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CYP2D6 Enzyme Polymorphisms and their Effect on Opiate Metabolism

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by

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Abstract

The purpose of this research and systematic literature review is to determine if pharmacogenetic testing for the CYP2D6 enzyme responsible for the metabolism of several opiates leads to differences in serum levels, side effects, and treatment outcomes for patients with acute or chronic pain. In this review, the Pubmed and Embase databases were searched from January 1, 2014, to November 1, 2019. Exclusion criteria included studies published before 2014 and those not peer-reviewed. For this review, 11 studies were included with designs such as prospective and retrospective cohorts, randomized control trials, systematic reviews, and meta-analyses. Much of the presented research indicates an association between CYP2D6 phenotypes and differential treatment outcomes. Poor CYP2D6 metabolizers are shown to be at increased risk of analgesic failure contrasted with ultra-rapid metabolizers demonstrating better analgesic control; however, they had a higher risk of side effects and toxicity. Conflicting data is also demonstrated as well as a lack of conclusions that can be drawn for more intermediate metabolizers. We know the gene that codes for CYP2D6 is one of many that can affect opiate metabolism. More research is needed that encompasses all of these genes in order to make the findings more applicable to clinical practice.

Keywords: CYP2D6, polymorphisms, opioid, metabolism, pain, analgesia

Introduction

Opioid involved fatalities have been on a steady rise nationally since the late 1990s. The CDC estimates more than 130 people per day die of an opioid-induced overdose in the United States (Center for Disease Control and Prevention [CDC], 2018). Unfortunately, prescription opioids acquired by both legal and illegal means have had a significant contribution to this crisis. Since its highest point in 2016, prescription-related overdose deaths have been holding steady at roughly 17,029 people in 2017 (CDC, 2018).

The expansion of access to naloxone, treatment for opioid abuse disorder, and the revision of prescription guidelines all aim to reduce opioid overdose deaths. However, prescribers still find it challenging to strike the delicate balance between adequately treating the patient's pain while simultaneously minimizing unwanted side effects, including addiction and overdose. Pharmacogenomic testing for variations in opiate metabolism before the onset of opiate therapy offers a potential solution at mitigating this challenge.

The cytochrome p450 system represents a family of enzymes responsible for the metabolism of many medications. One member of this family, the CYP2D6 enzyme, plays an integral role in the pharmacokinetics of the opiate drug class. Research has identified over 100 alleles for the CYP2D6 gene (Crews et al., 2014), and clinical trials have demonstrated the functional impact on the opiate metabolism of many; however, not all. Most clinical trials have adopted the star (*) allele nomenclature to identify specific CYP2D6 haplotypes that correlate to a metabolism activity score, and thus a predicted phenotype. Table 1 summarizes the relationship genotype to activity scores and phenotypes.

Table 1
Phenotypes and their Correlating Activity Score and Genotypes

Phenotype	Total Activity Score	Haplotype Examples
Poor Metabolizer (PM)	0	CYP2D6*4, CYP2D6*5, CYP2D6*6
Intermediate Metabolizer (IM)	0.5	CYP2D6*10, CYP2D6*9
Extensive Metabolizer (EM)	1.0-2.0	CYP2D6*2
Ultrarapid Metabolizer (UM)	> 2.0	CYP2D6*2N

Table 1 derived from "CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients," by R. Balyan, M. Mecoli, R. Venkatasubramanian, V. Chidambaran, N. Kamos, S. Clay, D. Moore, J. Mavi, C. Glover, P. Szmuk, A. Vinks, and S. Sadhasivam, 2017, *Pharmacogenomics, Volume 18*, p. 339. Copyright 2017 by Future Science Group.

This literature review intends to explore how an individual's genetic variability in the CYP2D6 enzyme influences the pharmacokinetics and pharmacodynamics of opioids and the clinical application of said variabilities to improve the treatment of acute and chronic pain while minimizing the probability of side effects and pharmacotherapy failure.

Statement of the Problem

Pharmacogenomic testing has shown much promise as a tool that can help clinicians make better prescribing decisions. Clinical and commercial use of this testing tool has been available for psychotropics as early as 2009, and coverage by insurance, including Medicare, is becoming more and more common. However, this testing has yet to be used clinically at the initiation of opiate therapy for pain management. Research has proven that the mechanism by which CYP2D6 polymorphisms affect opiate metabolism; however, the clinical utility of this test and the implication on patient outcomes is undetermined.

Research Question

In adults with chronic or acute pain, is there statistical evidence that pharmacogenetic testing for CYP2D6 polymorphisms can lead to better clinical outcomes for pain management with opiates vs. current trial and error prescribing practices?

Methods

A 5-year systematic literature review was conducted utilizing PubMed and Embase databases for publications dated from January 1, 2014, to November 1, 2019. MeSH and free-text terms used to search include: "polymorphisms, genetic," "pharmacogenetics," "analgesics, opioid," "pharmacogenomic testing," and "cytochrome p-450 CYP2D6". Articles selected for review include those relating to CYP2D6 polymorphisms and their effect on opioid pharmacokinetic and pharmacodynamic parameters. Study design and clinical application further narrowed the reviewed studies only to include peer-reviewed articles or reviews.

Literature Review

A review of the literature identifies several different opiates that have their metabolism altered by CYP2D6 polymorphisms. The drugs identified include tramadol, codeine, oxycodone, hydrocodone, fentanyl, methadone, and morphine. Whether this translates to superior clinical outcomes as opposed to the current trial and error methodology is currently undetermined.

Theme One: **CYP2D6 Polymorphisms and Opioid Pharmacokinetics**

Crews et al. (2014) provided an update to the systematic review they completed in 2012 regarding opiate metabolism and CYP2D6 polymorphisms to create opiate prescribing guidelines accounting for patient CYP2D6 phenotype. Codeine is a prodrug that is converted to its active metabolite of morphine by the CYP2D6 enzyme. Two studies are sited stating the amount of morphine produced from codeine is decreased in PMs when compared to EMs, thus decreasing

the amount of analgesia concurrently produced. Also noted was a decrease in GI side effects in PMs vs. EMs. Other side effects, such as sedation, nausea, and dry mouth, showed no difference between PMs and EMs. Codeine is converted to morphine by CYP2D6 at a much higher rate when comparing UMs and EMs, increasing the risk of toxic levels. As such, this guideline has recommended using analgesic alternatives to codeine in those who are PMs or UMs.

