UNDERSTANDING EXPOSURE TO PHARMACOGENETICALLY ACTIONABLE OPIOIDS IN PRIMARY CARE

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Pharmacogenetic testing has the potential to improve pain management through addressing wide interindividual variations in responses to pharmacogenetically actionable opioids, ultimately decreasing costly adverse drug effects and improving responses to these medications. A recent review of pharmacogenomics in the nursing literature highlighted the need for nurses to more fully embrace the burgeoning field of pharmacogenomics in nursing research, clinical practice, and education. Despite the promise of pharmacogenetic testing, significant challenges exist for evaluating outcomes related to its implementation, including oversimplification of medication exposure, the complexity of patients' clinical profiles, and the characteristics of healthcare contexts in which medications are prescribed. A better understanding of these challenges could enhance the assessment and documentation of the benefits of pharmacogenetic testing in guiding opioid therapies. This dissertation is intended to address the challenges of evaluating outcomes of pharmacogenetic testing implementation and the need for nurses to lead pharmacogenomic-related research. The dissertation purpose was to advance the sciences of nursing, pain management, and pharmacogenomics through the development of a typology of common patterns of medication exposure to known pharmacogenetically actionable opioids (codeine & tramadol). A qualitative, person-oriented approach was used to retrospectively analyze six months of electronic health record and pharmacogenotype data in 30 underserved adult patients. An overarching typology with eight groups of patients that had one of five opioid prescription patterns (singular, episodic, switching, sustained, or multiplex) and one of three types of medical

emphasis of care (pain, comorbidities, or both) were identified. This typology consisted of a description of multiple common patterns that compare and contrast salient factors of exposure and the emphasis of why individuals were seeking care. Furthermore, in an aggregate descriptive analysis evaluating key clinical profile factors, these patients had complex medical histories, extensive healthcare utilization, and experienced significant polypharmacy. These findings can aid in addressing challenges related to the implementation of pharmacogenetic testing in clinical practice and point to ways in which nurses can take the lead in pharmacogenomics research. Findings also provide a foundation for future studies aimed at developing medication exposure measures to capture its dynamic nature and identifying and tailoring interventions in this population.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADDs	Atypical antipsychotic drugs
ADHD	Attention Deficit Hyperactive Disorder
CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP2D6	Cytochrome P450 2D6
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
FDA	United States Food and Drug Administration
GI	Gastrointestinal
ICD-9	International Classification of Diseases, Ninth Revision
IM	Intermediate metabolizer
NM	Normal metabolizer
PGRN	Pharmacogenomics Research Network
PGxA	Pharmacogenetically actionable
PM	Poor metabolizer
PONV	Post-operative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	Standard deviation
UM	Ultra-rapid metabolizer

CHAPTER 1

This chapter introduces the dissertation topic of the development of a typology of common patterns of exposure to known pharmacogenetically actionable opioid medications (codeine and tramadol) in a primary care setting. The chapter provides a discussion of the significance of the topic, identifies the purpose of the dissertation, and outlines the study methods.

Background & Significance

Significance of Pain

Pain is a prevalent, costly, and inadequately managed health problem. The most common reason Americans seek healthcare is pain,[1] "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms."[2] Acute pain is a protective sensation alerting an individual to a possible or actual tissue injury lasting a short period of time, whereas chronic pain is pain or discomfort lasting long beyond its useful and protective function.[3, 4] Chronic pain affects 100 million people in the United States and produces annual costs of $635 billion, making it the most prevalent and costly health condition.[3] Additionally, one in four, or 76.2 million, Americans have experienced pain lasting longer than 24 hours.[1, 5] Approximately 50% of individuals with acute or chronic non-cancer pain experience inadequate management of their pain.[4, 6] Inadequate pain management leads to an array of negative consequences such as development of chronic pain syndromes, decreased functional status and health-related quality of life, disability, increased demands on the health system, and economic burdens including increased healthcare expenditures and disability compensation.[3, 4, 7]

Pain & Pharmacogenomics

It is crucial for pain management science to incorporate the rapidly evolving field of pharmacogenomics, the study of individual genetic variations associated with drug

metabolism and response.[8] One reason for inadequately managed acute or chronic pain is genetic variation.[8-11] Genetics can influence the pharmacodynamics and pharmacokinetic disposition of opioids.[12] Genetic variations are associated with adverse drug effects and poor drug response, ultimately leading to poor patient outcomes.[11, 13]

Opioid medications have been a mainstay for the treatment of pain for years. Unfortunately, there are wide individual variations in analgesic efficacy and adverse drug effects to commonly prescribed opioids that are known to be pharmacogenetically actionable, such as codeine and tramadol which have evidence based guidelines to guide prescribing decisions based on pharmacogenetic test results.[10] Approximately 10% of Caucasians receive inadequate or no analgesia from codeine due to genetic variations in the CYP2D6 enzyme metabolizing the drug to its active form, morphine.[14-16] Furthermore, 3% of Caucasians ultra-rapidly metabolize codeine due to genetics, which increases the incidence of drug-related adverse events and reactions.[17] Like codeine, tramadol is metabolized by the same CYP2D6 enzyme and people have varied clinical responses due to genetic variations.[18, 19]

Implementing Pharmacogenetic Testing in Clinical Practice

International and national guidelines for medication dosing adjustments based on pharmacogenetic test results exist,[20] but have not been widely implemented in practice.[21-24] It is broadly believed that making dose and medication adjustments based on pharmacogenetic testing can improve clinical and economic outcomes through decreasing costly adverse drug reactions and improving medication response.[8, 25-28] As pharmacogenetic testing becomes more integrated within routine clinical practice, it will be necessary to further evaluate its impact on clinical and economic outcomes that are related to the use of pharmacogenetically actionable opioids.[29, 30] However, there have been numerous methodological challenges noted when evaluating the effects of

pharmacogenetic testing, including medication exposure measurement errors and the complexity of patients, clinical context, and diseases being treated.[28, 31, 32]

Medication exposure. Medication exposure can be defined as the condition of being subjected to a medication. Medication exposure includes multiple factors such as the medication and dose prescribed, the medication regimen, and changes in the regimen over time.[33] Although there is no standardized measure for medication exposure, medication exposure is dynamic and can change from day to day or month to month. Consequently, an exposure measure should capture medication use beyond a single event.[34]

In general, studies and meta-analyses evaluating the efficacy or effectiveness of pharmacogenetic testing have oversimplified medication exposure and fail to capture its dynamic and heterogeneous state in relation to actual or predicted outcomes.[26, 35, 36] To date, only a handful of data-based articles have reported on exposure to known pharmacogenetically actionable medications, including opioids.[26-28, 36] These studies have counted the number of patients taking such medications. Among 52,942 primary care patients, for example, 65% of patients received a prescription for at least one pharmacogenetically actionable medication and at least 23% were prescribed three or more during a 5-year period.[36] More than 10% of these patients received a prescription for tramadol or codeine.[36] In another study of 1,013 primary care patients at high risk for starting statin therapy, 75% were prescribed tramadol and 48% were prescribed codeine at least once during a 20-year period.[23] Other studies have evaluated characteristics of opioid exposure (e.g., dose[37-41]; co-administered analgesics and other medications[39, 41, 42]; dosing schedule[38]; and whether a medication was discontinued[43]); however, these studies have all used traditional variable-oriented approaches to data analysis. Variable-oriented approaches use the variable (e.g., total number of patients taking opioid medications) as the main conceptual and analytic unit, resulting in a failure to capture

the holistic view, complexity, and the interplay among variables (factors) of medication exposure at the person level.[44]

Contextual factors. Understanding contextual influences, or the factors that are not directly part of existing evidence-based pharmacogenetic guidelines, can increase certainty of the relationship between outcomes and the implementation of pharmacogenetic testing.[45] Unfortunately, clinical guidelines that are used as a foundation for practice changes are limited in relation to the context in which medications are prescribed.[46] Contextual factors, such as a patient's clinical profile, have the ability to influence medication exposure to pharmacogenetically actionable opioids and confound outcomes being evaluated to determine benefits of the implementation of pharmacogenetic testing.[28, 31, 32] Currently, studies are limited in exploring or including contextual influences that could impact outcomes related to the use of pharmacogenetic testing to guide opioid therapies in clinical practice.

Using A Person-oriented Approach to Understand of Medication Exposure

A person-oriented approach (consisting of 2 components – person-oriented theory and person-oriented methods) is ideal for more completely understanding the realities of exposure to pharmacogenetically actionable opioids in which salient factors and needs occurring at the level of the whole person can be captured through the development of typologies.[44, 47, 48] Person-oriented approaches view the individual as an organized whole, functioning and developing as a totality, with the totality being formed by all factors involved.[44] For example, knowing a patient is taking tramadol (measured either as *no/yes* tramadol or as taking *no vs. one* medication known to be pharmacogenetically actionable) fails to reflect the true regimen complexity. A prescription for tramadol might be written as 25 mg daily with instructions to increase by 25 mg every three days until a final dose of 100 mg is reached. Additionally, individuals experiencing pain often seek new opioid prescriptions or modifications to medication

regimens from multiple providers[49]; thus, identifying where the opioid prescription originated and where adjustments to opioid regimens are made is important (e.g., emergency department, specialty clinic). Therefore, to truly reflect the complexity of the regimen and to classify the pattern of exposure appropriately, it is necessary to understand a wide array of information such as complete prescription details (e.g., whether the medication dose was increased or reduced, whether it was discontinued and another started, prescriber), clinical responses (e.g., adverse events), and health care utilization (e.g., where modifications to regimen were made; need for clinic, hospital, emergency department visits). In a person-oriented approach, typologies are developed to organize these factors[47, 50] to understand patterns and commonalities.[50]

This approach can be beneficial to clinicians, researchers, and policy makers since they are continuously challenged to address the health needs of individuals and populations without a comprehensive picture of the relevant factors.[51] Developing a typology will provide important baseline information to more comprehensively understand factors most salient in determining how medication exposure unfolds over time as well as meaningful subgroups of individuals that share common patterns of medication exposure.

Topical Fit to National Priorities

Understanding medication exposure to pharmacogenetically actionable opioids meets national nursing research priorities. The National Institute of Nursing Research's Strategic Plan emphasizes the need to explore multiple factors, including health determinants such as psychological, physiological, genomic, and environmental factors, that influence health promotion and self-management of acute and chronic conditions such as pain.[52] Because medication management is a significant component of self-management, identifying the multidimensional and complex patterns of medication exposure is a necessary step to inform strategies to improve health promoting and self-

management behaviors.[52-54] Thus nurse scientists are in a unique position to provide a holistic, person-oriented evaluation of medication exposure of individuals receiving pharmacogenetically actionable medications. This will aid in identifying factors most salient in determining how exposure unfolds over time and understanding the health needs of individuals seen in primary care who experience acute or chronic pain.

This research also addresses key research issues identified in the Summary Report of the NIH-sponsored 2014 Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain. This Report highlighted the need to more comprehensively understand drug-related, genetic, and other patient-related factors affecting the use of opioids in managing pain.[55] There is a paucity of research in this area. Therefore, detecting common patterns of exposure to pharmacogenetically actionable opioid medications and related factors will contribute to the advancement of the interdisciplinary sciences of nursing, pain management, and pharmacogenomics more broadly.

Aims of the Dissertation

The overarching goal of this dissertation is to advance the sciences of nursing, pain management, and pharmacogenomics through developing a typology describing common patterns of exposure to known pharmacogenetically actionable opioid medications (tramadol and codeine). To achieve this goal, three different yet related manuscripts were developed and are presented as Chapters 2, 3, and 4 within this dissertation.

Chapter 2 consists of a comprehensive review of the state of the science of pharmacogenomics as reflected in the nursing literature, with specific aims to critically examine: (1) the concepts of pharmacogenomics and pharmacogenetics; (2) pharmacogenomic and pharmacogenetic clinical practice applications; and (3) nursing's responsibilities in pharmacogenomics and pharmacogenetics. The primary purpose of

Chapter 3 was to employ a qualitative person-oriented approach to develop a typology that identified meaningful subgroups that shared common patterns of medication exposure within a sample of patients newly prescribed a pharmacogenetically actionable opioid in primary care clinics part of a safety-net health system. And finally, the goal of **Chapter 4** was to describe the context in which pharmacogenetically actionable opioids were prescribed, including patients' comorbidities, healthcare utilization, and polypharmacy, in a large safety-net health system.

In the following sections of this chapter, the theoretical and methodological basis and approaches of obtaining data and conducting analyses to develop the typology of medication exposure to pharmacogenetically actionable opioids are discussed.

Approach

Theoretical & Methodological Basis

A person-oriented approach was used in lieu of a more traditional variable-oriented approach. In a person-oriented approach, the individual is the analytic unit and patterns of salient factors related to the phenomenon of interest are used to divide a heterogeneous sample into subgroups that share common characteristics.[44, 56] In a variable-oriented approach, variables that capture theoretical constructs are the primary analytic units and relationships among these variables are investigated. Although the strengths of variable-oriented approaches are well known and include the power of inferential statistics and model testing to yield causal inferences, only analyzing pairwise relationships among variables and ignoring patterns at the person level can fail to reflect the complex ways variables are inter-related within subgroups.[57]

The person-oriented approach has two components; theory and methods.[48] Person-oriented theory, rooted in develomental psychology, consists of the following tenets: (1) The structure and dynamics of behavior are partly specific to individuals; (2) the phenomenon being studied is complex and is conceptualized as involving many

factors interacting at various levels that may be mutually related in a complicated manner; (3) there is lawfulness and structure to intra-individual constancy and change as well as inter-individual differences in constancy and change; (4) processes develop in a lawful way and can be described as patterns; (5) meaning of the involved factors is defined by the interactions among these factors; and (6) some patterns occur more frequently whereas others occur less frequently than expected.[44, 48] Person-oriented research methods based on person-oriented theory focus on individual cases or homogeneous groups. Though many data analytic techniques based on a person-oriented theory are quantitative in nature (e.g., configural frequency analysis), qualitative techniques, such as cross-case analysis,[58] provide another way of identifying and describing homogeneous subgroups within a larger population.

Factors to include in the person-oriented analysis were derived from the literature (see Figure 1-1). Patient factors are known to influence opioid prescribing and use including demographics[59-67], past medical history[68-75], and pharmacogenetic genotyping.[76, 77] Medication information important to determining exposure includes opioid dose, frequency, and duration over time[34, 37-43]; co-prescribed medications[39, 41, 42]; and prescriber.[49, 62, 78] Clinical response to opioids is assessed in terms of pain intensity[68-70, 72, 74, 75, 79, 80] and adverse events[68-70, 74, 75, 80] and these can impact healthcare utilization (clinic visits, emergency department visits, hospital admission).[49, 55, 79, 81]

Design

This was a retrospective, 6-month, longitudinal analysis of de-identified, electronic health records and DNA from banked blood samples. The electronic health records were housed and maintained at the Regenstrief Institute, and those records are linked to blood samples within the Indiana Biobank.

Sample

Inclusion criteria and rationale. Electronic health records were obtained from a cohort of patients meeting the following inclusion criteria:

1) First prescription of record for codeine or tramadol in primary care clinics within the past 5 years (1/1/10-12/31/14);
2) member of the Eskenazi Health's Health Advantage managed care program;
3) have a blood sample in the Indiana Biobank;
4) age 21 or older; and
5) no documentation of substance abuse in the electronic medical record.

Rationale for inclusion criteria. Eskenazi Health's Health Advantage is a managed care program, consisting of more than 52,000 members, providing high-quality, seamless medical care to low-income and uninsured residents of Indianapolis falling at or below 200% of the federal poverty level and not qualifying for any other assistance program.[82] This population was chosen because the members of Health Advantage must seek care at Eskenazi Health affiliated clinics for coverage and all health records that are part of this plan, including outpatient pharmacy records, are tracked, stored, and accessible through the Regenstrief Institute. Additionally, the Regenstrief Institute has the ability to include data from the Indiana Network for Patient Care, which captures health records and utilization outside of the Eskenazi Health system. The 5-year time frame to identify electronic health records meeting inclusion criteria was selected to help limit any external influences (e.g., legislative changes) that would change provider prescribing practices affecting medication exposure for the included cases. Additionally, codeine and tramadol were chosen because, at the time of this study, these are the only opioid medications with actionable pharmacogenetic information on FDA drug labels.[20] All trade and generic versions of each of the opioids will be included. For example, there are two different formulations for tramadol, tramadol

hydrochloride and tramadol hydrochloride with acetaminophen.[83] Prescriptions for either one will be used to identify eligible patients (cases). Electronic health records of individuals with known substance abuse will be excluded because this population may have distinct patterns of exposure and it will be difficult to ferret out whether their exposure to opioids is related to appropriate use for analgesia or for other non-medical reasons.[51]

Random selection and sampling. Random selection aided in ensuring the sample was representative of the Eskenazi Health primary care population. Eskenazi patients, 91% of whom are from Marion County, are broadly representative of underserved patients falling within the Index of Medical Underservice scale scores of 0 to 61.60, where 0 is completely underserved to 100 best served (62 or less qualifies as underserved).[84]

The Regenstrief Institute and Indiana Biobank provided a dataset of all electronic health records (*N* = 118) meeting the inclusion criteria. A multiple-case sample was produced through randomly selecting a subset of these records using a random numbers table. Published recommendations for a multiple-case sample ranges from 10-30 cases due to the required in-depth analysis as the complexities from larger samples would become unwieldy.[58] Thus, this study included data from 30 records (cases) for analysis.

Study Procedures

Institutional review and approval. Prior to beginning this research the Indiana University Human Subjects Office confirmed the study was non-human subjects research. Private, identifiable information was not accessible and only de-identified electronic health record data and de-identified samples were provided for use in this study. Thus, the research did not involve human subjects and IRB review was not required.[85]

Data use agreements. A data use agreement was signed with the Regenstrief Institute and the Indiana Biobank for the electronic health record data and blood samples. Regenstrief's data analyst abstracted and provided access to the de-identified data from electronic health records. The blood samples were released to the clinical pharmacology laboratory for pharmacogenetic genotyping.

