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Research Report

The past, present, and future of opioid prescribing: Perioperative opioid use in gynecologic oncology patients after laparotomy at a single institution from 2012 to 2021

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ABSTRACT

Objective: To describe the evolution of perioperative opioid management in gynecologic oncology patients after open surgeries and determine current opioid over-prescription rates.
Methods: Part one of this two-part study was a retrospective chart review of adult patients who underwent laparotomy by a gynecologic oncologist from July 1, 2012 to June 30, 2021, comparing changes in clinical characteristics, pain management and discharge opioid prescription sizes between fiscal year 2012 (FY2012) and 2020 (FY2020). In part two, we prospectively surveyed patients after laparotomy in 2021 to determine opioid use after hospital discharge.
Results: 1187 patients were included in the chart review. Demographic and surgical characteristics remained stable from FY2012 to FY2020 with differences notable for increased rates of interval cytoreductive surgeries for advanced ovarian cancer and decreased rates of full lymph node dissection. Median inpatient opioid use decreased by 62 % from FY2012 to FY2020. Median discharge opioid prescription size was 675 oral morphine equivalents (OME) per patient in FY2012 and decreased by 77.7 % to 150 OME in FY2020. Of 95 surveyed patients in 2021, median self-reported opioid use after discharge was 22.5 OME. Patients had an excess of opioids equivalent to 1331 doses of 5-milligram oxycodone tablets per 100 patients.
Conclusion: Inpatient opioid use in our gynecologic oncology open surgical patients and post-discharge opioid prescription size significantly decreased over the last decade. Despite this progress, our current prescribing patterns continue to significantly overestimate patients' actual opioid use after hospital discharge. Individualized point of care tools are needed to determine an appropriate opioid prescription size.

1. Introduction

Surgeons unwittingly contribute to the opioid epidemic through the over-prescription of opioids in the perioperative setting (Ladha et al., 2019; Thiels et al., 2017). Over-prescription contributes to excess opioids circulating in the patients' communities. (Brummett et al., 2017; Hasak et al., 2018; Khan et al., 2019; Brat et al., 2018; Sekhri et al., 2018; Rachel and Lipari, 2017; Bateman et al., 2016; Setnik et al., 2015) Gynecologic surgeries are no exception; numerous studies have demonstrated opioids prescribed in excess after both minor and major gynecologic procedures. (Griffith et al., 2018; As-Sanie et al., 2017).

In gynecologic surgery, the rate of persistent opioid use 3–6 months after surgery is 6–7 % (Wright et al., 2019; Chan et al., 2021). This would suggest that for every 14 patients who receive an opioid

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prescription after gynecologic surgery, one patient will develop persistent opioid use. Both the risk of a patient developing persistent opioid use and the risk of a family member suffering a drug overdose increase with increasing postoperative prescription size (Khan et al., 2019; Chan et al., 2021; Wen et al., 2020). In response to media attention and increased regulation, opioid prescribing rates nationally have decreased since 2012 (CDC Injury Center, 2021; Levy et al., 2015; Everson et al., 2020). Within gynecologic surgery, opioid prescribing rates have also decreased but on a delayed time frame (Arabkhazaeli et al., 2021; Thompson et al., 2018). Anecdotally we have observed a reduction in opioid prescription sizes in our own gynecologic oncology surgical practice in recent years, however given the ongoing devastating impact of opioids in the community, we hypothesized that there may still be room for improvement.

We undertook this two-part study to examine the evolution of perioperative opioid management over nine years in our gynecologic oncology division for patients undergoing open surgery. In the first part of this study, we utilized retrospective data to observe changes in our perioperative pain management and postoperative opioid prescribing from fiscal years 2012 (FY2012) to 2020 (FY2020). In the second part, we conducted prospective surveys of postoperative patients to determine if we are still over-prescribing opioids for home use.

2. Methods

We obtained institutional review board (IRB) approval to conduct a retrospective chart review (Part I) and prospective surveys (Part II) in this two-part study. This study was designed as a two-part study to allow for comparison of the survey population to a historical baseline population and to place our current prescribing patterns in this historical context.

In Part I, we included patients $\geq$ 18 years of age who underwent an open surgery performed by a gynecologic oncologist at our institution between July 1, 2012 and June 30, 2021. We focused on laparotomy patients as our current practice is to discharge all minimally invasive patients with $\leq$ 5 oxycodone tablets, while post-laparotomy opioid discharge prescriptions have not been standardized. We excluded patients if they were pregnant at the time of their surgery or were not primarily cared for by our gynecologic oncology inpatient service. We abstracted data from the medical record for eligible patients and compared outcomes between fiscal years 2012 (FY2012: July 1, 2012 to June 30, 2013) and 2020 (FY2020: July 1, 2020 - June 30, 2021).