One study included in the review found that after a dose of tramadol, the concentration-time curve for active metabolites in CYP2D6 PMs showed lower median plasma levels when compared to EMs. UMs also show higher peak plasma levels of tramadol as well as more significant analgesia and a more frequent occurrence of side effects such as nausea and miosis when compared to other phenotypes. Three prospective clinical trials found those with PM phenotypes fail to exhibit analgesia when dosed with tramadol as well.

Similar to the relationship of codeine and morphine, hydrocodone is converted to hydromorphone by the CYP2D6 enzyme. Peak concentrations of hydromorphone are lower in PMs compared to EMs after a dose of hydrocodone. However, this does not seem to affect the pharmacodynamics of analgesia with hydrocodone. Therefore, the data is insufficient to conclude whether PMs have less analgesia or UMs are at increased risk of toxicity when dosed with hydrocodone.

Lastly, CYP2D6 is responsible for the conversion of oxycodone to its active form of oxymorphone. Two studies have shown that PMs have lower peak concentrations of oxymorphone compared to EMs when doses with oxycodone. Two more studies utilizing experimentally induced pain in healthy volunteers found a different analgesic response when comparing EMs to PMs and UMs to EMs. However, prospective clinical studies have produced conflicting data stating that CYP2D6 phenotypes cannot be associated with variances in toxicity

and analgesia. Two more clinical studies done on postoperative pain and cancer-related pain found differences in analgesia, and side effects from oxycodone could not be associated with CYP2D6 phenotypes.

Therapy recommendations were assigned for each CYP2D6 phenotype, which is summarized in Table 2. Special considerations are given for pediatrics and breastfeeding due to considerable CYP2D6 activity variation in infants younger than one month. Although the amount is low and dependent on dose, codeine and its metabolites are secreted in breast milk. Mothers who are UMs may achieve higher serum morphine concentrations leading to higher breast milk concentrations. Fatal opioid poisonings in breastfed neonates by UM mothers have been documented, prompting the FDA to change codeine indications in these populations.

Limitations of this meta-analysis are that not all opiates metabolized by CYP2D6, and not all CYP2D6 variations are included. New evidence may have emerged since the publication of this article in 2014. There is also a potential conflict of interest as two authors have served as expert witnesses on legal cases involving codeine and have been compensated as such.

Table 2
Recommendations Based on Phenotype

Phenotype	Recommendations for codeine therapy	Classification of evidence	Alternative Considerations
UM	Avoid codeine use; risk for toxicity	Strong	Consider morphine or NSAIDs
EM	Use label-recommended dose based on age or weight.	Strong	N/A
IM	Use label recommended dose based on age or weight. Consider morphine or	Moderate	If using tramadol, monitor use for response

	nonopioid if treatment failure		
PM	Avoid codeine therapy. Decreased efficacy	Strong	Consider morphine or NSAIDs

Table 2 derived from "Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update," by K. Crews, A. Gaedigk, H. Dunnenberger, J. Leeder, T. Klein, K. Caudle, … T. Skaar, 2014, *Clinical Pharmacology & Therapeutics*, *95,* p. 379. Copyright 2014 by American Society for Clinical Pharmacology and Therapeutics.

Balyan et al. (2017) conducted a prospective observational study to determine how the pharmacokinetics of oxycodone are affected by CYP2D6 polymorphisms in postoperative children. Thirty children aged 2-17 years old who were to undergo either orthopedic, thoracic, urologic, or colorectal surgery were enrolled in the study with the expectation they would require IV access and postoperative analgesia with opiates. Exclusion criteria included a history of smoking, alcohol use, drug addiction, and the use of a CYP2D6 inhibitor or inducer within the past 14 days. Blood was drawn before surgery for the CYP2D6 genotype and phenotype determinations. One subject was represented as a poor metabolizer (PM), 13 as intermediate metabolizers (IMs), and 16 as extensive metabolizers (EMs). Participants were dosed according to label instructions for height and weight initially via IV, then PO postoperatively. Blood samples were taken at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after oxycodone administration for oxycodone and oxymorphone pharmacokinetic analysis. The analysis included measuring the peak concentration (Cmax), time to peak concentration (Tmax), terminal half-life (T1/2), and area under the curve (AUC) for oxymorphone and oxycodone. For standardization, these parameters were normalized by the actual oxycodone dose.

Results showed that EM phenotypes were found to have a significantly greater oxymorphone plasma level when compared to IM and PM phenotypes ($p = 0.02$ for Cmax, $p = 0.016$ for AUC 0-6, and $p = 0.026$ for AUC 0-24). Higher Total Activity Score (TAS) values

used to categorize phenotypes were found to be significantly associated with greater oxymorphone exposure. Lastly, EM phenotypes were shown to convert oxycodone to oxymorphone at a higher level when compared to PM and IM phenotypes ($p = 0.0007$ Cmax, $p = 0.001$ AUC 0-6, and $p = 0.004$ AUC 0-24).

Limitations of this study include the small number of extreme metabolizers; only one PM and no UMs were included. A second limitation is the inability to perform a direct prospective comparison with codeine since the use of codeine in children has been black boxed by the FDA due to its unpredictable adverse effects.

Stauble et al. (2014) conducted a cohort study to determine what clinical effects CYP2D6 had on the conversion of hydrocodone to hydromorphone in post-Cesarean section patients. The inclusion criteria for the study consisted of women with a BMI <40, who spoke either English or Spanish, who were to be scheduled for a C-section delivery and receiving hydrocodone postoperatively. Exclusion criteria included known drug abuse, allergy to hydrocodone, and medical disability. Blood was drawn three days post-delivery then analyzed for the GYP2D6 genotype and phenotype. Visual Analog Scale (VAS) scores were used to document pain control. The pain was treated with 800 mg of ibuprofen every 8h in addition to hydrocodone as needed. Plasma levels of hydrocodone and its metabolites, such as hydromorphone, were monitored following dosage. Statistical analyses were conducted by calculating means and SDs for all metabolites, relevant subject characteristics, and CYP2D6 phenotype.

