49-113.10) and POD14 (95% CI, 1.17-5.03), respectively.

CONCLUSIONS AND RELEVANCE A significantly lower frequency of postoperative opioid orders was observed from CUHK compared with OHSU across similar major head and neck procedures. This contrast encourages a careful examination of (1) cultural and patient expectations of pain control, (2) the metrics by which control is assessed, (3) industry and economic drivers of opioid use, and (4) alternatives to opioid pain regimens. A thoughtful shift in postoperative pain protocols that deemphasizes opioid use may be an opportunity to counter the epidemic of opioid abuse in the United States.

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Supplemental content

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The worsening opioid epidemic in the United States has led to a staggering number of overdose-related deaths. The Centers for Disease Control and Prevention estimates that more than 350 000 people have died of opioid overdose from 1999 to 2016. In 2016 alone, 40% of the 46 000 opioid-related deaths were related to opioid prescriptions.[1] This in part resulted from a substantial change in prescribing patterns for opioids, with a 4-fold increase from 1999 to 2014. This period marked a surge in choices of available opioids and a public call from major regulatory and governmental bodies to consider pain as the "fifth vital sign."[2,3] The death rate related to opioid overdose is higher than that for motor vehicle accidents and higher than AIDS-related death rates during the height of the human immunodeficiency virus epidemic.[4,5] As surgeons, we must increasingly engage in solutions for the current opioid epidemic given our unique, potential position to bridge health care, policy, and industry in this trial.[6] We are also the second largest subgroup of physicians involved in opioid prescribing.[7]

Otolaryngologists commonly prescribe opioids postoperatively, with the 2 combinations of hydrocodone with acetaminophen and oxycodone with acetaminophen representing the most commonly prescribed formulations.[8,9] Up to 10% of opioid-naive patients prescribed postoperative narcotics will continue to take them 1 year following surgery despite undergoing low-risk surgeries.[10-12] Chronic opioid use in otolaryngology care is present in 6% of cases.[13] The current epidemic appears to be most profound within the United States, with no significant data from Europe or Asia to indicate an opioid epidemic in these regions.

The prescribing patterns of all medical specialties must be evaluated, and this process includes the review of postoperative pain management for patients undergoing major head and neck procedures. Comparison with international pain management practices can illuminate opportunities for more judicious utilization of opioid and nonopioid pain medications. Given the paucity of surgical data comparing the opioid prescribing patterns between countries, we sought to evaluate and compare the prescription patterns for postoperative head and neck surgery patients at 2 institutions—1 in the United States and 1 in the Hong Kong Special Administrative Region (SAR)—to highlight the differences in practice.

In this study, we determined differences in postoperative pain regimens between an international and domestic surgical program for patients undergoing head and neck surgical procedures.

Key Points

Question How do opioid-ordering patterns differ across a US and Hong Kong institution after head and neck surgery?

Findings In this cohort study, a significantly lower rate of opioid orders was observed at the Chinese University of Hong Kong compared with Oregon Health and Science University. Compared with baseline, the differences were significant at both postoperative days 6 and 14.

Meaning The markedly higher rate of opioid orders in the United States after head and neck surgery is likely driven by industry influence, health care and legislative pressure, and societal expectations regarding pain control, with an opportunity for surgeons to impart widespread positive change on responsible opioid use.

Methods

Study Design and Participants

We identified eligible patients via query of the Chinese University of Hong Kong (CUHK) and Oregon Health and Science University (OHSU) electronic medical record systems. This retrospective cohort study included patients undergoing head and neck surgery at 2 academic institutions from July 1, 2013, to August 31, 2017. The reported diagnoses included malignant and benign tumors of the major salivary glands, upper aerodigestive tract, cutaneous head and neck sites, and regional metastatic disease to the neck alone. Reported surgical procedures included glossectomy, laryngectomy, mandibulectomy, maxillectomy, parotidectomy, pharyngectomy, thyroidectomy, tonsillectomy, local soft-tissue excision, neck dissection, tracheostomy, and regional and free tissue transfer. Patient age and sex information was collected.

This study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong SAR, and the Oregon Health and Science University Institutional Review Board, Portland, Oregon. A waiver of informed consent was granted by both the ethics committee and institutional review board at each institution for this review of electronic medical record data.

