



# Evidence-based opioid prescribing guidelines after lung resection: a prospective, multicenter analysis

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**Background:** Opioid prescribing guidelines have significantly decreased overprescribing and post-discharge use after cardiac surgery; however, limited recommendations exist for general thoracic surgery patients, a similarly high-risk population. We examined opioid prescribing and patient-reported use to develop evidence-based, opioid prescribing guidelines after lung cancer resection.

**Methods:** This prospective, statewide, quality improvement study was conducted between January 2020 to March 2021 and included patients undergoing surgical resection of a primary lung cancer across 11 institutions. Patient-reported outcomes at 1-month follow-up were linked with clinical data and Society of Thoracic Surgery (STS) database records to characterize prescribing patterns and post-discharge use. The primary outcome was quantity of opioid used after discharge; secondary outcomes included quantity of opioid prescribed at discharge and patient-reported pain scores. Opioid quantities are reported in number of 5-mg oxycodone tablets (mean  $\pm$  standard deviation).

**Results:** Of the 602 patients identified, 429 met inclusion criteria. Questionnaire response rate was 65.0%. At discharge, 83.4% of patients were provided a prescription for opioids of mean size 20.5 $\pm$ 13.1 pills, while patients reported using 8.2 $\pm$ 13.0 pills after discharge ( $P < 0.001$ ), including 43.7% who used none. Those not taking opioids on the calendar day prior to discharge (32.4%) used fewer pills (4.4 $\pm$ 8.1 *vs.* 11.7 $\pm$ 14.9,  $P < 0.001$ ). Refill rate was 21.5% for patients provided a prescription at discharge, while 12.5% of patients not prescribed opioids at discharge required a new prescription before follow-up. Pain scores were 2.4 $\pm$ 2.5 for incision site and 3.0 $\pm$ 2.8 for overall pain (scale 0–10).

**Conclusions:** Patient-reported post-discharge opioid use, surgical approach, and in-hospital opioid use before discharge should be used to inform prescribing recommendations after lung resection.

**Keywords:** Opioid prescribing; thoracic surgery; practice guidelines; lung cancer

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## Introduction

Opioid prescribing is a cornerstone of pain management after surgery. Yet, overprescribing remains a common occurrence with larger prescription sizes associated with higher opioid use as well as an increased risk of new persistent opioid use after surgery (1-4). Moreover, patients undergoing cardiac or general thoracic surgery are among the highest risk populations for new persistent opioid use (2,5-9) despite being among the least likely to be preoperative opioid users (10,11).

In an effort to reduce opioid use and improve patient safety, evidence-based guidelines have been developed to help mitigate overprescribing after surgery (12-17). Such guidelines have been particularly effective for general surgery procedures, many of which are performed in ambulatory or short-stay settings (13,15,17). In contrast, Brescia *et al.* (12) recently proposed recommendations for opioid prescribing after cardiac surgery where median hospital stay can be over a week (18). The authors showed that a stratified prescribing strategy guided by inpatient opioid use significantly decreased post-discharge opioid use without changes in pain levels and refill rate, an approach which may be similarly beneficial for general thoracic surgery patients. At present, the relationship between in-hospital opioid use and post-discharge use

after lung resection is not well understood. Variation in operative approach, including minimally invasive (MIS) versus open thoracotomy, yields a range of post-operative pathways, whereas cardiac surgery patients typically undergo median sternotomy for most operations performed. Recent efforts have thus aimed to better characterize opioid use and prescribing after general thoracic surgery (19-21); however, there is no consensus on appropriate opioid prescription quantities for patients undergoing lung resection.

In this prospective, multicenter study, we utilized a statewide quality collaborative to (I) characterize opioid prescribing and post-discharge use after thoracic surgery, (II) assess patient-reported pain scores after surgery, and (III) evaluate inpatient opioid use and operative approach as predictors of post-discharge opioid use. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1621/rc>).

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was deemed exempt by the University of Michigan Institutional Review Board (No. HUM00156194), and individual consent for this retrospective analysis was waived.