Results indicated that pain relief was correlated with plasma levels of hydromorphone, not hydrocodone. PMs were only able to create 0.66 ng/ml mean plasma level (SD 1.1) of hydromorphone, compared to 7.06 mean ng/ml (SD 11.9) from UMs. Plasma hydromorphone also showed a weak yet statistically significant inverse association with patient VAS scores.

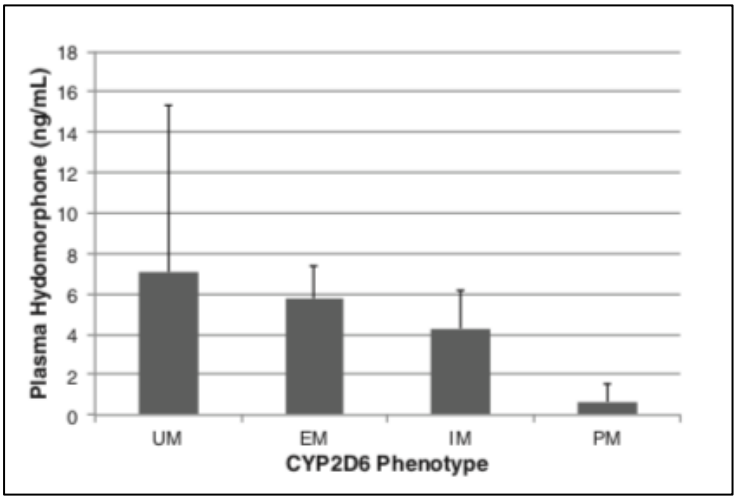

Figure 1. Plasma hydromorphone concentrations (ng/mL) in women after C-section operation based on their CYP2D6 genotype. Gene-dose effect is efident by the fact that ultra-rapid metabolizers (UM) have the greatest concentrations of hydromorphone followed by the extensive (EM), intermediate (IM), and poor metabolizers (PM). From "Hydrocodone in postoperative personalized pain management: Pro-drug or drug?" by M. Stauble, A. Moore, L. Langman, M. Boswell, R. Baumgartner, S. McGee…S. Jortani, 2014, *Clinica Chimica Acta, 429,* p. 28. Copyright 2014 by Elsevier.

Limitations of this study include inaccurate pain reporting by patients on VAS scores and the small representation of PM (3.2%) and UM (6.56%) phenotypes in the sample size. Although the homogeneous sample allowed for better comparative data, it cannot be generalized to the standard population.

Linares, Fudin, Daly, and Boston (2015) performed a randomized, crossover, double-blind, placebo-controlled study to identify how CYP2D6 phenotypes alter the pharmacokinetics of hydrocodone and hydromorphone with hopes the data could be used to create phenotype-specific dosing strategy. They also performed a meta-analysis through PubMed and Google Scholar to determine the therapeutic range of hydrocodone, which resulted in 24.16 ng/mL to 31.60 ng/mL with a CI of 95%.

Exclusion criteria for the study included any comorbidities, history of opioid, or substance abuse. CYP2D6 genotyping was performed before the initiation of the study. Results

identified 5 EM and 6 PM phenotypes, totaling 11 participants. Data from the 5 EM participants was used to synthesize 5 UM participants using a pharmacoepigenomic technique. An overnight fast and standardized breakfast was given to participants on the day of the study. Participants were not allowed food or drink items containing alcohol, nicotine, or caffeine for two days before the study. Baseline blood samples were drawn before 10 mg of hydrocodone was administered. Subsequent blood samples were drawn at 10, 20, 30, and 45 minutes as well as 1, 1.5, 2, 3, 5, 6.5, 8, and 24 hours.

Results showed that PMs had lower levels of plasma hydrocodone compared to EMs. Hydrocodone clearance was decreased by 60% in PMs and the half-life increased roughly 68% when compared to EMs. Using these results, combined with the results of the meta-analysis, Linares et al. then created an algorithm for personalized hydrocodone dosing. Step 1 includes determining the patient's CYP2D6 phenotype. Step 2 is to determine the target therapeutic hydrocodone plasma concentration. Lastly, step 3 is to use integrated clinical pharmacokinetics with pharmacogenetics to determine dose.

Limitations of this study are the small sample population, that 5 UMs were postulated from EM data instead of being evaluated in vivo with the other phenotypes, and that it does not account for possible tolerance to hydrocodone. The algorithm they proposed for oxycodone dosing is possibly useful but may be impractical to apply clinically. This algorithm also only accounts for one gene involved in hydrocodone metabolism when there is evidence that many others also involved.

Theme Two: **CYPD26 Polymorphisms and Pain Relief**

Ren et al. (2015) conducted a systematic review and meta-analysis to clarify the effects of genetic polymorphisms on pain management and adverse effects in patients with postoperative

pain. The systematic search was conducted on PubMed, Embase, ISI Web of Science, and the Cochrane Library databases. Publication dates up until January 31, 2014, were included so long as they were randomized, cohort studies done in perioperative patients treating pain with opioids. Several genes were included in the meta-analysis; however, since this review is only concerned with the CYP2D6 gene, only data analyzing this gene was summarized.

A total of six studies concerning CYP2D6 were summarized. The first study included in the analysis suggests poor metabolizers (PMs) had a weak analgesic effect while ultra-rapid metabolizers (UMs) attained immediate pain relief with the same dose codeine but had increased incidence of side effects. The second study found that PMs required more tramadol to attain the same analgesic effect compared to EMs. This finding was inconsistent with another study that found CYP2D6 genotypes did not significantly affect tramadol dosage, tramadol-induced side effects, and pain scores in postoperative patients. When using morphine, UMs consumed less opiate and had lower pain scores than other phenotypes, found the fourth study. Patients with CYP2D6 phenotype PM and EM showed no significant difference in oxycodone consumption when used postoperatively, found the fifth study. Lastly, CYP2D6 PMs were found to have decreased occurrence of nausea and vomiting; however, pain scores remained high for this phenotype.