Our Enhanced Recovery After Surgery (ERAS) pathway was implemented July 1, 2014.(Chapman et al., 2016) This pathway includes the use of epidurals or nerve blocks for postoperative pain management, restricted intraoperative fluid resuscitation, early postoperative ambulation, and administration of pre- and postoperative multi-modal oral analgesia.

In Part II, we conducted prospective surveys of open surgical patients who were cared for and discharged to home by our gynecologic oncology inpatient service from April to November 2021. We contacted eligible patients 2–4 weeks after surgery by telephone or at the time of a virtual postoperative visit. We excluded patients if they were readmitted to the hospital prior to when the survey was conducted or were still admitted a month after surgery. We used telephone interpreters as needed. We obtained verbal consent from each patient for participation and asked them the following four questions:

1. Did you have any opioid pain medication that you did not use/need? If so, how much?
2. The number of opioid pills you were given was: a) too few, b) just right, or c) too many?
3. Did you need a refill of the opioid medication? If so, was asking for a refill a) easy or b) challenging?
4. Approximately a month prior to surgery, were you using a prescription opioid pain medication on a daily basis?

The primary purpose of this survey was to ascertain a patient's actual (self-reported) opioid use at home and the number of unused pills that remained in a patient's possession after their surgical recovery. If a patient had unused opioid medication, the patient was counseled on proper disposal. The second and third questions assessed patient satisfaction with the opioid prescription size. The fourth question identified patients who were opioid-tolerant as defined by the Food and Drug Administration (FDA). We limited the survey to only four questions for simplicity and to foster successful completion. We entered survey responses and paired patient data into our institution's Research Electronic Data Capture (REDCap). If a patient was still utilizing opioid pain medication when the survey was conducted, we asked the patient to make an estimate regarding their total opioid use and requested permission to re-contact the patient in 1–2 weeks.

All oral and intravenous opioid medication use is presented as oral morphine equivalents (OME) for standardization. We used standard ratios of oral and intravenous medication to oral morphine to calculate OME (Table 1).

We used Stata to perform statistical analysis. We compared categorical variables using chi-square tests and Fisher exact tests as appropriate. We present continuous variables as medians with interquartile ranges and compare them using Wilcoxon rank-sum tests.

3. Results

3.1. Part I. The evolution of surgery and perioperative pain management from FY2012 to FY2020

Patient and surgical characteristics: we included data from 1187 patients who underwent open surgery between July 1, 2012 and June 30, 2021. There was no significant change in patient demographics between FY2012 and FY2020 (Table 2) with the exception of increases in the proportion of patients who identified as Black or African American, Native Hawaiian or Pacific Islander, or American Indian or Alaska Native. There was no change in the proportion of patients undergoing surgery for a malignant versus a benign diagnosis. From FY2012 to FY2020, there was no difference in the percentage of patients who underwent a hysterectomy (73.5 % vs 73.7 %, $p = 0.96$), at least one bowel resection (21.6 % vs 24.4 %, $p = 0.56$), and unilateral or bilateral oophorectomy (81.5 % vs 81.4 %, $p = 0.99$). We saw a significant reduction in rates of full pelvic (32.7 % vs 12.8 %, $p < 0.01$) and *para*-aortic (25.9 % vs 8.3 %, $p < 0.01$) lymph node dissection with a concurrent increase in sentinel lymph node mapping and biopsy (0 % vs 6.4 %, $p < 0.01$) from FY2012 to FY2020 (Fig. 1). Over this period, there was a decrease in rates of primary debulking surgeries performed (68.8 % vs 40.6 %, $p = 0.02$) for patients with stage III and IV ovarian, fallopian tube, and primary peritoneal carcinoma (Fig. 1).

Postoperative outcomes: the median length of hospital stay after surgery decreased from five days in FY2012 to four days in FY2020 ($p < 0.01$). Median units of red blood cells transfused in both fiscal years was zero. There was a similar rate of intensive care unit (ICU) postoperative admissions (14.8 % in FY2012 vs 11.5 % in FY2020, $p = 0.39$). Administration of postoperative oral or intravenous antibiotics (either for surgical prophylaxis or treatment of infection) did not vary from

Table 1
Conversion of common opioids to oral morphine equivalents (OME).