Regenstrief electronic health records data. Six months of electronic health record data for each individual were obtained – starting with the first prescription date through the following six months. Regenstrief's clinical data analysts used a process to de-identify dates and times through date offsets. Instead of using actual dates/times for any particular health record, a random number was assigned and attached to the calendar for every associated event. Importantly, the temporal relationship between subjects and events was kept in the study data while de-identifying actual dates. For example, the number 8 might be randomly selected for a patient seen on January 15th and February 15th. The dates in the dataset would appear as January 23rd (15 + 8) and February 23rd, thus de-identifying the actual dates while still preserving the temporal sequencing of events, including the time lag between encounters.

To reflect the person-level factors pertinent to medication exposure, data fields (factors) capturing the following were obtained from the electronic health records:

- Patient characteristics: Demographics of 1) age, 2) gender, 3) race/ethnicity, and 4) past medical history (ICD-9 codes).
- Medication characteristics (every time any prescription is prescribed and filled/refilled [opioids or other medications] in the 6-month time period specified above): 1) medication, 2) dose, 3) dose frequency, 4) route, 5) administration instructions, and 6) prescriber (a de-identified unique number for each prescriber).

- Clinical response (captured during each healthcare encounter over the 6-month time period): 1) any documented adverse events (based on ICD-9 codes), and 2) pain intensity.
- Healthcare utilization:
    - *Clinic visits* (each clinic visit in the 6-month time period): 1) name/specialty of clinic, 2) reason for visit (ICD-9 codes), 3) documented medication history (including over-the-counter medications), and 4) newly prescribed medications.
    - *Emergency department visit* (each occurrence in the 6-month time period): 1) reason for visit, 2) documented medication history, and 3) newly prescribed outpatient medications.
    - *Hospital admission* (each occurrence in the 6-month time period): 1) reason for visit, 2) documented past medical history, 3) newly prescribed outpatient medications, and 4) length of stay (calculated from admission and discharge dates).

Indiana Biobank blood samples. Cytochrome P450 2D6 (CYP2D6) pharmacogenetic genotype was determined for the 30 cases in this study. The CYP2D6 gene is highly polymorphic, therefore, we genotyped common variants that influence both codeine and tramadol drug disposition and response.[46] Samples of extracted DNA in the amount of 350 ng/sample and a concentration of 10 ng/µl were released to the clinical pharmacology laboratory for storage and analysis. The extracted DNA was further diluted to a final concentration of 5.8 ng/µl. Using Taqman Genotyping Assays (Applied Biosystems, Inc.) following the manufacturer's instructions and QuantStudio (Thermo Fisher Scientific, Inc., Grand Island, NY), genotyping was performed for the CYP2D6 alleles *2, *3, *4, *5, *6, *9, *10, *17, *29, and *41. These star alleles were

chosen because of their frequencies in Caucasian and African populations and their descendants.[86] Quality controls were run for each sample batch and repeated measures were conducted on 20% of samples for further validation. Based on the genotype results, the CYP2D6 activity score was determined for each case.[46]

Analysis

Data Management

Data were maintained on a secure data server in a limited access folder meeting standards for storing research-related electronic, protected health information regulated by the Health Insurance Portability and Accountability Act of 1996. There was no risk for loss of confidentiality since all data are de-identified.

Data Analysis

Sample characteristics were described using descriptive statistics (e.g., means, standard deviations, frequencies, and percentages) using SPSS™ 23.0 (IBM, Armonk, NY). The remaining data analysis was conducted in three iterative steps of 1) data condensation, 2) data display (creating matrices), and 3) drawing and verifying conclusions.[58] Data analysis was interactive with assistance and verification from dissertation co-chairs.

Using each of the 30 patients with all corresponding data fields (factors) as a case, a within-case analysis as described by Miles et al.[58] was completed. The goal of a within-case analysis is to "describe, understand, and explain what has happened in a single, bounded case (p. 100)."[58] To complete this, data was condensed (a process of selecting, simplifying, abstracting, and transforming the data into an interpretable format[58]) and organized in a case-by-time (time-ordered) meta-matrix in which patient characteristics (age, gender, race/ethnicity, CYP2D6 activity score) were on the vertical axis and all other factors (medication characteristics, clinical responses, healthcare utilization) were organized by month on the horizontal axis. The case-by-time matrix

allowed for development of an in-depth (narrative) description of each case posing which factors seem to be most salient in determining how opioid exposure unfolds over time.

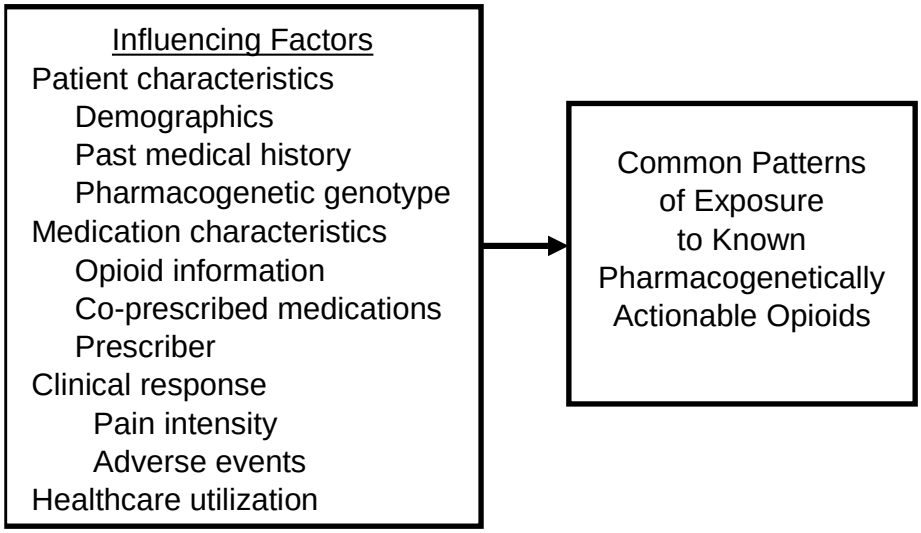
In typology construction, the phenomena should be understood and explained with meaningful relationships derived from empirically founded groups or clusters of cases.[50] Using the narrative data in the case-by-time meta-matrix from the within-case analysis, cross-case analytic procedures were applied.[58] Cross-case analysis seeks to determine whether multiple cases cluster into groups sharing certain patterns or configurations providing the ability to deepen the understanding and explanation of similarities and differences across multiple cases.[58] The cases were examined for repeating patterns of factors of exposure to the opioids and cases that share patterns were juxtaposed by moving rows in a partially-ordered meta-matrix. Cases that are clustered in this way were examined as a group to determine similarities and differences. If the cases shared similar patterns in factors of exposure, the patterns were considered a common trajectory. The goal of the cross-case analysis was to identify a parsimonious number of trajectories with common features without forcing the groupings or producing finely grained distinctions. Each trajectory was examined for critical factors that influence exposure to the opioids and a detailed descriptive narrative of each trajectory was constructed. These data were presented in a two-by-two variable matrix in which each column and row represented different factors detailing exposure to known pharmacogenetically actionable opioids.

Trustworthiness of Research

Trustworthiness of the research was further established through a series of published techniques[87], including establishing credibility, transferability, dependability, and confirmability. Credibility (confidence in the truth of the findings) was evaluated during frequent meetings with the dissertation co-chairs. At each meeting we discussed emerging patterns to see if the investigator's conclusions were consistent with both co-

chairs' conclusions. Transferability (showing findings have applicability in other contexts) was evaluated by thorough review from interdisciplinary partners (i.e., pharmacologist and health economist) and will need to be further evaluated through validation studies with different medications and/or populations. Dependability (findings are consistent and could be repeated) was achieved by the investigator documenting detailed analytic memos throughout the analysis process to identify his thoughts about how the data was structured into clusters, patterns, or themes.[54] Confirmability (findings are shaped by data and not researcher bias) was realized through a rigorous, written self-examination of biases and presuppositions that was discussed with both dissertation co-chairs, and then bracketed during data analysis. Frequent meetings were held with both co-chairs to review all cases independently and discuss and compare each of our conclusions in order to achieve intersubjective consensus. All analytic notes were also reviewed by the co-chairs and appropriate guidance was provided.

Figure 1-1.
Conceptual Framework



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CHAPTER 2

This chapter presents the results of the manuscript, “Pharmacogenomics in the Nursing Literature: An Integrative Review,” which has been published in the August, 2014 issue of *Nursing Outlook.*

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Abstract

Pharmacogenomics is a rapidly growing component of personalized medicine and nurses must be competent to deliver genomic-focused nursing care. The purpose of this manuscript was to conduct an integrative review of pharmacogenomics in the nursing literature. A comprehensive search of the nursing literature was conducted using the key words *pharmacogenomics* and *pharmacogenetics.* A total of 47 unique articles were included. Articles represented mainly narrative reviews, with limited discussions of the implications for nursing practice, education, or research. As such, they provide limited direction for advancing either clinical practice or scientific inquiry. This review serves as a call to action for more systematic and empirical publications addressing pharmacogenomics in nursing practice, education, and research. Nurses must be involved in and contribute to interdisciplinary conversations and burgeoning clinical practice initiatives related to pharmacogenomics.

Keywords: Pharmacogenomics, pharmacogenetics, personalized health care, nursing implications

Pharmacogenomics in the Nursing Literature: An Integrative Review

Pharmacogenomics, a key component of personalized medication prescribing, provides the opportunity to individualize drug therapy through choosing the right drug and the right dose for the right person. This approach supersedes the traditional "one size fits all" approach and has potential to address the 20% to 95% of genetic-associated variability in drug disposition.[1, 2] Pharmacogenomics facilitates the identification of the most optimal treatments to decrease costly adverse drug events and side effects, with potential to improve medication adherence and ultimately improve patient outcomes while decreasing costs of care.[3-5]

Pharmacogenomics is the study of genomic variation associated with drug response, allowing for an understanding of how the genomic composition(s) of an individual or population affects the pharmacokinetic and pharmacodynamic responses to drugs.[6, 7] Pharmacogenomics examines the entire genome and thus allows for the identification of variations in multiple genes affecting drug response.[8] The term pharmacogenomics is often used interchangeably with pharmacogenetics; however, the concepts have distinct differences, with pharmacogenetics having a narrower focus. Pharmacogenetics is described as the study of variations of single genes influencing specific drug receptors and individual variability in drug response.[6, 9]

Pharmacogenomics is increasingly being applied to clinical settings as a component of personalized health care. In 2000, the National Institutes of Health supported the development of the Pharmacogenomics Research Network (PGRN). The PGRN is composed of interdisciplinary scientific groups focused on understanding how an individual's genes affect drug response.[10] The PGRN's work is being translated into practice through the Clinical Pharmacogenetics Implementation Consortium (CPIC). Currently, CPIC provides 17 evidence-based guidelines for gene and drug pairs, thus helping clinicians understand how genetic test results should be used to optimize drug

therapy.[11] These guidelines address both individual medications (e.g., codeine and warfarin) and classes of drugs (e.g., selective serotonin reuptake inhibitors).[12, 13] In addition to these guidelines, more than 100 medications now incorporate pharmacogenetic information on their product labels.[14] Institutions in the United States, Canada, and Europe are using pharmacogenetic tests to guide medication-prescribing practices.[15]

Three foundational documents support the relevance and importance of pharmacogenomics for nurses at all levels and specialties: (1) *Genetics/Genomics Nursing Scope and Standards of Practice*[6]; (2) *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators*[16]; and (3) *Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees.*[17] For example, as the largest group of healthcare providers, nurses are increasingly expected to understand and translate genomic developments into effective strategies benefiting patient care across clinical specialties and settings. Advanced practice nurses prescribe medications, and all registered nurses administer medications, provide education, promote adherence, and serve as the first line of defense in initiating actions to prevent, recognize, and treat adverse drug effects. Thus, nurses have a professional responsibility to apply pharmacogenomics to clinical practice, education, and research.

For nursing to make clinical and scientific contributions, a baseline understanding of the knowledge discovery regarding pharmacogenomics in nursing is essential. The purpose of this integrative review was to provide a thorough examination of the state of the science of pharmacogenomics as reflected within the nursing literature. Specific aims were to critically examine within the nursing literature: (1) the concepts of pharmacogenomics and pharmacogenetics; (2) pharmacogenomic and pharmacogenetic clinical practice applications; and (3) nursing's responsibilities in pharmacogenomics and pharmacogenetics.

Methods

Computer-based searches of the nursing literature were conducted in PubMed, the Cumulative Index to Nursing and Allied Health (CINAHL), and Ovid Nursing. The keywords used were *pharmacogenomics* or *pharmacogenetics.* Article inclusion criteria were (1) full-length article published in a nursing journal, (2) English-language, and (3) including content relevant to pharmacogenomics and/or pharmacogenetics. Nursing journals were identified through the three databases searched by selecting the appropriate journal category/subset limits to only include nursing journals. Nursing journals were chosen for inclusion because research has shown that these journals are highly circulated and read by nurses, and they reflect both the nursing and biomedical literature.[18] Exclusion criteria included: (1) editorials and abstracts; (2) duplicate publications; and (3) no exploration of pharmacogenomics or pharmacogenetics beyond the definition or no detailed discussion of the concepts.

The search yielded a total of 136 articles. Titles were screened to remove duplicates (*n* = 56). Abstracts of the remaining 80 articles were reviewed to eliminate ones not meeting inclusion criteria (*n*=12). The remaining 68 articles were read in full, with another 21 eliminated due to not meeting inclusion criteria. The resulting 47 articles were included in this review. Figure 2-1 outlines the search results and detailed screening process.

Data were abstracted from each article by the first author and verified by the second author. Discrepancies were resolved through discussion. Data were organized in tables to address the three specific aims of this review. These data were analyzed and integrated through coding, categorizing, and summarizing to reach conclusions. Each aim corresponds with a like-numbered table (e.g., Aim 1 and Table 2-1).

Abstracted data for Table 2-1 included information about the author(s), year, national origin of author(s), article type, purpose, and the definitions used for

pharmacogenomics and/or pharmacogenetics. If the purpose was not stated within the article itself (excluding abstract), “not stated” was noted in this column. If the authors did not define the concepts, those columns were left blank. Table 2-1 shows data for articles published in the last year (2013) and the complete table is available upon request from the authors.

Table 2-2 was created to summarize discussions about clinical practice presented in the articles and included information about patient population, medication classes, and practice guidelines described in the article. Patient populations were grouped into five different categories (mental health, cardiovascular, oncology, surgical/anesthesia, and obstetrics). Because most articles referred to adults only, we noted especially where pediatric patients were included within Table 2-2. The clinical practice guideline discussions were coded as (1) not discussed, (2) partially discussed (briefly mentioned the need or actual practice guidelines), or (3) detailed discussion (provided detailed examples of practice guidelines).

Data abstracted into Table 2-3 included the implications of pharmacogenomics for nursing practice. Articles were reviewed for (1) focus on functional role in nursing – direct care nurses or nurses in general (with no particular focus on a nursing role), advanced practice nurses, and/or researchers; (2) focus of implications (practice, education, research); and (3) the temporal saliency of the implications. Examples of practice implications included topics such as patient assessment, education, and integrating knowledge for the purpose of prescribing medications. Education implications included discussions around implementing pharmacogenomic content in nursing curricula, continuing education, and certification and licensing exams. Research implications included discussions of the impact of pharmacogenomic knowledge on research or directions for future research.

Results

Description of Sample

This literature review resulted in a homogeneous sample of articles, with 91.5% (*n* = 43) being narrative reviews.[4, 19-60] No narrative review article included a description of systematic evaluation methods such as search strategies used, number of articles retrieved, and reasons for attrition or final sample selection.[61] The remaining articles included 4% (*n* = 2) case studies[53, 62], 2% (*n* = 1) a conceptual framework[63], and 2% (*n* = 1) an in vitro pharmacogenetic study.[64] According to Melnyk & Fineout-Overholt's *Rating System for the Hierarchy of Evidence*[65], only one article[64] provided Level III evidence through representing an in vitro pharmacogenetic study, whereas all other articles provided the lowest level of evidence, Level VII, or narrative and/or opinion manuscripts. The majority were published after 2009 (66%, *n* = 31) and originated in the United States (87%, *n* = 41). However, there were four different countries represented – Brazil, New Zealand, United Kingdom, and the United States - and 4% (*n* = 2) of the articles[45, 57] represented international collaborations. These findings support the international relevance of this topic.

Overall, the purpose of most articles was to review or explore clinical aspects of pharmacogenomics and/or pharmacogenetics. However, 40% (*n* = 19) did not have a clearly articulated purpose. One article[31] included a purpose statement within the abstract but not within the text of the article.

Only two articles described a theoretical foundation. Davies and colleagues[63] presented a conceptual framework to "incorporate pharmacologic findings and pharmacogenetic evidence related to atypical antipsychotic drugs (ADDs) into advanced psychiatric nursing practice" (p. 98). Davies, Conley, and Roth[64] used a systematic approach to conduct in vitro pharmacogenetic experiments to determine whether allelic variants in the 5-hydroxytryptamine receptor altered the pharmacology of certain ADDs.

Aim 1 Results: Concepts of Pharmacogenetics and Pharmacogenetics

As shown in Table 2-1, there was wide variation in conceptual definitions. Pharmacogenomics was defined in 21% (*n* = 10) of articles, pharmacogenetics in 25.5% (*n* = 12), both concepts defined in 25.5% (*n* = 12), and neither concept was defined in 25.5% (*n* = 12). One article, Beery and colleagues[23], used the two concepts interchangeably and referred to them as "*pharmacogenetic/pharmacogenomic...*" Both the terms pharmacogenomics and pharmacogenetics were most widely used in describing the science or study of genetic variations and the effects on drug responses. In addition, these concepts were described in relation to the clinical applicability and its effect on treatment outcomes.

Three distinct attributes, or defining characteristics, emerged from the definitions of pharmacogenomics and pharmacogenetics. These included (1) science/study, (2) genomic/genetic, and (3) pharmacology. Science is defined as "knowledge or system of knowledge covering general truths of general laws"[66] whereas study is defined as "such application in a particular field or to a specific subject."[67] Sixty-two percent (*n* = 29) of articles defined pharmacogenomics and/or pharmacogenetics using these terms.