The significant limitations of this publication include the fact that confidence intervals and p-values were not included for the individual studies, which makes it difficult to gauge the strength of their findings. Statistical analysis was performed for other genes included in this meta-analysis; however, none were included for the CYP2D6 gene. Also, the inability to analyze non-genetic factors that can change opiate pharmacodynamics was left out. Most

publications do not address these interactions, so they could not be included in the meta-analysis. Selective publication bias may be a further limitation.

Smith et al. (2019) designed a trial with a nonrandomized, open-label, prospective, and cluster design with the intent to evaluate whether pharmacogenetic guided prescribing leads to better pain management for chronic pain patients in primary care and specialty settings. Exclusion criteria included participants less than 18 years old and patients who had already undergone CYP2D6 genotyping. Chronic pain was defined as pain lasting longer or equal to 3 months seeking treatment at a participating clinic. Physicians referred patients meeting these criteria who had poorly controlled pain for which a change in therapy was indicated. CYP2D6 genotyping was carried out using a Luminex xTAG kit. Identified alleles were assigned an activity score for which was used to assign phenotypes. For participants taking a CYP2D6 inhibitor, phenotypes were individually refined by a pharmacist. The pharmacist then made recommendations to the prescribing practitioner regarding opioid use according to CYP2D6 phenotypes. Ultimately, the prescribing physician remained the decision-maker.

Data was collected at baseline and again after three months of treatment for 345 participants. Data was analyzed using a two-sample *t*-test, chi-square analysis, or Fisher's exact test when appropriate. Numerical data are presented as mean ± standard deviation. Findings showed that IMs and PMs that were prescribed tramadol or codeine via CYP2D6 phenotype guided recommendations were more likely to have a minimum 30% reduction in pain intensity when compared to current prescribing clinical practices ($p = 0.040$). However, this change was not seen in normal metabolizers who followed CYP2D6 phenotype recommendations for tramadol or codeine (-0.61 ± 1.39 vs. -0.54 ± 1.69; $p = 0.540$). When all CYP2D6 phenotypes taking tramadol and codeine were combined and compared to those of the usual care group, no

difference in pain composite pain intensity was noted (-0.72 ± 1.46 vs. -0.12 ± 1.32; p = 0.019). IMs and PMs that were prescribed tramadol, codeine, or hydrocodone based on their phenotype saw a more significant reduction in composite pain intensity (-0.84 ± 1.51) when compared to the usual care group (-0.12 ± 1.32; p = 0.019). In contrast, the improvement in pain for IMs and PMs prescribed oxycodone was less when compared to the usual care group (-0.02 ± 1.09 vs. -0.87 ± 0.67; p = 0.024) and nonexistent for normal metabolizers.

Limitations to this study include the nonrandomized, cluster design, the fact that patients were not blind to their phenotypes, that medication assessments did not include OTC analgesics, and the long-acting or short-acting formulations were not specified.

Choi et al. (2017) performed a systematic review and meta-analysis that analyzed several gene polymorphisms, including those affecting CYP2D6, in attempts to analyze how these genes impact opioid metabolism and pain response. The systematic search was conducted using Web of Science, PubMed, and Ovid via Embase databases between the dates of April 2015 through June 2016. Studies that were included must have reported on postoperative or intraoperative opioid use and genotyping for single nucleotide polymorphisms for many genes, including CYP2D6. Exclusion criteria included abstract only articles, literature reviews, meta-analyses, and articles not written in English. There was no limitation on publication year. All articles were individually assessed for risk of bias, and p values of < 0.05 were considered statistically significant.

Eight studies were included in the meta-analysis that evaluated CYP2D6 polymorphisms. Choi et al. (2017) were unable to create a Forest plot with these studies as the studies used different standards to characterize metabolizer phenotypes. Two of these studies found no significant difference between phenotypes and opioid metabolism while the remainder did. One

analyzed CYP2D6 genotypes and their response to postoperative analgesia with IV oxycodone. The second evaluated CYP2D6 polymorphisms' effect on tramadol metabolism and postoperative pain control. Another study, in particular, found the effect of more than 40 different CYP2D6 polymorphisms had a profound effect on morphine metabolism and requirements for pain management.

Limitations outlined by the authors include heterogeneity of the studies that could not offer a comprehensive picture of how polymorphisms from multiple genes offer a combined effect on opioid metabolism and that demographic data for individual articles could not be retrieved. Further limitations include incredibly brief summaries of the articles concerning CYP2D6, missing findings from the included articles, missing statistical values such as confidence intervals, risk ratios, and p-values, and that publication bias was not assessed for each article.

Vieria, Fragoso, Pereira, and Medeiros (2018) conducted an evidence-based review of the literature using the PubMed, Evidence-Based Medicine Guidelines, and Google databases. MESH terms used to search include "cancer pain," "polymorphism," "genetic," and "gene polymorphism." Clinical guidelines, systematic reviews, meta-analyses, and clinical trials published before January 2018 were included. Exclusion criteria included articles that did not include the term "polymorphism" within the abstract, and any article referencing non-cancer pain. Evidence and recommendations were classified according to The American Family Physician's (AFP) Strength of Recommendation Taxonomy, where Level of Evidence 1 indicates quality studies and evidence-oriented decision; Level of Evidence 2 indicates limited quality studies, patient-oriented evidence; and Level of Evidence 3 indicates other evidence.

Numerous guidelines cited evidence concerning the effect of CYP2D6 polymorphisms on opiate metabolism. The National Comprehensive Cancer Network from January 2018 recognizes that poor and slow CYP2D6 metabolizers have reduced analgesic response, and ultra-rapid metabolizers are at increased risk for toxicity. The European Palliative Care Research Collaborative (EPCRC) guidelines indicate that poor metabolizers are at risk for decreased pain control efficacy when using codeine or tramadol. The EPCRC acknowledges that gene polymorphisms other than those from CYP2D6 can be accountable for variation in opiate metabolism, some of which may have yet to be discovered. The World Health Organization recognizes that those who are poor CYP2D6 metabolizers are less likely to achieve analgesia as they can have up to a 14-fold lower concentration of active metabolites. The Center for Disease Control notes that equianalgesic dose conversions do not take into account all pharmacokinetic variabilities related to genetics and are meant only to be an estimation.