Medication Data Accrual

Data on pain and anxiolytic medication orders and prescriptions were collected, including those that were active as of preoperative day 1 (PRE1), postoperative day 6 (POD6), and postoperative day 14 (POD14). The rationale for selecting these distinct perioperative times was the institutional differences in hospital length of stay, which is a common variation across international programs. As such, examining pain management data at time of discharge would introduce bias via comparison of patients at significantly different time points postoperatively. The examined drug classes included opioids, tramadol hydrochloride, paracetamol or acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, serotonin and norepinephrine reuptake and/or serotonin selective reuptake inhibitors, and tetracyclic and/or tricyclic antidepressants.

In addition, we collected data on utilization of gabapentinoids at OHSU. These agents were not used within the CUHK program and therefore were not included within a comparative analysis of the 2 institutions. Tramadol, a Schedule IV drug (per the Drug Enforcement Administration) was analyzed separately from Schedule II opioids (eg, oxycodone, hydrocodone, methadone, hydromorphone, and morphine). The potential for abuse of and dependence on tramadol is considered much lower than for Schedule II opioids.[14]

Table 1. Characteristics of Head and Neck Surgery Patients at OHSU and CUHK

Characteristic	Patients, No. (%)	
	OHSU (n = 567)	CUHK (n = 253)
Age, mean (SD), y	60.1 (16.4)	59.4 (14.3)
Women	185 (32.6)	95 (37.5)
Preoperative opioid prescription[a]	87 (15.3)	4 (1.6)
Preoperative diagnosis by site[b]		
Parotid or submandibular gland neoplasm	58 (10.2)	10 (4.0)
Oral cavity	141 (24.9)	116 (45.8)
Pharyngoesophageal or laryngeal	52 (9.2)	42 (16.6)
Oropharyngeal	107 (18.9)	15 (5.9)
Cutaneous	65 (11.5)	0
Sinonasal and orbit	36 (6.3)	1 (0.4)
Thyroid	44 (7.8)	45 (17.8)
Neck	64 (11.3)	24 (9.5)
Procedure type[c]		
Glossectomy	66 (11.6)	73 (28.9)
Laryngectomy	25 (4.4)	23 (9.1)
Mandibulectomy	45 (7.9)	28 (11.1)
Maxillectomy	37 (6.5)	16 (6.3)
Parotidectomy	96 (16.9)	16 (6.3)
Pharyngectomy	50 (8.8)	30 (11.9)
Thyroidectomy	34 (6.0)	57 (22.5)
Tonsillectomy	57 (10.1)	11 (4.3)
Neck dissection	317 (55.9)	184 (72.7)
Tracheostomy	47 (8.3)	75 (29.6)
Local, regional, or free tissue transfer	121 (21.3)	118 (46.6)
Other[d]	136 (24.0)	60 (23.7)

Abbreviations: CUHK, Chinese University of Hong Kong; OHSU, Oregon Health and Science University.

[a] Patients for whom an opioid medication order was active 1 day prior to surgery.

[b] Includes malignant and benign diagnoses.

[c] Many patients underwent multiple procedures. Procedure frequencies therefore sum to greater than cohort total.

[d] Includes major head and neck procedures including orbital exenteration, cutaneous malignancy excision, and lateral temporal bone resection.

Outcomes

The primary outcomes of interest were active opioid inpatient orders and/or prescriptions present on PRE1, POD6, and POD14, with comparison between the CUHK and OHSU programs. The pattern of orders for tramadol, paracetamol or acetaminophen, NSAIDs, and anxiolytics over the same times was also analyzed.

Patient Covariates

We included information on patient age, sex, institution, diagnosis, procedure type, active PRE1 opioid orders, and ordering of nonopioid anxiolytics and analgesics in this analysis. Comorbidity, tobacco, alcohol, chemotherapy, and radiotherapy information were unavailable for this cohort and may affect opioid demand and drug metabolism.

Statistical Analysis

Opioid, tramadol, acetaminophen or paracetamol, NSAID, and anxiolytic orders among CUHK and OHSU cohorts were compared at PRE1, POD6, and POD14 using a χ^2 test. Multivariate logistic regression was used to identify variables associated with opioid and other medication orders at PRE1, POD6, and POD14, and odds ratios (ORs) and 95% CIs are reported. Analysis was conducted using Stata SE, version 14.2 (StataCorp). $P < .05$ was considered statistically significant.