Opioid	Equivalent OME
PO Hydrocodone 1 mg	1
PO Oxycodone 1 mg	1.5
PO Hydromorphone 1 mg	4
PO Tramadol 1 mg	0.25
PO Codeine 1 mg	0.15
IV Hydromorphone 1 mg	20
IV Fentanyl 1mcg	0.3

Abbreviations: PO = Per os, or by mouth. IV = Intravenous.

Table 2
Characteristics of open surgical patients for fiscal years 2012 and 2020.

Characteristic	Fiscal Year 2012 (n = 162)	Fiscal Year 2020 (n = 156)	P value
Age (years)	60 (51, 66)	56 (44, 64)	0.05
Body mass index	27.3 (23.7, 33.5)	27.5 (23.4, 33.2)	0.82
Diabetes diagnosis	24 (14.8 %)	24 (15.4 %)	0.89
Hispanic ethnicity	24 (15.1 %)	34 (22.1 %)	0.11
Race			<0.01
White or Caucasian	89 (54.9 %)	88 (56.4 %)	
Asian	22 (13.6 %)	16 (10.3 %)	
Black or African American	14 (8.6 %)	21 (13.5 %)	
Native Hawaiian or Pacific Islander	1 (0.6 %)	3 (1.9 %)	
American Indian or Alaska Native	4 (2.5 %)	8 (5.1 %)	
Other or Unknown/Declined	32 (19.7 %)	20 (12.8 %)	
Language			0.23
English	129 (79.6 %)	130 (83.3 %)	
Spanish	18 (11.1 %)	13 (8.3 %)	
Chinese (Mandarin and Cantonese)	4 (2.5 %)	8 (5.1 %)	
Other	11 (6.8 %)	5 (3.2 %)	
Medicaid insurance	69 (42.6 %)	53 (34.0 %)	0.11
Medicare insurance	40 (24.7 %)	33 (21.2 %)	0.45
Cancer diagnosis	107 (66.0 %)	104 (66.7 %)	0.91
Primary cancer organ			0.55
Ovary, Fallopian tube, Primary peritoneal	55 (51.4 %)	54 (51.9 %)	
Uterus, Sarcoma	32 (29.9 %)	24 (23.1 %)	
Cervix	10 (9.3 %)	16 (15.4 %)	
Borderline ovarian tumor	4 (3.7 %)	3 (2.9 %)	
Vulva, Vagina	0 (0)	0 (0)	
Gastrointestinal	5 (4.7 %)	7 (6.7 %)	
Other	1 (0.9 %)	0 (0 %)	

FY2012 to FY2020 (23.5 % vs 23.7 %, p = 0.96). From FY2012 to FY2020, alvimopan (an opioid receptor antagonist at the bowel that is administered as part of our ERAS pathway) use increased for those patients who underwent a bowel resection (0 % vs 37 %, p < 0.01). Nasogastric tubes were utilized less frequently from FY2012 to FY2020 (18.5 % vs 9.7 %, p = 0.02). Post-discharge emergency room (ER) visits (8.6 % vs 11.5 %, p = 0.39) and inpatient readmissions (11.1 % vs 10.3 %, p = 0.81) did not vary from FY2012 to FY2020.

Postoperative pain management: use of thoracic epidurals remained consistent from FY2012 to FY2020 (51.9 % vs 53.8 %, p = 0.72) while transverse abdominis plane (TAP) blocks were performed more frequently (3.1 % vs 33.8 %, p < 0.01, Fig. 2). Opioid patient-controlled analgesia (PCA) use significantly decreased over this time period (61.1 % vs 14.1 %, p < 0.01). Use of non-opioid adjuncts postoperatively increased from FY2012 to FY2020 including use of acetaminophen (79.6 % vs 99.4 %, p < 0.01), non-steroidal anti-inflammatory drugs (35.2 % vs 83.3 %, p < 0.01), and gabapentin (3.7 % vs 95.5 %, p < 0.01). The median total amount of oral and intravenous opioid medication used by patients in the hospital (intra- and postoperatively) decreased from 436 OME in FY2012 to 165.5 OME in FY2020 (p < 0.01). Adjusting for lengths of hospital stay, the median OME used per day also decreased from FY2012 to FY2020 (78.7 vs 42.2 OME per day, p < 0.01, Fig. 3). In FY2012, extended-release opioid medications were utilized in the inpatient setting to treat postoperative pain in 3.1 % of patients versus 0 % in FY2020 (p = 0.03). Additionally, 35.8 % of patients received more than one immediate-release opioid medication (e.g. oxycodone and tramadol) in the immediate postoperative setting in FY2012 versus 14.7 % in FY2020 (p < 0.01).