## Data source

Clinical data were collected through the Michigan Society of Thoracic and Cardiovascular Surgeons (MSTCVS) Quality Collaborative. Initially developed in 2001 as a cardiac surgeon-led quality improvement effort embedded within the MSTCVS, it has grown to become a statewide, multidisciplinary, large-scale collaborative that has expanded to now include general thoracic surgery since 2014. The Quality Collaborative data warehouse is composed of standardized harvest files sent from each of the participating sites to the Society of Thoracic Surgeons (STS) national database.

Patient-reported outcomes (PROs) were captured via questionnaires administered at 30-day clinic follow-up.

### Highlight box

#### Key findings

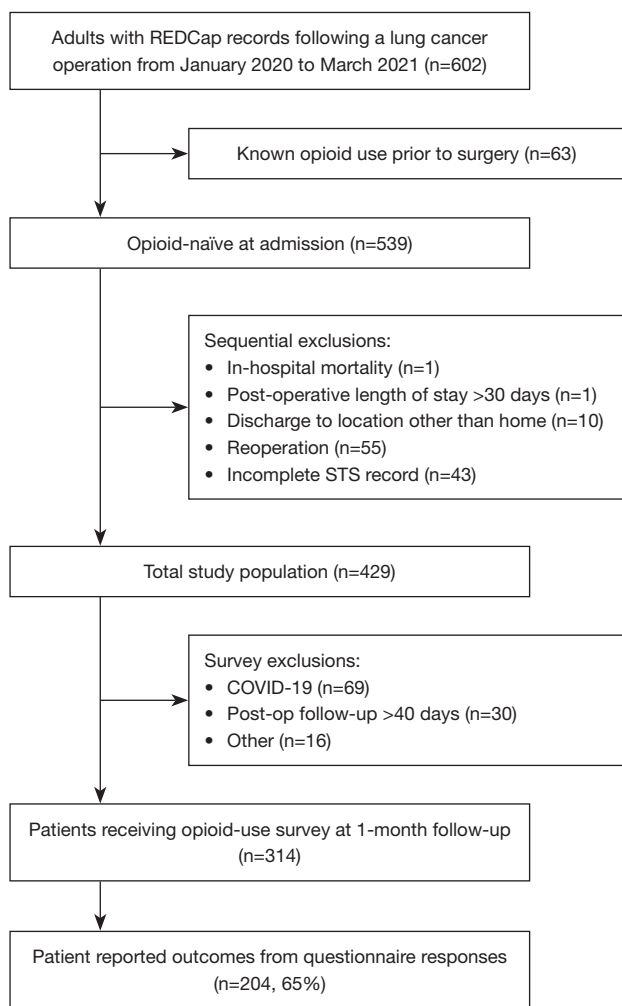
- In this statewide, quality improvement study, patients reported using significantly fewer opioids than they were prescribed at discharge including nearly half of patients who required none.

#### What is known and what is new?

- Implementation of opioid guidelines have significantly decreased overprescribing and post-discharge use; however, limited recommendations exist for general thoracic surgery.
- Patient-reported outcomes and in-hospital data prior to discharge were used to develop opioid prescribing recommendations and then distributed to participating institutions.

#### What is the implication, and what should change now?

- Evidence-based guidelines should be used to inform opioid prescribing after lung cancer resection.



**Figure 1** Patient population diagram with sequential exclusions. REDCap, Research Electronic Data Capture; STS, Society of Thoracic Surgeons.

Questionnaire items included (I) post-operative pain scores, (II) quantity and duration of post-discharge opioid use, and (III) pain medication storage and disposal. Data managers at each site also collated information including in-hospital opioid use before discharge, prescription size at discharge, and prescription refills after discharge. All patients receiving an opioid prescription were provided an Opioid Start Talking form and reviewed with a provider prior to discharge. Current state law allows prescription sizes up to 7-days for treatment of acute post-operative pain, where a Michigan Automated Prescription System (MAPS) report is required for prescriptions exceeding a 3-day supply.

Questionnaire responses and opioid prescription and use

data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the MSTCVS Coordinating Center (22). Patient responses and opioid-specific information were then linked to STS data from the Quality Collaborative by unique record identification numbers as well as dates of surgery and discharge.

