Gynecologic Oncology 183 (2024) 9–14

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Impact of pharmacogenomic profiles on post-surgical pain following laparotomy for gynecologic pathology

Gretchen E. Glaser [a,*], Brandon Maddy [a], Amanika Kumar [a], Karen Ishitani [a], Maureen A. Lemens [a], Kristine Hanson [b], Ann M. Moyer [c], Elizabeth Habermann [b], Sean C. Dowdy [a,b]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN, United States of America
[b] Robert D. and Patricia E. Kern Center for the Science of Healthcare Delivery, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA
[c] Division of Laboratory Genetics/Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States of America

HIGHLIGHTS

- Pharmacogenomics is an emerging field which may be used to individualize postoperative pain management.
- CYP2D6 metabolizer status correlated with milligram morphine equivalents of opioids consumed in the 24 h following laparotomy for gynecologic pathology.
- Genes such as *OPRM1 and COMT* may hold promise for further personalization of opioid prescribing.

ARTICLE INFO

Article history:
Received 22 December 2023
Received in revised form 23 February 2024
Accepted 3 March 2024
Available online xxxx

Keywords:
Pharmacogenomics
Opioids
Surgery
CYP2D6
Postoperative

ABSTRACT

Objectives. The aim of this prospective study was to compare perioperative opioid use in women by status of *CYP2D6*, a highly polymorphic pharmacogene relevant to opioid metabolism.

Methods. Patients undergoing laparotomy were prospectively recruited and provided a preoperative saliva swab for a pharmacogenomic (PGx) gene panel. Postoperative opioid usage and pain scores were evaluated via chart review and a phone survey. Pharmacogenes known to be relevant to opioid metabolism were genotyped, and opioid metabolizing activity predicted by *CYP2D6* genotyping. Patient and procedural factors were compared using Fisher's exact and Kruskal-Wallis tests.

Results. The 96 enrolled patients were classified as ultra-rapid ($N = 3$, 3%), normal (58, 60%), intermediate (27, 28%), and poor (8, 8%) opioid metabolizers. There was no difference in surgical complexity across *CYP2D6* categories ($p = 0.61$). Morphine Milligram Equivalents (MME) consumed during the first 24 h after perioperative suite exit were significantly different between groups: ultrarapid metabolizers had the highest median MME (75, IQR 45–88) compared to the other three groups (normal metabolizers 23 [8–45], intermediate metabolizers 48 [20–63], poor metabolizers 31 [12–53], $p = 0.03$). Opioid requirements were clinically greater in ultrarapid metabolizers during the second 24 h and last 24 h but were statistically similar ($p = 0.07$). There was no difference in MME prescribed at discharge ($p = 0.22$) or patient satisfaction with pain control ($p = 0.64$) between groups.

Conclusions. A positive association existed between increased CYP2D6 activity and in-hospital opioid requirements, especially in the first 24 h after surgery. This provides important information to further individualize opioid prescriptions for patients undergoing laparotomy for gynecologic pathology.

1. Introduction

Gynecologic surgery for both benign and malignant conditions is associated with postoperative pain [1]. Inability to adequately control postoperative pain is a major patient dissatisfier and highlights the need to identify best practices for perioperative pain control while also reducing total opioids prescribed [2]. Enhanced Recovery After

* Corresponding author at: Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States of America.
E-mail address: glaser.gretchen@mayo.edu (G.E. Glaser)
Social media:

https://doi.org/10.1016/j.ygyno.2024.03.001
0090-8258/

Surgery (ERAS) protocols have revolutionized the perioperative management of gynecologic patients and includes a multimodal pain management strategy to reduce opioid requirements [3]. Outpatient opioid prescribing protocols such as our tiered guideline approach further reduce opioid administration for the full postoperative period without affecting patient-perceived pain control or refill rates [4].

While inpatient and outpatient opioid prescribing guidelines are effective to reduce opioid administration and use in patients with postoperative pain from gynecologic surgery, true individualization has not been achieved [4,5]. Pharmacogenomics (PGx) is an emerging field in individualized medicine concerned with genetic variations in drug-metabolizing enzymes, transporters, receptors, and drug targets that may partly explain inter-individual variation in drug efficacy and toxicity [6]. Variation in genes that encode enzymes known to process opioids may result in poor pain control for some patients even when receiving high doses of opioid medications, with life-threatening adverse effects from even small doses of the same medication for others [7]. The majority of opioid medications used for acute postoperative pain are known to be processed by enzymes encoded by *CYP2D6* and *CYP3A4*, with a more recent discovery of *OPRM1* and *COMT* [6,8,9]. CYP2D6 metabolizer status has been shown in prior studies to correlate with postoperative opioid consumption, pain control, and adverse effects [5,10,11]. In addition to tiered prescribing and the use of non-opioid and non pharmaceutical pain relief strategies, pharmacogenomics can improve individualized post-operative pain control strategies.