Preoperative and post-discharge pain management: there were more patients in FY2012 than in FY2020 who had a diagnosis of "chronic pain" (15.1 % vs 3.5 %, p < 0.01) on their medical record problem list, although was no difference in the percentage of patients with an opioid prescription on their preoperative home medication list from FY2012 to FY2020 (38.9 % vs 31.4 %, p = 0.16). The median prescription size at the time of hospital discharge decreased by 77.7 % from 675 OME in FY2012 (equivalent to 90 doses of 5 mg oxycodone tablets) to 150 OME in FY2020 (equivalent to 20 doses of 5 mg oxycodone tablets, Fig. 4). The refill rate did not increase (17.3 % vs 18.6 %, p = 0.76). We also observed a decrease in the frequency of prescribing more than one immediate release opioid medication for home (12.3 % FY2012 to 0 % FY2020, p < 0.01).

3.2. *Part II. Assessing over-prescription of opioid medication*

One hundred surveys were attempted and ninety-five surveys were successfully completed from April 2021 to November 2021. We utilized telephone interpreters for twelve (12.6 %) patients. Twenty-seven percent of respondents had an opioid on their preoperative home medication list, but only 4.2 % were taking the medication consistently enough to meet the FDA definition of opioid tolerance. A hysterectomy was performed for 66.3 % of respondents, a bowel resection for 15.8 %, and a unilateral or bilateral oophorectomy for 85.3 %. Forty-four percent of respondents had a benign diagnosis. Three patients (3.2 %) were still requiring opioid pain medication at the time the survey was completed. A best estimate was provided by the patient regarding their anticipated total opioid use and two patients were successfully contacted again 1–2 weeks later and their updated total opioid use was acquired.

The self-reported median OME used by patients at home after hospital discharge was 22.5 (equivalent to 3 doses of 5 mg oxycodone tablets, the star icon in Fig. 4). The range of OME used was 0–1200, or the equivalent of 0–160 doses of 5 mg oxycodone tablets. Thirty-seven percent of patients did not use any opioid medication after hospital discharge. The majority of respondents (77.9 %) had unused doses of their initial discharge opioid prescription. The refill rate in survey respondents was 12.6 %. The amount of unused opioids retained by patients from their initial prescription and any refills ranged from 3.8 to 937.5 OME (the equivalent of 0.5 to 125 doses of 5 mg oxycodone tablets). This equates to 1331 excess doses of 5 mg oxycodone tablets per 100 patients. Thirty-three patients (34.7 %) used zero OME the day before leaving the hospital, yet 93.9 % of them were given an opioid prescription at hospital discharge.

When we queried patients about their satisfaction with the prescription size they were given, 42.1 % reported the size was "just right," 12.6 % felt they had received "too few," and 45.3 % felt that the prescription size had been "too many." Of those that had leftover opioids from their initial prescription, 41.9 % still felt that their initial prescription size was adequate in size and half of respondents (55.4 %) felt that they had been prescribed too many.

4. Discussion

Prescription of excess postoperative opioids is associated with risk of persistent opioid use and overdose among patients and their families. (Khan et al., 2019; Rachel and Lipari, 2017; Wright et al., 2019; Chan et al., 2021) From FY2012 to FY2020, we observed a significant reduction of opioids used by our open surgical patients in the immediate postoperative period. We reduced our median post-discharge opioid prescription size by 77.7 % from FY2012 to FY2020, without an increase in refill rate. Our prospective survey data identifies ongoing over-prescription of opioids post-discharge with an excess of prescribed opioids equivalent to 1331 doses of 5 mg oxycodone tablets per 100 patients. This suggests that we could further decrease the median prescription size by an additional 85 % to meet our patients' self-reported opioid use and decrease the excess of opioids we are introducing into our patients' communities.

Notably, our patients' opioid use in the hospital began to decrease in FY2014 (Fig. 3) while our opioid prescriptions did not decrease in size until FY2017 (Fig. 4), lagging behind national trends (CDC Injury