A variety of terms was used to describe the genetic/genomic attributes of pharmacogenomics and pharmacogenetics. Genetics is defined as the study of individual genes and their impact on a single-gene disorder, whereas genomics is the study of all genes in the human genome and their interactions with each other and the environment.[6] The concept and knowledge of genomics is much broader than genetics and these differences were not reflected in the definitions of pharmacogenomics and pharmacogenetics, thus obscuring any differentiation or clarity between the two concepts.

The definitions of pharmacogenomics included the terms chromosomal, gene, genes, genomic, genetic, genotype, DNA/RNA, and polymorphisms to describe

variations in individuals' genetic profiles. The definitions of pharmacogenetics used very similar terms: gene, genes, genetic, and DNA. Again, this variety of terms obscured clarity and led to inconsistencies within and between the definitions.

In addition to the knowledge of genetics and genomics, an understanding of the pharmacology of medications is essential. Pharmacology pervades all aspects of the study and use of drugs in humans, and this aspect is studied by considering the pharmacokinetic and pharmacodynamic effects of medications.[68] Within the definitions of pharmacogenomics and pharmacogenetics, these drug relationships were described in a variety of ways using terms including: variations in drug toxicity, drug behavior, adverse drug reactions, drug effects, and drug responsiveness.

Overall, the definitions of the two concepts, pharmacogenomics and pharmacogenetics, were not sufficiently distinguished so as to clarify the concepts as being distinct from one another. Standing alone, the three defining characteristics – study/science, genetic/genomic, and pharmacology - should lead to each individual concept[69]; unfortunately, these defining attributes did not always provide the clarity needed to differentiate between pharmacogenomics and pharmacogenetics.

Aim 2 Results: Pharmacogenomic and Pharmacogenetic Clinical Practice Applications

Fifty-seven percent (*n* = 27) of articles focused on specific patient populations (see Table 2-2). The remaining articles (43%) either provided a broader overview crossing multiple patient populations or referred to no particular patient population. The application of pharmacogenomics in the pediatric population was discussed only in three articles (6%).[55, 58, 70] In articles focusing on specific populations, mental health and cardiovascular patients were the most frequently discussed. In addition, anticoagulants, psychotropic medications (e.g., antidepressants and antipsychotics), opioids, and antihypertensives were the medication classes most emphasized.

The use of interdisciplinary clinical practice guidelines to guide medication dosing based on pharmacogenetic results was not discussed in most articles, with only 19% (*n* = 9) addressing either the need for or use of clinical practice guidelines. Warfarin dosing guidelines (warfarindosing.org) were the most frequently mentioned.[23, 33, 39, 41, 53] Kelly[38] was the only article specifically addressing the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine dosing. These CPIC guidelines were noted to be useful in facilitating translation of pharmacogenomic knowledge to clinical practice.[11] The first CPIC guideline was established in 2010, and thus we recognize that articles published prior to this date would not reflect these guidelines.

Aim 3 Results: Nursing's Responsibilities in Pharmacogenomics and Pharmacogenetics

Thirty-six articles (76.5%) included a discussion of nursing implications affecting direct care nurses or nurses in general. Advanced practice nurse (APN) implications were presented in 42.5% (*n* = 20) of articles, yet only 4% (*n* = 2) specifically addressed the role of the nurse researcher.

Discussions about nursing implications were organized into three categories – practice, education, and research. Only one article provided detailed discussion[30], and another briefly discussed implications for all three categories.[60] No other articles addressed all three categories.

Practice implications were discussed in 94% (*n* = 44) of the articles, with an overwhelming consensus that nurses need to have the ability to apply pharmacogenomic knowledge in practice such as in nursing assessments and detailed patient and family histories.[4, 21, 26, 30, 32, 40, 41, 43, 48, 52-55, 58] In addition, several articles noted that it is essential for nurses to have a keen ability to evaluate the effectiveness of pharmacogenomic treatments such as patient responses to medications and

identification of drug reactions.[31, 33, 36, 43, 47, 48, 53, 55, 58] Others noted that nurses are and will continue to be integral to providing patient and family education around this topic, including interpretation of pharmacogenetic results, providing information on medications, and explaining why others are taking different medications or dosages for the same condition.[33, 54, 63] Finally, several articles noted that APNs who prescribe medications should have a fundamental understanding of the principles of pharmacology and genetics in order to incorporate patient environment and genetics when selecting medications and dosages.[22, 32, 39, 49, 70]

Implications for nursing continuing education were less frequently included (25.5%, *n* = 12 articles). Recommendations were that pharmacogenomic and pharmacogenetic information should be reflected in educational initiatives preparing nurses at all levels[4, 44, 48] and in nursing curricula.[23, 56] Suggestions for incorporating this content into nursing curricula included the need for faculty to have additional education and specific training regarding the application of genomic models to practice.[41] Finally, the articles noted that education should include ethical and legal aspects of genomic medicine because nurses will be held legally and professionally responsible for understanding the pharmacogenomics of drugs administered.[19, 27]

Research implications were discussed in 32% (*n* = 15) of articles. These articles noted that nurses are integral to the success of personalized medicine and should conduct and participate in collaborative research.[4, 22, 60] The need for pharmacogenomic studies to evaluate the effectiveness of genetic and genomic technologies, information, interventions, and outcomes was discussed.[26, 50, 63, 64] Specifically, articles recommended that future studies explore the safety, efficacy, and effectiveness of pharmacogenomic treatments to provide evidence of clinical utility.[29, 36, 50, 64] A final research recommendation was to study the ethical, legal, and social implications of the use of pharmacogenomics.[29, 30]

In regard to the temporal saliency of these implications, the majority of the implications were provided in the context of the future (62%, n = 29). In these articles, pharmacogenomics and pharmacogenetics were seen as far off in the future rather than in the here and now of clinical practice, education, or research. Twenty-eight percent (*n* = 13) of articles presented nursing implications for current practice and 10% (*n* = 5) of articles included both.

Discussion & Future Directions

The overall conclusion of this integrated review is that a call to action is needed for nurses to fully embrace the burgeoning interdisciplinary field of pharmacogenomics. Our current literature is limited in number, type, and scope of articles. Narrative reviews are criticized for their possible selection bias, wherein all available information is not reviewed and instead authors may preferentially cite data to support certain points or opinions.[71] The overwhelming lack of theory and empirical studies greatly limits the establishment of a robust foundation to build upon. Although nurses may be publishing theoretical and/or data-based articles in journals that are not nursing-specific (i.e., interdisciplinary journals), the overwhelming majority of articles in nursing journals reiterated rather than systematically reviewed existing information and did not generate theoretical or empiric knowledge. This stands in stark contrast to the knowledge being generated in other fields. For example, Preskorn and Hatt[72] conducted a search of PubMed with the keyword pharmacogenomics and found a significant increase in knowledge as represented by the growing number of annual publications since the late 1990s. Approximately 400 articles were published in 2000, which increased to nearly 1,300 publications in 2012. When we repeated their search in PubMed on January 20, 2014, results yielded 1,370 publications in 2013, indicating the immediate and growing relevance of pharmacogenomics. Thus, our overwhelming conclusion is that, although

pharmacogenomic knowledge has exploded over the last decade, articles published in nursing journals do not reflect this trend.

As nursing embraces pharmacogenomics, it is crucial that consistent terms and definitions be used. Similar to other disciplines[73], conceptual confusion between pharmacogenomics and pharmacogenetics was evident. In the nursing literature, these two concepts were used interchangeably and defined inconsistently, with different terms used to describe the same or similar key attributes. This conceptual confusion of central concepts contributes to difficulties in developing a foundational framework. Pharmacogenomic studies investigate multiple genes or the entire genome and can be useful in examining how genetic variations effect drug response among populations, for instance, how drugs may affect different racial or ethnic groups.[8] Pharmacogenetic studies can provide a more focused approach by identifying individual gene variation and its influence on a certain medication, such as a CYP2D6 variation effect on the metabolization of codeine. Our recommendation for future work is for nursing to use agreed-upon definitions of pharmacogenomics and pharmacogenetics from national organizations such as the American Nurses Association[6], National Human Genome Research Institute[8], or the Pharmacogenomics Knowledge Base website supported by the National Institutes of Health (NIH).[13]

The available literature did provide a variety of examples of how to apply pharmacogenomics to practice, education, and research. However, articles provided only a superficial expression of the roles and responsibilities outlined in the International Society of Nurses in Genetics (ISONG) and American Nurses Association's *Genetics/Genomics Nursing Scope and Standards of Practice*[6], the *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators*[16], and *Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees.*[17] These guidelines provide the detailed nursing scope of practice in

genomics and minimum genetic and genomic competencies expected of every nurse, with the latter providing specific competencies for advanced practice nurses, clinical nurse leaders, educators, administrators, and scientists. For example, nurses should be able to help patients understand how results of pharmacogenetic tests may impact medication changes and/or dose changes in addition to ensuring patients possess and are using the correct medications and doses. Advanced practice nurses must be able to advocate for pharmacogenetic testing and base medication prescriptions on those results. Further work is needed to more clearly elucidate nursing's roles and responsibilities in the body of literature addressing pharmacogenomics in nursing.

Advancing and implementing components of personalized health care, such as pharmacogenomics, largely depends upon contributions from interdisciplinary stakeholders.[74, 75] Pharmacogenomics is directly relevant to the work nurses do every day and the research priorities of the National Institute of Nursing Research.[76] The key role nurses play in promoting self-management during acute and chronic illness was emphasized in a recently released request for applications, RFA-NR-14-002, Centers of Excellence in Self-Management Research (http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-14-002.html). Because medication management is a key component of self-management, pharmacogenomics is pertinent to nurses' contributions in promoting self-management. Clinical care, education, and research interventions must address the issue of pharmacogenomics for nurses and nursing research to continue to promote excellence in nursing care.

Policy makers, educators, and nursing administrators in health care systems need to ensure that nurses are appropriately prepared to participate in interdisciplinary conversations and initiatives related to pharmacogenomics in health care. It is important that licensing examinations and advanced specialty certifications reflect current trends in health care, therefore having pharmacogenomic-related content is important. This

content should be based on the competencies documents listed above.[6, 16, 17] Educators should integrate pharmacogenomic information into the curriculum, such as pharmacology courses, simulations, and clinical experiences. Administrators must ensure policies are up to date and support or provide additional continuing education resources so nurses develop and remain competent in pharmacogenomics.

Limitations

The conclusions from this review should be interpreted in the light of some limitations. Articles published only in nursing journals were included. We recognize nurses may be publishing in non-nursing journals and nursing books. This review does not reflect that work or work published by other disciplines. Moreover, this review does not represent ongoing or existing unpublished work, published editorials or abstracts, or dissertations. The review was limited to only articles published in English and thus is not representative of other non-English articles.

Conclusion

This integrative review was the first to evaluate the state of the science of pharmacogenomics in the nursing literature. The findings identified the limitations of the nursing literature and suggest a call to action is needed for nursing to recognize and embrace this important and burgeoning field. Pharmacogenomics can no longer be looked at as a practice on the horizon since it is already being implemented in a variety of capacities. To meet responsibilities for practice, education, and research, nurses must engage in interdisciplinary conversations involving pharmacogenomics. Research aimed at the nursing implications of pharmacogenomics is needed to support the developing responsibilities of nurses in practice.

Figure 2-1.
PRISMA Diagram of Search Strategy

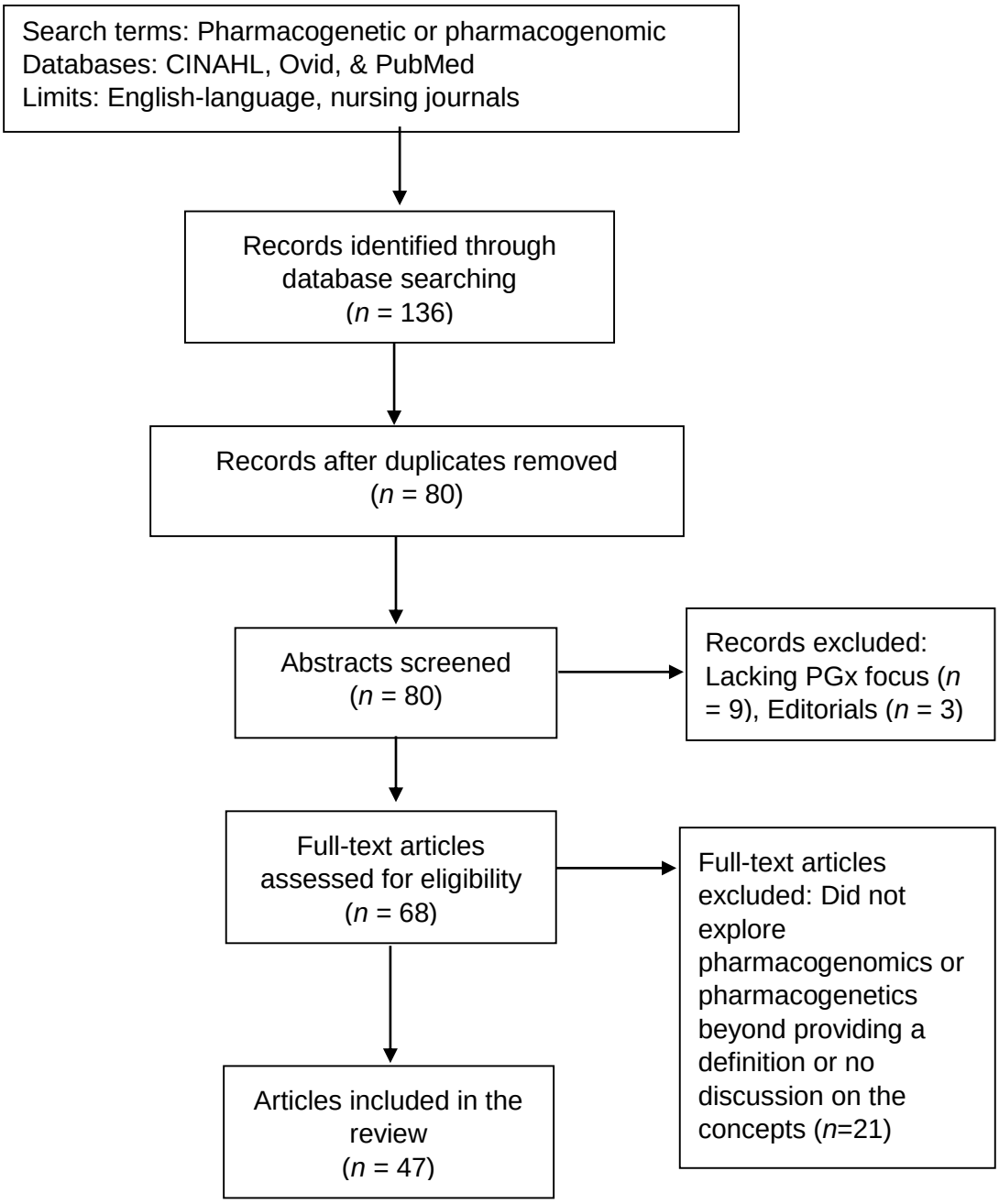

Table 2-1.
Evaluating the Concepts of Pharmacogenomics and Pharmacogenetics in Nursing Articles Published in 2013

Author, Date Country	Type of Article	Purpose	Definition of Pharmacogenomics	Definition of Pharmacogenetics
Chadwell, 2013 U.S.A	Narrative Review	Provide an overview of personalized medicine, its relevance to advanced nursing practice, and resources related to personalized medicine, including genetics and genomics.	the general study of all the many different genes that determine drug behavior	the study of inherited differences in drug metabolism and response
Cheek, 2013 U.S.A.	Narrative Review	Focus on how pharmacogenomics can help nurses provide better care for patients.	tailoring medications to a patient's genomic information, is a significant and growing area of research with the potential to improve patient outcomes	the field of study dealing with the variability of responses to medications due to variation in single genes
Kaplan et al., 2013, U.S.A.	Narrative Review	Review the pharmacology of tamoxifen, the genetics and physiology of CYP2D6, and the clinical implications of both for women with hormone receptor-positive breast cancer.		