### Study population

Patients undergoing lung cancer resection between January 2020 to March 2021 were identified across 11 participant centers. Patients taking opioids at the time of admission (i.e., not opioid-naïve) were excluded from this analysis. Additional sequential exclusions included patients undergoing reoperation, postoperative length of stay (LOS) greater than 30 days, discharge to location other than home, in-hospital mortality during the index admission, and patients with an incomplete STS record (Figure 1). Former cigarette smokers were defined as those patients who quit smoking cigarettes greater than 30 days prior to surgery. Major psychiatric disorder refers to a formal psychiatric diagnosis requiring regular behavioral therapy, counseling, and/or pharmaceutical treatment (e.g., depression, anxiety, bipolar disorder).

### Statistical analysis

Clinical characteristics and opioid prescription and use data were collected for all patients as described above. Primary outcomes for this study were opioid prescription size and patient-reported opioid use after discharge. Secondary outcomes included in-hospital opioid use day before discharge, prescription refills before follow-up, duration of opioid use after discharge, and patient-reported pain scores. Pain assessment included pain in the first week after surgery (e.g., none, minimal, moderate, or severe) as well as incisional pain and overall body pain for the week immediately prior to follow up (e.g., 0 denoting no pain and 10 denoting worst pain).

Opioid prescription and use quantities were converted to oral morphine equivalents to standardize across individual sites, with the data quantified as the number of 5-mg oxycodone pills and presented as mean  $\pm$  standard deviation unless otherwise stated. Two-tailed Student's *t*-test, nonparametric Wilcoxon rank sum test, and chi-square testing for categorical data were used for comparisons as appropriate with  $P < 0.05$  considered to be statistically significant. Cochran-Armitage test was used to detect trends

**Table 1** Patient characteristics

Variable	Overall (n=429)	Responders (n=204)	Non-responders (n=225)	P value
Age, years	67.0±9.1	68.2±8.7	66.0±9.3	0.600
Female	226 (52.7)	118 (57.8)	108 (48.0)	0.030
BMI, kg/m <sup>2</sup>	28.0±6.1	29.3±6.6	29.8±5.5	0.470
Race				0.100
Caucasian	382 (89.0)	190 (87.7)	192 (86.2)	
Black	36 (8.4)	16 (7.8)	20 (8.9)	
Race other than Black or Caucasian	18 (4.2)	6 (2.9)	12 (5.3)	
Not stated	4 (0.9)	3 (1.5)	1 (0.02)	
Diabetes	81(18.9)	44 (21.6)	37 (16.4)	0.180
Hypertension	275 (64.1)	133 (65.2)	142 (63.1)	0.650
Cerebrovascular disease	54 (12.6)	34 (16.7)	20 (8.9)	0.010*
Aortic or peripheral vascular disease	48 (11.2)	22 (10.8)	26 (11.6)	0.810
Congestive heart failure	22 (5.1)	15 (7.4)	7 (3.1)	0.047*
Major psychiatric disorder	96 (22.4)	61 (29.9)	35 (15.6)	<0.001*
Smoking status				0.850
Never	70 (16.3)	34 (16.7)	36 (16.0)	
Former	257 (60.0)	124 (60.8)	133 (59.1)	
Current	102 (23.8)	46 (22.5)	56 (24.9)	
Procedure				0.85
Minimally invasive surgery	356 (83.0)	171 (83.8)	185 (82.2)	
Open thoracotomy	44 (10.3)	20 (9.8)	24 (10.7)	
Not reported	30 (7.0)	13 (6.4)	17 (7.6)	
Post-operative length of stay, days	4.2±3.3	3.7±2.8	4.7±3.6	0.10

Data expressed as mean ± standard deviation, or total number (percentage). \*, P<0.05. BMI, body mass index.

in prescription refill rate. Data analysis was performed using MATLAB (R2021a; MathWorks, Natick, MA).

## Results

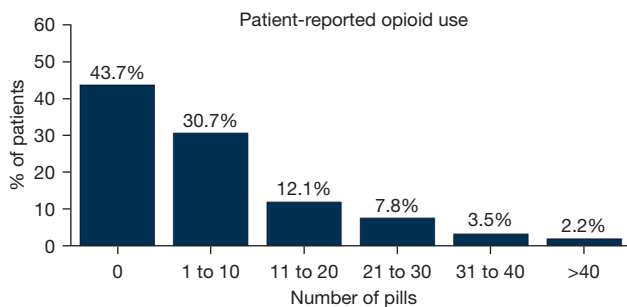
From the study cohort of 602 patients, there were 539 patients considered to be opioid naïve. Following additional sequential exclusions, the resulting population included 429 patients. Due to staff limitations and follow-up imposed by the COVID-19 pandemic, there were 314 patients who received surveys with a questionnaire response rate of 65%.