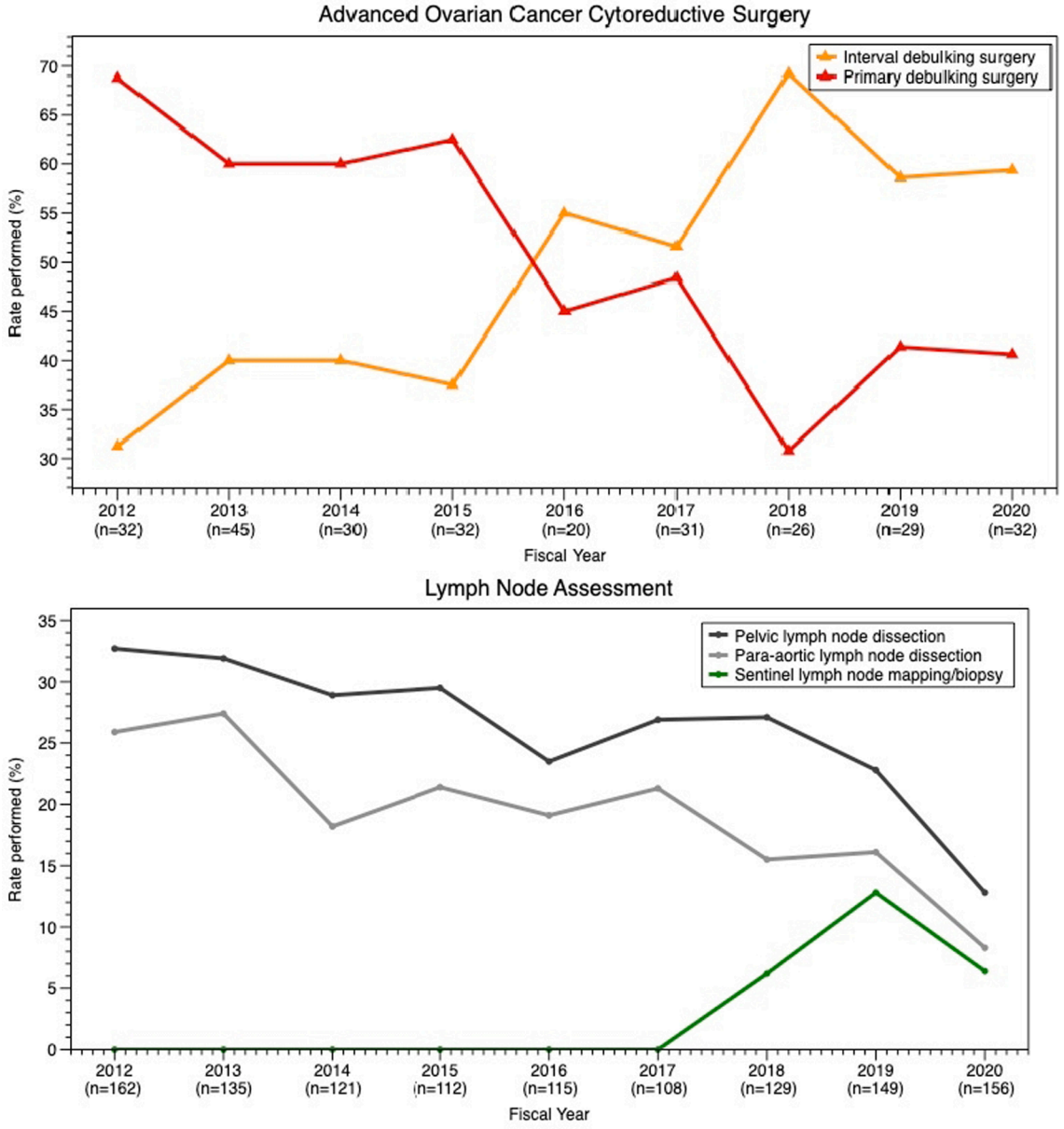

Fig. 1. Trends in procedural complexity from FY2012 to FY2020, number of patients listed beneath each fiscal year. A) Lymph node evaluation. B) Cytoreductive surgeries for advanced epithelial ovarian cancer.

Center, 2021). Multiple factors likely contribute to this reduction in opioid use and this timeline. Our ERAS pathway was launched in 2014 and likely contributed to this decrease in opioid use via increased utilization of opioid-sparing adjunct medications and opioid-sparing pain management modalities. Chapman et al., 2016; Kay et al., 2020; Lefkowits et al., 2018; Hillman et al., 2019 The introduction of electronic prescribing at our institution in 2019 may also have contributed to the changes observed. Prior to this, there was significant concern for discharging patients to remote locations without an adequate opioid prescription. The effects of electronic prescribing on opioid prescribing rates in other studies though has been mixed. Everson et al., 2020; Danovich et al., 2019 Increased popular press coverage of the risks of opioids undoubtedly impacted both patients' and providers' desire to decrease opioid use and comfort with smaller post-discharge opioid prescriptions.(Michael Forsythe, 2021; Benner, 2021; Keefe, 2017).

