CYP2D6 Drug-Gene and Drug-Drug-Gene Interactions Among Patients Prescribed Pharmacogenetically Actionable Opioids

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Abstract

Purpose: When codeine and tramadol are used for pain management, it is imperative that nurses are able to assess for potential drug-gene and drug-drug-gene interactions that could adversely impact drug metabolism and ultimately pain relief. Both drugs are metabolized through the CYP2D6 metabolic pathway which can be affected by medications as well the patient's own pharmacogenotype. The purpose of this brief report is to identify drug-gene and drug-drug-gene interactions in 30 adult patients prescribed codeine or tramadol for pain.

Methods: We used three data sources: (1) six months of electronic health record data on the number and types of medications prescribed to each patient; (2) each patient's CYP2D6 pharmacogenotype, and (3) published data on known CYP2D6 gene-drug and drug-drug-gene interactions.

Results: Ten patients (33%) had possible drug-gene or drug-drug-gene interactions. Five patients had CYP2D6 drug-gene interactions indicating they were not good candidates for codeine or tramadol. In addition, five patients had potential CYP2D6 drug-drug-gene interactions with either codeine or tramadol.

Conclusion: Our findings from this exploratory study underscores the importance of assessing and accounting for drug-gene and drug-drug-gene interactions in patients prescribed codeine or tramadol.

Keywords: Drug-gene interaction, drug-drug-gene interaction, pharmacogenomics, pharmacogenetic testing, opioid, pain management, polypharmacy

Drug-gene and drug-drug-gene interactions can interfere with patients' abilities to metabolize codeine and tramadol for pain relief. Drug-gene interactions (DGIs) are defined as the influence of a patient's genetic makeup on the ability to metabolize or clear a drug.[1] Drug-drug-gene interactions (DDGIs) are defined as the effect of a patient's genetic makeup and another medication in their regimen (e.g., cytochrome P450 inhibitor or inducer) on that patient's ability to metabolize or clear a certain medication.[1] A medication that is a cytochrome P450 inhibitor prevents the abilities of a drug metabolizing enzyme (e.g., CYP2D6) to metabolize a medication, whereas a medication that is an inducer increases the abilities of an enzyme to metabolize a medication.[2] Therefore, DDGIs can alter a person's drug metabolizing status (e.g., changing a person from a normal to a poor metabolizer) and increase the risk of adverse events such as treatment non-response or toxicity.[3] Understanding both drug-gene and drug-drug-gene interactions are beneficial in predicting medication response. Current efforts to implement widespread pharmacogenetic testing in clinical practice require that nurses be knowledgeable about this field.[4]

The goal of implementing pharmacogenetic testing in clinical practice is to help address wide interindividual variations in response to medication therapies. Ideally, this testing would lead to improved clinical and economic outcomes through avoidance of adverse drug effects and medication non-response.[5-7] However, current clinical practice guidelines for pharmacogenetic testing account for drug-gene interactions but do not account for the complexity of patients' medication regimens.[8] Polypharmacy, or the concurrent taking of multiple medications, may increase the potential for adverse drug effects or medication non-response as a result of known or unknown drug-drug-gene interactions.[9] For example, a person with a normal pharmacogenotype may not adequately metabolize a given medication if they are taking a concurrent medication that inhibits or induces the metabolic pathway for that given medication. While there is a paucity of research exploring drug-gene and drug-drug-gene interactions in the context of pain management, clinicians and researchers must consider the potential impact of both when evaluating the effects of codeine and tramadol for pain relief.

The purpose of this brief report was to identify drug-gene and drug-drug-gene interactions in 30 adult patients prescribed codeine or tramadol for pain. Two pharmacogenetically actionable opioids (i.e., codeine and tramadol) were chosen as exemplar medications because they have evidence-based guidelines to guide drug or dosage changes based on pharmacogenetic test results.[10]

Methods

Design & Setting

This study was a retrospective analysis of 6-months of de-identified data from electronic health records (EHRs) and banked DNA specimens from a random selection of patients who were newly prescribed a pharmacogenetically actionable opioid in a primary care clinic within a large public health system that provides care for an underserved and low income population. Due to the de-identified

nature of this study, it was deemed non-human subjects research by the Office of Human Subjects Research.

Sample

The sample included 30 patients randomly selected from the population of patients who met the following inclusion criteria: 1) part of a managed care program for individuals falling at or below 200 percent of the federal poverty level, 2) first prescription of record for codeine or tramadol in at least one of the primary care clinics within the health system, 3) had a banked blood sample, 4) age 21 and older, and 5) had no documentation of substance abuse in the electronic health record. A 'first prescription of record' was defined as either codeine or tramadol being prescribed between January 1, 2010 and December 31, 2014 and no information in the patient's record that indicated that either medication had been previously prescribed.