Table continues

Kelly, 2013 U.S.A.	Narrative Review	Not stated.	the study of how an individual's genetic inheritance affects the body's response to drugs	
Mutsatsa et al., 2013 U.K.	Narrative Review	Review the progress made in research towards understanding how genetic factors influence psychotropic drug response.		science dedicated to the identification of genes influencing response to medication
Santos et al., 2013 Brazil, U.S.A.	Narrative Review	Introduce nurses to how - genomics is currently integrated into cancer care from prevention to treatment and the influence on oncology nursing practice.	study of how genomic factors (including SNPs) and acquired mutations in tumors determine an individual’s response or toxicity to drugs	
Turner, 2013 U.S.A.	Narrative Review	Review the risks in child and adolescent psychiatric prescribing and review how analysis of medication interactions with the CYP450 enzyme system can improve safety and efficacy.	an area of science focused on studying variations in genes that impact individual drug response, identifying new drug transporters, and studying metabolizing enzymes	

Table 2-2.
Summary of Pharmacogenomic Clinical Practice Discussions in the Nursing Literature

Author, Date	Patient Population[1]	Medication Classes	CPIC/Practice Guidelines[2]
Ama et al., 2010	surgical patients (pseudocholinesterase deficiency, malignant hyperthermia, analgesics, PONV*),	anesthetics, opioids, antidepressants	□
Anderson, 2011	obstetrics	opioids	□
Anderson-Pompa, 2008	surgical patients – malignant hyperthermia	anesthetics	□
Beery, et al., 2004			□
Beery, et al., 2011		opioids, anticoagulants, antidepressants	◘
Bray et al., 2008	mental health	psychotropic medications	□
Chadwell, 2013		anticoagulants	□
Cheek, 2013	cardiovascular, mental health, HIV*, oncology	antiplatelet, anticoagulant, antidepressants, antiretroviral	□
Chummun, 2011		opioids	□
Davies et al., 2010	mental health	antipsychotics	◘
Davies et al., 2011	mental health	antipsychotics	□
Ensor et al., 2009	cardiovascular	antiplatelet	□
Fleeman et al., 2009		anticoagulants, antipsychotics, antidepressants, and tamoxifen	◘
Frazier et al., 2004		antihypertensives	□
Frazier et al., 2009	cardiovascular	antihypertensives	□
Howe, 2011	cardiovascular	antihypertensives, digoxin, anticoagulants, antiplatelet, lipid-lowering agents, & antiarrhythmic	□

Table continues

Howington et al., 2011		cancer agents for leukemia & breast CA, antivirals, Anticoagulants, antihypertensives	◘
Howland, 2006	mental health	antidepressants & antipsychotics	□
Kaplan et al., 2013	oncology – breast cancer	tamoxifen	◘
Kayser, 2007	cardiovascular	anticoagulants, antiplatelets, antihypertensives, & antiarrhythmic	□
Kelly, 2013		opioid	◘
Krauter et al., 2011	mental health - depression	antidepressants	◘
Kudzma, 2001	Cardiovascular disease – hypertension	antihypertensives	□
Kudzma et al., 2009		anticoagulant, Opioids, Statin drugs, tacrine, cancer treatments (azathioprine, irinotecan, 5-Fluorouracil)	■
Kurnat-Thoma, 2011		anticoagulant	□
Landino et al., 2011	mental health	psychotropic medications	□
Lea, 2000			□
Lea, 2005		opioids	□
Lea, 2009		chemotherapy, cetuzimab, and herceptin	□
Lea et al., 2011		anticoagulant, anticonvulsants, antidepressants, antihypertensives, analgesics, cancer therapy	□
Miaskowski, 2009	cancer pain	opioids	□
Mutsatsa et al., 2013	mental health	antipsychotics, antidepressants, & mood stabilizers	□

Table continues

Nicol, 2003		antipsychotics, antidepressants, anticoagulants, opioid, proton pump inhibitor, antiseizure medications	□
Novak, 2007			□
O'Malley, 2011		antiplatelet	□
Petska, 2010			□
Prows et al., 2004			□
Prows, 2008		psychotropic medications & anticoagulants	□
Prows et al., 2008	cardiovascular	anticoagulant & antihypertensives	■
Prows et al., 2009	mental health – pediatric	psychotropic medications	□
Prows, 2011	oncology	tamoxifen, Antidepressants, chemotherapy	□
Read, 2002			□
Santos et al., 2013	oncology	chemotherapy agents and adjuvants	□
Theoktisto, 2009	ADHD* - pediatric	psychotropic & psychostimulant medications	□
Turner, 2013	mental health - pediatric	psychotropic medications	□
Wung, 2002	cardiovascular	antihypertensives & Statins	□

[1]Patient population: All patient populations are adults unless noted as including pediatric patients.

[2]Extent of Discussion: No discussion (□) – no mention of clinical practice guidelines for nurses; Partial discussion (◘) – briefly mention clinical practice guidelines; Detailed discussion (■) – provides detailed discussion or examples of clinical practice guidelines

*PONV – Post-operative nausea and vomiting; ADHD – Attention Deficit Hyperactive Disorder

Table 2-3.
Pharmacogenomic Nursing Implications as Discussed in Nursing Literature

Author, Date	Nursing Role			Focus of Implications			Future	Now
	Nurses	Advanced Practice Nurses	Researcher	Practice	Education	Research		
Ama et al., 2010		X		X	X		X	
Anderson, 2011		X		X		X	X	
Anderson-Pompa, 2008	X			X		X	X	
Beery et al., 2004		X		X		X	X	
Beery et al., 2011	X			X	X		X	X
Bray et al., 2008	X			X		X	X	X
Chadwell, 2013		X		X	X		X	
Cheek, 2013	X			X			X	
Chummun, 2011	X	X		X			X	
Davies et al., 2010	X	X		X		X		X
Davies et al., 2011			X			X		X
Ensor et al., 2009	X			X			X	
Fleeman et al., 2009	X					X	X	
Frazier et al., 2004	X	X	X	X	X	X	X	
Frazier et al., 2009	X			X		X	X	
Howe, 2011	X	X		X				X
Howington et al., 2011	X			X				X
Howland, 2006a	X			X			X	
Howland, 2006b	X	X		X			X	
Kaplan et al., 2013	X			X		X		X
Kayser, 2007	X			X			X	
Kelly, 2013	X			X				X

Table continues

Krauter et al., 2011	X	X	X				X
Kudzma, 2001	X		X				X
Kudzma et al., 2009	X		X	X			X
Kurnat-Thoma, 2011	X		X	X	X	X	
Landino et al., 2011		X	X				X
Lea, 2000	X		X			X	
Lea, 2005	X		X				X
Lea, 2009	X	X	X	X		X	
Lea et al., 2011	X	X		X		X	
Miaskowski, 2009	X		X			X	
Mutsatsa et al., 2013	X	X	X			X	
Nicol, 2003	X		X	X		X	
Novak, 2007		X	X			X	
O'Malley, 2011		X	X		X	X	
Petska, 2010	X		X			X	
Prows et al., 2004	X		X			X	
Prows, 2008	X		X			X	
Prows et al., 2008	X		X	X		X	X
Prows et al., 2009	X		X				X
Prows, 2011	X		X				X
Read, 2002	X		X	X		X	
Santos et al., 2013	X		X			X	
Theoktisto, 2009		X	X		X	X	X
Turner, 2013		X	X		X	X	X
Wung, 2002	X		X	X	X	X	

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CHAPTER 3

This chapter presents the results of the manuscript, “Moving Toward Widespread Implementation of Pharmacogenetic Testing: Understanding Patterns of Exposure to Pharmacogenetically Actionable Opioids.”

Abstract

Understanding and capturing the dynamic nature of medication exposure is a key component in evaluating the impact of pharmacogenetic testing on improving patient outcomes. The goal of this study was to generate a complex description of the unfolding of medication exposure over time in persons newly prescribed the pharmacogenetically actionable opioids of codeine or tramadol using a qualitative person-oriented approach. We used qualitative within- and cross-case analyses of six months of retrospective data from de-identified electronic health records and pharmacogenetic genotype data from banked DNA samples of 30 adult patients. We identified an overarching typology with eight groups of patients that had one of five opioid prescription patterns (singular, episodic, switching, sustained, or multiplex) and one of three types of medical emphasis of care (pain, comorbidities, or both). The findings highlighted the heterogeneity and variations among the sample prescribed these medications and advanced the argument that medication exposure is not static, but rather dynamic and multidimensional. The knowledge gained can be used to guide the development of medication exposure measures and inform studies seeking to identify and develop personalized interventions in this population.

Keywords: Medication exposure, pharmacogenomics, opioid, clinical implementation, pain management

Moving Toward Widespread Implementation of Pharmacogenetic Testing: Understanding Patterns of Exposure to Pharmacogenetically Actionable Opioids

Evidence-based guidelines have been developed for the use of pharmacogenetic testing to guide the prescription of certain opioid therapies in clinical practice. Pharmacogenetic testing identifies individual genetic variations that are associated with drug metabolism and response.[1] Pharmacogenetic testing is a particularly promising approach to help address wide interindividual differences in responses to some opioid medications and could thus lead to improved analgesia and mitigate costly adverse drug effects.[2] Pharmacogenetically actionable opioids are those that have strong evidence based guidelines to guide drug or dosing changes based on pharmacogenetic test results.[3, 4] Codeine and tramadol are two commonly used pharmacogenetically actionable opioids.

Medication exposure can be broadly characterized as the condition of being subjected to a medication. Medication exposure includes multiple factors such as the medication and dose prescribed, the medication regimen, and changes in the regimen over time.[5] Despite the fact that medication exposure is a multidimensional process that changes over time, measures of medication exposure typically capture single event medication prescriptions as a dichotomous variable (yes/no prescribed) or medication counts (total number of medications prescribed).[6, 7]

To date, studies of the potential efficacy and effectiveness of pharmacogenetic testing have been limited by the failure to examine the complexities of medication exposure and the lack of an adequate measure of medication exposure.[8-11] For example, Schildcrout et al.[11] used medication counts of 56 different medications, including tramadol and codeine, to predict the number of potential adverse drug events that could be avoided through preemptive pharmacogenetic testing. Additionally, in a study that sought to model the benefits of pharmacogenetic testing on antidepressants, exposure

to selective serotonin reuptake inhibitors (SSRIs) was captured dichotomously through an on/off treatment measure.[10]

Pharmacogenetic studies have also failed to consider factors that are likely to influence the effects of pharmacogenetic testing on patient outcomes including the complexity of patient's clinical profile and the healthcare context in which the medication is prescribed.[6, 12, 13] For example, the cost of pharmacogenetic testing may be a challenge in low resource facilities or those that treat patients with complicated medical histories and multiple comorbidities, such as is often the case in federally qualified or safety-net health systems.[14] Further, the outcomes of pharmacogenetic testing for opioid exposure are likely to be influenced by the non-pain-related conditions for which patients are being treated using non-opioid pharmacologic agents. For example, the potential for drug-drug interactions are likely to increase in patients treated for a number of comorbidities and this risk could impact medication exposure patterns.[15]

Therefore, a different, more complex conceptualization of opioid exposure is needed to guide subsequent development of improved measures of opioid exposure.[6, 16] One research approach that captures the complexities of health-related dynamic phenomena is the person-oriented approach. This approach is based on two assumptions. First, that persons should be considered holistically; that is, all aspects of their being – their genetic makeup, histories, and behaviors, as well as the contextual risk and protective factors they encounter – interact synergistically to constitute human experience.[17] Second, that human functioning is fluid over time due to developmental processes and constant changes in the person-environment system.[18] The person-oriented approach seeks to uncover common patterns of interacting characteristics and behaviors in heterogeneous samples by identifying subgroups within the sample that share common patterns.[17, 19] The subgroups are often then presented in a typology to allow for an in-depth description of the characteristic patterns of each group. The

person-oriented approach can use either pattern-based quantitative methods (e.g., latent class analysis, cluster analysis, or configural frequency analysis) or qualitative methods (e.g., within-case and cross-case analysis) to identify meaningful subgroups within heterogeneous samples.[17, 20, 21]

In health-related research, the person-oriented approach provides an alternative to the more traditional variable-oriented approach in which variables represent characteristics or behaviors that vary within groups or across time and are the primary analytic unit of study. In variable-oriented approaches, linear relationships among variables are studied and model testing yields causal inferences.[22] Person-oriented methodologists argue that variable-oriented approaches are limited by the assumption that samples are homogenous in regards to the relationships among variables and by the fact that group statistics and aggregate data do not allow inferences about any one case.[23, 24] A person-oriented approach, which clusters persons with similar characteristics, can provide conclusions about subgroups that are interpretable at the level of the individual.[17, 19] While a variable-oriented approach could identify factors that predict the efficacy of pharmacogenetic testing, a person-oriented approach will yield a typology of subgroups that cluster on relevant characteristics of medication exposure, capture the complex nature of exposure to pharmacogenetically actionable opioids, and account for the context in which the exposure to these medications occur.

Our goal was to generate a complex description of the unfolding of medication exposure over time in persons newly prescribed codeine or tramadol. The primary purpose of this study was to employ a qualitative person-oriented approach to develop a typology that identified meaningful subgroups that share common patterns of medication exposure within a sample of patients newly prescribed a pharmacogenetically actionable opioid.

Methods

This retrospective, 6-month, longitudinal analysis of de-identified, electronic health records and banked DNA samples used a qualitative, person-oriented approach and did not require Institutional Review Board review. The theoretical and methodological components of the person-oriented approach are described in detail elsewhere.[25]

Setting

This study was conducted in a large, Midwestern safety-net healthcare system where widespread implementation of pharmacogenetic testing was occurring. This setting was chosen because this health system predominately serves low-income, or uninsured or underinsured individuals who are at greater risk for poor health, emergency room visits, frequent hospital admissions, and adverse outcomes from disease and their treatments.[26-28] This healthcare system also has the advantage of having robust data repositories allowing for linkage of patients' health records to banked DNA samples.

Sample

A multiple-case sample was produced through randomly selecting a subset of de-identified electronic health records and banked DNA samples from patients (cases). Inclusion criteria for cases were: 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 primary care clinics part of a large safety-net health system; 3) had a banked blood sample; 4) age 21 and older; and 5) had no previous documentation of substance abuse in the electronic medical 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. Cases with known substance abuse were excluded because that population may have distinct

patterns of exposure and it would have been difficult to determine whether their exposure to opioids was related to appropriate use for analgesia or for other non-medical reasons.[29] There were a total of 118 cases that met the inclusion criteria. Published recommendations for a multiple-case sample range from 10-30 cases due to the required in-depth analysis as the complexities from larger samples would become unwieldy.[21] Thus, this study included data from 30 cases.

Data & Research Processes

Data that reflected factors pertinent to exposure to pharmacogenetically actionable opioids were obtained for each of the 30 cases from existing data repositories and through completion of CYP2D6 pharmacogenetic genotyping of DNA samples. Factors with potential to influence exposure to opioids were identified through an extensive review of the literature, including patient characteristics (e.g., demographics, past medical history, and pharmacogenetic genotype)[30-34], medication characteristics (opioid information, co-prescribed medications, changes in drug regimen, drug-drug interactions)[16, 35, 36], clinical responses (e.g., pain intensity and adverse drug effects)[37], and healthcare utilization.[38]

The main data repository accessed for data was the Indiana Network for Patient Care, which is an information exchange that captures and integrates varying levels of data from the safety-net health system and from more than 25,000 physicians, 106 hospitals, 110 clinics and surgery centers as well as other healthcare providers across Indiana.[39] Additionally, other clinical and administrative data repositories from the safety-net health system directly associated with the managed care program were accessed. A trained clinical data analyst accessed all data and used an existing process to de-identify it prior to releasing it to the research team. All electronic health records and DNA samples were provided a unique study identification number, allowing for the linkage of the two. Additionally, all dates reflecting interactions with the system of care were shifted

by a random number unknown to the investigators. This allowed for the timing of events (e.g., healthcare utilization dates, prescription dispense dates) to remain accurate in sequence while de-identifying the exact dates.

Electronic health records. Six months of electronic health record data for each case were extracted – starting with the date of the new prescription for either codeine or tramadol and ending six months later. To reflect the person-level factors pertinent to medication exposure, we obtained all data fields (factors) over the six months that captured patient characteristics, medication characteristics, clinical responses, and healthcare utilization. Each of these is described below.

Patient characteristics included age, gender, race, ethnicity, and past medical history. The age of the individual at the time of the first prescription for tramadol and codeine was used. Additionally, the past medical history recorded at every healthcare encounter was captured through documented International Classification of Diseases – 9th Revision (ICD-9) codes.

Medication characteristics were captured through medication data from repositories that contain records from both health systems and outpatient pharmacies. The data included all available medication names, dose, dose frequency, route, supply amount, administration instructions, prescriber, and dates that the prescription was written and then dispensed. Additionally, any medication history (medication reconciliation) documented during a healthcare encounter was also provided.

Clinical responses potentially influenced by opioids included any documented adverse drug events and pain intensity ratings. Documented ICD-9 codes that were indicative of potential adverse drug events in individuals taking an opioid[40, 41] during each healthcare encounter were used to determine if an adverse drug event occurred. Also, all documented pain intensities by the providers were included in the analysis.

Data reflecting healthcare utilization were also captured. Because the data included in this study was de-identified, specific clinic names and locations were not provided. Each location point of care was given a unique location identification number, as well as categorized as primary care clinic, specialty clinic, emergency department, or inpatient hospitalization. The date and ICD-9 codes for admit diagnosis/chief complaint(s) for each visit were specified.

Pharmacogenetic genotype. CYP2D6 genotype was determined for all 30 cases in this study. The CYP2D6 gene is highly polymorphic, therefore, we genotyped common variants that influence both codeine and tramadol drug disposition and response.[3] Samples of extracted DNA in the amount of 350 ng/sample and a concentration of 10 ng/µl were released from a biobank to the research team for storage and analysis. The extracted DNA was further diluted to a final concentration of 5.8 ng/µl. Using 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), genotyping was performed for the CYP2D6 alleles *2, *3, *4, *5, *6, *9, *10, *17, *29, and *41. These star alleles were examined because of their frequencies in Caucasian and African populations and their descendants.[42] Quality controls were run for each sample batch and repeated assays were conducted on 20% of samples for further validation. For the genotyping, there was a 99.4% call rate. Based on the genotype results, a CYP2D6 activity score was calculated.[3] Additionally, patients' medication regimens were examined for cytochrome P450 drug-drug interactions that would alter the CYP2D6 enzyme activity.[43] For drug-drug interactions with strong inhibitors of the pharmacogenetically actionable opioid, a final activity score of 0 was assigned. For drug-drug interactions with moderate inhibitors of the pharmacogenetically actionable opioid, the CYP2D6 genotype activity score was multiplied by 0.5 to

determine the final activity score. These final activity scores were then used to determine the drug metabolizing phenotype for each patient.[44]

Data analysis. Sample characteristics were described with descriptive statistics using SPSS™ 23.0 (IBM, Armonk, NY). The remaining data analysis was conducted by three of the research team members using the following iterative steps: 1) data condensation, 2) data display (creating matrices), and 3) drawing and verifying conclusions.[21]

Using all available data, within-case and cross-case analyses as described by Miles and colleagues[21] were performed. The goal of a within-case analysis is to "describe, understand, and explain what has happened in a single, bounded case (p. 100)."[21] To complete this, the investigator condensed the data by selecting, simplifying, abstracting, and transforming it into an interpretable format. The investigator organized all data in a case-by-time (time-ordered) meta-matrix in which patient characteristics (age, gender, race/ethnicity, CYP2D6 activity score) were displayed on the vertical axis and all other factors (medication characteristics, clinical response, healthcare utilization) were organized by month on the horizontal axis. The case-by-time matrix allowed for visualization of all factors over the 6-month time period and the development of an in-depth narrative description of each patient based on the salient factors that determined how the patients' opioid exposure unfolded over time.