### Patient demographics

Among the survey responders (n=204), mean age was

68.2±8.7 years, 57.8% female, body mass index (BMI) 29.3±6.6 kg/m<sup>2</sup>, and predominately Caucasian, 87.7% (Table 1). Hypertension (65.2%), major psychiatric disorder (29.9%), and diabetes (21.6%) were the most common comorbidities. The majority of patients were former cigarette smokers (60.8%) compared to current (22.5%) or never smokers (16.7%). Most patients underwent MIS operations (n=171) versus open thoracotomy (n=20). None of the patients meeting inclusion criteria were discharged with chest tubes remaining in place.

Among the survey non-responders (n=225), there were fewer female respondents (48.0% vs. 57.8%, P=0.030) and a lower proportion with a history of cerebrovascular disease (8.9% vs. 16.7%, P=0.010), congestive heart failure (3.1% vs. 7.4%, P=0.047), and major psychiatric disorder (15.6% vs. 29.9%,



**Figure 2** Distribution of patient-reported opioid use after discharge.

$P < 0.001$ ). Average post-operative LOS was not significantly different between groups ( $4.7 \pm 3.6$  vs.  $3.7 \pm 2.8$  days,  $P = 0.10$ ).

### Opioid prescribing and refills

At discharge, 83.4% of patients were provided a prescription for opioids with mean size of  $20.5 \pm 13.1$  pills (Figure S1). Of these patients, 90.0% reported filling their prescription. Patients who were provided a prescription for opioids at discharge were more likely to need a refill before follow up compared with patients who were not prescribed any opioids at discharge (21.5% vs. 12.7%). For patients prescribed opioids at discharge, refill rate was unrelated to the initial prescription size ( $P = 0.748$ ).

### Pain scores and duration of opioid use

The majority of patients described their pain as moderate (51.2%) during the first week after surgery compared to none (3.0%), minimal (21.2%), and severe (24.6%). Pain scores for incisional pain and overall body pain during the week immediately prior to follow up were  $2.4 \pm 2.5$  and  $3.0 \pm 2.8$  (scale 0 to 10), respectively. Most patients reported using opioids for less than 2 weeks after discharge with 33.8% reporting <1 week, 36.0% for 1–2 weeks, 12.9% for 2–3 weeks, 6.5% for 3–4 weeks, and 10.8% for >4 weeks. Post-operative, non-narcotic pain adjuncts included PO acetaminophen (91.6%), IV acetaminophen (29.1%), PO nonsteroidal anti-inflammatory drugs (NSAIDs, 17.2%), IV ketorolac (24.2%), and PO gabapentin (48.1%).

### Opioid use after discharge

Patient-reported opioid use was  $8.2 \pm 13.0$  pills after discharge (Figure 2), significantly fewer than the  $20.5 \pm 13.1$  pills

prescribed at discharge ( $P < 0.001$ ). This included 43.7% of patients who reported using no opioids after discharge. There was no difference in the number of pills used after discharge between those undergoing MIS and open thoracotomy ( $8.2 \pm 13.2$  vs.  $8.0 \pm 11.1$  pills, respectively;  $P = 0.84$ ); however, stratification of opioid use into categories of 10 pill increments revealed that a higher proportion of open thoracotomy patients used 11 to 20 pills compared to 1 to 10 pills ( $P = 0.007$ ; Figure S2).

