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RESEARCH

Evaluation of the impact of *CYP2D6* testing on outcomes in patients taking opioids

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ABSTRACT

Background: *CYP2D6* affects metabolism of several opioids; however, the clinical impact of genetic variants on efficacy has limited evidence in large patient populations.
Objective: This study aims to assess the impact of CYP2D6 phenotype on pain response in an elective pharmacogenomics (PGx) screening population prescribed opioids.
Methods: A retrospective review was conducted on hospitalized patients with *CYP2D6* genotyping, prescribed either codeine, tramadol, hydrocodone, or oxycodone within 24 months prior to PGx testing and through 36 months after results. Pain scores were abstracted on a 10-point analog scale and categorized into 3 cohorts (mild, moderate, and severe) based on their baseline pain score. Baseline pain score was measured within 30 min of each opioid dose administration. Percentage changes in pain scores from baseline to 6, 12, 24, and 48 hours following each respective opioid dose administration were analyzed. Morphine milligram equivalents (MME) were averaged amongst the days of opioid administration.
Results: A total of 8062 patients were analyzed. Oxycodone was the most administered (4856, 41%). Mild pain cohort poor metabolizers (PMs) had significant increase in pain scores compared to normal metabolizers (NMs) at all hours from baseline ($P < 0.001$). PMs in moderate and severe pain cohorts had significantly decreased pain score reduction than NMs at all hours from baseline ($P < 0.001$). PMs had significantly higher MME compared to NMs in these cohorts (15 vs. 10, $P < 0.001$).
Conclusion: CYP2D6 PMs had significantly less pain score reduction. CYP2D6 genotyping can lead to effective use of opioids in pain management and may display greater impact on efficacy of oxycodone than previously studied. Full implication of PGx testing is limited by the study's retrospective nature. PMs across all pain intensity cohorts had significantly less reduction in pain scores from baseline compared to NMs ($P < 0.05$). These results encourage further investigation into prospective pre-emptive *CYP2D6* testing regarding effective pain management by optimizing opioid administration.

Background

Acute and chronic pain is a widespread crisis in the United States affecting over 50 million adults.[1] Managing a condition that can be so debilitating requires a multimodal approach, usually with the involvement of opioids.[2] However, successfully managing both acute and chronic pain remains challenging. According to the CDC, 8.1% of emergency department (ED) visits from 2019 to 2020 led to opioid prescriptions upon discharge.[3] Despite treatment, nearly 7% of U.S. adults still suffer from uncontrolled high-impact chronic pain, which is severely restricting individuals from their daily activities.[2]

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Key Points

Background:

- *CYP2D6* is a polymorphic gene that encodes the enzyme, CYP2D6, responsible for the metabolism of commonly used opioids: tramadol, codeine, hydrocodone, and oxycodone.
- For CYP2D6 poor metabolizers, Clinical Pharmacogenetics Implementation Consortium guidelines provide strong recommendations to avoid tramadol and codeine usage and an optional recommendation to use an alternative opioid for hydrocodone if no response. Variants in *CYP2D6* did not show clinical significance for the efficacy of oxycodone when evaluated for this guideline.
- Oxycodone is metabolized by CYP2D6 but has less evidence for correlation to a clinical impact on efficacy to provide guideline dosing recommendations.

Findings:

- CYP2D6 poor metabolizers (PMs) experienced statistically significant less reduction in pain scores compared to normal metabolizers (NMs) after opioid administration.
- CYP2D6 PMs despite larger average morphine milligram equivalents consumption did not have similar pain reductions as NMs.
- Results from this study suggest CYP2D6 genotyping has clinical utility in opioid prescribing for pain management for both acute and chronic pain patients.

Suboptimal pain control can lead to greater risk of morbidity and mortality.[4] Although clinicians are considering the risks of medication adverse effects and opioid overprescribing, effective pain management should not suffer as a result.

Pharmacogenomics (PGx) is the study of genetic variants and the impact on medication metabolism. *CYP2D6* is a polymorphic gene that encodes the enzyme, CYP2D6, responsible for the metabolism of commonly used opioids. Most notably, codeine and tramadol are metabolized from relatively inactive compounds to more active metabolites, morphine and O-desmethyltramadol, respectively. Given the polymorphic nature of *CYP2D6*, no function, loss of function, gene deletion, and gene duplication are possible resulting in a range of phenotypes from poor to ultra-rapid metabolizer (UM). The U.S. Food and Drug Administration and Clinical Pharmacogenetics Implementation Consortium (CPIC) provide recommendations to avoid both codeine and tramadol in CYP2D6 poor metabolizers (PMs) due to the possibility of diminished analgesia.[5-7] A similar effect is seen with hydrocodone and oxycodone, though the parent drugs and metabolites are both pharmacologically active, and evidence suggests the relative impact of CYP2D6 is less pronounced for hydrocodone and oxycodone.[8] CPIC guidelines endorse monitoring for hydrocodone efficacy with the potential need to switch to a noncodeine opioid; however, oxycodone yields no recommendation due to the lack of evidence PGx impacts analgesic response or risk of adverse effects.[7] However, a recent study by Nahid *et al.* suggests that *CYP2D6* may have a greater clinical impact on hydrocodone and oxycodone pain response than previously thought.[9] The clinical impact of CYP2D6 phenotype on opioid efficacy and the means by which PGx testing can guide pain management are not yet fully understood for hydrocodone and oxycodone. Therefore, a retrospective analysis was conducted to identify efficacy (reduction in pain scores) of codeine, tramadol, hydrocodone, or oxycodone amongst patients with CYP2D6 genotyping.