Using the narratives developed in the within-case analysis, cross-case analytic procedures were then applied. Cross-case analysis is used to cluster multiple cases into groups that share certain patterns or configurations.[21] The goal of the cross-case analysis is to identify a parsimonious number of groups with common features without forcing the groupings or producing finely grained distinctions. A partially-ordered meta-matrix was developed to stack the within-case (case-level) narratives to more easily compare across the different cases. Considering the definition of medication exposure,

the three research team members examined all prescription data from the pharmacogenetically actionable opioids (i.e., dose, timing of fills/refills, and supply amounts) displayed in the narrative columns of the matrix to identify repeating patterns of opioid exposure and, using an iterative process and group discussion, juxtaposed the rows that shared patterns. Cases that clustered in this way were examined as a group to determine similarities and differences. If the cases shared similar configurations in factors of exposure, the configurations were considered a common pattern. Five common patterns of exposure to pharmacogenetically actionable opioids were identified through detailed written descriptions and discussions among research team members to achieve intersubjective consensus.[21] The patterns, which are described below, were labeled by the research team as singular, episodic, switching, sustained, and multiplex.

The research team also determined that the patients differed significantly in the focus of their medical care in regards to their pain, and that these differences were important in understanding the complexities of the exposure patterns. With a return to the data, the team observed patterns related to medical histories, type and indication for all medications prescribed, clinical responses, and type and reasons for healthcare encounters. It was determined that there were three main types of medical focus of care: a medical emphasis on pain, a medical emphasis on other comorbidities, and a medical emphasis on both pain and comorbidities. The cases that evidenced the five patterns of exposure were thus subdivided according to the type of medical emphasis of care. The groups were displayed on a two-by-two variable matrix (Table 3-1) in which the columns represented the opioid prescription patterns and the rows represented the types of medical emphasis of care. Each case was placed in the appropriate cell by one member of the research team and confirmed by the other two team members. The final product of the analysis, therefore, was a typology of eight groups of patients that share common exposure patterns and types of medical emphasis of care.

Results

Sample

The sample included 30 adults (14 males, 16 females) aged 23 to 65 years who had been prescribed tramadol (*n* = 24) or codeine (*n* = 6). Eighteen of the patients were White, 11 were Black, and one was Biracial. Twenty-six were Not Hispanic/Latino, one was Hispanic/Latino (*n* = 1), and three were of unknown ethnicity. The CYP2D6 metabolizing phenotypes for 20 patients were normal metabolizers (activity score: 1-2), six were poor metabolizers (activity score: 0), two were intermediate metabolizers (activity score: 0.5), and two patients were ultra-rapid metabolizers (activity score: > 2). Mean time between when the pharmacogenetically actionable opioid prescription was written and dispensed was 1.6 days.

The Typology

The typology consists of eight groups of patients that had one of five opioid prescription patterns and one of three types of medical emphasis of care. The pharmacogenetically actionable opioid prescription patterns were labeled Singular, Episodic, Switching, Sustained, and Multiplex. The three types of medical emphasis of care were labeled Pain, Comorbidities, and Both. The defining characteristics of each of the patterns of opioid prescriptions and types of medical emphasis of care are displayed in Table 3-1. Each group is represented by a cell that includes patterns of opioid prescription according to the type of medical emphasis of care. In the following sections we provide further descriptions of each group. Individual patients are referred to by their study case number. Table 3-2 and Table 3-3 provides sample characteristics and Table 3-4 provides case exemplars to illustrate the essential characteristics of each of the eight groups that comprise the typology.

Singular/Pain. Two patients were placed in this group because they received one, time-limited prescription for the pharmacogenetically actionable opioid while their

medical emphasis of care was largely attributed to pain-related conditions. Both patients within this group were White males and one was a CYP2D6 normal metabolizer and the other was an intermediate metabolizer of the pharmacogenetically actionable opioids.

Both patients received a prescription for tramadol for a limited period of time (≤30 day supply). In one case, Patient 21, a 54-year-old man and a CYP2D6 intermediate metabolizer, was prescribed tramadol 50 mg tablet every 4 to 6 hours as needed for pain, whereas the other patient, Patient 26, a 61-year-old man and CYP2D6 normal metabolizer, was prescribed tramadol 50 mg tablet to be taken each night for severe pain. Neither of the patients received another prescription for a pharmacogenetically actionable opioid over the 6 month time frame, although each was prescribed an additional time-limited medication often used concomitantly to treat painful conditions such as naproxen (NSAID), cyclobenzaprine (muscle relaxant), and gabapentin (anticonvulsant).

The singular opioid exposure pattern for this group occurred in the context of an emphasis of care on their pain-related conditions. The focus of their medical visits was on pain-related conditions such as cervicalgia, paresthesia, and carpal tunnel syndrome, and their medical histories were otherwise limited. They had one to three health care visits over the six-month period.

Singular/Comorbidities. Four patients were placed in this group because they received one, time-limited prescription for a pharmacogenetically actionable opioid while the emphasis of their care was largely attributed to non-pain related comorbidities. The patients in this group included two White and two Black men. Three patients were CYP2D6 normal metabolizers of pharmacogenetically actionable opioids, and one patient was considered a poor metabolizer due to a drug-drug interaction.

Each patient in this group received a prescription for either tramadol (*n* = 3) or codeine (*n* = 1) for a circumscribed period of time (10-30 days). None received an

additional prescription of a pharmacogenetically actionable opioid. Other than one patient who was prescribed cyclobenzaprine for muscle spasms 3 months following a tramadol prescription, no other medications for pain or discomfort were prescribed to any patient within this group.

The singular opioid exposure pattern for the four patients in this group occurred in the context of a medical emphasis on non-pain-related comorbidities. While their pain was treated as described above, the focus of much of their treatment was on other diseases or illnesses. Some of the patients were treated for several conditions affecting multiple body systems. For example, Patient 14, a 62-year-old White man, sought care for dermatophytosis on the foot, hypertension, diabetes, and diabetic retinopathy. Others were treated for one overarching comorbidity such as HIV. The patients in this group had between 5 and 10 different visits during the six-month period and were prescribed between 6 and 10 different medications. One patient had a cytochrome P450 drug-drug interaction between codeine and bupropion, which was prescribed as a smoking cessation aid. Bupropion is a strong inhibitor of codeine and could reduce its analgesic effects.

Singular/Both. Three patients were placed in this group because they received one, time-limited prescription for a pharmacogenetically actionable opioid while the medical emphasis of their care was on both pain and other comorbidities. Two of the patients in this group were White women, and one was a White man. All the patients were CYP2D6 normal metabolizers of the pharmacogenetically actionable opioids.

Each patient in this group received a prescription for tramadol (n = 2) or codeine (n = 1) for a relatively short period of time (6-15 days). None of the patients received another prescription for a pharmacogenetically actionable opioid or any other opioid, and few had other medications prescribed for pain. Patient 06, a 40-year-old White female,

and Patient 24, a 40-year-old White male, were also prescribed gabapentin for fibromyalgia and neuralgia, respectively.

The singular opioid pattern occurred for these three patients in the context of a medical emphasis on both pain and other comorbidities. These patients had 4 to 10 visits for various reasons. For example, Patient 30, a 61-year-old White woman, visited a primary care clinic three times for abdominal pain related to an infection and esophageal reflux; an outpatient specialty clinic five times for abdominal pain, chest pain, neuralgia/neuritis, and shortness of breath; and the emergency department once for abdominal pain and rectal bleeding. The patients were prescribed 9 to 12 different medications for different comorbidities. For example, Patient 06, a 40-year-old White woman, was prescribed 12 different medications for pain, depression, thyroid disease, vitamin supplementation, infection, and allergies.

Episodic/Pain. Three patients were placed in this group because they received multiple intermittent or discontinuous prescriptions for pharmacogenetically actionable opioids while their emphasis of care was largely attributed to pain-related conditions. The patients in this group included two Black women and one White man. Two patients were CYP2D6 normal metabolizers and one was considered an ultra-rapid metabolizer of the pharmacogenetically actionable opioids.

Each patient in this group received at least two separate prescriptions for tramadol several months apart. For example, Patient 5, a 46-year-old Black woman who was a CYP2D6 ultra-rapid metabolizer, was prescribed and filled a 30-day supply of tramadol 50 mg 1 tablet every 8 hours as needed for pain in August, and did not receive or fill another prescription for tramadol until 5 months later (January). Two of the patients were also prescribed an opioid other than tramadol over the 6-month time frame. For example, Patient 10, a 51-year-old Black female, was prescribed oxycodone and

codeine. All three of the patients also received an anti-inflammatory medication used to treat pain such as naproxen, ibuprofen, or piroxicam.

The episodic opioid exposure pattern for the three patients in this group occurred in the context of a medical emphasis on pain-related conditions. The focus of the healthcare visits was primarily on their joint pain (e.g., shoulder and leg/knee). At these visits, they rated their pain from 7/10 to 10/10. For example, Patient 10, a 51-year-old Black female, sought care three times at the primary care clinic and 1 time at a specialty care clinic for joint pain in the left leg. At two of the primary care visits, she reported a pain intensity rating of 10/10. The patients in this group had two to five visits healthcare visits over the six-month period.

Episodic/Both. Ten patients were placed in this group because they received and/or refilled multiple intermittent, or discontinuous, prescriptions for pharmacogenetically actionable opioids while having a medical emphasis of care on both pain and other comorbidities. The patients in this group included nine women and one man. Six of the patients were White and four were Black. Eight of the patients were CYP2D6 normal metabolizers, two were poor metabolizers due to CYP2D6 genotype variation, and two additional patients were considered poor metabolizers due to a drug-drug interaction with a strong inhibitor of the opioid.

Each patient in this group received at least two separate prescriptions for tramadol (*n* = 8) or codeine (*n* = 2) that were prescribed or refilled several months apart. For example, Patient 18, a 56-year-old White woman, was given a 30-day prescription for Tramadol 50 mg 1 tablet twice a day as needed for pain that she refilled over three months later. Patient 01, a 61-year-old White woman, received and filled two separate prescriptions for tramadol over four months apart. Five days following the second prescription, she had a primary care visit related to an adverse effect of the opioid, but the details of the adverse effect are unknown. In addition to the pharmacogenetically

actionable opioids, most of the patients in this group were prescribed other pain medications including anti-inflammatory medications such as ibuprofen, piroxicam, or naproxen.

The episodic opioid exposure pattern for this group occurred in the context of a medical emphasis on both pain and other comorbidities. The pharmacogenetically actionable opioids were prescribed at primary care visits mostly associated with either joint or lower back pain, but there were also multiple healthcare encounters for non-pain related conditions such as hypertension, diabetes, and depression. The patients in this group had between 1 to 11 visits and were prescribed between 4 to 19 different medications. Patient 07, a 62-year-old Black female, and Patient 11, a 54-year-old White female, both had a cytochrome P450 drug-drug interaction between diphenhydramine and tramadol. Diphenhydramine is a strong inhibitor of tramadol. The other non-pain-related medications were most commonly prescribed to manage hyperlipidemia and hypertension. For example, Patient 15, a 60-year-old-Black woman consistently filled two medications for hyperlipidemia (atorvastatin and ezitimbe) and two medications for hypertension (amlodipine and hydrochlorothiazide) in addition to filling medications to treat her joint pain (tramadol, naproxen, and piroxicam).

Switching/Both. Three patients were placed in this group because they were prescribed a short-term supply of a pharmacogenetically actionable opioid that was followed shortly after (< 30 days) with a different opioid prescription while their emphasis of care was attributable to both pain and other comorbidities. This group included two women and a man. Two of the patients were Black, and one was Biracial/Hispanic. Two patients were CYP2D6 normal metabolizers and one patient was considered a poor metabolizer due to a drug-drug interaction.

Each patient in this group received a prescription for tramadol (n = 2) or codeine (n = 1) with a short supply (≤ 10 days). Soon after they filled the pharmacogenetically

actionable opioid, they received a new prescription for a different opioid. Oxycodone/acetaminophen was the new opioid prescribed for two of the patients and hydrocodone/acetaminophen was the new opioid prescribed to the third patient. For example, Patient 16, a 53-year-old Black woman, was prescribed an 8-day supply of tramadol 50 mg 1 tablet every 6 hours for pain as needed, and less than 1 month later was prescribed a 5-day supply of oxycodone/acetaminophen. This patient had a potential cytochrome P450 drug-drug interaction between the tramadol and fluoxetine. Fluoxetine is a strong inhibitor of tramadol, meaning the tramadol could potentially have reduced analgesic effects. Some patients received pain medications other than opioids, such as anti-inflammatory medications (NSAIDs). For example, Patient 03, a 51-year-old Hispanic woman, received prescriptions for tramadol, hydrocodone, and ibuprofen.

The switching opioid exposure pattern for these four patients occurred in the context of a medical emphasis on both pain and other comorbidities. They had 4 to 6 health care visits over the 6-month period, and each received at least 10 medications for multiple indications. For example, Patient 13, a 51-year-old woman, was prescribed or refilled 24 different medications for indications that included pain, hypertension, hyperlipidemia, diabetes, depression, and others.

Sustained/Both. Two patients were placed in this group because they were prescribed pharmacogenetically actionable opioids for extended or continuous periods of time while having a medical emphasis of care on both pain and other comorbidities. Both of the patients in this group were White men, and one was a CYP2D6 normal metabolizer whereas the other was considered an intermediate metabolizer due to a drug-drug interaction.

Each patient in this group received a prescription for tramadol that they filled at least three times with a total supply of at least 60 days during the six-month period. For example, Patient 27, a 65-year-old White man, filled a prescription for a 30-day supply of

tramadol 50 mg to be taken once a day as needed for severe pain for three consecutive months. Patients in this group were prescribed few other pain medications, with a maximum of two additional medications for pain over the 6 month period. Patient 23, a 52-year-old White male, had a P450 drug-drug interaction between tramadol and duloxetine, with duloxetine being a moderate inhibitor of tramadol.

The sustained opioid exposure pattern for these four patients occurred in the context of a medical emphasis on both pain and other comorbidities. These patients had 6 to 10 healthcare encounters for pain-related conditions such as fibromyalgia, carpal tunnel syndrome, and joint pain, as well as for non-pain related conditions such as diabetes, depression, and hypertension. They received between 7 and 20 medications for multiple indications. For example, Patient 23 was prescribed 20 different medications for conditions such as fibromyalgia, hypertension, hyperlipidemia, depression, anxiety, and a sleep disorder. This patient also had cytochrome P450 interaction between duloxetine and tramadol. Duloxetine is a moderate inhibitor of tramadol, meaning it can decrease the analgesic effects of tramadol.

Multiplex/Both. Three patients were placed in this group because they were prescribed a markedly complex regimen of pharmacogenetically actionable opioids while their medical emphasis of care was on both pain and other comorbidities. Two patients in this group were White men, whereas the other patient was a Black women. Two patients were normal metabolizers and one was an ultra-rapid metabolizer of the pharmacogenetically actionable opioids.

Two patients in this group received prescriptions for tramadol and one received prescriptions for codeine. The opioid patterns of these three patients represented some combination of the episodic or sustained patterns with some incremental dose adjustments. For example, Patient 17, a 54-year-old White man and ultra-rapid metabolizer, received a prescription for tramadol with an increasing dose. He was

instructed to take ½ tablet for 3 days, then ½ tablet twice a day for 3 days, then ½ tablet three times a day for 3 days, then ½ tablet every 6 hours as needed for pain. In addition, the pharmacogenetically actionable opioid was complemented by at least one additional opioid for all the patients. For example, Patient 09, a 30-year-old White male had received two prescriptions, approximately a month apart, for a 6-day supply of codeine/acetaminophen to be taken every 4 to 6 hours as needed for pain. In between those prescriptions, he was prescribed hydrocodone, and he was prescribed oxycodone at the same time as the second codeine prescription. Over the six month time frame these patients received 6 to 8 different prescriptions for pain, including the pharmacogenetically actionable opioids and other opioids (e.g., hydrocodone, oxycodone, fentanyl, hydromorphone), acetaminophen, anti-inflammatory medications (e.g., naproxen, ibuprofen), and other adjuvant medications (e.g., cyclobenzaprine, capsaicin cream).

The multiplex exposure pattern for these three patients occurred in the context of a medical emphasis on both pain and other comorbidities. They were treated for pain-related conditions such as cervicalgia, lumbago, myalgia, and abdominal pain as well as a variety of non-pain-related conditions. All were being treated for depression and anxiety with medications such as amitriptyline, venlafaxine, trazadone, lorazepam, and alprazolam. The co-occurring psychiatric and pain conditions led to significant healthcare utilization as the patients in this group had 12 to 21 visits over the 6-month time period. Patient 09, for example, a 30-year old White male, had nine different healthcare encounters for depression, cervicalgia, and suicidal ideation within 27-days. Six of the visits were to the emergency department, two were to the primary clinic, and one was to a specialty clinic for depression. Overall, these patients received prescriptions for between 11 to 15 different medications.

Discussion

The purpose of this study was to understand the nuances and complexity of exposure to tramadol and codeine - two opioid medications for which there are clear pharmacogenetically based guidelines. We found eight exposure patterns based on opioid prescription patterns and the medical emphasis (or focus) for which care was being sought. The patterns we uncovered show how the interactions between these salient factors unfolded over a six month period; thus, the typology yielded a more complex understanding of meaningful subgroups of individuals with differing patterns of exposure to pharmacogenetically actionable opioid medications than prior measures of medication exposure. Our study findings have generated information not previously described in the field and suggest that a shift is needed in the way medication exposure has been conceptualized.