The goal of this study is to examine the current and potential future therapeutic relevance of PGx testing for gynecologic oncology surgical patients in order to improve patient clinical care with more effective and efficient prescribing of opioid medications.

2. Methods

This study was approved by the Mayo Clinic Institutional Review Board. Patients age ≥ 18 with a planned laparotomy for gynecologic pathology were prospectively recruited at a single institution. Patients provided written informed consent and HIPAA authorization prior to initiation of any study-specific procedures. Enrollment was set at 100 patients a priori based on available funding for this exploratory pilot. Analysis was limited to patients who underwent surgery following study enrollment.

All participants provided a one-time saliva swab for a PGx multigene panel performed in a CLIA-approved/CAP-accredited laboratory before surgery. Genotyping was performed via a PGx panel including *CYP2D6*, *CYP3A4*, *OPRM1*, and *COMT*. Opioid metabolizing activity was predicted based on phenotypes derived from *CYP2D6* genotyping for each participant. CYP2D6 metabolizer statuses were defined as ultra-rapid metabolizer, normal metabolizer, intermediate metabolizer, or poor metabolizer. These groups corresponded with previously defined CYP2D6 activity scores: ≥2.25 for ultrarapid, 1.25–2 for normal, 0.5–1 for intermediate, and 0 for poor metabolizer statuses [12]. All patients were managed perioperatively using the Enhanced Recovery After Surgery (ERAS) protocol at our institution [4,13]. Supplemental Table S1 shows full details in the RECOvER checklist format [14]. For pain control, this protocol includes preoperative administration of acetaminophen and celecoxib and postoperative wound infiltration with bupivacaine. Gabapentinoids are not routinely used secondary to recent evidence of increased risk in older patients after major surgery [15,16]. Intraoperative regional analgesia is not routinely used. Immediately after surgery, patients receive scheduled acetaminophen and NSAIDs unless they had a contraindication, and oral opioids (oxycodone 5-10 mg) as needed every four hours. If patients have breakthrough pain (pain >7 > 1 h after receiving oxycodone), our ERAS protocol states that they should receive hydromorphone 0.4 mg IV once, with a repeat dose after 20 min if ineffective. IV patient-controlled analgesia is only used if patients have continued pain desite two doses of IV hydromorphone [13]. At the time of discharge, patients receive opioid medications based on a tiered prescription guideline approach developed at our institution [4]. For patients who have undergone laparotomy, this includes no opioid prescription for those who have not used this medication within 24 h before hospital discharge, and a prescription for oxycodone 5 mg × 10 tablets if patients are still requiring opioid treatment to manage pain.

The primary outcomes were in-hospital postoperative opioid use and pain scores, evaluated across CYP2D6 metabolizer statuses. Secondary analysis evaluated differences across CYP3A4 phenotypes (normal vs intermediate to normal), *OPRM1* genotypes (rs179971 AA vs rs1799971 AG), and *COMT* genotypes (rs4680 AA, rs4680 GA, rs4680 GG). In-hospital factors including time between exit from the postoperative anesthesia care unit (PACU) and hospital discharge, postoperative medication administration, and pain scores were obtained from the electronic medical record. Opioids administered in hospital and opioid prescriptions at discharge were evaluated as morphine milligram equivalents (MME). Postoperative pain scores were measured on an analog scale from 0 (no pain) to 10 (worst possible pain). In-hospital opioids were evaluated as total MME administered and pain scores were evaluated as maximum score within each of the following time periods: first 24 h following PACU exit (0–24 h), second 24 h following PACU exit (>24 to 48 h), and last 24 h of hospitalization; values in the second 24 h after PACU exit were only calculated for patients who were discharged >24 h after PACU exit. Patient records were examined for simultaneous administration of strong inhibitors of CYP2D6 (bupropion and fluoxetine) and non-opioid pain medications (acetaminophen, ibuprofen, ketorolac, gabapentin.

Patient demographics, surgical factors, and discharge opioid prescriptions were evaluated via electronic chart review. A phone survey planned for 21–35 days after discharge captured opioid use after surgery, pain control following discharge, and satisfaction with pain control. Post-discharge pain control was captured on a scale from 0 (not controlled at all) to 10 (completely controlled).