The systematic reviews and meta-analyses also indicated a CYP2D6 effect on opiate metabolism. Major conclusions drawn from these studies include that ultra-rapid metabolizers and poor metabolizers should avoid tramadol, codeine, hydrocodone, and oxycodone as it can lead to analgesic failure or increased side effects (Level of Evidence 2). Tramadol analgesia is dependent on CYP2D6 activity and is not recommended for UMs (Level of Evidence 3). Codeine, morphine (Level of Evidence 2), and methadone (Level of Evidence 1) have also been shown to be affected by the CYP2D6 phenotype; however, it does not specify to what extent. Acknowledgment is made that additional considerations are needed for those with hepatic and renal impairment.

One clinical trial was included that discussed CYP2D6 polymorphisms and how they affect the pharmacokinetics of tramadol. The prospective cohort study found that the

CYP2D6*10 genotype associated with intermediate metabolism showed a significant impact on tramadol analgesia following postoperative gastrectomy (Level of Evidence 2). CYP2D6 polymorphisms and their effect on opiate pharmacokinetics received a Recommendation Level A regarding codeine, tramadol, oxycodone hydrocodone, and methadone citing the evidence that PM phenotypes are at increased risk of treatment failure. At the same time, UM metabolizers are at higher risk for toxicities due to higher serum concentrations of active metabolites. The authors used this evidence to propose an algorithm approach to the management of pain that incorporates polymorphism screening when pain persists despite the use of strong opiates, NSAIDs, and other pain adjuvants or when intolerable side effects are experienced.

Limitations of this article are that statistical and publication bias assessments were not performed, and articles concerning non-cancer pain were excluded making the applicable setting for this research rather narrow.

Theme Three: **CYP2D6 Polymorphisms and Adverse Effects**

Dagostino et al. (2018) conducted a retrospective cohort study in attempts to understand how CYP2D6 genotyping could help in predicting the efficacy and side effects in Italians with chronic low back pain treated with codeine/acetaminophen or oxycodone. Two hundred twenty-four participants were enrolled in the study, 75 males and 130 females. CYP2D6 genotyping was performed initially then classified into phenotypes. Exclusion criteria included those with a possible drug to drug interaction (n=13) and genotyping failure (n=15). One hundred ninety-six participants remained, 66 men and 130 women. Of these, 97 were prescribed codeine/acetaminophen, and 99 were prescribed oxycodone or oxycodone/naloxone. Patients who reported side effects or no pain relief in the first visit after the prescription was administered were considered as the “Case” group (n=27), and those who reported adequate pain relief were

considered the "Control" group (n=169). Also, worth noting is that 15% of participants across both groups were prescribed additional medications other than the opioid.

The phenotype make-up of the Case group is as follows: 78% EMs, 15% IMs and PMs combined, and 7% UMs. The Control group was made of 80% EMs, 17% IMs and PMs, and 3% UMs. CYP2D6 phenotypes between the genders showed no significant differences (Case, Fisher's exact test $p = 0.304$; Control, Fisher's exact test $p = 0.302$). Haplotypes *6 (PM) and *9 (IM) were significantly overrepresented in the Case group, making them more likely to experience treatment failure. The occurrence of the *2N haplotype (UM) was 7% in the Case group compared to only 3% in the Control group, making it at increased risk for side effects. Diplotypes for CYP2D6*1/*11 (EM), *4/*6 (PM), and *41/*2N (UM) were also associated with increased toxicity or treatment failure.

Table 3
CYP2D6 Haplotype Distribution in Case and Control Groups and their Association with Benefit/No Benefit Status

Allele	Case	Control	OR	95% Lo	95 % Hi	χ^2	*p*-value
*1	20 (35%)	129 (38%)	1.000	1.000	1.000	0.092	0.761
*4	7 (13%)	66 (20%)	0.730	0.291	1.831	1.157	0.282
*2	9 (17%)	61 (18)	0.973	0.415	2.282	0.077	0.782
*41	6 (11%)	38 (11%)	1.045	0.387	2.817	0.001	0.971
*35	3 (6%)	20 (6%)	0.921	0.248	3.429	0.040	0.841
*5	1 (2%)	8 (2%)	0.678	0.079	5.829	0.159	0.690
*9	3 (6%)	4 (1%)	5.760	1.111	29.870	5.358	0.021
*10	0 (%)	4 (1%)	0.000	0.000	0.000	0.744	0.389
*2N	2 (4%)	3 (1%)	4.795	0.710	32.380	3.142	0.076
*1N	0(%)	2 (1%)	0.000	0.000	0.000	0.000	1.000
*6	3 (6%)	1 (0%)	81.340	3.356	1,971.000	19.400	0.011
*15	0 (%)	1 (0%)	0.000	0.000	0.000	0.000	1.000
*35	0 (%)	1 (0%)	0.000	0.000	0.000	0.000	1.000

Table 3 derived from "CYP2D6 genotype can help to predict effectiveness and safety during opioid treatment for chronic low back pain: results form a retrospective study in an Italian cohort," by C. Dagostino, M. Allegri, V. Napolini, S. D'Agnelli, B. Bignami, A. Mutti, R. van

Schaik, 2018, *Pharmacogenomics and Personalized Medicine, Volume 11,* p. 186. Copyright 2018 by Dovepress.

Limitations of this study include a minimal sample size in the "Case" group, only 27 of 196 patients. The retrospective design did not include a prospective component where drug adjustments could be addressed, or no effect/side effects could be better defined. Bias outlined by the author could be related to the inappropriate drug selection by the prescribing physician in the study.

Sauver et al. (2017) used a population of participants from the Mayo Clinic Right Drug, Right Dose, Right Time Protocol (RIGHT Protocol). They performed a retrospective cohort to examine the relationship between poor pain control and different CYP2D6 phenotypes in order to create data that can be applied to generalized populations in real-world clinical practice settings.

Participants in this study who were prescribed an opioid analgesic between the dates of 07/01/2013 and 06/30/2015 that contained either codeine, oxycodone, hydrocodone, or tramadol contributed blood samples that were analyzed for different CYP2D6 polymorphisms. Exclusion criteria included people utilizing a CYP2D6 inhibitor within the past year. Phenotypes were classified as follows: PM, IM-EM, and UM. Adverse effects such as vomiting, nausea, rash, itching, and throat swelling, as well as analgesic failure, were also reviewed without knowledge of patient phenotypes. Phenotype and outcome associations were evaluated using Chi-square tests and logistic regression.