Our findings confirm the importance of measuring exposure as a dynamic concept, rather than a dichotomous or single exposure variable as has been done in prior studies. The variations between the pharmacogenetically actionable opioid prescription patterns (e.g., singular, episodic, switching, sustained, and multiplex) highlight the nuances and multi-dimensional nature of medication exposure and the reason why exposure measures should capture changes over time.[16] For example, the 'Episodic pattern' involved varying periods of time over the six months in which the patients had interruptions in their opioid therapies. In contrast, the 'Singular pattern' included only one time limited prescription for the opioid and the 'Sustained pattern' involved prolonged periods of opioid use. Previous studies evaluating the effectiveness of pharmacogenetic testing have oversimplified medication exposure through dichotomous measures (e.g., yes/no an individual is taking a medication) or by medication count.[8, 9, 11] For example, if medication exposure is captured at a single point in time, then continuous exposure or non-exposure to the drug would be assumed after

the baseline measurement. This would not account for any discontinuation or interruptions of opioid therapies as were noted in the Singular, Episodic, and Switching patterns. As evidenced by the patterns identified in this study, previously used measures fail to capture the dynamic and heterogeneous state of medication exposure and potentially lead to misclassification of the medication exposure.[16] Thus, future medication exposure measures must go beyond dichotomous measures and capture the length and pattern of exposure to a pharmacogenetically actionable opioid.

The differences in medical emphasis of care between patterns raises concerns about the complexity of evaluating the clinical implementation of pharmacogenetic testing and its effects on opioid-related outcomes. The identified differences within the medical emphasis of care highlighted the importance of interactions among various medications used in complex treatment regimens, healthcare encounters, and reasons for seeking care. Pain and opioid use rarely occurs in isolation from other comorbidities or co-prescribed medications.[45, 46] Largely, the subgroups had complicated medication regimens with evidence of polypharmacy. In certain instances, such as those patients with an emphasis of care on both pain and comorbidities, it could be difficult to distinguish what drug or drug-drug interaction is causing a particular adverse drug effect or medication non-response. Therefore, due to the heterogeneity and complexity of this population, it is likely that the benefits of pharmacogenetic testing may be difficult to fully capture as there are many confounding factors to be considered when evaluating clinical implementation of pharmacogenetic testing.

Additionally, a common method of predicting treatment outcomes of pharmacogenetically actionable opioids is through stratifying the population based on genotype-driven drug metabolizing phenotypes (i.e., poor, intermediate, extensive (normal), ultra-rapid metabolizers).[47] The identified patterns show an alternative way to stratify or control for confounding factors in individuals receiving pharmacogenetically

actionable opioids. If we solely relied on the common use of the CYP2D6 genotype activity score to determine drug metabolizing phenotypes in this study, there would have been four resulting groups – ultra-rapid metabolizers (*n* = 2), normal metabolizers (*n* = 25), intermediate metabolizers (*n* = 1), and poor metabolizers (*n* = 2). These data are consistent with population level frequency estimates in similar race/ethnic groups.[3] Although the poor metabolizers fell within the same pattern of exposure (Episodic/Both), the two ultra-rapid metabolizers fell within two different patterns (Episodic/Pain and Multiplex/Both) and the normal metabolizers fell within all eight, distinctly different patterns. In addition, the five cytochrome P450 drug-drug interactions of moderate to strong inhibitors of tramadol or codeine would not have been captured. The methods we used could be applied to better understand exposure to other non-opioid or pharmacogenetically actionable medications.

In general, this study also addressed a call to action to explore research strategies that aid in capturing heterogeneity across patients who use opioids and identifying meaningful subgroups that may respond differently to treatments.[48] To our knowledge, no other studies have employed a qualitative, person-oriented approach to explore patterns of medication exposure with data coming from existing clinical and administrative data repositories. While the person-oriented approach cannot determine causation between medication exposure and clinical responses, this approach proved useful in identifying subgroups and comparing and contrasting salient factors of exposure. The identified patterns and subgroups can inform future studies that seek to develop a medication exposure measurement tool to account for confounding factors when evaluating clinical outcomes and costs of the implementation of pharmacogenetic testing, as well as in genomic association studies linking genes to opioid-induced side effects (e.g., constipation, nausea, or vomiting). Importantly, the subgroups can inform studies that seek to identify and tailor interventions in this population, thereby allowing

for more personalized health care and ultimately better pain management outcomes. For example, due to the identified complexities between the pharmacogenetically actionable opioid, polypharmacy, and extensive healthcare utilization, individuals falling within the Multiplex/Both pattern may benefit from personalized health coaching or coordinated pain management approaches across multiple providers. Individuals falling within the Singular/Pain pattern may require a significantly less intense intervention, such as a brief medication education intervention at or immediately after clinic discharge.

Our findings need to be interpreted in light of some limitations. While this qualitative, person-oriented approach identified subgroups that shared common patterns that reveal some of the intricacies and nuances of medication exposure and implications for pharmacogenetic testing, we recognize at the current stage of development of this typology we cannot make statements related to the prevalence of patients that would fall within each pattern or causal/predictive statements related to outcomes. With further development and validation, however, we believe a typology such as this could be used to tie group membership to clinical or economic outcomes such as medication response or costs of care. For example, Jonzon & Lindblad[49] employed a person-oriented approach to identify subgroups of women who had exposure to sexual assault during their childhood. These investigators identified six different subgroups based on varying patterns of risk and protective factors (i.e., severity of child sexual abuse, severity of child physical abuse, coping, social support) and then determined that subgroup membership was significantly associated with adulthood outcomes such as psychological and psychosomatic symptoms and healthcare utilization. Similarly, with further research, we propose that groups that differ in medication exposure will likely have different outcomes related to pharmacogenetic testing and may require different strategies to ensure that the benefits of the testing are fully realized. A Singular/Pain group, for example, may be found to experience optimal analgesia following the use of

pharmacogenetic testing to select the most appropriate opioid therapy and may require minimal monitoring of pain response; whereas achieving optimal analgesia in the Multiplex/Both group may be more challenging as comorbidities and irregular health utilization would have to be considered in the monitoring of pain response and determining its relationship to the medication and dose that was selected based on pharmacogenetic testing.

There is limited generalizability beyond individuals who are prescribed either tramadol or codeine in the primary care setting at a safety-net healthcare system. Given the small sample size, further research is needed to further develop the typology in larger populations or those taking different pharmacogenetically actionable medications (e.g., amitriptyline). Furthermore, the retrospective nature and use of existing electronic health records also contributes to the limitations of this study. It was difficult to assess accuracy of the data (e.g., accuracy of ICD-9 codes as admit diagnosis) as well as whether certain data were missing within the electronic data sources. The way we assessed the inclusion criteria of "first prescription of record" assumed that all patients' past healthcare records were captured within the Indiana Network for Patient Care. Also, we were only able to capture medication exposure through pharmacy records, thus we assumed that if a medication was prescribed and filled, the patient was actively taking that medication as prescribed. Ultimately, there was no true way of knowing whether the individuals were actually taking the opioid medication. In addition, electronic health records provide important clinical and administrative information, however, these sources lack information on patient perspectives.[50] For example, data elements related to the intensity, duration, distress, and quality of an individual's pain, along with their level of functioning, are not consistently documented or not captured within the electronic health record. Additionally, we were also limited in capturing potential medication side effects. Therefore, we were limited in capturing patient perspectives

related to their pain and response to the opioid medication. These will be important factors to include in future research.

Conclusion

We sought to expand the knowledge of medication exposure by employing an innovative, person-oriented approach to identify a typology of common patterns of exposure to pharmacogenetically actionable opioids in primary care. As a result, we identified eight typical patterns of medication exposure that highlighted the heterogeneity and variations among the sample prescribed these medications. Study findings advance the argument that medication exposure is not static, but rather dynamic and multidimensional. This is particularly meaningful when determining a medication exposure measure when evaluating the utility of pharmacogenetic testing and its impact on selecting and dosing pharmacogenetically actionable opioids. Additionally, the patterns serve as a means to stratify individuals into meaningful subgroups of medication exposure. Therefore, these patterns can inform future studies that seek to personalize care through identifying and tailoring interventions in individuals prescribed pharmacogenetically actionable opioids. Finally, our approach could be applied to other medications and other patients groups.

Table 3-1.

Typology of Exposure to Pharmacogenetically Actionable Opioids

		Pharmacogenetically Actionable Opioid Prescription Pattern[1]				
		Singular	Episodic	Switching	Sustained	Multiplex
Medical Emphasis of Care[2]	Pain	One, time-limited prescription for the PGxA opioid and reasons for care are largely attributed to pain-related conditions.	Intermittent, or discontinuous, prescriptions for PGxA opioids and reasons for care are largely attributed to pain-related conditions.			
	Comorbidities	One, time-limited prescription for the PGxA opioid and reasons for care are largely attributed to non-pain related illnesses or diseases.				
	Both	One, time-limited prescription for a PGxA opioid and reasons for care largely attributed to both pain and other co-occurring illnesses or diseases.	Intermittent, or discontinuous, prescriptions for PGxA opioids and reasons for care largely attributed to both pain and other co-occurring illnesses or disease.	Short-term supply of PGxA opioid followed by a new/different opioid and reasons for care largely attributed to both pain and other co-occurring illnesses or diseases.	Extended periods of uninterrupted prescriptions or refills of the PGxA opioid and reasons for care largely attributed to both pain and other co-occurring illnesses or diseases.	Combination of PGxA opioid patterns and reasons for care largely attributed to both pain and other co-occurring illnesses or diseases.

Table continues

PGxA: Pharmacogenetically actionable.

[1] Pharmacogenetically Actionable Opioid Prescription Pattern was determined from prescription data including dose, timing of fills/refills, and supply amounts over the 6-month time period.

[2] Medication Emphasis of Care was determined from patterns in data representing medical histories, type and indication for all medications prescribed, clinical responses, and type and reasons for healthcare encounters over the 6-month time period.

Table 3-2.
Sample Characteristics by Exposure Pattern

	Singular/ Pain	Singular/ Comorbid	Singular/ Both	Episodic/ Pain	Episodic/ Both	Switching/ Both	Sustained/ Both	Multiplex/ Both	Total
N	2	4	3	3	10	3	2	3	30
Age (years)									
Mean	57.5	52.8	47	47	51	49.3	58.5	48.3	50.9
(SD)	(4.9)	(12.8)	(12.1)	(3.6)	(11.9)	(4.7)	(9.2)	(16.3)	(10.4)
Range	54-61	34-62	40-61	44-51	23-62	44-53	52-65	30-61	23-65
Sex *n* (%)									
Male	2 (100)	4 (100)	1 (33.3)	1 (33.3)	1 (10)	1 (33.3)	2 (100)	2 (66.7)	14 (46.7)
Female	---	---	2 (66.7)	2 (66.7)	9 (90)	2 (66.7)	---	1 (33.3)	16 (53.3)
Race *n* (%)									
White	2 (100)	2 (50)	3 (100)	1 (33.3)	6 (60)	---	2 (100)	2 (66.7)	18 (60)
Black	---	2 (50)	---	2 (66.7)	4 (40)	2 (66.7)	---	1 (33.3)	11 (36.7)
Biracial	---	---	---	---	---	1 (33.3)	---	---	1 (3.3)
Ethnicity *n* (%)									
Not Hispanic	2 (100)	3 (75)	3 (100)	2 (66.7)	9 (90)	2 (66.7)	2 (100)	3 (100)	26 (86.7)
Hispanic	---	---	---	---	---	1 (33.3)	---	---	1 (3.3)
Unknown	---	1 (25)	---	1 (33.3)	1 (10)	---	---	---	3 (10)
PGxA Opioid *n* (%)									
Tramadol	2 (100)	3 (75)	2 (66.7)	3 (100)	8 (80)	2 (66.7)	2 (100)	2 (66.7)	24 (80)
Codeine	---	1 (25)	1 (33.3)	---	2 (20)	1 (33.3)	---	1 (33.3)	6 (20)

SD = standard deviation; PGxA = Pharmacogenetically Actionable

Table 3-3.
CYP2D6 Activity Score, Drug-Drug Interactions, and Drug Metabolizing Phenotype by Exposure Pattern

	Singular/ Pain	Singular/ Comorbid	Singular/ Both	Episodic/ Pain	Episodic/ Both	Switching/ Both	Sustained/ Both	Multiplex/ Both	Total
N	2	4	3	3	10	3	2	3	30
CYP2D6 Genotype Activity Score									
0	---	---	---	---	2 (20)	---	---	---	2 (6.7)
0.5	1 (50)	---	---	---	---	---	---	---	1 (3.3)
1.0	---	2 (50)	---	---	3 (30)	2 (66.7)	1 (50)	2 (66.7)	10 (33.3)
1.5-2	1 (50)	2 (50)	3 (100)	2 (66.7)	5 (50)	1 (33.3)	1 (50)	---	15 (50)
>2	---	---	---	1 (33.3)	---	---	---	1 (33.3)	2 (6.7)
P450 DDI with Opioid									
None	2 (100)	3 (75)	3 (100)	3 (100)	8 (80)	2 (66.7)	1 (50)	3 (100)	25 (83.3)
Moderate	---	---	---	---	---	---	1 (50)	---	1 (3.3)
Strong	---	1 (25)	---	---	2 (20)	1 (33.3)	---	---	4 (13.3)
Final Phenotypes									
UM	---	---	---	1 (33.3)	---	---	---	1 (33.3)	2 (6.7)
NM	1 (50)	3 (75)	3 (100)	2 (66.7)	6 (60)	2 (66.7)	1 (50)	2 (66.7)	20 (66.7)
IM	1 (50)	---	---	---	---	---	1 (50)	---	2 (6.7)
PM	---	1 (25)	---	---	4 (40)*	1 (33.3)	---	---	6 (20)

Data reported as *n* (%).
PGxA = Pharmacogenetically Actionable; DDI: Drug-drug interaction; PM = Poor Metabolizer; IM = Intermediate Metabolizer; NM = Normal Metabolizer; UM = Ultra-rapid Metabolizer
*The two patients who had a CYP2D6 genotype activity score of 0 were not the same patients who had a DDI with a strong inhibitor.

Table 3-4.
Case Exemplars by Exposure Pattern

Pattern	Exemplar
Singular/Pain	Patient 26 was a 61-year-old White male and CYP2D6 normal metabolizer. He had a one, time limited prescription for tramadol and had a history of cervicalgia. He sought care at the primary care clinic for this condition and was prescribed tramadol 50 mg to be taken at night for severe pain. The pain intensity documented at this visit was 5/10. In addition to the new tramadol prescription, 2 other medications for pain were prescribed at this visit – naproxen and cyclobenzaprine. All three prescriptions were filled. Over the 6 month period, there were no additional healthcare encounters or medications prescribed or filled.
Singular/Comorbidities	Patient 19 was a 34-year-old Black male and CYP2D6 normal metabolizer. He had a one, time-limited prescription for codeine and suffered from a number of comorbidities, including HIV/AIDS, Hepatitis B and C, seborrheic dermatitis, constipation, and back and shoulder pain. He sought care at the primary care clinic for HIV disease and back ache. At this visit he rated his pain intensity as a 10/10. He was prescribed a 30 day supply of codeine/acetaminophen to be taken as needed for pain. In addition, he was also prescribed bupropion and conjugated estrogen. All three of these medications were filled, and other than the mentioned codeine prescription, there was no evidence of any pain medications prescribed or filled over the 6 month period; however, his medication regimen consisted of 9 other medications that were regularly filled. In the same time period, there were a total of 2 primary care visits and 3 specialty clinic visits for diagnoses other than pain (e.g., HIV). There was one cytochrome P450 drug-drug interaction between bupropion (strong inhibitor) and codeine/acetaminophen. This interaction led to Patient 19’s phenotype change from a CYP2D6 normal metabolizer to a poor metabolizer.

Table continues

Singular/Both	Patient 30 was a 61-year-old White female and CYP2D6 normal metabolizer had multiple comorbidities such as coronary artery disease, asthma, esophageal reflux, depression, and a number of pain conditions (headache, neuralgia, abdominal pain). She had a one, time limited prescription for 15-day supply for tramadol prescribed at a primary care visit for esophageal reflux, H. pylori infection, headache and neuralgia. Also at this visit she was prescribed 8 additional medications such as prednisone, amitriptyline, esomeprazole, 2 asthma medications, and 2 anti-infective medications. All were filled the day after the primary care visit. Following that visit there were multiple additional healthcare encounters for both pain and non-pain-related conditions, including 3 visits to the primary care clinic, 5 visits to specialty care clinics, and 1 emergency department visit. Despite the frequent healthcare encounters, the only additional prescription provided was for esomeprazole and there were no new prescriptions for tramadol or any other pain medications.
Episodic/Pain	Patient 29, a 44-year-old White male and CYP2D normal metabolizer, had a history of knee pain and hypertension. He sought care at the primary care clinic for joint pain in his left leg. At this visit he rated his pain intensity as an 8/10 and was prescribed a short-term (7-day) supply of tramadol to be taken every 6 hours as needed for pain. Additionally, naproxen to be taken twice a day. Both of these prescriptions were filled, along with a prescription for lisinopril. In the following 6-months, there were an additional 3 primary care visits and 1 specialty clinic visit – all for joint pain/osteoarthritis. Furthermore, there were 2 documented pain intensities of 7 and 10/10. Three months following the original tramadol prescription, there was a new order for a 15-day supply of tramadol to be taken every 6 hours as needed for pain. Also at this time there was evidence that the naproxen prescription was refilled.

Table continues

Episodic/Both	Patient 04 was a 57-year-old Black female and CYP2D6 normal metabolizer. She was prescribed codeine/acetaminophen at a primary care visit for depressive disorder, hypertension, and joint pain. At this visit the reported pain intensity was documented as 7/10. Also prescribed were 1 antihypertensive medication (hydrochlorothiazide) and 2 psychiatric medications (desvenlafaxine and risperidone). All medications were filled, with a 10 day supply of codeine being dispensed. Approximately one month following the initial visit, there was another primary care visit with a documented pain intensity of 6/10, a specialty clinic visit for venereal disease, and 2 inpatient hospitalizations lasting longer than 1 month for cervicalgia. One month following discharge from the hospital, there was a primary care visit for Herpes Zoster, with a pain rating of 10/10 was reported. Subsequently, a 10 day supply of codeine, along with an antiviral, was prescribed and filled. In total, there were 8 different medications part of the medication regimen and a total of 6 healthcare encounters.
Switching/Both	Patient 03, a 44-year-old Black male and CYP2D6 normal metabolizer, was prescribed codeine/acetaminophen, to be taken as needed for pain, at a primary care visit for gout and hypertension. At this visit, a pain intensity of 10/10 was recorded. The codeine prescription was filled with a 3-day. Less than a week later, the patient sought care in the emergency department for foot pain, and was subsequently prescribed a 5 day supply of oxycodone/acetaminophen. Three weeks later, the patient returned to the primary care clinic with a pain intensity of 8/10 and a 5 day supply of oxycodone/acetaminophen was prescribed and filled. In addition to these opioids, there were 8 different medications prescribed and consistently filled to manage conditions such as hypertension, heart failure, and gout.