Patient and procedural factors were compared by CYP2D6 metabolizer status, CYP3A4 phenotype, *OPRM1* genotype, and *COMT* genotype and using Chi-square, Fisher's exact, and Kruskal-Wallis tests.

Statistical analysis was performed using version 9.4 of SAS (SAS Institute, Cary NC). *P*-values of <0.05 were considered statistically significant.

3. Results

100 patients were prospectively enrolled, of which 96 underwent surgery and were included in the study. Patients were grouped according to their CYP2D6 metabolizer status, classified as ultra-rapid ($N = 3$, 3%), normal (58, 60%), intermediate (27, 28%), and poor (8, 8%) opioid metabolizers (Table 1). Patient demographics, pre-operative assessments, and surgical factors are shown in Table 2. Over two thirds of patients (66, 69%) underwent complex cytoreductive surgery, while 30 (31%) had staging laparotomy, and one-fifth (19, 20%) underwent colon resection. The majority of patients (91, 95%) had a final postoperative diagnosis of cancer. Median length of stay after surgery was 3 days (IQR 2–5), with 71 (74%) of patients staying >48 h after exit from the post-anesthesia care unit (PACU). There was no difference in surgical complexity ($p = 0.61$) or length of hospitalization ($p = 0.50$) across CYP2D6 metabolizer statuses (Table 2), and all patients were administered nonopioid pain medications during hospitalization. (Table 3).

The overall median MME consumed in the first 24 h after PACU exit was significantly different between CYP2D6 metabolizer groups. While the overall median MME consumed during this time period was 30 (IQR 13–53), patients in the ultrarapid metabolizer group consumed a median 75 MME (IQR 45–88) which was higher than normal (median 23; IQR 8–45), intermediate (48; 20–63), and poor (31; 12–53) metabolizers($p = 0.03$). MME used by patients during the second 24 h after PACU exit and the last 24 h of hospitalization were not significantly different between groups, but higher in the ultrarapid

Table 1
CYP2D6 metabolizer status and activity score.

			N
CYP2D6 metabolizer status	**CYP2D6 activity score**	**Effect on Response**	2
Ultrarapid Metabolizer	**3**	Drugs metabolized by CYP2D6 would be eliminated at an increased rate and carry an increased risk of therapeutic failure.	
	2.5		1
		Prodrugs activated by CYP2D6 would have a greater proportion of active drug available and carry an increased risk of side effects.	
Normal Metabolizer	**2**	Patients would be expected to have an average or normal response to the drug and risk of side effects.	39
	1.5		17
	1.25		2
Intermediate Metabolizer	**1**	Drugs metabolized by CYP2D6 would be eliminated at a decreased rate and carry a risk of increased side effects.	22
	0.5		5
Poor Metabolizer	**0**	Prodrugs activated by CYP2D6 would have a lesser proportion of active drug available and carry an increased risk of therapeutic failure.	8
Total			96

metabolizers ($p = 0.07$ for both, Fig. 1) In the whole cohort, 69 (72%) received oxycodone during their hospitalization and 33 (34%) received hydromorphone; 27 (28%) received both oxycodone and hydromorphone. There was no significant difference in administration of these drugs between *CYP2D6* phenotypes (Table 3). In addition to these medications, 42 (44%) received tramadol and 4 (4%) received fentanyl. For 9 patients (9%), tramadol was the only opioid administered.

Postoperative pain scores did not differ significantly between *CYP2D6* phenotype groups with a median of 7 (IQR 5–8) in the first 24 h ($p = 0.29$), 5 (IQR 4–7) in the second 24 h ($p = 0.12$), and 4 (IQR 3–6) in the last 24 h of hospitalization (p = 0.12). Possible confounding factors for adequate pain control were examined and found to be not significantly different between groups, including simultaneous prescription of strong CYP2D6 inhibitors ($p = 1.00$) and use of prescription pain medications between study enrollment and surgery ($p = 0.31$). None of the patients with ultrarapid metabolism were taking strong CYP2D6 inhibitors simultaneously with opioid medications during hospitalization. (Table 3).

At hospital discharge, 72 (75%) of patients received an opioid prescription, with no difference between groups ($p = 0.75$), and median total MME consumed in the outpatient period was 8 (IQR 0–50) also with no difference across CYP2D6 metabolizer categories ($p = 0.44$). Eleven percent of patients surveyed reported receiving an opioid refill or new prescription after dismissal. Despite this low use of opioids in the outpatient setting, patients reported having excellent pain control, rating their satisfaction with pain a median of 9 (IQR 8–10) ($p = 0.64$) out of a best possible score of 10. Fewer patients in the CYP2D6 ultrarapid metabolizer group (67%) used non-prescription pain medications after hospital dismissal than the other groups (73%–98%, $p = 0.002$, Table 3).