Objective

The primary objective was to evaluate the change in pain scores, as a surrogate for pain control, following each respective opioid dose administration during a hospital admission between CYP2D6 phenotypes. The secondary objective was to evaluate differences in the average morphine milliequivalents (MME) between the CYP2D6 phenotypes. This protocol was approved by Sanford Health's Institutional Review Board (STUDY00003625).

Methods

This was a retrospective, single cohort study conducted at a single health system located in the Upper Midwest of the United States. Data were collected by automated data abstraction for all hospitalized patients within the electronic health record (EHR) with *CYP2D6* results, who were prescribed either codeine, tramadol, hydrocodone, or oxycodone. Opioids were included based on having CPIC recommendations and/or the frequency of usage. Opioids prescribed for acute or chronic pain within 24 months prior to testing and through 36 months after results of *CYP2D6* testing were eligible for inclusion. Pain scores were collected from inpatient hospital encounters, excluding scores recorded in ambulatory and outpatient care settings. Data elements were abstracted from the EHR from January 2017 to December 2023, whereby all data was reliably populated and standardized.

PGx assay

PGx testing has been offered through an in-house laboratory since 2014 as a single gene or panel-based test; the panel originally included four genes but has evolved over time to 14 genes.[10] PGx testing methodology was based on single nucleotide polymorphism genotyping [Standard BioTools Inc, South San Francisco, CA]. *CYP2D6* allele coverage has included *2, *3, *4, *5 (gene deletion), *6, *9, *10, and *41 in all iterations of the CYP2D6 assays; CYP2D6 alleles *17, *29 were added in subsequent years.[11] The list of alleles was derived from CPIC guidelines, allele tier recommendations from the Association for Molecular Pathology, and definitive level of evidence of alterations in enzyme function. Copy number variance was tested to assess duplications; however, the specific allele duplicated was not distinguishable. Patients with a range of CYP2D6 phenotypes due to duplication were excluded; however, this impacted <1% of patients. Categorization of phenotypes from diplotypes was derived from CPIC

guidelines. PGx testing results are stored as discrete values within the laboratory results section of a secure EHR platform.

Medication data

The administration of the four opioids of interest – codeine, tramadol, hydrocodone, or oxycodone – were abstracted from inpatient encounters from the medication administration record (MAR). Opioid naïve and patients on previous opioid therapies were included. Patients that did receive opioids but not any of the four of interest were excluded from this study. Codeine, tramadol, hydrocodone, and oxycodone orders were abstracted from each patient encounter. Dosing for range orders (i.e., oxycodone 5–10 mg every 4 hours prn) were more difficult to obtain and required a cross check with the MAR. If unable to determine the dose administered from a dose range, the lower dose was assumed to be given. Concurrently administered CYP2D6 strong inhibitors were similarly collected to account for phenoconversion of CYP2D6 phenotype.

Phenoconversion

Phenoconversion occurs when a drug causes inhibition or induction of a metabolizing enzyme such that it changes the expected phenotype.[12,13] Strong concurrent CYP2D6 inhibitors (i.e. paroxetine, bupropion, fluoxetine) were taken into consideration when assessing a patient's CYP2D6 phenotype. Other strong CYP2D6 inhibitors such as quinidine and terbinafine were not represented in the phenoconversion analysis due to a very low frequency in our population. A patient's clinical phenotype was considered to be a CYP2D6 PM while concurrently on one of these agents. For the purpose of this analysis, we defined a phenoconverting medication to be concurrent if ordered within the previous 60 days of one of the four opioids of interest being ordered. Moderate CYP2D6 inhibitors that may change a patient's phenotype to a CYP2D6 intermediate metabolizer (IM) were not included in the analysis. Sensitivity analyses were not conducted to validate enzyme activity. However, previous literature suggests CYP2D6 activity scores should be converted to zero in the presence of strong inhibitors which correlates to a PM.[12,13] Analysis was conducted after phenoconversion was accounted for.

MME data

MME conversion calculations were based on the Center for Disease Control and Prevention's 2022 guidelines.[14] After dose normalization across opioid types, total administration was normalized by dividing the total sum of MME from all sources of the four opioids of interest by the number of days between when the patient started and stopped taking opioids in a given encounter. An opioid was considered administered on documentation of administration on the MAR. Time increments between the first and last dose were rounded up to one as to not bias patients given a single administration of oral agents as compared to iteratively administered doses intravenously. The distribution of MME was skewed right; therefore, Wilcoxon signed-rank tests were used to evaluate initial median differences in MME between CYP2D6 phenotypes.

Pain data

Pain severity was determined by abstracting pain scores on a 10-point analog scale. Pain scores were categorized into mild (scores 1–3), moderate (scores 4–6), and severe (scores 7–10) consistent with existing literature.[15] Baseline pain severity was determined by the pain score within 30 minutes with every new opioid dose. The percentage changes in pain scores were calculated for every new dose from pain scores at baseline and duration of time from baseline and then compared to normal metabolizers (NMs). Evaluation was accomplished through *t*-tests, analyzing the pain score preopioid and postopioid administration in each of the CYP2D6 metabolizer statuses. The average pain scores were compiled into different time groups: 6, 12, 24, and 48 hours post opioid administration and were compared to baseline pain scores. The percentage change in pain scores were analyzed between each time interval and compared between CYP2D6 phenotypes. NM was considered the reference group.