Table continues

Sustained/Both	Patient 23, a 52-year-old White male who was a CYP2D6 normal metabolizer, had a history of fibromyalgia, depression, hypertension, and coronary artery disease who was prescribed tramadol 50 mg to be taken as needed for pain, at a primary care visit for coronary atherosclerosis. In addition, multiple other medications were prescribed, resulting in 10 different medications part of the medication regimen. The 20 day supply of tramadol was filled/refilled a total of 4 times. After the initial visit, there were a total of 2 additional primary care visits and 7 specialty clinic visits for diagnoses such as abdominal pain, neuralgia, major depression, anxiety, and hypertension. Overall, there were a total of 20 different medications for multiple chronic conditions as part of the medication regimen over the 6 month period. There were also four different potential cytochrome P450 drug-drug interactions, one of which was between duloxetine (moderate inhibitor) and tramadol. This interaction led to Patient 23's phenotype change from a CYP2D6 normal metabolizer to an intermediate metabolizer. The other drug-drug interactions were between duloxetine (inhibitor) and metoprolol, omeprazole (inhibitor) and clopidogrel, and esomeprazole (inhibitor) and clopidogrel.

Table continues

Multiplex/Both	Patient 08, a 61-year-old Black female who is a CYP2D6 normal metabolizer, was prescribed tramadol 50 mg to be taken as needed for pain, at a primary care visit for hyperparathyroid, hypertension, and osteoarthritis. At this visit there was a documented pain intensity of 8/10 and other medications prescribed included lorazepam and cyclobenzaprine. All 3 medications were filled. The tramadol prescription was refilled with a 17 day supply approximately 1 month after the original fill date. 10 days after the refill, there was a visit to a specialty clinic for polyarthritis and new prescription for a 28 day supply hydrocodone was provided. Less than a week later, the patient returned to the primary clinic for osteoarthritis and a 7 day supply for hydromorphone was prescribed for fibromyalgia. There were 2 more prescriptions for 15 day supplies of hydromorphone provided a month apart in the following 2 months. Less than a month after the third prescription for hydromorphone, and approximately 3 months following the last tramadol refill, there was a new prescription written for tramadol. This prescription was filled and then refilled 3 weeks later. In addition to the opioids, this patient had evidence of filling prescriptions for an anti-inflammatory (indomethacin), muscle relaxant (cyclobenzaprine), antirheumatic (leflunomide), and a benzodiazepine (lorazepam) medications over the 6 months. Overall, this patient's medication regimen consisted of 11 different medications, 6 of which were for pain. There were also 12 healthcare encounters – 6 visits to the primary care clinic, all for pain-related conditions, and 6 to specialty clinics, which only 3 of those visits were related to pain. Additionally, during 4 of the visits there were documented pain intensity ratings ranging from 8-9/10.

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CHAPTER 4

This chapter presents the results of the manuscript, “Comorbidities, Healthcare Utilization, and Medication Regimens in Underserved Primary Care Patients Prescribed Pharmacogenetically Actionable Opioids.”

Abstract

Despite the promise of pharmacogenetic testing, significant challenges for evaluating the outcomes related to its implementation exist, including the complexity of patients' clinical profiles. The purpose of this study was to describe the context in which pharmacogenetically actionable opioids (codeine and tramadol) are prescribed, including patients' comorbidities, healthcare utilization, and medication regimens, in a large safety-net health system. We used 6 months of electronic health record and CYP2D6 pharmacogenetic genotype data from 30 adult patients to evaluate their number and type of comorbidities, healthcare encounters, and medications prescribed. Findings showed that patients had multiple comorbidities, with all patients experiencing 2 or more comorbidities and 57% (*n* = 17) experiencing 5 or more. On average, patients had 6.9 healthcare encounters and were prescribed 10 different medications over a 6-month time period. Five patients (17%) had potential drug interactions that could have affected their CYP2D6 drug metabolizing status. Findings indicated that complex medical histories, extensive healthcare utilization, and the number of co-prescribed medications in patients prescribed pharmacogenetically actionable opioids could potentially confound the desired clinical and economic benefits of pharmacogenetic testing. Therefore, future research and clinical implementation of pharmacogenetic testing to guide opioid therapies must control or account for these important factors.

Keywords: Pharmacogenomics, pharmacogenetic testing, clinical implementation, opioid, pain management, comorbidities, healthcare utilization, polypharmacy

Comorbidities, Healthcare Utilization, and Medication Regimens in Underserved Primary Care Patients Prescribed Pharmacogenetically Actionable Opioids

Pharmacogenetic testing has the potential to improve pain management through addressing wide interindividual variations in responses to pharmacogenetically actionable opioids such as codeine and tramadol.[1] Pharmacogenetic testing aids in the identification of individual genetic variations that affect drug disposition and response and thus could improve clinical and economic outcomes by improving medication responses and decreasing adverse drug effects.[2-4] Pharmacogenetically actionable medications are those for which there are evidence-based guidelines to guide drug or dosage changes based on pharmacogenetic test results.

Despite the promise of pharmacogenetic testing, the complexity of patients' clinical profiles can confound its desired clinical and economic benefits.[3, 5, 6] Three patient clinical profile factors likely to influence the outcomes of pharmacogenetic testing are patient comorbidities, healthcare utilization, and medication regimens. Comorbidities are common since pain rarely occurs in isolation from other conditions. Multiple pain and non-pain comorbidities can lead to significant variability in clinical responses and complicate healthcare utilization and costs of care.[7] In addition, patients who experience pain are often treated by a number of providers during multiple healthcare encounters and prescribed several different medications to manage their pain and other comorbid conditions.[8] Furthermore, 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 interactions.[9] Although a better understanding of these three factors could enhance the effectiveness of pharmacogenetic testing used to improve pain management[10], these factors are not currently considered in clinical guidelines for pharmacogenetic testing[11] and no studies

to date have described these factors in a group of patients being prescribed pharmacogenetically actionable opioids.

The goal of this study was to describe in detail the comorbidities, healthcare utilization, and medication regimens of patients who had been prescribed tramadol or codeine in a primary care clinic within a large safety-net health system. The primary care clinics provided an optimal setting for the study as they served an underserved population with complex clinical profiles that are likely to complicate the implementation of pharmacogenetic testing which is underway within the setting.

Methods

Design & Setting

This study was a retrospective, secondary analysis of 6-months of de-identified data from electronic health records and banked DNA specimens from a randomly selected sample of patients who were newly prescribed a pharmacogenetically actionable opioid in a primary care clinic within a large safety-net health system. The data were collected as part of a study that sought to identify a typology of meaningful subgroups that shared common patterns of exposure to these medications.[12] The safety-net health system primarily serves low-income and vulnerable patients and, at the time of this study, was in the process of implementing widespread pharmacogenetic testing for 30 different target medications.[13] This system has robust data repositories that allowed for capturing information such as medical histories, medication records and healthcare utilization from patients' comprehensive health records and for linking electronic health records to DNA samples. Due to the de-identified nature of this study, it was deemed non-human subjects research by the Indiana University Office of Human Subjects Research.

Sample

The sample included 30 patient records randomly selected from a pool of 118 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 large safety-net 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 Sources & Procedures

Six months of electronic health record data for each patient were obtained from comprehensive data repositories. The six-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 electronic health record data from more than 25,000 individual providers, 106 hospitals, and 110 clinics and surgery centers.[14] 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 safety-net health system. Furthermore, the electronic health records were linked to banked DNA specimens obtained from the biobank. All data were de-identified

by the data analyst through existing processes prior to being released to the research team.

Patient characteristics. Demographic characteristics at the time of the new prescription for the pharmacogenetically actionable opioid, including age, gender, and race, were extracted from electronic health records. The time between the first encounter within the safety-net health system and the first prescription for the pharmacogenetically actionable opioid was calculated as an indicator of how long patients had been followed within the health system.

Comorbidities. The comorbidities experienced by the patients during the six-month time period were identified by the International Classification of Diseases – 9th Revision (ICD-9) codes recorded as part of the problem or diagnoses list and/or chief complaint with each healthcare encounter. The ICD-9 codes were aggregated by pain and non-pain diagnoses and descriptive analysis (frequencies) were used to determine the occurrences of each comorbid condition.

Healthcare utilization. Healthcare encounters occurring within six months following the new opioid prescription were determined through a de-identified location number indicating where a service was provided. The encounters were classified as primary care clinic, specialty care clinic, emergency department, or inpatient hospitalization. Clinic sites classified as specialty care included, but were not limited to, cardiology, hematology, neurology, mental health, urology, and orthopedics. Each healthcare encounter was linked to a chief complaint or admit diagnosis through an ICD-9 code(s) so that the reason of the visit could be determined. Mean number and frequencies for total visits, as well as pain-related visits, were calculated for each type of clinic (i.e., primary care, specialty care, emergency).

Medication regimens. 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, including the pharmacogenetically actionable opioids, was determined over the six month time period. Because widespread implementation of pharmacogenetic testing for 30 different target medications was being implemented within the safety-net health system[13], we categorized medications as pharmacogenetically actionable or other. We also classified type of medication based on its indication and reported frequency of patients taking each type. Furthermore, for those patients who were prescribed a certain medication type (e.g., pain medications, cardiac medications, psychiatric medications, etc.), the mean number and range of medications for that type was determined.

CYP2D6 drug interactions and phenotypes. We also reviewed each patient's medication regimen to determine if any potential cytochrome P450 drug-drug interactions (DDI) that would alter the CYP2D6 enzyme activity were present.[15] We noted a potential DDI was present if two medications had known P450 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 DDI present.

Data from the identified drug-drug interactions were then used to calculate the final CYP2D6 enzyme activity score and CYP2D6 drug metabolizing phenotype. The activity score is used to identify the drug metabolizing phenotype classification and is determined by the sum of values assigned to each CYP2D6 allele making up the diplotype.[11] Therefore, we completed CYP2D6 genotype on the banked DNA specimens for all patients in this study. 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 drug disposition and response, as well as their frequencies in the Caucasian, African and their descendant populations.[16] We completed quality controls for each sample batch and repeated assays for 20% of samples. There was a genotyping sample call rate of 99.4%. The genotype results were then used to calculate the CYP2D6 enzyme activity score.[11] This activity score was then adjusted based on the occurrence of any drug-drug interactions. For drug-drug interactions with strong inhibitors of the opioid, the final activity score of 0 was assigned. For drug-drug interactions with moderate inhibitors of the opioid, the CYP2D6 enzyme activity score was multiplied by 0.5 to identify the final activity score.[17] Consequently, the drug metabolizing phenotype for each patient was then determined from the final activity score.[11]

Results

The sample consisted of 30 adults, nearly evenly divided in terms of gender (Table 1), and of whom 40% were Black or Biracial. Ages ranged from 23 to 65 years, with a mean of 50.9 years (SD = 10.4). Of the pharmacogenetically actionable opioids, 24 patients were prescribed tramadol, and six were prescribed codeine. The time between the first encounter within the safety-net health system and the first prescription for either tramadol or codeine was a mean of 14.5 years (SD = 10.9; range = 0 – 34.7 years; median = 13.8 years). The time between the pharmacogenetically actionable opioid prescription and the medication being dispensed was a mean of 1.6 days.

Comorbidities

The patients in the sample typically experienced multiple comorbidities. Table 4-1 presents the 19 most frequently occurring comorbidities. In terms of non-pain comorbidities, 63% of the sample was diagnosed with hypertension and 50% were diagnosed with depression. In terms of pain-related comorbidities, 63% experienced joint

pain/osteoarthritis. Many of the patients were diagnosed with multiple co-occurring painful and non-pain-related comorbidities (Figure 4-1). All of the patients (100%) had at least two or more comorbidities, and 17 (57%) had five or more. Furthermore, 23 patients (77%) had two or more non-pain comorbidities and 22 patients (73%) had two or more documented pain-related comorbidities.

Healthcare Utilization

The patients in this sample had frequent healthcare utilization over the 6-month period (Table 4-2). The total number of healthcare encounters ranged from 1 to 21 different visits, with an average of 6.9 healthcare encounters per patient, or slightly more than one per month on average. Of these visits, there was an average of 3.7 visits to primary care clinics, 2.7 visits to specialty clinics, and 0.5 visits to the emergency department. Visits attributed to pain accounted for less than half of the healthcare visits, however, pain complaints accounted for 86% of emergency department visits. One patient had inpatient admissions of 18 and 24 days for cervicalgia (not reflected in Table 4-2).

Medication Regimens

The patients in the sample received an average of 10 different medication prescriptions with a range of 2 to 24 medication prescriptions over the 6-month time period indicating significant polypharmacy within the sample (Table 4-3). A mean of 3.0 different pain medications were prescribed per patient, of which one was either codeine or tramadol per inclusion criteria (Table 4-3). Furthermore, medications for cardiovascular conditions were prescribed for 77% (n = 23) of the sample; these patients were prescribed an average of 2.9 medications 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.

Figure 4-2 highlights the total number of medications per patient as well as the total number of medications identified as pharmacogenetically actionable as part of the widespread implementation of pharmacogenetic testing within the safety-net health system. Fifty percent (*n* = 15) of patients were only taking one pharmacogenetically actionable medication, which was either codeine or tramadol. Moreover, 30% (*n* = 9) of the patients were taking two different pharmacogenetically actionable medications, 13% (*n* = 4) were taking three different pharmacogenetically actionable medications, and nearly 7% (*n* = 2) were taking five different pharmacogenetically actionable medications.

Genotype and medications affected CYP2D6 metabolizer status. The pharmacogenetic genotyping identified most patients as normal metabolizers (*n* = 25). The five remaining patients had genetic variations affecting their CYP2D6 drug metabolizing status, making them CYP2D6 poor metabolizers (*n* = 2), intermediate metabolizers (*n* = 1), or ultra-rapid metabolizers (*n* = 2). These data are consistent with population level frequency estimates in similar race/ethnic groups.[11] However, after reviewing patients' medication regimens, five (17%) additional patients had potential CYP2D6 drug-drug interactions with either codeine or tramadol (Table 4-4). Additionally, in two patients there were potential CYP2D6 drug-drug interactions involving metoprolol. Thus, a total of eight patients (27%) could be classified as CYP2D6 poor (*n* = 6) or intermediate metabolizers (*n* = 2) based on the totality of contextual information available.

Discussion

The goal of implementing pharmacogenetic testing in clinical practice is to help address wide interindividual variations in response to medication therapies such as tramadol and codeine. Ideally, this testing would lead to improved clinical and economic outcomes through optimal analgesia and avoidance of adverse drug effects and medication non-response. However, a number of factors that comprise patients' clinical

profiles can confound the desired outcomes of pharmacogenetic testing.[3, 10] To our knowledge, our findings are a first to provide a detailed description of the comorbidities, healthcare utilization, and medication regimens that might influence the outcomes of pharmacogenetic testing in an underserved population prescribed pharmacogenetically actionable opioids. Our findings begin to quantify the contextual complexity of this patient population.

Our findings clearly indicate that the patients in this sample had complex comorbidities and healthcare utilization. All patients had at least two pain and/or non-pain comorbidities, and 57% had five or more. These rates are significantly higher than have been reported elsewhere. The National Council on Aging[18], for example, reports that 80% of older adults have at least one chronic condition and 68% have two or more. In addition, most of the patients in our study had significant healthcare utilization. Our finding that the participants had an average of 6.9 healthcare encounters in six months is more than four times the average of 3.01 outpatient clinic visits per patient each year as reported by Ashman et al.[19] Our finding of significant polypharmacy exceeds national data where an average of 4 unique medications are prescribed per person every year[20] and is comparable to findings from other studies with patients seeking treatment for pain.[7, 21] For example, Davis and colleagues[7] studied 1,211,483 adults in 23 different pain cohorts (e.g., HIV-associated pain, cancer pain, migraine) and found an average of 3.5 pain medications prescribed during the one year study period.

Polypharmacy can also increase the potential for undesirable consequences.[8] Five different patients were identified with potential CYP2D6 drug-drug interactions with the pharmacogenetically actionable opioids. These interactions occurred with either a strong or moderate inhibitor of the CYP2D6 enzyme, which would likely result in no or decreased analgesic effects from tramadol or codeine.[11] These patients' responses to the pharmacogenetically actionable opioid would be similar to those responses of the

two patients with two non-functional CYP2D6 alleles; thus CYP2D6 drug-drug interactions have the ability to confound the associations between variants identified through pharmacogenetic testing and medication responses. These data underscore the importance of multi-drug, multi-gene approaches to implementing pharmacogenetic testing to fully address patients' needs.

Implications for Research

In populations with complex clinical profiles, a number of methodological issues need to be considered to study the outcomes of pharmacogenetic testing. For example, to determine if such testing could decrease healthcare utilization by facilitating optimal analgesia, it would be essential to distinguish between visits associated with pain and the pharmacogenetically actionable medication(s) and visits associated with other symptom(s) or disease(s). The finding in our study that less than half of visits to primary care and specialty care clinics were attributed to pain suggests that evaluating the aggregation of all visits over a specified period of time will not be sufficient. For example, one patient had a total of 6 healthcare encounters over the six month period of time, with four of the visits to manage uncontrolled hypertension and two visits to address and manage pain. For this patient, the aggregate total of 6 healthcare encounters would not be the best indicator of healthcare encounters to determine the effects of pharmacogenetic testing on healthcare utilization.