As would be expected based on the known rarity of genetic variants and homogeneous enzyme activity of *CYP3A4*, there were no differences in opioid use or pain scores during any postoperative period between the normal ($n = 89$) and intermediate ($n = 7$) cohorts [17,18]. Standardized genotype to phenotype classifications for *OPRM1* and *COMT* have yet to be defined as of the latest Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [9], but we did see a difference in opioid use in the second 24 h after PACU exit for the two *OPRM1* genotypes (median 15 MME [IQR 8–28] among rs1799971 AA vs. 8 [IQR 0–16] among rs1799971 AG, $p = 0.04$). Inpatient opioid requirements did not vary across the three *COMT* genotypes in our study. Opioids prescribed and used as outpatients and patient satisfaction scores were equivalent for both *OPRM1* genotypes and all three *COMT* genotypes (Supplemental Tables S2–S7).

4. Discussion

PGx has the potential to improve efficacy and reduce side effects of medications by using an individual's genotype and determined phenotype to inform personalization and optimization of drug therapy. This could even further enhance the inpatient (ERAS®) and outpatient postoperative opioid prescribing guidelines that have been created for this population [4,15]. In this study we showed that MME consumed during the first 24 h after PACU exit was significantly different between

Table 2
Demographics, pre-operative assessments, and surgical factors by CYP2D6 phenotype. Unless otherwise noted, summary statistics are displayed as N (column percentage).

	CYP2D6 metabolizer status					
	Ultrarapid Metabolizer (N = 3)	Normal Metabolizer (N = 58)	Intermediate Metabolizer (N = 27)	Poor Metabolizer (N = 8)	Total (N = 96)	P-value
Age, mean (SD)	59.3 (12.1)	62.4 (11.2)	62.6 (10.2)	68.3 (6.3)	62.9 (10.6)	0.486[1]
BMI, n (%)						0.719[2]
<25	0 (0.0%)	26 (44.8%)	11 (40.7%)	4 (50.0%)	41 (42.7%)	
25 to <30	1 (33.3%)	16 (27.6%)	8 (29.6%)	1 (12.5%)	26 (27.1%)	
30+	2 (66.7%)	16 (27.6%)	8 (29.6%)	3 (37.5%)	29 (30.2%)	
History of any prior opioid use [3]	0 (0.0%)	16 (27.6%)	10 (38.5%)	0 (0.0%)	26 (27.4%)	0.144[2]
History of prior chronic pain syndrome diagnosis [3]	0 (0.0%)	3 (5.2%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	0.689[2]
History of any prior surgery	1 (33.3%)	38 (65.5%)	17 (63.0%)	5 (62.5%)	61 (63.5%)	0.749[2]
Surgical complexity						0.605[2]
Staging Laparotomy	1 (33.3%)	21 (36.2%)	6 (22.2%)	2 (25.0%)	30 (31.3%)	
Complex Cytoreductive	2 (66.7%)	37 (63.8%)	21 (77.8%)	6 (75.0%)	66 (68.8%)	
Colon resection	1 (33.3%)	9 (15.5%)	6 (22.2%)	3 (37.5%)	19 (19.8%)	0.301[2]
Cancer	3 (100.0%)	55 (94.8%)	26 (96.3%)	7 (87.5%)	91 (94.8%)	0.635[2]
Length of hospitalization (days)						0.502[1]
Median (IQR)	4 (2, 6)	3 (2, 5)	4 (2, 5)	4 (3, 5)	3 (2, 5)	
Range	2, 6	0, 15	1, 16	3, 7	0, 16	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value; [3]History of any prior opioid use and history of prior chronic pain syndrome missing for $N = 1$.

Table 3
Medications and pain during hospitalization and post-discharge by CYP2D6 phenotype. Unless otherwise noted, summary statistics are displayed as N (column percentage).