Results

During the study period, 820 patients were included. These patients had undergone head and neck surgical procedures—567 patients from OHSU and 253 patients from CUHK (**Table 1**). The day before surgery (PRE1), active opioid orders were present for 15.3% of OHSU patients compared with 1.6% of CUHK patients (OR, 11.3; 95% CI, 4.09-31.10). Both institutions treated a broad range of benign and malignant diseases, with fewer oropharyngeal and cutaneous malignancies observed at CUHK. Table 1 reports the range of procedures performed—many patients underwent multiple procedures (eg, glossectomy with neck dissection and free tissue flap reconstruction). Hence, the inclusion of procedure into subsequent opioid analyses had to consider that individual procedure classification may not reflect the entire complexity of the operation performed.

Perioperative Comparison of Active Medication Orders by Institution

Table 2 lists results from comparison of PRE1, POD6, and POD14 opioid, tramadol, acetaminophen or paracetamol, NSAID, and anxiolytic orders by institution. A higher proportion of patients at OHSU had active opioid orders at all 3 times compared with CUHK (**Figure**) (PRE1: 95% CI, 4.09-31.10; POD6: 95% CI, 228.51-11 959.01; and POD14: 95% CI, 77.12-1276.52). More than 70% of OHSU patients had opioid orders at POD6 (492 [86.8%]) and POD14 (405 [71.4%]) compared with less than 1% at CUHK (1 [0.4%] and 2 [0.8%], respectively). The contrast between ordering patterns at OHSU and CUHK was greatest for opioids, but a difference was also seen for tramadol orders, which were less frequently ordered at OHSU (PRE1: 95% CI, 0.02-0.32; POD6: 95% CI, 0.02-0.15; and POD14: 95% CI, 0.02-0.20) at all 3 times. Postoperatively, the proportion of patients receiving acetaminophen or paracetamol, NSAIDs, and anxiolytics did not differ significantly between institutions.

Factors Associated With Postoperative Opioid Orders

In univariate modeling, various procedures (parotidectomy, thyroidectomy, tonsillectomy, tracheostomy, flap reconstruction, glossectomy, and neck dissection), institution (OHSU vs CUHK), and medication orders (tramadol, acetaminophen or paracetamol, NSAIDs, and anxiolytics) predicted the odds of opioid orders (eTable in the Supplement). Each of these independent variables was dropped into a multivariate model with institution as the only other independent variable (**Table 3**). All procedures except for flap reconstruction ceased to be significant indicators—it is possible that flap reconstruction may be a surrogate variable for length and complexity of proce-

Table 2. PRE1, POD6, and POD14 Active Medication Orders

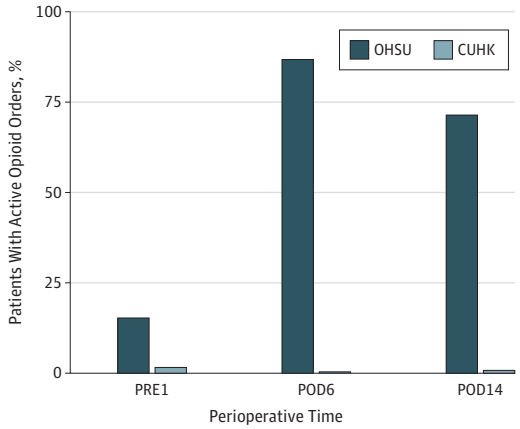
Drug Order	Patients, No. (%) OHSU (n = 567)	CUHK (n = 253)	OR (95% CI)[a]
Opioids			
PRE1	87 (15.3)	4 (1.6)	11.3 (4.09-31.10)
POD6	492 (86.8)	1 (0.4)	1653.12 (228.51-11 959.01)
POD14	405 (71.4)	2 (0.8)	313.75 (77.12-1276.52)
Tramadol			
PRE1	2 (0.4)	12 (4.7)	0.07 (0.02-0.32)
POD6	5 (0.9)	34 (13.4)	0.06 (0.02-0.15)
POD14	4 (0.7)	24 (9.5)	0.07 (0.02-0.20)
Acetaminophen or paracetamol			
PRE1	77 (13.6)	24 (9.5)	1.50 (0.92-2.43)
POD6	375 (66.1)	185 (73.1)	0.72 (0.52-1.00)
POD14	349 (61.6)	171 (67.6)	0.77 (0.56-1.05)
NSAIDs			
PRE1	31 (5.5)	30 (11.9)	0.43 (0.25-0.73)
POD6	96 (16.9)	41 (16.2)	1.05 (0.71-1.57)
POD14	83 (14.6)	39 (15.4)	0.94 (0.62-1.42)
Anxiolytics			
PRE1	31 (5.5)	11 (4.3)	1.27 (0.63-2.57)
POD6	72 (12.7)	20 (7.9)	1.69 (1.01-2.85)
POD14	40 (7.1)	15 (5.9)	1.20 (0.65-2.22)

Abbreviations: CUHK, Chinese University of Hong Kong; OHSU, Oregon Health and Science University; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; POD, postoperative day; PRE1, day before surgery.