Additionally, in our surgical data we observed a decrease in primary cytoreductive surgeries for advanced ovarian cancer and in systematic pelvic and paraaortic lymph node dissections. These shifts in surgical care (and likely decrease in surgical complexity) came after sentinel papers in gynecologic oncology demonstrated similar survival for patients who underwent surgery or chemotherapy for the initial treatment of advanced ovarian cancer(Vergote et al., 2010; CHORUS 2015) and after sentinel lymph node mapping in endometrial cancer was prospectively validated (FIRES 2017). Vergote et al., 2010; Kehoe et al., 2015; Rossi et al., 2017 However, other markers of procedural complexity (i.e. rates of hysterectomy and bowel resections, ICU admissions, red blood cell transfusions, use of antibiotics, ER visits and inpatient readmissions) remained consistent from FY2012 to FY2021 and it is unclear what effect this evolution of care had on patient opioid use.

As we look to the future and our commitment to decrease our contribution to the opioid epidemic, we must continue to focus on best practices for opioid prescribing at hospital discharge. The Opioids After Surgery Workshop at Johns Hopkins University, the Michigan Opioid Prescribing Engagement Network (Michigan OPEN), and several research studies have developed modern recommendations for

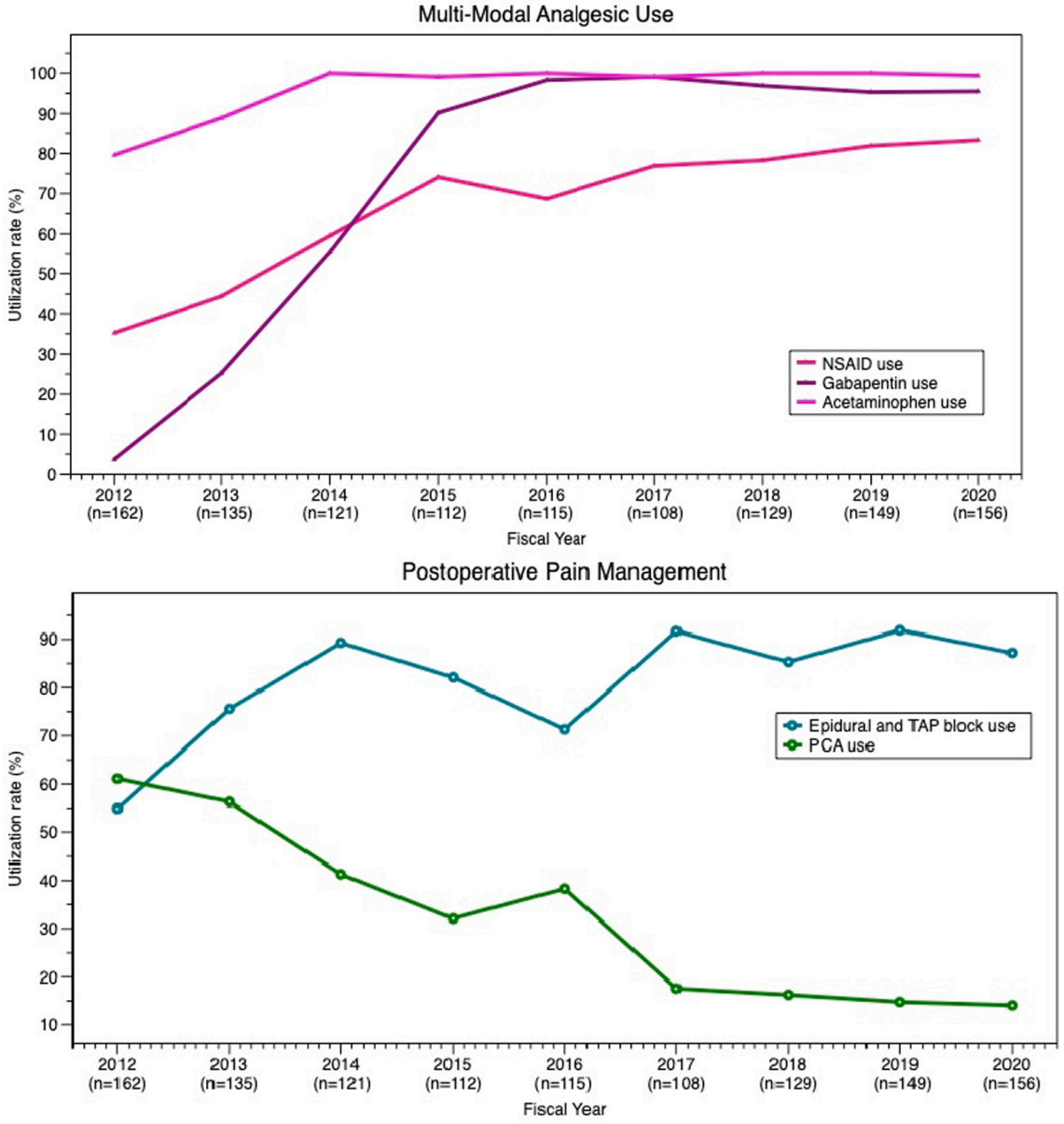

Fig. 2. Trends in postoperative pain management from FY2012 to FY2020, number of patients listed beneath each fiscal year. A) Postoperative pain management with epidurals, transverse abdominis plane (TAP) blocks, and opioid patient controlled analgesia (PCAs). B) Administration of oral multi-modal analgesia.

postoperative opioid prescribing with a suggested range of opioid tablets. Hill et al., (2017); Overton et al., (2018); Network et al., (2021); Hill et al., (2018); Thiels et al., (2018); Boitano et al., (2020) For example, Michigan OPEN recommends a post-discharge prescription of 0–10 doses of 5 mg oxycodone tablets after an open hysterectomy. However, there will ultimately be some patients who need larger prescriptions (e.g. 33 % of our patients used more than 10 doses of 5 mg oxycodone tablets) and there are currently no reliable evidence-based point-of-care tools to aid providers in identifying who those patients might be.