Multivariate analysis

Potential covariates were considered as relevant in multivariate modeling including patient age, sex, the opioid of interest, and the total daily MME, and whether the patient was on a concurrent benzodiazepine regardless of drug. To determine if a benzodiazepine was concurrently ordered with an opioid, the same criteria were utilized as with concurrent strong CYP2D6 inhibitors. That is, if a benzodiazepine was ordered within 60 days of an opioid order, it was considered concurrent. Type and dose of benzodiazepine were not separately analyzed. These variables were chosen based on theoretical relevance, understanding that certain contextual variables such as comorbidities or indications may play a part, but would be difficult to standardize given the complexities of pain management in an inpatient setting. Beyond theoretical relevance, initial evidence of statistical association with pain percentage difference from baseline was also specified as part of the criterion using Spearmen correlation tests for numeric variables and analysis of variance tests for categorical variables. Pain percentage difference 24 hours from medication administration was selected as a proxy for pain change for covariate inclusion and was used as justification for modeling the outcomes of both pain percentage difference as well as MME.

There were two repeated measure effects in the data that needed to be adjusted for. First, patients could have had multiple encounters whereby we used the unique patient identifier as a random effect. Second, patients could have multiple doses administered in a given encounter whereby we used the unique encounter level identifier as a random effect. Using identified and tested covariates, whilst adjusting for the two repeated measures, mixed-effects linear regression was used to isolate the independent effect of CYP2D6 phenotype on the dependent variables of pain percentage difference from baseline. A similar method was used for modeling MME differences, whereby the unique patient identifier was treated as a random effect; however, there was no need to treat the unique encounter level identifier as MME was aggregated at the encounter level.

Table 1
Baseline characteristics

Characteristic	Statistic
IQR	
Age	58 (44–68)
MME	7.5 (5–10)
N (%)	
Patients	8062
CYP2D6 metabolizer phenotype	
Poor	564 (7)
Intermediate	3153 (39)
Normal	4187 (52)
Ultra-rapid	158 (2)
On phenoconverting drug	1337 (17)
CYP2D6 metabolizer phenotype - phenoconverted	
Poor	1795 (22)
Intermediate	2646 (33)
Normal	3493 (43)
Ultra-rapid	128 (2)
Sex	
Female	5305 (66)
Male	2757 (34)
Drug type	
Codeine	135 (1)
Hydrocodone	4222 (36)
Oxycodone	4856 (41)
Tramadol	2523 (21)
On concurrent benzodiazepine	3114 (39)
Pain baseline group - all doses	
1–3	11,769 (17)
4–6	32,331 (46)
7–10	26,518 (38)

Abbreviation used: IQR, interquartile range.

Results

There were 8062 distinct patients totaling 14,989 inpatient encounters, which resulted in 70,618 doses administered of the four opioids of interest included in final analysis. The majority of patients were female with the average age of 58 years (Table 1). For baseline pain scores, 16.66% had mild pain, 45.78% had moderate pain, and 37.56% had severe pain. The average number of encounters per patient was 1.86 and the average number of opioid orders was 8.76. Tramadol, hydrocodone, and oxycodone were commonly administered medications accounting for 21%, 41%, and 36%, respectively. Codeine was infrequently administered (1% of orders). Nearly 40% of patients were concomitantly prescribed a benzodiazepine. CYP2D6 phenotypes at baseline were as follows: 7% were PMs (n = 564), 39% IMs (n = 3153), 52% NMs (n = 4187), and 2% UMs (n = 158). Approximately 17% of patients were on a strong CYP2D6 inhibitor, therefore increasing the percentage of PMs to 22% when accounting for phenoconversion (Table 1). All analyses for pain scores and MME incorporated phenoconversion.

Pain scores

PMs across all pain intensity cohorts had significantly less pain improvement from baseline compared to NMs ($P < 0.05$) (Table 2). In the mild pain cohort, PMs had an increase in pain scores, compared to NMs 6 hours (3.9% vs. −6.8%), 12 hours (12.2% vs. −1.7%), 24 hours (15.1% vs. 0.6%), and 48 hours from baseline (15.2% vs. 0.4%) (all $P < 0.05$). In the moderate pain cohort, PMs had less pain reduction than NMs 6 hours (−15.6% vs. −20.9%), 12 hours (−11.9% vs. −17.3%), 24 hours (−13.7% vs. −20.1%), and 48 hours from baseline (−15.6% vs. −22.8%) (all $P < 0.001$). In the severe pain cohort, PMs had less pain reduction than NMs 6 hours (−23.1% vs. −25.2%), 12 hours (−22.4% vs. −25.5%), 24 hours (−24.9% vs. −27.6%), and 48 hours from baseline (−26.9% vs. −30.4%) (all $P < 0.001$) (Figure 1).

Relevant potential covariates were analyzed for statistical associations with pain percentage difference from baseline. There was a small negative association ($r = -0.09$, $P < 0.001$) between age and the percentage change in pain scores. The MME of each specific opioid order also had a small correlation with percentage change in pain scores ($r = 0.05$, $P < 0.001$). Males had significantly greater reduction in pain scores than females, −21.4% compared to −15.5%, respectively ($P < 0.001$). Those on a concurrent benzodiazepine had significantly less pain improvement than those who did not (−18.0% vs. −19.8%, respectively, $P < 0.001$). The type of opioid proved to be significantly associated with pain percentage change ($P < 0.001$). When examining specific drug effects on pain percentage change, codeine had the highest pain percentage reduction (−23.7 ± 40.0), followed by hydrocodone (−20.8 ± 37.1), oxycodone (−18.8 ± 34.3), and tramadol (−16.7 ± 42.9). As such, other demographics were included as covariates in the mixed effects linear regression models (Supplemental Table 1).