Adverse effects or inadequate pain control was reported in 35% of PMs and 34% of UMs compared to only 18% of IM-EMs. This was broken down further to show that 17% with a PM or UM phenotype reported inadequate analgesia compared to 8% of IM-EM phenotypes ($p = 0.05$). Furthermore, 19% of PMs or UMs experienced an adverse symptom compared to 12% of

IM-EMs ($p = 0.25$). After adjustments were made for age and sex, it was found that PMs and UMs were 2.4 times more likely to experience either an adverse effect or inadequate pain management compared to IM-EMs (OR: 2.40; 95% CI: 1.35, 4.28).

The limitation of this study includes possible inadequate reporting by patients or practitioners in the medical records that lead to a high potential for misclassification. Documentation of medication compliance was also missing. The Luminex kit used for genotyping does not include all CYP2D6 alleles, which has the potential to misclassify phenotypes. Lastly, many of the opioids prescribed were used in conjunction with other medications.

Lloyd, Hotham, Hall, Williams, and Suppiah (2017) performed a literature review to decipher how several genetic variations can contribute to variation in opiate dosage requirements, therapy outcomes, adverse effects for chronic malignant and nonmalignant pain in adults over 18 years old. They focused their search on the five most commonly prescribed opiates: codeine, tramadol, oxycodone, morphine, and fentanyl.

Medline and Embase databases were used to conduct this literature search. Exclusion criteria included studies that mentioned addiction, abuse or withdrawal, drugs other than the above named, studies that included participants with acute, induced, or postoperative pain, and studies without full-text access. Since this review included a number of other genes not of concern for this review, only the studies addressing CYP2D6 are summarized.

Four studies addressed the effect of CYP2D6 phenotypes on participants using tramadol to treat postherpetic neuralgia (PHN). One of these four indicated that the CYP2D6*4 haplotype (PM) was significantly associated with lower pain relief from pain characterized as burning, squeezing, tingling, and pins and needles (all p values < 0.05), and was not associated with

tramadol-induced adverse events. A conflicting study indicated the *4 haplotype (PM) was associated with adverse effects such as somnolence ($p = 0.009$), dizziness ($p = 0.007$), injection site reactions ($p = 0.015$), headache ($P = 0.039$) and nausea and vomiting ($p = 0.017$). Two studies indicated no correlation between the CYP2D6*10 haplotype (IM) and pain with rest or movement, or similar adverse effects (all p values > 0.1). This makes it unlikely there is a correlation between the *10 haplotype and PHN treatment outcomes with tramadol. The most recent of the studies indicated a significant correlation with allodynia ($p = 0.029$) and pins and needles type pain ($p = 0.03$) in the CYP2D6*2 haplotype (EM). However, all of the pain subtypes also showed an association with decreasing mean pain scores over time.

When considering opiates as a class of medications being used to treat chronic and malignant pain, a cohort study on Caucasian patients showed no significant association between several genes, including CYP2D6, and opioid dose, pain scores, and side effects. When considering oxycodone independently, a Japanese cohort found there was no association between CYP2D6*10 (IM) and CYP2D6*2 (EM) and oxycodone trough concentrations (12 hours post-dose). However, a significant association between trough oxymorphone and a higher ratio of oxymorphone to oxycodone was seen in EMs ($p = 0.04$) compared to IMs ($p = 0.02$). Lastly, a cross-sectional study of 450 Caucasian participants showed that PMs had lower concentrations of oxymorphone and noroxymorphone (both metabolites of oxycodone) compared to EMs and UMs ($p < 0.001$). PMs also had a lower oxymorphone: oxycodone ratio ($p < 0.001$). However, there was no significant difference in the haplotypes and the oxycodone dose required for analgesia, pain scores, or side effects.

One limitation of this review was that the search terms for pain, such as low back pain, neuralgia, neuropathic pain, and musculoskeletal pain, may have led to the exclusion of studies for other chronic pain.

Discussion

The CYP2D6 enzyme is one of many enzymes that make up the P450 system, which is responsible for the metabolism and clearance of numerous compounds such as steroids, hormones, fatty acids, and medications. Genetic variations can affect the enzymatic activity of CYP2D6, causing increased or decreased drug metabolism. Opiates such as tramadol, fentanyl, methadone, codeine, oxycodone, morphine, and hydrocodone are all metabolized by the CYP2D6 enzyme. It is postulated that those who are poor CYP2D6 metabolizers (PMs) would, therefore, have a decreased plasma serum levels of active metabolites and decreased analgesic effect, resulting in higher dose requirements to achieve treatment success. PMs should also show a decreased occurrence of side effects for these same reasons. Conversely, those who are ultra-rapid metabolizers (UMs) should exhibit increased plasma serum levels and increased analgesic effect, as well as an increased occurrence of side effects and risk of toxicity. Intermediate (IMs) and extensive metabolizers (EMs) lie somewhere in between these two extremes.

Do CYP2D6 Polymorphisms Affect the Pharmacokinetics of Opiates?

The updated systematic review done by Crews et al. (2014), offers several studies that show evidence that CYP2D6 polymorphisms alter the metabolism of codeine, tramadol, and oxycodone; along with one study that indicated insufficient evidence of the same for hydrocodone. It is postulated that the variability between drugs could be related to their roles as a prodrug. This review also noted variabilities between people of the same CYP2D6 diplotype.

Possible explanations for this include other gene variabilities involved in the metabolism of opiates. The data to recommend increased dosages of opiate to PM metabolizers is also insufficient.

Since codeine had been black boxed by the FDA for use in children in 2013, the prospective observational study done by Baylan et al. (2017), aimed to find other options for postoperative analgesia. Their results indicate that the CYP2D6 phenotype significantly affects the conversion of oxycodone to its active metabolite oxymorphone. EMs were found to have significantly higher plasma levels than IMs and PMs, and higher CYP2D6 TAS values were significantly associated with higher oxymorphone plasma levels. Additionally, it is noted that different populations have different occurrences of CYP2D6 phenotype; 29% of Ethiopians (Akilillu et al., 1996) and 20% of Saudi Arabians (Mclellan, Oscarson, Seidegard, Evans & Ingleman-Sundberg, 1997) compared to 1-7% of Caucasians (Leon, Dinsmore, & Wedlund, 2003) are UMs. Populations with a higher prevalence of CYP2D6 ultra-rapid metabolism are at higher risk for toxicity from these drugs.