Data & Procedures

Six months of EHR data for each patient were obtained from comprehensive data repositories. The 6-month time period started with the date of the new prescription for either codeine or tramadol and ended six months later. Data were accessed, extracted, and de-identified by a trained data analyst. The main repository where data originated was the Indiana Network for Patient Care, which is a large, multi-institutional information exchange that captures EHR data from more than 25,000 individual providers, 106 hospitals, and 110 clinics and surgery centers.[11] The repository allows for capturing information about patients' healthcare encounters across multiple clinics and health systems and information about medication orders and/or dispensing data from the safety-net health system, other health systems, and outpatient pharmacies within the region where this study was conducted. Other sources included clinical and administrative data repositories associated with the managed care program and public health system. The EHR data were linked to existing DNA specimens obtained from the biobank.

Patient characteristics and medication regimens. Demographic characteristics at the time of the new prescription for the pharmacogenetically actionable opioid were extracted from the EHR, including age, gender, and race. The medication regimen prescribed for each patient was identified through data elements including medication name, dose, dose frequency, route, administration instructions, and fill or refill dates. The mean number and range of medications prescribed per patient was determined over the 6-month time period. We also classified type of medication based on its indication (e.g., pain medications, cardiac medications, psychiatric medications, etc.) and calculated frequencies, mean number, and range of medications for that type.

CYP2D6 drug-gene interaction. A DGI occurs when the metabolization or clearance of a medication is influenced by a gene or genes.[1] In this study, we identified the effects of a patient's cytochrome P450 2D6 (CYP2D6) genotype on their ability to metabolize or clear codeine or tramadol. Both codeine and tramadol are considered prodrugs, meaning they are inactive and will not produce analgesic effects until metabolized into the active form of the drug. Therefore, we completed CYP2D6

genotype analyses on the banked DNA specimens for all patients in this study. The genotype results were then used to calculate the CYP2D6 enzyme activity score.[10] The activity score is used to identify the drug metabolizing status (i.e., phenotype) classification and is determined by the sum of values assigned to each CYP2D6 star allele making up the diplotype.[10] The drug metabolizing status classification includes ultra-rapid (activity score: >2), normal (activity score: 1-2), intermediate (activity score: 0.5), and poor (activity score: 0). The genotyping was performed for the CYP2D6 star alleles *2, *3, *4, *5, *6, *9, *10, *17, *29, and *41 using the QuantStudio (Thermo Fisher Scientific, Inc., Grand Island, NY) and following the manufacturer's instructions of the Taqman Genotyping Assays (Applied Biosystems, Inc., Foster City, CA). These star alleles were chosen because they have common variants that influence both codeine and tramadol drug disposition and response, as well as their frequencies in Caucasian, African and their descendant populations.[12] We completed quality controls for each sample batch and repeated assays for 20% of samples. We had a genotype call rate, defined as the proportion of genotypes per marker with non-missing data[13], of 99.4%. This underscores the quality of our samples and genotyping procedures.

CYP2D6 drug-drug-gene interactions. A DDGI occurs when there is an interaction between an individual's CYP2D6 genotype and a medication that affects a person's ability to appropriately metabolize a different medication (e.g., codeine, tramadol).[1] In this study, we identified a potential DDGI was present if two medications had known CYP2D6 interactions and that the supply amount dispensed for each medication overlapped. For example, if a 30-day supply of tramadol was dispensed 10 days following a 60-day supply of fluoxetine being dispensed, we assumed that these two medications would be taken concurrently and coded these data as a DDGI present. The Flockhart Table™ for cytochrome P450 drug interactions served as the reference for identifying DDGIs in this sample (http://medicine.iupui.edu/clinpharm/ddis/main-table).[2]

To determine the effects of the DDGI on the CYP2D6 drug metabolizing status, we then adjusted the CYP2D6 enzyme activity score (identified from the CYP2D6 genotyping processes described above) for each patient based on identified DDGIs that would alter the CYP2D6 enzyme activity.[2] For drug interactions with strong inhibitors of the opioid, the final activity score of 0 was assigned. For drug interactions with moderate inhibitors of the opioid, the CYP2D6 enzyme activity score was multiplied by 0.5 to identify the final activity score.[14] Consequently, the drug metabolizing status for each patient was then determined from the final activity score.[10]

Results

The sample consisted of 30 adults (16 female), of whom 60% were White and 40% were Black or Biracial. The mean age was 50.9 years (SD = 10.4; range = 23 – 65 years). The majority of patients were prescribed tramadol (*n* = 24), with fewer prescribed codeine (*n* = 6). Patients received an average of 10 different medication prescriptions over the 6-month time period (range = 2-24). A mean of 3 different pain medications were prescribed per patient, of which one was either codeine or tramadol per

inclusion criteria. Apart from the pain medications, the most common class of medications prescribed were for cardiovascular conditions (*n* = 23, 77% of sample), with 2.9 medications per patient for indications such as hypertension, dyslipidemia, and anticoagulation. In addition, 60% (*n* = 18) of the sample were prescribed medications for psychiatric problems such as depression or anxiety.