Twelve separate multivariate mixed-effects models were fit on pain percentage difference from baseline for each unique combination of levels of aggregation (baseline pain severity and time from baseline). Given that PMs were the only phenotype that showed reliable and consistent difference from NMs, the data were limited to only those levels. Limiting the data to only NMs and PMs simplified the issue of multiple comparisons. In the mild pain cohort, the independent effect of PM status was significantly associated with pain percentage change 6, 12, and 24 hours from baseline ($P < 0.001$), but only marginally at 48 hours from baseline ($P = 0.05$) (Supplemental Table 1). In the moderate pain cohort, the independent effect of PM status was significantly associated with pain percentage change 6, 12, 24, and 48 hours from baseline ($P < 0.001$) (Supplemental Table 1). In the severe pain baseline cohort, the independent effect of PM status was significantly associated with pain percentage change 6, 12, 24, and 48 hours from baseline ($P < 0.01$) (Supplemental Table 1). The effects of each contextual covariate across all models suggest very minor influence. Within all model results, the trend of age suggested that older patients had more pain reduction (mean $P = 0.081$). Males tended to have less pain reduction compared to females (mean $P = 0.111$).

MME

All MME comparisons can be observed in Table 3. In the mild pain cohort, there were no significant differences in MME ($P > 0.05$). In the moderate pain cohort, the only metabolizer status that differed from NMs (MME = 13.6) was PMs (MME = 15) ($P < 0.001$). In the severe pain cohort, PMs (MME = 17.5) and IMs (MME = 15) significantly differed from NMs (MME = 12.5) ($P < 0.0001$) (Figure 2).

Table 2
Pairwise CYP2D6 metabolizer status and pain percentage reduction

Time from opioid administration	NM control		CYP2D6 comparator			Pain score difference (NM − Comparator)	*P*
	n	Percent difference pain score from baseline	Metabolizer	n	Percent difference pain score from baseline		
Mild baseline pain (1–3)							
6 h	4045	−6.8	Poor	1888	3.9	−10.8 (−13.6, −7.9)	<0.001 ***
			Intermediate	3058	−5.1	−1.8 (−4.2, 0.7)	0.33
			Ultra-rapid	168	−11.4	4.6 (−3.8, 12.9)	0.33
12 h	3046	−1.7	Poor	1440	12.2	−13.9 (−17.4, −10.5)	<0.001 ***
			Intermediate	2251	0.9	−2.6 (−5.6, 0.4)	0.18
			Ultra-rapid	137	−7.6	5.8 (−4.9, 16.6)	0.29
24 h	2777	0.6	Poor	1302	15.1	−14.5 (−18.1, −10.9)	<0.001 ***
			Intermediate	2019	3.3	−2.7 (−5.9, 0.4)	0.18
			Ultra-rapid	126	−4.7	5.3 (−4.1, 14.6)	0.27
48 h	1999	0.4	Poor	956	15.2	−14.8 (−19, −10.7)	<0.001 ***
			Intermediate	1476	1.5	−1.2 (−4.8, 2.4)	0.52
			Ultra-rapid	94	−12.5	12.8 (2.7, 22.9)	<0.05 *
Moderate baseline pain (4–6)							
6 h	11,766	−20.9	Poor	6936	−15.6	−5.2 (−6.3, −4.2)	<0.001 ***
			Intermediate	8809	−20.0	−0.9 (−1.9, 0.1)	0.13
			Ultra-rapid	485	−21.9	1 (−2.1, 4.1)	0.53
12 h	9638	−17.3	Poor	6015	−11.9	−5.4 (−6.7, −4.2)	<0.001 ***
			Intermediate	7188	−17.0	−0.3 (−1.5, 0.8)	0.6
			Ultra-rapid	425	−19.7	2.3 (−1, 5.6)	0.33
24 h	9209	−20.1	Poor	5674	−13.7	−6.4 (−7.6, −5.2)	<0.001 ***
			Intermediate	6814	−19.5	−0.6 (−1.7, 0.5)	0.6
			Ultra-rapid	401	−19.0	−1.1 (−4.4, 2.2)	0.6
48 h	7122	−22.8	Poor	4307	−15.6	−7.3 (−8.6, −6)	<0.001 ***
			Intermediate	5233	−22.5	−0.4 (−1.7, 0.9)	1
			Ultra-rapid	307	−23.9	1 (−2.7, 4.7)	1
Severe baseline pain (7–10)							
6 h	8908	−25.2	Poor	6623	−23.1	−2.1 (−2.9, −1.3)	<0.001 ***
			Intermediate	7442	−24.7	−0.5 (−1.3, 0.3)	0.29
			Ultra-rapid	296	−27.5	2.3 (−0.8, 5.5)	0.29
12 h	8052	−25.5	Poor	6145	−22.4	−3.1 (−3.9, −2.2)	<0.001 ***
			Intermediate	6768	−24.5	−1 (−1.8, −0.1)	0.06
			Ultra-rapid	265	−27.6	2.1 (−1.4, 5.7)	0.23
24 h	7865	−27.6	Poor	6024	−24.9	−2.7 (−3.5, −1.8)	<0.001 ***
			Intermediate	6633	−27.7	0.2 (−0.7, 1)	0.7
			Ultra-rapid	260	−30.8	3.2 (0, 6.4)	0.11
48 h	6612	−30.4	Poor	5057	−26.9	−3.5 (−4.4, −2.6)	<0.001 ***
			Intermediate	5537	−30.3	−0.1 (−1.1, 0.8)	1
			Ultra-rapid	202	−30.6	0.2 (−3.1, 3.5)	1

Abbreviation used: NM, normal metabolizer.
Note: Difference in reduction of pain scores compared between CYP2D6 metabolizer status and NMs as the reference. Data are presented as mean difference in pain reduction and range.
NMs as reference group.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Three separate mixed effects models were fit for each pain baseline cohort whereby MME was regressed on relevant covariates and CYP2D6 phenotype and patient identifier as a random effect. A log transformation was applied to MME to account for its right-skewed distribution. In the mild pain cohort, CYP2D6 phenotype did not associate with MME ($P = 0.9$). In the moderate and severe pain cohorts, PMs had significantly higher MME as compared to NMs ($\beta = 0.11$ [0.06, 0.15], $\beta = 0.2$ [0.13, 0.28], $P < 0.001$) (Supplemental Table 2).