	CYP2D6 metabolizer status					
	Ultrarapid Metabolizer (N = 3)	Normal Metabolizer (N = 58)	Intermediate Metabolizer (N = 27)	Poor Metabolizer (N = 8)	Total (N = 96)	P-value
Hospitalization						
Opioids administered between PACU exit and discharge						
Any	3 (100.0%)	47 (81.0%)	27 (100.0%)	7 (87.5%)	84 (87.5%)	0.053[1]
Oxycodone	2 (66.7%)	37 (63.8%)	24 (88.9%)	6 (75.0%)	69 (71.9%)	0.078[1]
Hydromorphone	2 (66.7%)	16 (27.6%)	13 (48.1%)	2 (25.0%)	33 (34.4%)	0.156[1]
Tramadol	0 (0.0%)	23 (39.7%)	14 (51.9%)	5 (62.5%)	42 (43.8%)	0.233[1]
Fentanyl	0 (0.0%)	3 (5.2%)	0 (0.0%)	1 (12.5%)	4 (4.2%)	0.339[1]
MME 0–24 h after PACU exit						0.029[2]
Median (IQR)	75 (45, 88)	23 (8, 45)	48 (20, 63)	31 (12, 53)	30 (13, 53)	
Range	45, 88	0, 106	0, 107	0, 117	0, 117	
MME >24–48 h after						0.069[2]
PACU exit [3]						
Median (IQR)	61 (30, 80)	10 (0,23)	20 (8, 23)	18 (4, 25)	13 (8, 25)	
Range	30, 80	0, 100	0, 60	0, 123	0, 123	
MME last 24 h of hospitalization						0.066[2]
Median (IQR)	38 (30, 40)	8 (0, 15)	8 (0,20)	15 (4, 35)	8 (0, 20)	
Range	30, 40	0, 76	0, 45	0, 43	0, 76	
Other medications administered between PACU exit and discharge						
Non-opioid pain medications	3 (100.0%)	58 (100.0%)	27 (100.0%)	8 (100.0%)	96 (100.0%)	N/A
Strong CYP2D6 inhibitors	0 (0.0%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	2 (2.1%)	1.000[1]
Was taking prescription pain medications prior to original surgery after study enrollment [4]	1 (33.3%)	4 (6.9%)	3 (11.5%)	0 (0.0%)	8 (8.4%)	0.311[1]
Maximum pain score 0–24 h post-PACU exit						0.291[2]
Median (IQR)	8 (8, 8)	6 (5, 8)	7 (6, 8)	7 (5, 8)	7 (5, 8)	
Range	8, 8	2, 10	3, 10	4, 10	2, 10	
Maximum pain score > 24–48 h post-PACU exit [3]						0.115[2]
Median (IQR)	7 (7, 8)	5 (4, 7)	6 (5, 7)	5 (3, 7)	5 (4, 7)	
Range	7, 8	2, 9	3, 10	3, 9	2, 10	
Maximum pain score last 24 h of hospitalization						0.116[2]
Median (IQR)	7 (7, 7)	5 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)	
Range	7, 7	0, 8	0, 7	2, 7	0, 8	
Post-discharge						
Opioid prescription at time of hospital dismissal						0.752[1]
No	0 (0.0%)	13 (22.4%)	8 (29.6%)	3 (37.5%)	24 (25.0%)	
Yes, one opioid prescription	3 (100.0%)	44 (75.9%)	19 (70.4%)	5 (62.5%)	71 (74.0%)	
Yes, two or more opioid prescriptions	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	
Total MME prescribed at discharge						0.216[2]
Median (IQR)	75 (75, 160)	75 (23, 75)	50 (0, 90)	36 (0, 60)	60 (11, 75)	
Range	75, 160	0, 260	0, 150	0, 90	0, 260	
Total MME consumed after discharge [4]						0.442[2]
N	3	57	26	8	94	
Median (IQR)	38 (8, 136)	10 (0, 50)	0 (0, 45)	0 (0, 53)	8 (0, 50)	
Range	8, 136	0, 260	0, 113	0, 85	0, 260	
Received any prescription opioid pain medications after leaving the hospital (refills or new prescription) [5]	0 (0.0%)	8 (14.0%)	1 (4.0%)	1 (12.5%)	10 (10.8%)	0.593[1]
Used non-prescription pain medications after hospital dismissal [6]	2 (66.7%)	56 (98.2%)	19 (73.1%)	7 (87.5%)	84 (89.4%)	0.002[1]
How adequately did pain medication control pain after hospital dismissal? [4,7]						0.638[2]
Median (IQR)	8 (8, 10)	8 (7, 10)	9 (8, 10)	10 (9, 10)	9 (8, 10)	
Range	8, 10	1, 10	2, 10	5, 10	1, 10	

[1]Fisher Exact *p*-value; [2]Kruskal-Wallis p-value; [3]MME and maximum pain 24–48 h after PACU discharge are missing for N = 5 patients discharged before 24 h after PACU exit; [4]Prescription pain medications prior to surgery, total MME consumed after discharge, and pain control after hospital dismissal missing for N = 1; [5]Prescription opioid pain medications after leaving the hospital missing for N = 3; [6]Non-prescription pain medications after hospital dismissal missing for N = 2; [7]Pain control scale: 0 = not controlled at all, 10 = completely controlled.