Further investigation is needed to develop such a decision aid. Ideally, this decision aid would be easy to use, incorporate readily available objective data from the medical record, reduce the excess of opioids prescribed to patients, and reduce disparities in prescribing. It is well documented that there is racial disparity in opioid prescribing (Pletcher et al., (2008); Friedman et al., (2019)) The specialty of obstetrics and gynecology is not exempt from these inequalities in clinical care. Badreldin et al., (2019) A postoperative opioid decision aid should ameliorate, not perpetuate, existing disparities in the management of pain. Our gynecologic oncology division is currently in the process of validating an opioid prescription size decision aid which incorporates age of the patient and the amount of OME used the day before discharge. Prescribers and patients could use this decision aid together to choose, free of implicit bias, an appropriate opioid prescription size for home.

A strength of our study is the incorporation of a large volume of data to best demonstrate the changes in clinical care that have occurred in the last decade and how that compares to our decrease in opioid prescription sizes for home. Additionally, our prospective surveys used verbal consent at the time of patient contact, which reduced the risk of introducing bias via the Hawthorne effect. Conversely, a limitation of our study is our reliance on patients' self-reported opioid use, but our findings are consistent with other published outcomes in gynecologic surgery Hillman et al., (2019). Another limitation is that our identified refill rate is exclusive to refills filled by our own institution's providers, but we accounted for this in our prospective surveys by directly querying patients on a need for a refill. Also our length of stay is relatively long

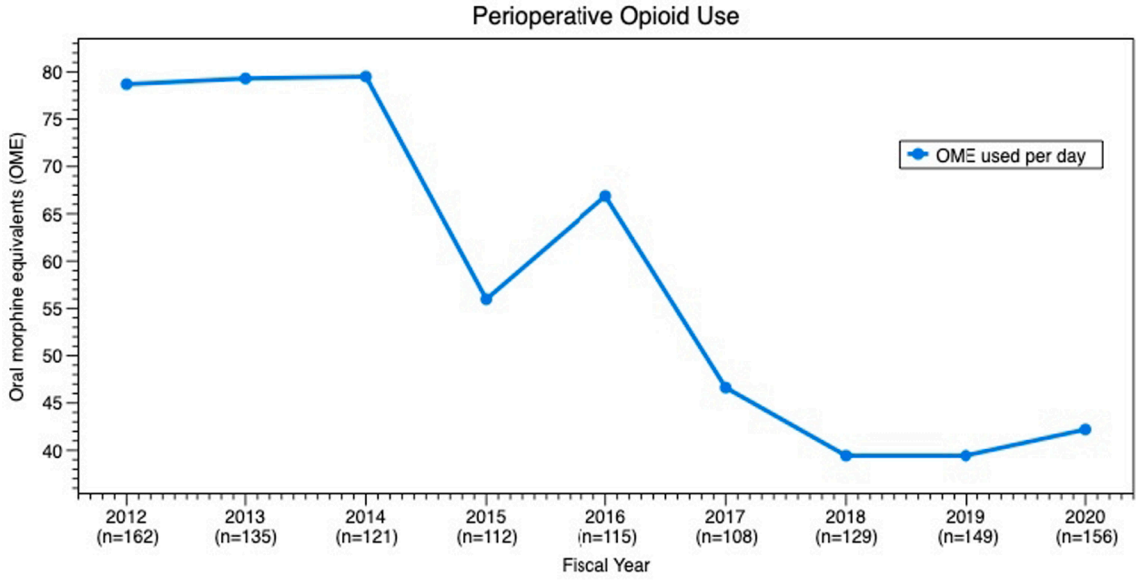

Fig. 3. Median intraoperative and postoperative opioid use by day, adjusting for hospital length of stay. Opioid use expressed in oral morphine equivalents (OME). Number of patients listed beneath each fiscal year.