Discussion

Our results show CYP2D6 PMs had a lower percentage of pain score reduction in all three cohorts (mild, moderate, and severe baseline pain) compared to NMs for patients receiving codeine, tramadol, hydrocodone, and/or oxycodone. Many covariates were taken into consideration including age, sex, drug type, and concurrent benzodiazepine usage. There is a potential that these results may be impacted by the type of opioid administered as there is a difference in potency among the opioids. However, multivariate analysis identified CYP2D6 phenotype as the only covariable accountable for these significant differences, minimizing these concerns. Besides *CYP2D6* genotype, an important consideration for what may impact patients' pain scores over time is the quantity of opioids a patient receives. MME consumption was similar amongst all phenotypes in the mild pain cohort. However, unlike the other cohorts, PMs in the mild pain cohort had a significant increase in their pain scores over time compared to NMs. The moderate and severe pain cohorts overall did see a decrease in pain scores after opioid administrations, with PMs seeing less reduction

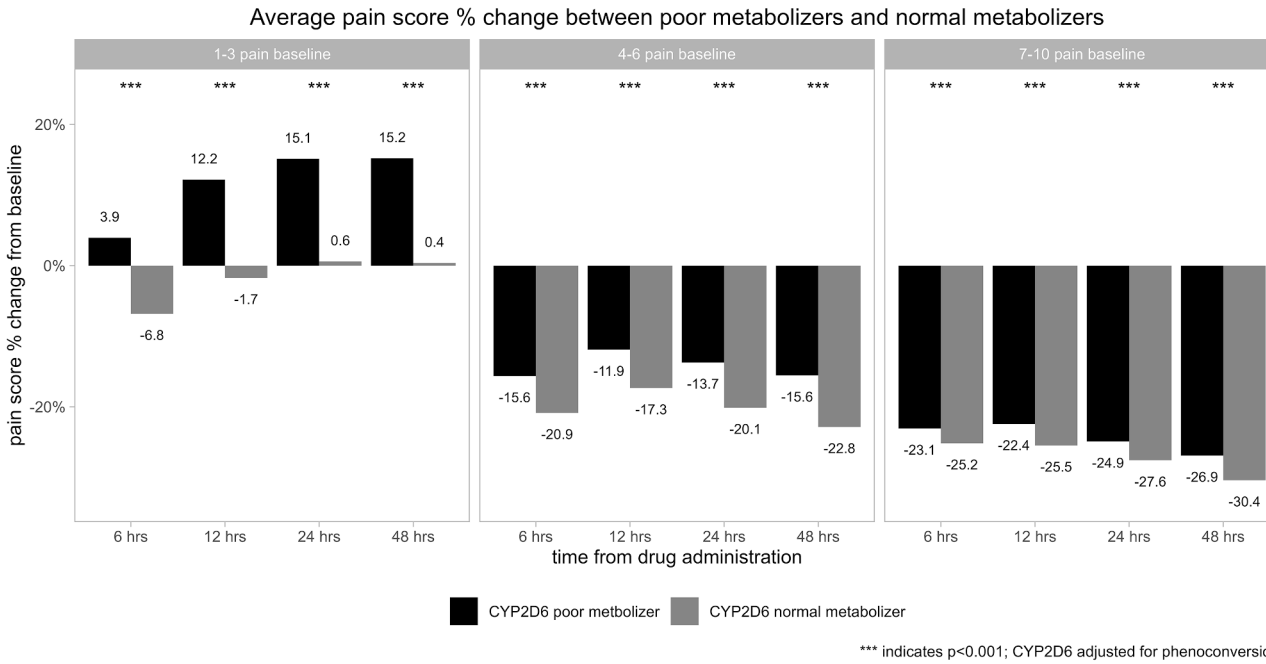

Figure 1. Average pain score percentage change between poor metabolizers and normal metabolizers. Comparison of percentage changes in pain scores between CYP2D6 poor and normal metabolizers from baseline pain scores to multiple time points post per opioid order. Patients are subcategorized based on their baseline pain severity.

than NMs. The changes in pain scores within the moderate and severe pain cohorts between PMs and NMs may be seen as less clinically significant with differences being <30%. However, PMs were administered significantly more MME on average than NMs, which supports the assertion that decreased CYP2D6 metabolism leads to decreased opioid efficacy. Within the severe pain cohort, NMs saw more pain score reduction compared to PMs and this difference grew over time. At 6 h, the difference in pain score reduction was 2.1 and had grown to 3.5 at 48 h. This growth in difference over time may highlight a trend for patients with decreased CYP2D6 metabolism have decreased pain management from these opioids.