CYP2D6 metabolizer groups. This pilot data adds to the mounting evidence that CYP2D6 metabolizer status is an important determinant when considering the choice and amount of opioid to prescribe. As was shown in previous studies, many patients do not consume the opioids prescribed to them, increasing the risk for diversion and misuse [4,19]. At the current time, without proven ways to personalize the amount of opioid prescribed, patients receive a standardized MME upon discharge, including in our cohort. Pgx information may help inform postoperative practices, reducing overall opioid prescribing, dependence, and diversion [20].

In the cytochrome *p*450 gene family, *CYP3A4* has few described genetic variants but *CYP2D6* is highly polymorphic and has over 130 core allelles and significant differences in allele frequencies between geographically, ancestry, and ethnically diverse groups [21–23]. The predicted CYP2D6 phenotypes for opioid metabolism are based on diplotypes and categorized into ultrarapid, normal, intermediate, and poor metabolizers based on their activity score [9]. (Table 1) Each CYP2D6 metabolizer category defines how quickly a drug will be metabolized or activated based on the predicted enzyme activity of its corresponding gene. Ingreater than 60,000 subjects across 173 reports worldwide, the

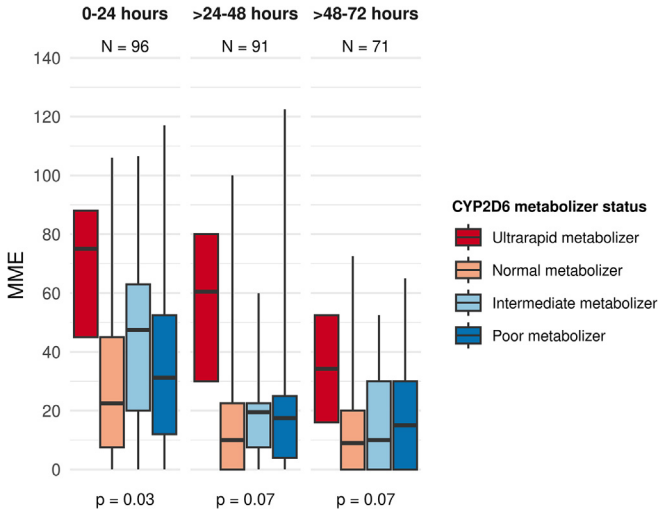

Fig. 1. Morphine milligram equivalents (MME) administered in the first 24-h period (0–24 h), second 24-h period (>24–48 h), and third 24-h period (>48–72) hours after exit from the PACU, compared by CYP2D6 metabolizer status. Only patients with post-PACU LOS ≥24 h are included in the second 24-h period, and only patients with post-PACU LOS ≥48 h are included in the third 24-h period.

distribution of metabolizer status included 1–21% ultrarapid, 67–90% normal, 0.4–11% intermediate, and 0.4–5.4% poor [24].

In the context of these phenotypes, not all opioids are affected similarly. For example, codeine requires activation by CYP2D6 to be efficacious, whereas oxycodone may be both activated and metabolized by the same gene in a complex pathway of simultaneous phase 1 and phase 2 metabolism [25]. In the case of codeine, ultrarapid metabolizers may be considered to be at an elevated risk for respiratory depression from standard doses due to their higher than typical ability to convert codeine to morphine. On the other hand, someone categorized as a poor or intermediate metabolizer may not have adequate pain relief from a standard dose of codeine. The examination of oxycodone is more complex, recognizing that this drug may be both metabolized and activated by CYP2D6 enzymes. A prior study demonstrated this complexity with similar responses and side effects in patients with ultrarapid and poor metabolizer statuses [26]. While level A evidence exists for codeine and tramadol prescribing guidelines based on CYP2D6 status, others such as oxycodone do not have recommended prescribing actions at present [27].

In addition to CYP3A4 and CYP2D6, OPRM1 and COMT have recently been discovered to participate in opioid processing. These additional genes function differently from the cytochrome *p*450 enzymes, with OPRM1 affecting opioid receptors and COMT encoding for neurotransmitter enzymes. These two genes require further validation before they will be clinically actionable, but their activity in opioid processing may provide further information in our quest for individualization [9].