[a] χ^2 analysis used.

dure. In the multivariate regression model for POD14 opioid orders, we observed a large OR and 95% CI for the indicator POD6 variable (OR, 480.97; 95% CI, 59.19-3908.74) that suggested multicollinearity between POD6 and POD14 opioid orders because most patients with POD6 opioid orders also had POD14 orders. In the final multivariate regression models, institution (OHSU vs CUHK) remained a significant indicator of active opioid orders on POD6 and POD14 after adjusting for PRE1 opioid orders, flap reconstruction, and POD6 anxiolytic orders.

Figure. Proportion of Patients With Active Opioid Orders at Oregon Health and Science University (OHSU) Compared With Chinese University of Hong Kong (CUHK) at 3 Perioperative Times



Comparison by institution showed a significantly higher proportion of opioid orders at OHSU vs CUHK at all times: day before surgery (PRE1): 95% CI, 4.09-31.10; postoperative day 6 (POD6): 95% CI, 228.51-11 959.01; and postoperative day 14 (POD14): 95% CI, 77.12-1276.52.

Discussion

This study demonstrates a significant difference in opioid prescribing patterns for head and neck surgical patients treated in a US and a Hong Kong institution. We found that by postoperative day 6, only 1 patient (0.4%) at CUHK had an active opioid order, whereas 86.8% of OHSU patients at the same time had active orders. In the United States, we are facing a public health threat in the opioid epidemic that is complex in causality, stakeholder mix, and solutions. The findings of this study signal a potential for our specialty and the medical profession as a whole to rebalance pain management options and thereby reduce the availability of opioids that are easily abused.

A 2017 publication in the *New England Journal of Medicine* provided an overview of historical litigation against the pharmaceutical industry—a major stakeholder and alleged contributor in the ongoing opioid crisis.[15] Class action and government-led suits against opioid manufacturers have won settlements on the grounds of deceptive marketing,[16] lack of responsible safeguards against abuse, and downstream profiting from the treatments that address opioid addiction, with much of the cost incurred by public health budgets.[17] Although the sum of settlements in the past 2 decades has neighbored $1 billion, the industry maintains $13 billion in annual revenue. Other countries, including mainland China, are not immune to pharmaceutical advertising that underemphasizes the addictive properties of opioids; the Hong Kong SAR may have preemptively suppressed industry influence in pain

Table 3. Multivariate Logistic Regression Models for POD6 and POD14 Opioid Orders

	OR (95% CI)	
Model Variable	POD6 (n = 820)	POD14 (n = 820)
Institution[a]	4271.10 (380.04-47 999.70)	330.35 (79.67-1369.82)
Preoperative opioid order[b]	4.77 (1.23-18.57)	1.70 (0.92-3.14)
Flap reconstruction performed	2.02 (0.83-4.92)	1.29 (0.77-2.17)
Anxiolytic POD6 order	13.02 (1.49-113.10)	2.42 (1.17-5.03)

Abbreviations: CUHK, Chinese University of Hong Kong; OHSU, Oregon Health and Science University; OR, odds ratio; POD, postoperative day.

[a] Odds ratios for institutions indicate that OHSU patients had a higher probability of opioid orders at POD6 and POD14.

[b] Patients for whom an opioid medication order was active 1 day before surgery.

management practices to a large degree, learning from a long and fluctuating epidemic of heroin abuse that spanned over a century. As such, both patients and health care clinicians in Hong Kong may presently have a heightened awareness of addiction risk and a more balanced view on pain management options. In the United States, there would be value for innovative strategies that engage pharma in the fight against opioid abuse—a difficult aspiration when it conflicts with short-term economic goals.