Decreased pain score reductions in CYP2D6 PMs point to the possibility of decreased pain control as compared to NMs. CPIC guidelines currently only give strong recommendations to avoid tramadol and codeine use in PMs for they may not receive any analgesic effect and should use an alternative if opioid therapy is warranted.[7] Current evidence is weaker for hydrocodone and CPIC guidelines recommend to start with standard dosing, and if no response, use an alternative.[7] Per CPIC guidelines, oxycodone has "insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time."[7] In our study, hydrocodone and oxycodone represented three-fourths of all opioid administrations, thus the effect demonstrated in the study was most

Table 3
Pairwise Wilcoxon testing of morphine milligram equivalents and CYP2D6 metabolizer status

CYP2D6 metabolizer status	NM median MME/Day	CYP2D6 treatment median MME/Day	Diff	*P*
Mild baseline pain (1–3)				
Poor	7.50 (n = 670)	7.50 (n = 214)	0 (0, 0)	1
Intermediate		10.00 (n = 487)	0 (0, 0)	0.92
Ultra-rapid		10.00 (n = 34)	0 (−2.5, 2.5)	1
Moderate baseline pain (4–6)				
Poor	13.625 (n = 4192)	15.00 (n = 1895)	0 (0, 2.5)	<0.001 ***
Intermediate		11.25 (n = 3202)	0 (0, 0)	0.58
Ultra-rapid		15.00 (n = 169)	0 (0, 2.5)	0.58
Severe baseline pain (7–10)				
Poor	12.5 (n = 1606)	17.50 (n = 970)	2.5 (1.5, 2.5)	<0.001 ***
Intermediate		15.00 (n = 1280)	0 (0, 0)	0.22
Ultra-rapid		10.00 (n = 58)	0 (−2.5, 2.5)	0.86

Abbreviations used: MME, morphine milligram equivalents; NM, normal metabolizer.
Note: Difference in average daily MME administered between CYP2D6 metabolizer status and NMs as the reference. Data are presented as median MME and range.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

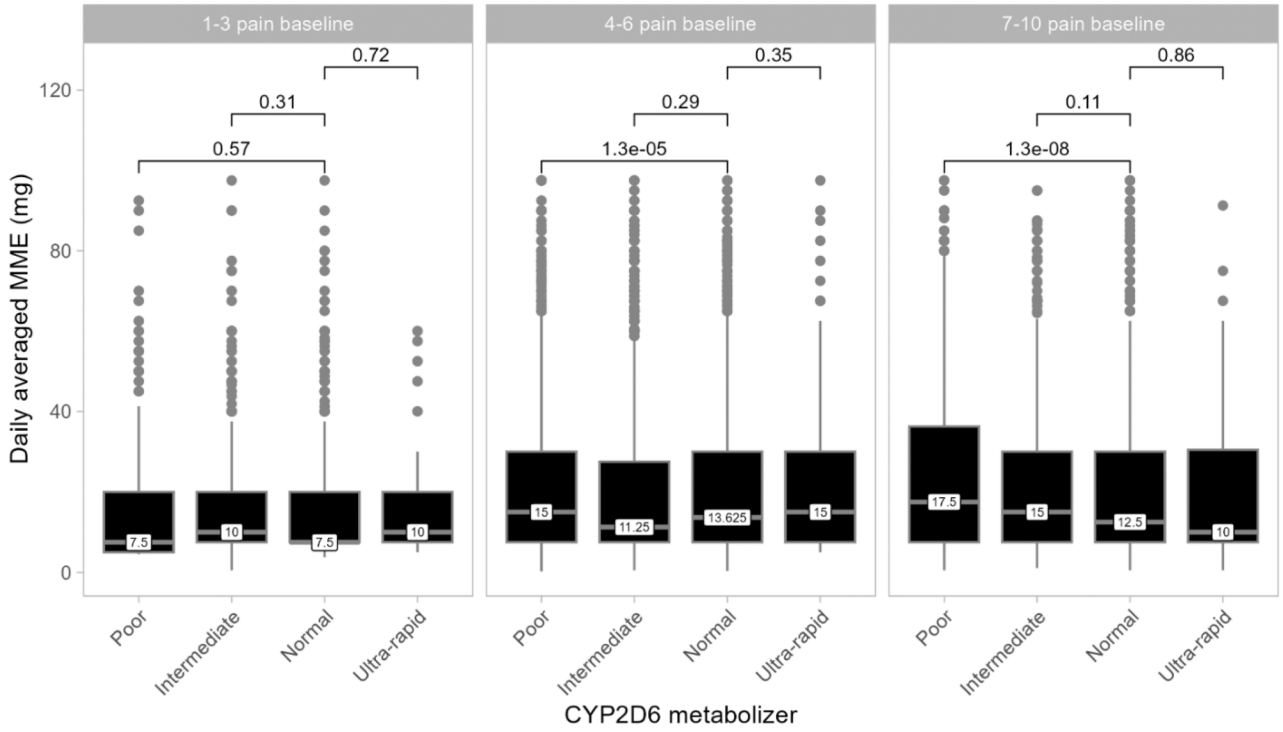

Figure 2. Daily average morphine milligram equivalents (MME) stratified across CYP2D6 metabolizer and pain severity. Comparison of daily average MME administered based on CYP2D6 phenotype and baseline pain severity cohort. CYP2D6 normal metabolizers are the reference for statistical difference. Phenoconversion was incorporated into the CYP2D6 metabolizer status.

attributable to these opioids, which have less published evidence compared to codeine and tramadol. Our study suggests that *CYP2D6* may play a larger role in optimizing pain management with oxycodone and hydrocodone than previously realized.[7]