While codeine and tramadol have clinical recommendations based on CYP2D6 phenotypes, recommendations have not been established for some of the most common opioids used in the postoperative setting, including oxycodone. This study combined with others in multiple fields could help support recommendations based on CYP2D6 phenotypes [11]. We know this works well in other disease types, as a large number of PGx variants with demonstrated clinical utility have been incorporated into drug labeling by the US Food and Drug Administration (FDA), including for nephrology, anticoagulation, and anticholesterol therapies [28].

In addition to guiding individualization of opioid prescribing, this data may help us optimize supplemental perioperative pain control strategies for selected patients. A randomized controlled trial of wound infiltration of liposomal bupivacaine with or without intrathecal analgesia in a similar patient population was recently completed at our organization and will inform the discussion of how best to manage immediate perioperative pain.

Strengths of this study include a population of patients who underwent surgery of similar complexity at one institution with well-established inpatient and outpatient opioid prescribing guidelines [4,13]. Information was collected prospectively, and physicians and patients were not informed of the metabolizer status until after surgical recovery. Weaknesses include the expected small number of patients in the ultra-rapid and poor metabolizer categories which may have limited the statistical power of our analyses. Type of opioid prescribed and order of prescription was not dictated, thereby introducing heterogeneity into the results. Finally, while all patients also used non-opioid pain medications, some patients may have taken less than others, which may have affected MME consumed.

As the availability of high throughput genomics technology becomes more widespread and the associated cost of genetic testing more economical, opportunities for patients to have precision genomic information to guide healthcare decisions is expected to increase, including choice and dose of medications [29,30].

Author contribution

GG and SD conceived the project idea and obtained IRB approval. KI and ML enrolled patients and completed patient surveys. GG, BM, KH, AM, and EH completed the chart review and survey information compilation, as well as conducted data analysis. GG wrote the manuscript. BM, AK, EH, KH, and SD all participated with edits of the manuscript and offered mentorship for completion of the project.

Funding

Center for Individualized Medicine, Mayo Clinic, Rochester, MN.

CRediT authorship contribution statement

Gretchen E. Glaser: Formal analysis, Data curation, Conceptualization, Writing – original draft. **Brandon Maddy:** Formal analysis, Data curation, Writing – review & editing. **Amanika Kumar:** Investigation, Writing – review & editing. **Karen Ishitani:** Investigation, Data curation. **Maureen A. Lemens:** Investigation, Data curation, Writing – review & editing. **Kristine Hanson:** Methodology, Formal analysis, Writing – review & editing. **Ann M. Moyer:** Formal analysis, Writing – review & editing. **Elizabeth Habermann:** Methodology, Investigation, Formal analysis, Conceptualization, Writing – review & editing. **Sean C. Dowdy:** Investigation, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.03.001.

References

[1] S. As-Sanie, S.R. Till, E.L. Mowers, et al., Opioid prescribing patterns, patient use, and postoperative pain after hysterectomy for benign indications, Obstet. Gynecol. 130 (2017) 1261–1268.
[2] L. Massicotte, K.D. Chalaoui, D. Beaulieu, J.D. Roy, F. Bissonnette, Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy, Acta Anaesthesiol. Scand. 53 (2009) 641–647.