Hydrocodone is a prodrug that is metabolized into its active metabolite hydromorphone by CYP2D6. Stauble et al. (2014) found that mean plasma levels of hydromorphone in PMs was much lower than that of UMs, which correlated to the amount of pain relief reported by patients. Linares at al. (2015) also evaluated the relationship of CYP2D6 phenotypes to hydrocodone and subsequent hydromorphone levels. Their results were similar in that PMs were shown to have lower plasma levels of hydrocodone, significantly increased hydrocodone clearance, and half-life compared to EMs.

Do CYPD26 Polymorphisms Affect Pain Relief from Opiates?

The review in this section included two systematic reviews and meta-analyses, one evidence-based review, and one prospective cohort. Systematic reviews represent some of the highest levels of research evidence available. They are a comprehensive survey of relevant studies that are assessed and dissected by a specific methodology to synthesize findings.

The systematic review presented by Ren et al. (2015) put for evidence that PMs are at increased risk of analgesic failure when dosed with codeine and tramadol in comparison to UMs and EMs. This was demonstrated by decreased patient pain scores and increased consumption of opiate. Likewise, UMs were shown to consume less morphine and reported lower overall pain scores. There was also evidence that CYP2D6 phenotypes did not affect postoperative pain relief and no difference between PM and EM oxycodone consumption postoperatively. Unfortunately, no statistical values were included in Ren et al.'s critique of these studies, making it challenging to compare evidential strength.

A systematic review done by Choi et al. (2017) included eight studies, two of which found no significance in oxycodone and tramadol metabolism postoperatively for CYP2D6 phenotypes, while the remaining six studies found statistical significance for the same. Choi et al. (2017) defined "statistically significant" as $p < 0.05$; however, statistical values and more specific findings for the individual studies were left out. This, again, makes it difficult to compare the strength of the evidence set forth.

The evidence-based review conducted by Viera et al. (2018) is the only article to include guidelines created by cited evidence in their review. All four of the meta-analyses were found to have evidence of varying strengths that the treatment efficacy of opiates such as tramadol, codeine, hydrocodone, oxycodone, morphine, and methadone was affected by CYP2D6 phenotype. The highest level of evidence (Level 1) was found for methadone. These findings

were enough to give a Recommendation Level A for PM and UM metabolizers to avoid these opiates. The prospective clinical trial indicated that IMs showed a significant impact on tramadol analgesia, which is a bit counterintuitive as one would suspect the extreme metabolizers (PMs and UMs) to show the most variance in this regard.

The trial created by Smith et al. (2019) was unique in that it was carried out in primary care and specialty clinic settings and allowed the physician to remain the decision-maker on prescriptive practices based on CYP2D6 phenotyping and pharmacist input. This makes it the most applicable to real-life clinical scenarios. However, what gives this study its uniqueness also gives its limitations in the nonrandomized and unblinded study design. The results indicate that CYP2D6 pharmacogenetic testing was beneficial to those with IM and PM phenotypes at lowering pain intensity when prescribed tramadol or codeine. This benefit was not seen in NMs as they do not exhibit increased or decreased CYP2D6 enzyme activity, leading authors to conclude the benefit seen in IMs and PMs was due to the pharmacogenetic testing intervention.

Do CYP2D6 Polymorphisms Affect the Incidence of Adverse Effects

A retrospective cohort done by Dagostino et al. (2018)'s demonstrated that PM and IM phenotypes were more likely to experience treatment failure with the use of codeine/acetaminophen, oxycodone, or oxycodone/naloxone for chronic low back pain. UMs were also at increased risk for side effects. Stauver et al. (2017) took a somewhat different approach and did not differentiate between adverse effect and pain relief when comparing phenotypes in their retrospective cohort. This led to results that showed the extreme metabolizers, UMs and PMs, reported increased incidence of adverse effects and inadequate pain control compared to their more moderate counterparts, the IMs and EMs. This makes it difficult to distinguish whether it was the PMs or UMs that reported the increased incidence of side

effects or inadequate analgesia. One would postulate that the PMs reported the inadequate analgesia and, the UMs reported the side effects; however, the way this data was presented made it impossible to draw that conclusion.

The literature review conducted by Lloyd et al. (2017) presented somewhat mixed results. PMs were shown to have decreased pain relief from postherpetic neuralgia; however, it also showed an increased incidence of opiate side effects. PMs were also shown to have decreased plasma concentrations of oxymorphone; however, this did not translate to a correlation to increased pain scores, increased dose requirements, and decreased adverse events. Two studies showed no correlation to pain relief and adverse effects in IMs, which is to be expected as IMs are not extreme metabolizers. Other studies concluded no correlation between CYP2D6 phenotypes and pain scores, adverse effects, plasma levels, and dose requirements. This is the only study included in this review that points towards CYP2D6 polymorphisms not affecting analgesia, plasma levels, and side effects.

Overall, the evidence in this review supports the theory that CYP2D6 polymorphisms affect the metabolism of numerous opiates leading to variances in serum levels and resulting analgesia and side effects. It is important to note that the CYP2D6 is not responsible for the metabolism of all opiates. Opiates such as oxymorphone, buprenorphine, and hydromorphone, as well as NSAIDs, are all metabolized by other P450 enzymes and, therefore, will not be affected by CYP2D6 polymorphisms (Crews et al., 2014). Also worth consideration are the numerous other genes involved in opiate metabolism. For example, polymorphisms exist for the catechol-O-methyltransferase (COMT) gene that is involved in the degradation of opiate metabolites and the OPRM-1 gene that codes for opiate receptors. It is the combined effort of

these genes and more that create the serum levels, analgesia, and adverse effects experienced by patients.

Application to Clinical Practice

The opioid crisis that began in the 1990s was a multifactorial issue created by pharmaceutical companies, doctors, pharmacists, and patients alike. In 2017, 47,600 people died from an opiate-related overdose, with 17,029 of these deaths directly related to a prescription acquired by legal means (CDC, 2018). The number of prescriptions related to opiate deaths is down-trending; however, the number of opiate-related deaths continues to rise as people now turn to heroin as it is cheaper and easier to acquire.