There have been previous conflicting conclusions on the impact of CYP2D6 interacting medication on opioids. One prospective observational trial by Johnson and colleagues evaluated ED patients with either pain or nausea and found significantly higher visual analogue scale pain scores for hydrocodone in individuals taking a CYP2D6 major inhibitor. The same effect was not observed for oxycodone.[16] There were notable limitations as only 125 patients received oxycodone, 3 were determined PMs at baseline, and 30 out of the total of 502 patients were determined to have taken at least one CYP2D6 inhibitor within 48 hours of the ED visit.[16] Nevertheless, the study found that the efficacy of hydrocodone, but not oxycodone, was impacted by decreasing CYP2D6 function. Our findings regarding oxycodone and hydrocodone more closely align with a study by Nahid *et al.*, which was a large retrospective cohort study of the impact on CYP2D6 metabolism and strong inhibitors on opioids.[9] Patients taking a CYP2D6 inhibiting antidepressant concurrent with either codeine, tramadol, or hydrocodone were shown to display almost double the crude rate of pain-related ED visits.[9] Importantly, the study also found that patients on oxycodone with phenoconversion showed a 1.75-fold increase in pain-related ED visits compared to concurrent use with other antidepressants which did not inhibit CYP2D6; therefore, not leading to phenoconversion.[9] There is an assumption that inadequate pain relief was experienced from discharge opioid orders that led to revisits for similar pain related disease states. This study along with our data points to a pattern of inadequate pain management in patients prescribed codeine, tramadol, hydrocodone, and oxycodone along with a concurrent strong CYP2D6 inhibitor.

Our study included a variety of patients based on their indication for opioid use. Included were patients prescribed opioids for short term indications such as trauma or post-surgery. The study also included those continuing their home opioid regimens for chronic pain conditions or cancer pain. The relative heterogeneous indications may explain how our study was able to show statistically significant results compared to a previous study that explicitly looked at only one patient population. One such study found no significant difference between CYP2D6-guided opioid dosing for patients suffering with cancer pain.[17] The variety of indications for opioid therapy and large study may have been able to draw out the impact of CYP2D6 metabolism on pain scores that cannot be seen in smaller single indication populations. Further research is warranted to see if these are clinically impactful on patients of either acute or chronic conditions requiring opioid treatment.

Our study results align with the CPIC codeine and tramadol recommendations with PMs compared to NMs. PMs, having greatly reduced CYP2D6 metabolism, are expected to have 96% lower plasma concentrations of morphine with codeine administration in comparison to NMs and IMs.[18] With this decrease in the active metabolite, diminished analgesic effect is expected and CPIC guidelines and the FDA Table of

Pharmacogenetic Associations, both take the position that codeine should have reduced efficacy.[7,19] This may not be as clinically meaningful as it was the least prescribed but still had a large effect with the highest overall pain percentage reduction (−23.7/−40). Although the evidence is strong specifically for codeine and tramadol in the guidelines, trends of CYP2D6 metabolism impacting pain score reduction were still seen overall in this study despite majority of the population receiving hydrocodone and oxycodone. This indicates that the relationship between hydrocodone and oxycodone and *CYP2D6* may play a larger role than previously shown and despite currently lacking a defined CPIC guideline dosing recommendation.

The growth in pain score reduction difference over time may highlight a trend for patients requiring chronic pain management may benefit from alternative analgesic therapy if having decreased CYP2D6 metabolism. Other avenues for pain management in these patients may have to be explored such as maximizing other analgesics including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). For these individuals that despite a higher MME with codeine, tramadol, hydrocodone, and oxycodone and do not have the same reduction in pain scores, more potent opioids may be of consideration.

Limitations

Given the retrospective design and a real-world clinical population, there were inherent limitations to this study. Incomplete or missing data was no exception to our study. The documentation of pain scores was sparse in the outpatient setting; therefore, we limited data to inpatients where pain scores were more reliably captured. Within the inpatient data, the following pain scores post opioid administration were missing: 13% at 6 hours, 26% at 12 hours, 29% at 24 hours, and 44% at 48 hours. No data imputation was done to statistically account for missing data. Other comorbidities and indications were not analyzed as this would be difficult to standardize given the indication for use of opioids in our patient population was not limited. These variables may impact underlying causes of pain and have a role in an individual's response to opioid administration.

A second limitation is that there were several factors for pain response that this study could not account for. Patients received other analgesics (e.g., acetaminophen and NSAIDs) including other opioids (e.g., fentanyl and hydromorphone) that we did not account for within the MME analysis during their hospitalization. Regardless, it did not distort the trends that were seen in CYP2D6 phenotypes, pain scores, and MME. This provides more applicability to real life situations where patients would receive alternative analgesics for optimal pain management. Other genetic factors outside CYP2D6 metabolism were not available for most of the participants in this study. For instance, the catechol-O-methyltransferase (COMT) is an enzyme that some sources suggest may impact efficacy of opioids. However, a guideline review of previous studies did not find an association between COMT and MME.[20] In addition, *CYP3A4* results were not available for majority of the participants. CYP3A4 has a role in metabolism of some opioids such as hydrocodone and oxycodone. However, the impact of genetic variants in this gene on clinical outcomes is poorly understood at this time leading to lack of guidelines for dosing recommendations.