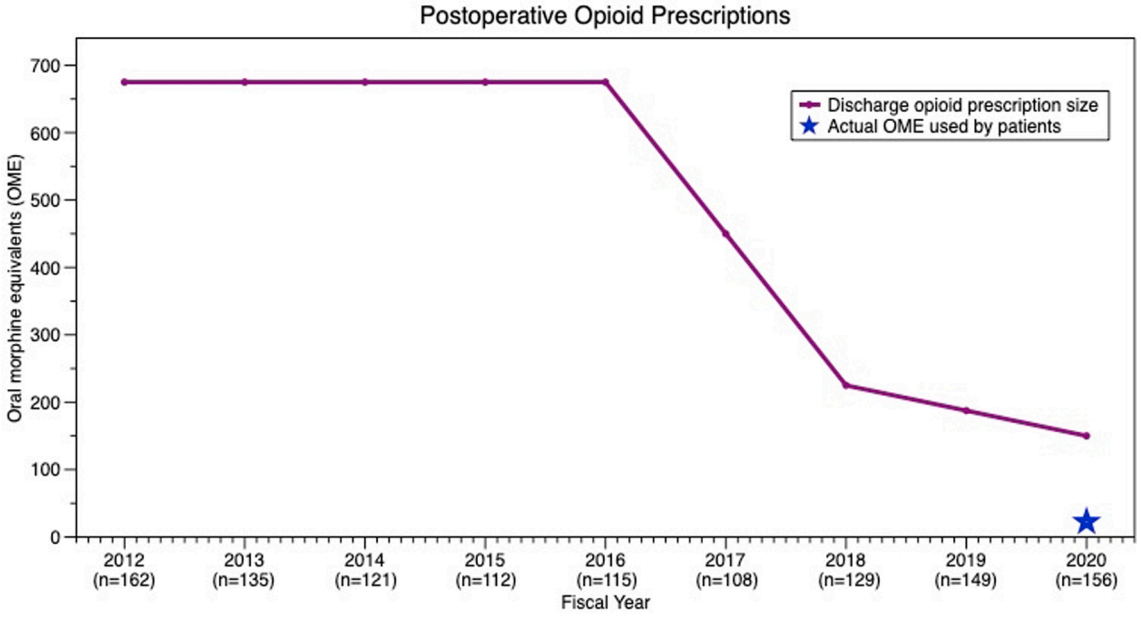

Fig. 4. Trends in opioid prescription size at time of hospital discharge from FY2012 to FY2020 with self-reported opioid use obtained from prospective surveys. The blue star denotes self-reported OME use by patients in the prospective survey portion of this study. Number of patients is listed beneath each fiscal year. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(median of 4 days in FY2020) and our ICU admission rate is relatively high (notably we do not have a stepdown unit), which may limit the generalizability of our findings.

We believe this study should bring attention to evolving opioid prescribing practices in gynecologic surgery and highlight the need for continued improvement. Despite a historical reduction in postoperative prescribing, we found that patients undergoing complex open surgical procedures for benign and malignant diagnoses still require significantly less opioid medication than they are prescribed. Persistent opioid use should be considered a surgical complication. We must continue to develop individualized approaches to opioid prescribing and partner with our patients to address each patient's pain management needs.

5. Disclosure of financial support

A small sum of financial support was obtained through a patient donation fund for gynecologic oncology research at UCSF. No commercial support was obtained.

CRediT authorship contribution statement

Allison H. Kay: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – original draft. **Alisha Othieno:** Methodology, Data curation, Writing – review & editing. **John Boscardin:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Lee-lynn Chen:** Conceptualization, Methodology,

Writing – review & editing. **Edwin A. Alvarez:** Conceptualization, Methodology, Resources, Writing – review & editing. **Megan Swanson:** Conceptualization, Methodology, Resources, Writing – review & editing. **Stefanie Ueda:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. **Lee-may Chen:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. **Jocelyn S. Chapman:** Conceptualization, Methodology, Investigation, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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