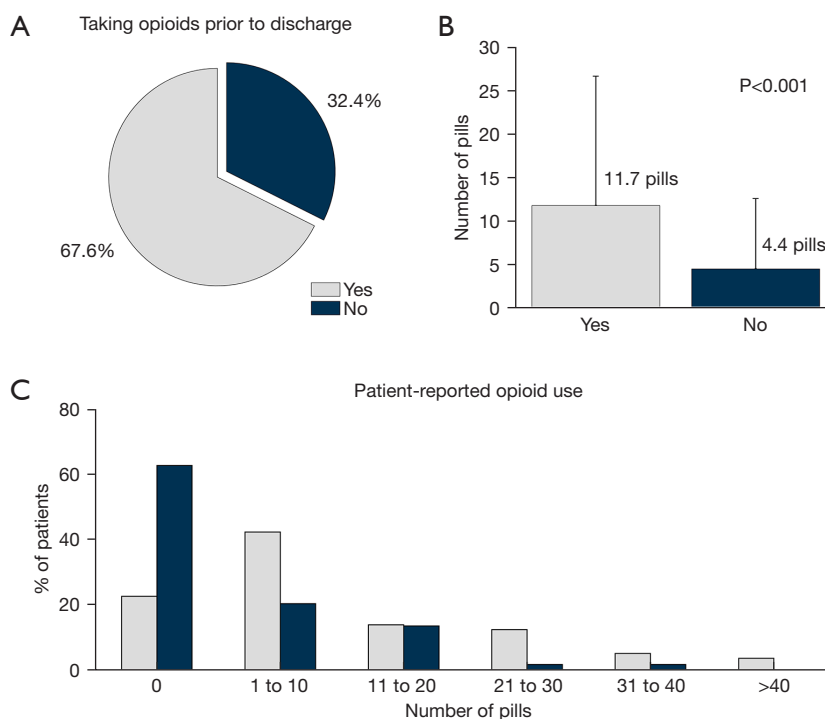
Approximately one-third of patients (32.4%) were not taking opioids in-hospital on the day prior to discharge (Figure 3A). After discharge, these patients used significantly fewer number of pills ( $4.4 \pm 8.1$  vs.  $11.7 \pm 14.9$  pills;  $P < 0.001$ ; Figure 3B) and had a higher proportion requiring no opioids after discharge (62.7% vs. 22.6%; Figure 3C), representing a nearly 3-fold increase over those who were taking opioids on the day prior to discharge.

Additional sub-analyses (Appendix 1) were performed to compare the effects of patient demographics and clinical factors on opioid prescribing and post-discharge use (Table S1). Findings included (I) patients undergoing robot-assisted operations used the fewest opioids ( $5.2 \pm 9.7$  pills,  $P = 0.004$ ); (II) more than 80% of patients with LOS >7 days required no opioids after discharge, with mean  $1.5 \pm 4.0$  pills; and (III) the type of resection performed was not associated with difference in post-discharge opioid usage ( $P = 0.835$ ).

## Discussion

In this assessment of opioid-prescribing practices in our general thoracic surgery statewide quality collaborative, patient-reported post-discharge opioid use was significantly less than discharge opioid prescribing, including nearly half of patients who used no opioids. We found that opioid refill rate was unrelated to prescription size at discharge, while few patients discharged without opioids required a subsequent prescription. In addition, opioid use on the day prior to discharge may be predictive of significantly less opioid use after discharge. Together these findings were used to develop guidelines (Figure 4), as presented here, which can be used to standardize opioid prescribing after lung cancer resection.

Opioid overprescribing after surgery is common and despite therapeutic intent, can serve as the sentinel event for new persistent opioid use (3,4). Thoracic surgery patients are among the highest risk population for new persistent opioid use (5), although among the least likely to be receiving opioids prior to surgery (10). Recent studies (8,9)