Third, not all phenotypes were accounted for within this analysis. Patients with an indeterminate CYP2D6 phenotype were excluded. Due to the small percentage of UMs, evidence from this study is not strong enough to draw conclusions regarding pain outcomes in comparison to NMs. In addition, moderate CYP2D6 inhibitors were not taken into account that may have phenoconverted some patients to present as an IM versus a NM. However, IMs and NMs did not have significant difference in reduction of pain scores where this seems less impactful on the significant difference still seen between PMs and NMs in pain reduction. Fourth, discrete dose data is challenging in retrospective chart reviews, which led to manual classification of dosing by a pharmacist. Finally, our results may not be generalizable to all patient populations given the study was conducted in a single healthcare organization comprising predominately patients of European descent. Reimbursement data was not collected in this study; therefore, no conclusions can be made about cost-effectiveness of implementation of testing within an organization.

Conclusion

PMs demonstrated significantly less pain improvement from opioid (codeine, tramadol, hydrocodone, and oxycodone) administration when compared to NMs, despite larger average MME in the moderate and severe baseline pain cohorts. PMs with baseline mild pain severities experienced increased pain despite opioid administration. Opioids are not strongly encouraged for mild pain severities, but this study further showed opioid usage should be strongly discouraged in this group for perceived lack of benefit. Oxycodone represented 41% of the opioids received in PMs and experienced significantly less reduction in pain scores than NMs. CYP2D6 phenotype may have a greater impact on the efficacy of oxycodone than previously studied. CYP2D6 genotyping may optimize opioid prescribing practices by limiting ineffective opioid administrations. These results strengthen the need for further investigation into prospective pre-emptive CYP2D6 testing regarding effective pain management with opioid administration with special emphasis on oxycodone and hydrocodone.

Ethical approval

This protocol was approved by Sanford Health's Institutional Review Board (STUDY00003625).

Disclosure

The authors declare no relevant conflicts of interest or financial relationships.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.japh.2025.102905.

References

1. U.S. Department of Health and Human Services. Executive summary executive summary pain management best practices inter-agency task force report best practices pain management best practices inter-agency task force report updates, Gaps, Inconsistencies, and Recommendations Pain Management Final Report. Available at: https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf; 2019. Accessed November 5, 2024.
2. Rikard SM, Strahan AE, Schmit KM, Guy Jr GP. Chronic pain among Adults- United States, 2019-2021. *MMWR Morb Mortal Wkly Rep*. 2023;72(15):379–385.
3. Santo L, Schappert SM. Opioids prescribed to adults at discharge from emergency departments: United States, 2017-2020. *NCHS Data Brief*. 2023;(461):1–8.
4. Baratta JL, Schwenk ES, Viscusi ER. Clinical consequences of inadequate pain relief: barriers to optimal pain management. *Plast Reconstr Surg*. 2014;134(4S-2):15S–21S.
5. FDA. Kima Pharmaceuticals International Limited. Codeine sulfate tablets [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022402s000lbl.pdf. Accessed September 4, 2024.
6. FDA. Janssen Research & Development LLC. Ultram (tramadol) [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata/fda.gov/drugsatfda_docs/label/2019/020281s045lbl.pdf. Accessed September 4, 2024.
7. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clin Pharmacol Ther*. 2021;110(4):888–896.
8. Kapil RP, Friedman K, Cipriano A, et al. Effects of paroxetine, a CYP2D6 inhibitor, on the pharmacokinetic properties of hydrocodone after coadministration with a single-entity, once-daily, extended-release hydrocodone tablet. *Clin Ther*. 2015;37(10):2286–2296.
9. Nahid NA, McDonough CW, Wei YJ, et al. Use of CYP2D6 inhibitors with CYP2D6 opioids: association with emergency department visits for pain. *Clin Pharmacol Ther*. 2024;116(4):1005–1012.
10. Van Heukelom J, Morgan J, Massmann A, et al. Evolution of pharmacogenomic services and implementation of a multi-state pharmacogenomics clinic across a large rural healthcare system. *Front Pharmacol*. 2023;14:1274165.
11. Petry NJ, Van Heukelom J, Schultz AJ, et al. Implementation of CYP2C19 and CYP2D6 genotyping to guide antidepressant use in a large rural health system. *Am J Health Syst Pharm*. 2024;81(16):723–732.
12. Cicali EJ, Elchynski AL, Cook KJ, et al. How to integrate CYP2D6 phenoconversion into clinical pharmacogenetics: a tutorial. *Clin Pharmacol Ther*. 2021;110(3):677–687.
13. Cicali EJ, Smith DM, Duong BQ, Kovar LG, Cavallari LH, Johnson JA. A scoping review of the evidence behind cytochrome P450 2D6 isoenzyme inhibitor classifications. *Clin Pharmacol Ther*. 2020;108(1):116–125.
14. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1–95.
15. Hay G, Korwisi B, Rief W, Smith BH, Treede RD, Barke A. Pain severity ratings in the 11th revision of the International Classification of Diseases: a versatile tool for rapid assessment. *PAIN*. 2022;163(12):2421–2429.
16. Monte AA, Heard KJ, Campbell J, Hamamura D, Weinshilboum RM, Vasiliou V. The effect of CYP2D6 drug-drug interactions on hydrocodone effectiveness. *Acad Emerg Med*. 2014;21(8):879–885.
17. Mosley SA, Cicali E, Del Cueto A, et al. CYP2D6-guided opioid therapy for adults with cancer pain: a randomized implementation clinical trial. *Pharmacotherapy*. 2023;43(12):1286–1296.
18. Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain*. 1998;76:27–33.
19. Table of pharmacogenetic associations. U.S. Food & Drug Administration. Available at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations; 2022. Accessed July 15, 2025.
20. Smith DM, Figg WD. Evidence regarding pharmacogenetics in pain management and cancer. *Oncologist*. 2023;28(3):189–192.

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