Because pain is an entirely subjective measurement, prescribers are put in a difficult position where they can prescribe too much opiate and risk patient dependence, or too little opiate in which the patient suffers from inadequately medicated pain. It was the goal of this paper to research a possible objective measure that could help guide the provider's prescriptive practices when it comes to opiates.

The evidence provided in this literature review indicates that the genetic polymorphisms that code for CYP2D6 PMs and UMs can have a statistically significant impact on the metabolism of certain opiates such as tramadol, codeine, hydrocodone, oxycodone, morphine, fentanyl, and methadone. PMs are shown to have lower serum levels of the active metabolite, resulting in higher pain levels and lower instances of adverse effects. Conversely, UMs are shown to higher levels of active metabolite leading to more effective analgesia and a higher risk of adverse effects and toxicity. The evidence supporting IM and EM phenotypes' effect on opiate metabolism is inconclusive.

The evidence regarding CYP2D6 pharmacogenetic testing is promising but has lengths to go regarding the clinical application. We know there are multiple enzymes responsible for opiate metabolism, yet research that accounts for the way these enzyme polymorphisms work together to account for treatment efficacy and side effects is lacking. It has also yet to be demonstrated how these polymorphisms relate to the occurrence of opiate dependence and addiction. Who is at risk? The PMs because of their higher requirement of medication to reach treatment success, the EMs because of their increased risk of side effects and toxicity, or both? The research outlined in this review is the first of many steps required in order to find these answers.

References

Akilillu, E., Persson, I., Bertilsson, L., Johansson, I., Rodrigues, F., Ingleman-Sundberg, M. (1996). Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. *Journal of Pharmacology and Experimental Therapeutics, 278*(1), 441-446. http://jpet.aspetjournals.org

Balyan, R., Mecoli, M., Venkatasubramanian, R., Chidambaran, V., Kamos, N., Clay, S., … Sadhasivam, S. (2017). CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. *Pharmacogenomics*, *18*(4), 337–348. http://dx.doi.org/10.2217/pgs-2016-0183

Center for Disease Control and Prevention. (2018). *Wonder Online Database: Mortality.* Retrieved from https://wonder.cdc.gov

Choi, S., Lam, D., Wong, S., Shiu, H., Wang, A., & Cheung, C. (2017). Effects of single nucleotide polymorphisms on surgical and post surgical opioid requirements – a systematic review and meta-analysis. *The Clinical Journal of Pain*, *33*(12), 1117-1130. http://dx.doi.org/10.1097/ajp.0000000000000498

Crews, K., Gaedigk, A., Dunnenberger, H., Leeder, J., Klein, T., Caudle, K., … Skaar, T. (2014). Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clinical Pharmacology & Therapeutics*, *95*(4), 376–382. http://dx.doi.org/10.1038/clpt.2013.254

Dagostino, C., Allegri, M., Napolioni, V., Dagnelli, S., Bignami, E., Mutti, A., & van Schaik, R. (2018). *CYP2D6* genotype can help to predict effectiveness and safety during opioid treatment for chronic low back pain: results from a retrospective study in an Italian cohort. *Pharmacogenomics and Personalized Medicine*, *Volume 11*, 179–191. http://dx.doi.org/10.2147/pgpm.s181334

Leon, D., Dinsmore, L., & Wedlund, P. (2003). Adverse drug reactions to oxycodone and hydrocodone in CYP2D6 ultrarapid metabolizers. *Journal of Clinical Psychopharmacology*, *23*(4), 420–421. http://dx.doi.org/10.1097/01.jcp.0000085421.74359.60

Linares, O., Fudin, J., Daly, A., & Boston, R. (2015). Individualized Hydrocodone Therapy Based on Phenotype, Pharmacogenetics, and Pharmacokinetic Dosing. *The Clinical Journal of Pain*, *31*(12), 1026–1035. http://dx.doi.org/10.1097/ajp.0000000000000214

Lloyd, R., Hotham, E., Hall, C., Williams, M., & Suppiah, V. (2017). Pharmacogenomics and Patient Treatment Parameters to Opioid Treatment in Chronic Pain: A Focus on Morphine, Oxycodone, Tramadol, and Fentanyl. *Pain Medicine*, *18*(12), 2369–2387. http://dx.doi.org/10.1093/pm/pnw317

Mclellan, R. A., Oscarson, M., Seidegard, J., Evans, D. A. P., & Ingelman-Sundberg, M. (1997). Frequent occurrence of CYP2D6 gene duplication in Saudi Arabians. *Pharmacogenetics*, *7*(3), 187–191. http://dx.doi.org/10.1097/00008571-199706000-00003

Ren, Z., et al. (2015). The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: A systematic review and meta-analysis. *Pain Physician. 18,* 131-152. https://www-ncbi-nlm-nih-gov.ezproxylr.med.und.edu/pubmed/25794200

Sauver, J., Olson, J., Roger, V., Nicholson, W., Black, J., Takahashi, P., … Bielinski, S. (2017). *CYP2D6* phenotypes are associated with adverse outcomes related to opioid medications. *Pharmacogenomics and Personalized Medicine*, *Volume 10*, 217–227. http://dx.doi.org/10.2147/pgpm.s136341

Smith, D., Weitzel, K., Elsey, A., Langaee, T., Gong, Y., Wake, D., … Cavallari, L. (2019). CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. *Genetics in Medicine*, *21*(8), 1842–1850. http://dx.doi.org/10.1038/s41436-018-0431-8

Stauble, M., Moore, A., Langman, L., Boswell, M., Baumgartner, R., Mcgee, S., … Jortani, S. (2014). Hydrocodone in postoperative personalized pain management: Pro drug or drug? *Clinica Chimica Acta*, *429*, 26–29. http://dx.doi.org/10.1016/j.cca.2013.11.015

Vieira, C., Fragoso, R., Pereira, D., & Medeiros, R. (2018). Pain polymorphisms and opioids: An evidence based review. *Molecular Medicine Reports*. http://dx.doi.org/10.3892/mmr.2018.9792