Physician and patient expectation of pain control may differ between the studied Hong Kong and US institutions. As described earlier, considering pain as the fifth vital sign has placed pressure on US health care professionals and hospitals to satisfy pain scales that have questionable validity or risk punitive, sometimes economic, consequences. Considering the opioid crisis and evidence of strong addictive properties, The Joint Commission and the Centers for Medicare & Medicaid Services no longer endorse pain as the fifth vital sign.[18] Approximately 15 years of this public assertion ingrained the concept in patient, nursing, physician, and societal behavior. Safer health care professional practices must be visibly supported by regulatory and policymaking bodies.

In this study, the proportion of postoperative patients receiving NSAIDs did not differ significantly between institutions. Cyclooxygenase-2 (COX-2) inhibitors were not widely used in either center; however, this drug class deserves study as a bridge to less reliance on opioids postoperatively. The appealing features of COX-2 inhibitors over traditional NSAIDs are the low risk for gastrointestinal bleeding and renal injury and lack of platelet inhibition, with the same anti-inflammatory properties.[19-21] A systematic review of postsurgical celecoxib, a COX-2 inhibitor, suggested improved pain control over acetaminophen in some studies and potentially reduced opioid consumption.[22] Unfortunately, serious cardiovascular events occurred in patients taking rofecoxib,[23] another COX-2 inhibitor, leading to the withdrawal of this drug from the market in 2004.

A recent large, prospective study comparing celecoxib with ibuprofen and naproxen in patients with arthritis responsive to anti-inflammatory agents demonstrated noninferiority of celecoxib with regard to cardiovascular events and reduced risk of gastrointestinal complications.[24] Critics have asserted that noninferiority to traditional NSAIDs does not necessarily translate to cardiac safety compared with no use of NSAIDs. However, this study was not approved for a placebo arm given that all included patients had known anti-inflammatory-responsive disease. Celecoxib and similar COX-2 inhibitors may become a useful complement to opioids in the postoperative setting and should be prospectively compared in randomized trials of patients undergoing head and neck surgery, aiming to reduce the requirement for opioids.

Limitations

The study had several limitations. The unavailability of comorbidity data, preoperative radiotherapy and chemotherapy information, and staging information for malignant tumors precludes analysis of their influence on postoperative opioid orders. It is also possible that the frequency of chronic pain conditions is higher in the OHSU group compared with the CUHK group. However, unless chronic pain was a comorbidity in the majority of OHSU patients, it is unlikely that this factor could account for the significant difference in opioid orders between institutions. We also accounted for opioid orders active up to the day before surgery (PRE1), which may have provided a partial proxy for unavailable preoperative pain data.

Another limitation of this study was the selection of discrete points for analyses—PRE1, POD6, and POD14. Planned hospital lengths of stay differ internationally and in our study required evaluation of medication orders relative to surgery date rather than date of discharge. By this design, we were unable to capture all postoperative opioid orders that were discontinued prior to POD6. Nevertheless, the near absence of active opioid orders at POD6 and POD14 for the CUHK group is an example of rapid opioid discontinuation postoperatively. As in prior studies, we were able to report opioid prescriptions but not opioid consumption.[25] Although this lack of data limits inference into patient behavior, our findings imply that there are markedly different approaches to pain control among these institutions and likely discrepant external forces that influence these decisions. The ordering pattern of opioid medications in the OHSU group likely mirrors the practice of many US institutions but does not provide information about actual patient use.

Finally, because we extracted medication orders from active medication lists within patients' electronic medical records, over-the-counter nonopioids, such as acetaminophen or paracetamol and NSAIDs, should have been captured with high fidelity. However, underreporting of these medications is also possible.

Conclusions

A significantly lower frequency of postoperative opioid orders was observed from CUHK (Hong Kong) compared with OHSU (United States) across similar major head and neck procedures. This stark contrast encourages a critical examination of (1) cultural and patient expectations of pain control, (2) the metrics by which control is assessed, (3) industry and economic drivers of opioid use, and (4) alternatives to opioid pain regimens. A thoughtful shift in postoperative pain protocols that deemphasizes opioid use may be an opportunity to counter the epidemic of opioid abuse in the United States.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). Opioid overdose. https://www.cdc.gov/drugoverdose/index.html. Updated October 23, 2017. Accessed March 14, 2018.