There were a total of 10 patients (33%) adversely affected by a DGI or DDGI. Adverse DGIs were present in 17% of the sample (n=5) (Table 1). Two patients were poor metabolizers, one patient an intermediate metabolizer, and two patients were considered ultra-rapid metabolizers. These patients would not be good candidates for codeine or tramadol due to the increased likelihood they would experience adverse drug effects or treatment non-response. The remaining patients were normal metabolizers (n=25) of the codeine or tramadol.

DDGIs were present in 17% of the sample (n=5) (Table 2). Based solely on the pharmacogenetic genotyping results, and not considering the effects of the DDGI on the patient's CYP2D6 drug metabolizing status, all of these patients were initially considered normal metabolizers. However, the identified DDGIs involved either a strong (*n* = 4) or moderate inhibitor (*n* = 1) of the prescribed opioid, which altered patients' CYP2D6 metabolizer status. As a result, four additional patients were ultimately classified as CYP2D6 poor metabolizers and one was classified as a CYP2D6 intermediate metabolizer.

Discussion

Findings from this exploratory study suggest that both drug-gene and drug-drug-gene interactions can be an issue in both clinical practice and research. Of note, 33 percent (*n* = 10) of our sample had altered CYP2D6 metabolizing status as a result of such interactions. Five different patients were identified with CYP2D6 drug-gene interactions and five additional patients were identified with potential CYP2D6 drug-drug-gene interactions with the pharmacogenetically actionable opioids. All interactions would result in altering their metabolizing status and result in no or decreased analgesia or enhanced side effects from tramadol or codeine.[10] These findings are consistent with larger studies evaluating similar interactions.[1, 9]

Our findings highlight a number of clinical and research considerations. The fact that numerous patients in this study had altered CYP2D6 metabolizing status underscores the potential benefits of implementing pharmacogenetic testing in practice. Without determining these patients CYP2D6 pharmacogenotype, these drug-gene and drug-drug-gene interactions would go undetected. In addition, this study provides important illustrations of why pharmacogenetic test results and complete medication regimens should be considered in tandem by nurses. Consequently, nurses need to consider drug-gene and drug-drug-gene interactions when assessing and educating patients about their medication regimens. Furthermore, future research is necessary to confirm and extend our findings. Studies that identify CYP2D6 drug-gene and drug-drug-gene interactions in a larger sample

and the impact of these interactions on patient outcomes (e.g., pain relief, adverse events) are warranted.

Conclusion

The findings from this exploratory study underscore the importance of assessing and accounting for drug-gene and drug-drug-gene interactions in patients prescribed codeine or tramadol. We found that pharmacogenetic test results that identified drug-gene interactions were only part of the story and that the complexity of complete medication regimens added significantly to understanding patients' abilities to appropriately metabolize these opioid medications. Therefore, future research and clinical guidelines must also account for potential for drug-drug-gene interactions.

Table 1. *Patients with Adverse Cytochrome P450 2D6 (CYP2D6) Drug-Gene Interactions*

CYP2D6 Drug Metabolizing Status	Patient ID	CYP2D6 Diplotype	CYP2D6 Activity Score	Prescribed PGxA Opioid	Clinical Interpretation
Poor Metabolizer	12	*4/*5	0	Tramadol	Patients are carrying no functional CYP2D6 alleles. Increased risk for lack of opioid efficacy.
	22	*4/*4	0	Codeine	
Intermediate Metabolizer	21	*5/*41	0.5	Tramadol	Patient carrying a reduced function CYP2D6 allele and a non-functional CYP2D6 allele. Increased risk for reduced opioid efficacy.
Ultra-rapid Metabolizer	5	*1/*17	>2	Tramadol	Patients are carrying more than 2 copies of functional CYP2D6 alleles. Increased risk for potential opioid toxicity.
	17	*2/*2xN	>2	Tramadol	

Note: This table only includes patients with adverse CYP2D6 drug-gene interactions and does not include patients (n = 25) who were considered to be normal CYP2D6 drug metabolizers.
PGxA: pharmacogenetically actionable

Table 2. *Patients with Cytochrome P450 2D6 (CYP2D6) Drug-Drug-Gene Interactions & Clinical Interpretations*