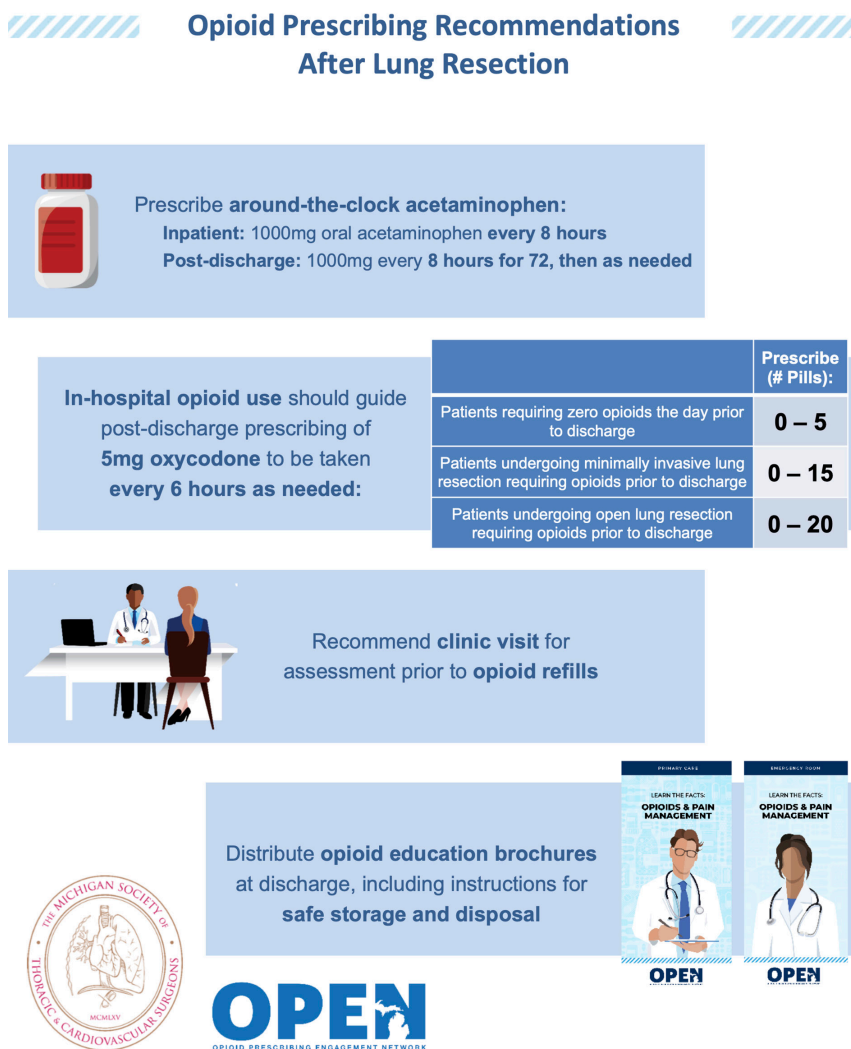
**Figure 3** Association between in-hospital use prior to discharge with patient-reported opioid use after discharge. (A) In-hospital opioid use prior to discharge, (B) average, and (C) distribution of patient-reported opioid use after discharge for patients taking (blue) or not taking (grey) opioids on the calendar day prior to discharge.

have suggested rates of new persistent opioid use may even be as high as 14% to 17% after lung resection, highlighting the urgent need for a more targeted approach to opioid prescribing. Opioid prescription sizes in our cohort were nearly 2.5-fold higher than actual patient-reported use, similar to Holst *et al.* (19) who reported median prescription sizes ranging from 1.5- to 3.5-fold higher than actual opioid consumption. Reducing prescription size at discharge, therefore, represents a high-impact area for improvement.

General surgery has been at the forefront of implementing standardized prescribing guidelines, reducing opioid prescribing by 40–60% across multiple studies (13,15–17). Their effectiveness has provided a template for the development of prescribing recommendations across other surgical subspecialties. In cardiac surgery, Brescia *et al.* (12) recently reported median prescription size decreased from 20 to 12 pills and median opioid use decreased from 3 to 0 pills with no change in refill rate or pain scores after the implementation of similar prescribing recommendations. These findings demonstrated the feasibility of implementing prescribing guidelines after more invasive procedures (i.e., via sternotomy) compared to

the ambulatory or short-stay procedures typical of general surgery (13,16). In comparison, thoracic surgery spans both MIS and open approaches with variable LOS, such that prescribing guidelines must be inclusive of all types of lung resection procedures performed.

In this study, we estimate that a threshold of 15 pills would be sufficient for nearly 80% of the patients in this cohort. Surprisingly, there was no difference in the mean number of pills used after discharge between MIS and open approaches, although a higher proportion of patients undergoing open thoracotomy used 11–20 pills. In addition, we found that patients not requiring any opioids prior to discharge used significantly fewer pills after discharge ( $4.4 \pm 8.1$  vs.  $11.7 \pm 14.9$ ) and were nearly three times more likely to not use any opioids after discharge. Moreover, nearly 70% of all patients used opioids for two weeks or less after discharge, suggesting a relatively short course for the majority of patients after surgery. Based on these data, we recommend a prescription size of 0–5 pills for patients not using opioids on the calendar day prior to discharge, and 0–15 pills for patients after MIS or 0–20 pills for patients after thoracotomy. As not all patient may be discharged



**Figure 4** Opioid prescribing, pain adjuncts, and patient safety recommendations for opioid-naïve patients undergoing lung resection in conjunction with the Michigan Opioid Prescribing Engagement Network (<https://michigan-open.org>).

with oxycodone, 15 pills correspond to approximately 5 mg of tramadol, 50 mg of hydrocodone, and 7.5 mg of codeine.