2. Molony SL, Kobayashi M, Holleran EA, Mezey M. Assessing pain as a fifth vital sign in long-term care facilities: recommendations from the field. *J Gerontol Nurs*. 2005;31(3):16-24. doi:10.3928/0098-9134-20050301-06

3. Tompkins DA, Hobelmann JG, Compton P. Providing chronic pain management in the "fifth vital sign" era: historical and treatment perspectives on a modern-day medical dilemma. *Drug Alcohol Depend*. 2017;173(suppl 1):S11-S21. doi:10.1016/j.drugalcdep.2016.12.002

4. Gawande AA. It's time to adopt electronic prescriptions for opioids. *Ann Surg*. 2017;265(4):693-694. doi:10.1097/SLA.0000000000002133

5. Centers for Disease Control and Prevention. The global HIV and AIDS epidemic, 2001. *JAMA*. 2001;285(24):3081-3083. doi:10.1001/jama.285.24.3081

6. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med*. 2018;178(5):667-672. doi:10.1001/jamainternmed.2018.0266

7. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, US, 2007-2012. *Am J Prev Med*. 2015;49(3):409-413. doi:10.1016/j.amepre.2015.02.020

8. Schwartz MA, Naples JG, Kuo CL, Falcone TE. Opioid prescribing patterns among otolaryngologists. *Otolaryngol Head Neck Surg*. 2018;158(5):854-859. doi:10.1177/0194599818757959

9. Svider PF, Arianpour K, Guo E, et al. Opioid prescribing patterns among otolaryngologists: crucial insights among the Medicare population [published online February 15, 2018]. *Laryngoscope*. doi:10.1002/lary.27101

10. Waljee JF, Li L, Brummett CM, Englesbe MJ. Iatrogenic opioid dependence in the United States: are surgeons the gatekeepers? *Ann Surg*. 2017;265(4):728-730. doi:10.1097/SLA.0000000000001904

11. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. *Arch Intern Med*. 2012;172(5):425-430. doi:10.1001/archinternmed.2011.1827

12. Pang J, Tringale KR, Tapia VJ, et al. Chronic opioid use following surgery for oral cavity cancer. *JAMA Otolaryngol Head Neck Surg*. 2017;143(12):1187-1194. doi:10.1001/jamaoto.2017.0582

13. Jiang X, Orton M, Feng R, et al. Chronic opioid usage in surgical patients in a large academic center. *Ann Surg*. 2017;265(4):722-727. doi:10.1097/SLA.0000000000001780

14. regulations.gov. Schedules of controlled substances: tramadol; schedule IV. https://www.regulations.gov/document?D=DEA-2013-0010-0001. Published October 25, 2013. Accessed July 25, 2018.

15. Haffajee RL, Mello MM. Drug companies' liability for the opioid epidemic. *N Engl J Med*. 2017;377(24):2301-2305. doi:10.1056/NEJMp1710756

16. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221-227. doi:10.2105/AJPH.2007.131714

17. Ausness RC. The role of litigation in the fight against prescription drug abuse. *West VA Law Rev*. 2014;(116):1117-1165.

18. Baker DW. Joint Commission Statement on Pain Management. https://www.jointcommission.org/joint_commission_statement_on_pain_management/. Published April 18, 2016. Accessed April 3, 2018.

19. Schug SA. The role of COX-2 inhibitors in the treatment of postoperative pain. *J Cardiovasc Pharmacol*. 2006;47(suppl 1):S82-S86. doi:10.1097/00005344-200605001-00015

20. Stoltz RR, Harris SI, Kuss ME, et al. Upper GI mucosal effects of parecoxib sodium in healthy elderly subjects. *Am J Gastroenterol*. 2002;97(1):65-71. doi:10.1111/j.1572-0241.2002.05265.x

21. Harris SI, Stoltz RR, LeComte D, Hubbard RC. Parecoxib sodium demonstrates gastrointestinal safety comparable to placebo in healthy subjects. *J Clin Gastroenterol*. 2004;38(7):575-580. doi:10.1097/00004836-200408000-00007

22. Straube S, Derry S, McQuay HJ, Moore RA. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol Scand*. 2005;49(5):601-613. doi:10.1111/j.1399-6576.2005.00666.x

23. Bresalier RS, Sandler RS, Quan H, et al; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352(11):1092-1102. doi:10.1056/NEJMoa050493

24. Nissen SE, Yeomans ND, Solomon DH, et al; PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519-2529. doi:10.1056/NEJMoa1611593

25. Lee JS, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. *J Clin Oncol*. 2017;35(36):4042-4049. doi:10.1200/JCO.2017.74.1363