Patient ID	CYP2D6 Diplotype	CYP2D6 Genotype Activity Score	CYP2D6 DIs	Final CYP2D6 Activity Score	Final CYP2D6 Drug Metabolizing Status	Clinical Interpretation
07	*1/*41	1.5	Diphenhydramine[1] – tramadol	0	Poor Metabolizer	Tramadol: Avoid medication due to lack of efficacy.
11	*2/*5	1	Diphenhydramine[1] – tramadol	0	Poor Metabolizer	Tramadol: Avoid medication due to lack of efficacy.
16	*1/*5	1	Fluoxetine[1] – tramadol	0	Poor Metabolizer	Tramadol: Avoid medication due to lack of efficacy.
19	*1/*4	1	Bupropion[1] – codeine	0	Poor Metabolizer	Codeine: Avoid medication due to lack of efficacy.
23	*1/*4	1	Duloxetine[2] – tramadol	0.5	Intermediate Metabolizer	Tramadol: Avoid medication due to reduced efficacy.

DI: Drug interaction; [1] CYP2D6 strong inhibitor: Final CYP2D6 Activity Score = 0; [2] CYP2D6 moderate inhibitor: multiply CYP2D6 Genotype Activity Score by 0.5 to determine Final CYP2D6 Activity Score.

References

1. Verbeurgt, P., Mamiya, T., & Oesterheld, J. (2014). How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. *Pharmacogenomics, 15*(5), 655-665.
2. Love, R. R., Desta, Z., Flockhart, D., Skaar, T., Ogburn, E. T., Ramamoorthy, A., . . . Jarjoura, D. (2013). CYP2D6 genotypes, endoxifen levels, and disease recurrence in 224 Filipino and Vietnamese women receiving adjuvant tamoxifen for operable breast cancer. *Springerplus, 2*(1), 52.
3. Brixner, D., Biltaji, E., Bress, A., Unni, S., Ye, X., Mamiya, T., . . . Biskupiak, J. (2016). The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. *J Med Econ, 19*(3), 213-228.
4. Levy, K., Decker, B., Carpenter, J., Flockhart, D., Dexter, P., Desta, Z., & Skaar, T. (2014). Prerequisites to implementing a pharmacogenomics program in a large healthcare system. *Clinical Pharmacology & Therapeutics, 93*(3), 307-309.
5. Arnaout, R., Buck, T. P., Roulette, P., & Sukhatme, V. P. (2013). Predicting the cost and pace of pharmacogenomic advances: an evidence-based study. *Clin Chem, 59*(4), 649-657.
6. Ross, S., Anand, S. S., Joseph, P., & Pare, G. (2012). Promises and challenges of pharmacogenetics: an overview of study design, methodological and statistical issues. *JRSM Cardiovasc Dis, 1*(2), 1-13.
7. Zdanowicz, M. (2010). *Concepts in Pharmacogenomics*. Bethesda, MD: American Society of Health-System Pharmacists.
8. Bahar, M. A., Setiawan, D., Hak, E., & Wilffert, B. (2017). Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics, 18*(7), 701-739.
9. Hocum, B. T., White, J. R., Jr., Heck, J. W., Thirumaran, R. K., Moyer, N., Newman, R., & Ashcraft, K. (2016). Cytochrome P-450 gene and drug interaction analysis in patients referred for pharmacogenetic testing. *Am J Health Syst Pharm, 73*(2), 61-67.
10. Crews, K. R., Gaedigk, A., Dunnenberger, H. M., Leeder, J. S., Klein, T. E., Caudle, K. E., . . . Skaar, T. C. (2014). Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther, 95*(4), 376-382.
11. Indiana Health Information Exchange. (n.d.). Indiana Network for Patient Care. Retrieved January 11, 2016, from http://www.ihie.org/indiana-network-for-patient-care
12. Hicks, J. K., Bishop, J. R., Sangkuhl, K., Muller, D. J., Ji, Y., Leckband, S. G., . . . Gaedigk, A. (2015). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clin Pharmacol Ther, 98*(2), 127-134.
13. Anderson, C. A., Pettersson, F. H., Clarke, G. M., Cardon, L. R., Morris, A. P., & Zondervan, K. T. (2010). Data quality control in genetic case-control association studies. *Nature protocols, 5*(9), 1564-1573.
14. Borges, S., Desta, Z., Jin, Y., Faouzi, A., Robarge, J. D., Philips, S., . . . Li, L. (2010). Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. *J Clin Pharmacol, 50*(4), 450-458.

Highlights

- CYP2D6 drug-gene and drug-drug-gene interactions can interfere with patients' abilities to metabolize codeine and tramadol for pain relief.
- 33% of the sample were affected by a CYP2D6 drug-gene or drug-drug-gene interaction.
- Findings suggest that both drug-gene and drug-drug-gene interactions can be an issue in both clinical practice and research.