Stratifying recommendations based on in-patient use further helps tailor prescribing to promote patient-centered care (12,17). Similarly, providing a range for prescription sizes (e.g., 0–15 pills) discourages one-size-fits-all guidelines that may discount experiences of the individual patient (11), promotes a more holistic approach to post-operative pain control, and allows for additional flexibility in clinical judgement. For example, although type of lung resection was not associated with post-discharge opioid use, patients undergoing robot-assisted procedures may actually use the fewest number of opioids after discharge while more than

80% of patients with LOS greater than 1 week used none. Surgical centers already familiar with stratified prescribing guidelines, as recently developed for cardiac surgery (12), may have already implemented and more readily adopt such recommendations. Nevertheless, in the setting of any clinical practice changes, future work should evaluate for changes in respiratory infection, emergency room visits, and readmissions secondary to inadequate pain control.

These recommendations are consistent with prior findings. Skelhorne-Gross *et al.* (23) recently described a standardized limited opioid prescription of 15 tablets of 2-mg hydromorphone after general thoracic surgery. Although smaller in size (n=122) with more elective

procedures excluding open surgery, they demonstrated adequate pain control and a refill rate of 17% with 54% of patients using no opioids after discharge, comparable to our findings here. In another report, Thiels *et al.* (14) proposed tiered guidelines with a standard dose of 20 tabs of oxycodone after MIS; however, there was considerable variability among low (0 tabs), standard, and high dose (40 tabs) tiers, with even larger prescription sizes after thoracotomy (low 5 tabs, standard 50 tabs, high 60 tabs). A follow up to this study (19) demonstrated average opioid use after discharge was only 28% to 67% of prescription size using the proposed guidelines. Others have also investigated ERAS (enhanced recovery after surgery) programs that do not routinely prescribe opioids at discharge for minimally-invasive foregut and lung resection procedures (21), with up to 72% of patients not taking opioids at home.

This study has several limitations. First, risk of recall bias is inherent with all studies involving PROs; however, surveys were collected at a fixed interval in the post-operative clinical course to standardize response times. Second, given the challenges presented by the COVID-19 pandemic, not all patients were provided surveys (314 out of 429 patients who met inclusion criteria); however, of those patients, 65% completed the questionnaires, a response rate which is identical to or better than previous studies using similar methodology (12,15). Moreover, the measured characteristics of the responder and non-responder groups were similar, with slightly fewer comorbidities, including major psychiatric disorders, observed for the latter group suggesting the PROs may even over-estimate opioid usage. Third, peri-operative use of pain adjuncts, including intercostal nerve blocks, may vary among different institutions, while benzodiazepine use at the time of admission, as well as prior but not current opioid or non-narcotic treatment of pain syndromes were not tracked as part of this study. Fourth, we do not account for socioeconomic difficulties and geographic populations, which could be associated with differences in obtaining opioid prescriptions, perioperative care, and even genetic variance. Finally, the proposed guidelines do not address pain recommendations for patients taking opioids prior to surgery, those with prolonged LOS, or discharge to location other than home. Nevertheless, these guidelines represent one of the largest, most robust datasets integrating data across 11 geographically diverse surgical centers with multiple surgeons, teams, and approaches, and thus, make recommendations widely generalizable to a variety of practice types.

## Conclusions

In summary, this multi-center, quality collaborative study proposes evidence-based opioid prescribing guidelines for patients undergoing lung cancer resection. These stratified recommendations aim to promote patient-centered care and improve safety by decreasing opioid overprescribing after general thoracic surgery.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). It was deemed exempt by the University of Michigan Institutional Review Board (No. HUM00156194), and individual consent for this retrospective analysis was waived.

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