[3] S.P. Bisch, C.A. Jago, E. Kalogera, et al., Outcomes of enhanced recovery after surgery (ERAS) in gynecologic oncology - a systematic review and meta-analysis, Gynecol. Oncol. 161 (2021) 46–55.
[4] G.E. Glaser, E. Kalogera, A. Kumar, et al., Outcomes and patient perspectives following implementation of tiered opioid prescription guidelines in gynecologic surgery, Gynecol. Oncol. 157 (2020) 476–481.
[5] R. Rocco, C.A. Thiels, D.S. Ubl, A.M. Moyer, E.B. Habermann, S.D. Cassivi, Use of pharmacogenetic data to guide individualized opioid prescribing after surgery, Surgery 166 (2019) 476–482.
[6] E.P. Sachtleben, K. Rooney, H. Haddad, et al., The role of pharmacogenomics in postoperative pain management, Methods Mol. Biol. 2547 (2022) 505–526.
[7] A.L. Dzierba, J.L. Stollings, J.W. Devlin, A pharmacogenetic precision medicine approach to analgesia and sedation optimization in critically ill adults, Pharmacotherapy 43 (11) (2023) 1154-116.
[8] M. Kane, Oxycodone therapy and CYP2D6 genotype, in: V.M. Pratt, S.A. Scott, M. Pirmohamed, B. Esquivel, B.L. Kattman, A.J. Malheiro (Eds.),Medical Genetics Summaries, 2012 , Bethesda (MD).
[9] K.R. Crews, A.A. Monte, R. Huddart, et al., Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy, Clin. Pharmacol. Ther. 110 (2021) 888–896.
[10] Y. Gasche, Y. Daali, M. Fathi, et al., Codeine intoxication associated with ultrarapid CYP2D6 metabolism, N. Engl. J. Med. 351 (2004) 2827–2831.
[11] D.M. Smith, K.W. Weitzel, A.R. Elsey, et al., CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial, Genet. Med. 21 (2019) 1842–1850.
[12] CYP2D6 Allele Definition Table and CYP2D6 Allele Functionality Table.
[13] E. Kalogera, J.N. Bakkum-Gamez, C.J. Jankowski, et al., Enhanced recovery in gynecologic surgery, Obstet. Gynecol. 122 (2013) 319–328.
[14] K.M. Elias, A.B. Stone, K. McGinigle, et al., The reporting on ERAS compliance, outcomes, and elements research (RECOvER) checklist: a joint statement by the ERAS ((R)) and ERAS((R)) USA societies, World J. Surg. 43 (2019) 1–8.
[15] G. Nelson, C. Fotopoulou, J. Taylor, et al., Enhanced recovery after surgery (ERAS(R)) society guidelines for gynecologic oncology: addressing implementation challenges – 2023 update, Gynecol. Oncol. 173 (2023) 58–67.
[16] C.M. Park, S.K. Inouye, E.R. Marcantonio, et al., Perioperative gabapentin use and in-hospital adverse clinical events among older adults after major surgery, JAMA Intern. Med. 182 (2022) 1117–1127.
[17] Y.S. Lin, A.L. Dowling, S.D. Quigley, et al., Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism, Mol. Pharmacol. 62 (2002) 162–172.
[18] J.K. Lamba, Y.S. Lin, K. Thummel, et al., Common allelic variants of cytochrome P4503A4 and their prevalence in different populations, Pharmacogenetics 12 (2002) 121–132.
[19] C.A. Thiels, D.S. Ubl, K.J. Yost, et al., Results of a prospective, multicenter initiative aimed at developing opioid-prescribing guidelines after surgery, Ann. Surg. 268 (2018) 457–468.
[20] J. Bates, J. Fudin, J.N. Patel, Integrating pharmacogenomics into precision pain management, Support. Care Cancer 30 (2022) 10453–10459.
[21] W.E. Evans, M.V. Relling, Pharmacogenomics: translating functional genomics into rational therapeutics, Science 286 (1999) 487–491.
[22] A.N. Werk, I. Cascorbi, Functional gene variants of CYP3A4, Clin. Pharmacol. Ther. 96 (2014) 340–348.
[23] B.W. Aruldhas, S.K. Quinney, S. Packiasabapathy, et al., Effects of oxycodone pharmacogenetics on postoperative analgesia and related clinical outcomes in children: a pilot prospective study, Pharmacogenomics 24 (2023) 187–197.
[24] A. Gaedigk, K. Sangkuhl, M. Whirl-Carrillo, T. Klein, J.S. Leeder, Prediction of CYP2D6 phenotype from genotype across world populations, Genet. Med. 19 (2017) 69–76.
[25] R. Huddart, M. Clarke, R.B. Altman, T.E. Klein, PharmGKB summary: oxycodone pathway, pharmacokinetics, Pharmacogenet. Genomics 28 (2018) 230–237.
[26] S. Merchant, C.A. Prows, F. Yang, et al., Association of CYP2D6 genotype predicted phenotypes with oxycodone requirements and side effects in children undergoing surgery, Ann. Transl. Med. 10 (2022) 1262.
[27] A.K. Wong, A.A. Somogyi, J. Rubio, J. Philip, The role of pharmacogenomics in opioid prescribing, Curr. Treat. Options Oncol. 23 (2022) 1353–1369.
[28] (FDA) USFaDA, Table of Pharmacogenomic Biomarkers in Drug Labeling, 2023.
[29] S.A. Morris, A.T. Alsaidi, A. Verbyla, et al., Cost effectiveness of pharmacogenetic testing for drugs with clinical pharmacogenetics implementation consortium (CPIC) guidelines: a systematic review, Clin. Pharmacol. Ther. 112 (2022) 1318–1328.
[30] K.B. Johnson, W.Q. Wei, D. Weeraratne, et al., Precision medicine, AI, and the future of personalized health care, Clin. Transl. Sci. 14 (2021) 86–93.