Similarly, consideration of the effects of polypharmacy on outcomes of pharmacogenetic testing would need to be considered in research studies. Patients in our sample were prescribed on average 10 different medications and, of these medications, an average of 3.0 different medications were prescribed for pain. While multimodal therapy is considered a best practice for managing pain[22, 23], this approach can complicate evaluation of potential adverse effects and medication responses which are desired outcomes of pharmacogenetic testing. For example, a patient may

experience adequate analgesia with an anti-inflammatory medication and pharmacogenetically actionable opioid, but researchers would need to determine the medication responses, including side effects, that are attributable to the opioid alone. The influence of multiple pain-related conditions with different etiologies on the testing outcomes would also need to be considered. Given the frequency of co-occurring pain conditions, for example, a pharmacogenetically actionable opioid may improve pain related to a musculoskeletal injury, for example, but not necessarily neuropathic pain, which may continue to lead to high healthcare utilization and costs.

Studies of pharmacogenetic testing thus will need to control or account for the confounding effects of clinical profile factors through more complex research designs (i.e., randomized controlled trials) and/or stratification methods (i.e., propensity score matching).[3, 24] These strategies would also require large sample sizes to fully realize the benefits of pharmacogenetic testing in this population.

Future research could also evaluate the use of multi-component interventions that partner pharmacogenetic testing with other components. Adding care coordination, medication adherence interventions, and family education and support could have a greater combined impact on clinical and economic outcomes than pharmacogenetic testing alone. Developing and testing such intervention packages would require the expertise of multiple disciplines, including nursing with their expertise in side effect/symptom management and self and family management of illness.

Implications for Clinical Practice

Our findings have several implications for clinical practice. The overall complexity of the clinical profiles of our sample, including high numbers of comorbidities, frequent healthcare utilization, and high rates of polypharmacy, likely reflect a low resource and medically vulnerable population treated in a safety-net system. Other studies have documented comparable findings noting complexities among comorbidities, healthcare

utilization, and polypharmacy in patients seeking care within safety-net health systems.[25, 26] These findings suggest that pharmacogenetic testing in such systems may be particular challenging but may offer specific benefits. For example, testing may tax the financial resources of such safety-net health systems but might show important long-term benefits by decreasing healthcare utilization related to adverse medication effects or non-response.

The complexity of the clinical profiles of populations offered pharmacogenetic testing, however, must be considered in its implementation. With the extensive healthcare utilization and polypharmacy, frontline providers must be attuned to ever changing medication regimens across multiple care transitions and assess for potential drug-drug interactions that may lead to adverse drug effects or medication non-response. For example, strategies such as the U.S. Food and Drug Administration step-wise approach to prevent drug-drug interactions could be integrated in clinical practice to aid in preventing cytochrome P450 drug interactions.[27] This approach includes taking a comprehensive medication history, identifying high risk patients, using available drug interaction references, and consulting pharmacists/drug information specialists.

Finally, because patients seek care in multiple outpatient settings such as primary care, specialty care, and emergency departments, availability of pharmacogenetic test results should be readily available across all care settings. As a result, having an infrastructure (i.e., meaningful use of electronic medical record, clinical decision support) will be essential in supporting the availability and use of pharmacogenetic test results.[28, 29] Given the average length of time (14.5 years) that patients within this sample have sought care at the safety-net health system, it is likely that these patients will continue to seek care within this system. Therefore, the availability of the patient's pharmacogenetic information could also be useful in the future when selecting and dosing other medications (i.e., metoprolol) or drug classes (i.e.,

selective serotonin reuptake inhibitors [SSRIs]) metabolized by the CYP2D6 enzyme. Furthermore, provider education on available pharmacogenetic tests available, when to order them, and interpretation and communication of test results should be widespread across settings and disciplines (i.e., physicians, pharmacists, nurses).[28]

Limitations

The findings should be interpreted in light of several study limitations. This was a secondary analysis of data from a small sample and only three clinical profile factors (comorbidities, healthcare utilization, and medication regimen) were evaluated. Although we used random selection of records to increase generalizability, the findings can only be generalized to populations prescribed pharmacogenetically actionable opioids in a safety-net health system and thus further research is needed to validate our findings in other populations. Additionally, while the data sources used were comprehensive and provided important clinical and administrative information, it was difficult to confirm the accuracy of the documentation (i.e., ICD-9 codes), determine whether data were missing (i.e., healthcare encounters not captured in data repositories), or if a patient was a non-Indiana resident previously prescribed tramadol or codeine at a facility not captured by Indiana Network for Patient Care.

Conclusion

We aimed to describe potential factors related to patients' clinical profiles that could complicate the evaluation of outcomes associated with implementation of pharmacogenetic testing in patients prescribed pharmacogenetically actionable opioids. The findings indicated that patients prescribed these medications generally have complex medical histories, extensive healthcare utilization, and are concurrently exposed to numerous medications over a six month period of time. Consequently, these findings underscore the importance of multi-drug, multi-gene approaches to implementation of pharmacogenetic testing. Moreover, these factors have the potential

to confound the outcomes of pharmacogenetic testing; therefore, future research and clinical implementation initiatives of this testing to guide opioid therapies must control or account for patients' comorbidities, healthcare utilization, and polypharmacy.

Table 4-1.
Sample Characteristics & Comorbidities (n = 30)

Gender	*n* (%)
Male	14 (46.7)
Female	16 (53.3)
Race	
White	18 (60.0)
Black	11 (36.7)
Biracial	1 (3.3)
Comorbidities	
Non-pain diagnoses	
Hypertension	19 (63.3)
Depression	15 (50.0)
Dyslipidemia	13 (43.3)
Diabetes	9 (30.0)
Gastrointestinal Reflux	7 (23.3)
Thyroid Disease	4 (13.3)
Hepatitis	4 (13.3)
Anxiety	3 (10.0)
Atherosclerosis	2 (6.7)
Asthma	2 (6.7)
COPD	2 (6.7)
Pain diagnoses	
Joint pain/osteoarthritis	19 (63.3)
Back pain/lumbago	12 (40.0)
Neuralgia/neuropathies	7 (23.3)
Fibromyalgia	5 (16.7)
Abdominal pain	5 (16.7)
Cervicalgia	4 (13.3)
Carpal Tunnel Syndrome	4 (13.3)
Rheumatoid Arthritis	2 (6.7)

Figure 4-1.
Total Number of Comorbidities per Patient

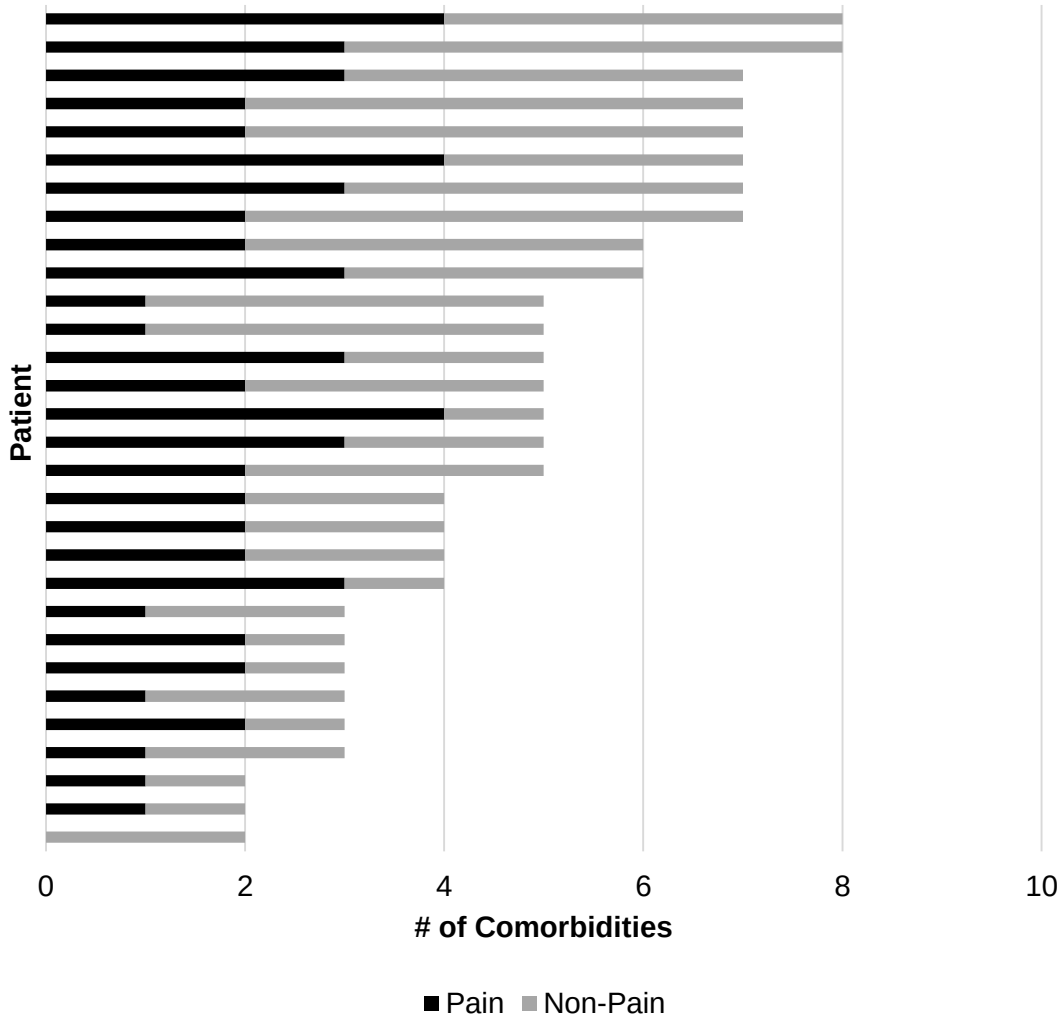

Figure 4-1. Figure shows total number of documented concurrent diagnoses for both non-pain and pain-related conditions for each of the 30 patients. Each bar represents an individual patient, as well as reflects their number of pain and non-pain conditions identified in Table 4-1. All patients had at least 2 or more documented comorbidities.

Table 4-2.
Healthcare Utilization by Outpatient Clinic Type Over 6 Months Following New Prescription of a Pharmacogenetically Actionable Opioid

	Mean # of visits (range)	# of Visits by Patient [*n* (%)]							
		0	1	2	3	4	5	6	≥7
Primary Care									
All visits	3.7 (1-8)	---	2 (6.7)	6 (20)	9 (30)	5 (16.7)	2 (6.7)	4 (13.3)	2 (6.6)
Pain-related visits	1.8 (0-6)	7 (23.3)	8 (26.7)	5 (16.7)	5 (16.7)	4 (13.3)	---	1 (3.3)	---
Specialty Clinic									
All visits	2.7 (0-10)	6 (20)	9 (30)	2 (6.7)	4 (13.3)	1 (3.3)	2 (6.7)	2 (6.7)	4 (13.3)
Pain-related visits	0.7 (0-4)	16 (53.3)	10 (33.3)	3 (10)	---	1 (3.3)	---	---	---
Emergency Dept.									
All visits	0.5 (0-10)	26 (86.7)	2 (6.7)	1 (3.3)	---	---	---	---	1 (3.3)
Pain-related visits	0.4 (0-8)	26 (86.7)	2 (6.7)	1 (3.3)	---	---	---	---	1 (3.3)
Total Clinic Visits									
All visits	6.9 (1-21)	---	2 (6.7)	1 (3.3)	2 (6.7)	4 (13.3)	2 (6.7)	7 (23.3)	12 (40)
Pain-related visits	3.0 (0-13)	5 (16.7)	6 (20)	6 (20)	3 (10)	3 (10)	2 (6.7)	2 (6.7)	3 (9.9)

Table 4-3.
Summary of the Type of Medications Prescribed

Medication Type	*n* (%) of Patients Prescribed Medication^	Mean # (range) of Medications per Patient*
Total medications	30 (100)	10.0 (2-24)
Pain medications	30 (100)	3.0 (1-8)
PGxA opioid	30 (100)	1.0 (1-1)
Additional opioids	13 (43.3)	1.5 (1-3)
Anti-inflammatory	14 (46.7)	1.6 (1-3)
Acetaminophen[ֆ]	2 (6.6)	1.0 (1-1)
Muscle Relaxant	6 (20)	1.0 (1-1)
Anticonvulsant	7 (23.3)	1.0 (1-1)
Other Adjuvant	5 (16.7)	1.0 (1-1)
Cardiac medications	23 (76.7)	2.9 (1-7)
Psychiatric medications	18 (60)	1.7 (1-3)
GI medications	11 (36.7)	1.4 (1-2)
Anti-infective medications	10 (30)	1.9 (1-5)
Endocrine medications	8 (26.7)	1.6 (1-3)
Respiratory medications	4 (13.3)	1.5 (1-2)
Other medications	21 (70)	2.7 (1-8)

^ Number of patients prescribed at least 1 medication per category.
* Total medications (mean & range) for those patients prescribed at least 1 medication per category.
[ֆ] Numbers do not include acetaminophen as a combination with another medication (e.g., hydrocodone/acetaminophen).
PGxA = pharmacogenetically actionable

Figure 4-2.
Total Number of Medications per Patient

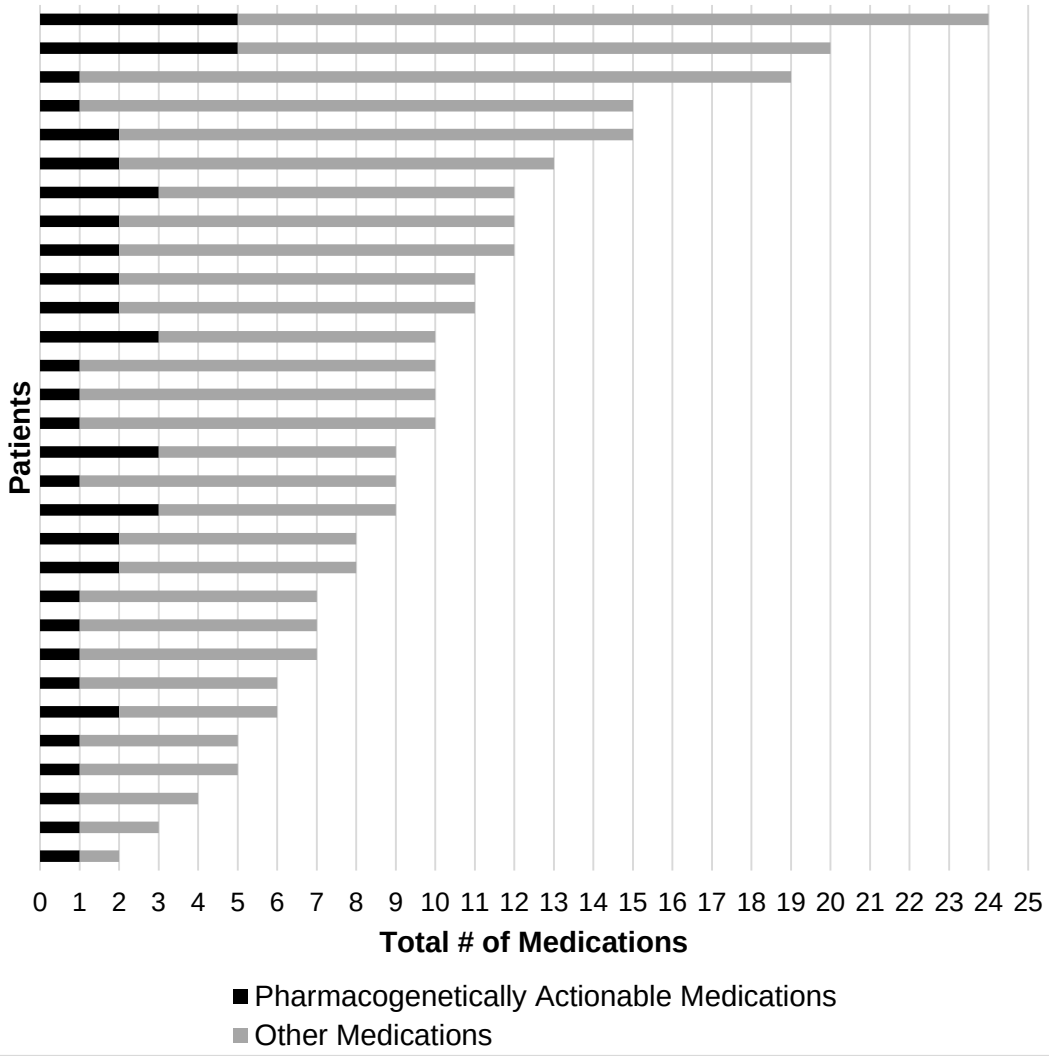

Figure 4-2. Figure shows total number of documented medications, including pharmacogenetically actionable or other medications (horizontal axis). Each bar represents a patient (vertical axis). All patients had at least 2 medications which one was the pharmacogenetically actionable opioid (codeine or tramadol).

Table 4-4.
Cytochrome P450 2D6 Drug-Drug Interactions & Clinical Interpretations

Patient ID	CYP2D6 Diplotype	CYP2D6 Genotype Activity Score	CYP2D6 DDIs	Final CYP2D6 Activity Score	CYP2D6 Drug Metabolizing Phenotype	Clinical Interpretation
07	*1/*41	1.5	Diphenhydramine[1] – tramadol Fluoxetine[1] – metoprolol Diphenhydramine[1] – metoprolol	0	PM	Tramadol: Avoid medication due to lack of efficacy. Metoprolol: Be alert to adverse drug effects (e.g., bradycardia, cold extremities).
11	*2/*5	1	Diphenhydramine[1] – tramadol	0	PM	Tramadol: Avoid medication due to lack of efficacy.
16	*1/*5	1	Fluoxetine[1] – tramadol	0	PM	Tramadol: Avoid medication due to lack of efficacy.
19	*1/*4	1	Bupropion[1] – codeine	0	PM	Codeine: Avoid medication due to lack of efficacy.
23	*1/*4	1	Duloxetine[2] – tramadol Duloxetine[2] – metoprolol	0.5	IM	Tramadol: Avoid medication due to lack of efficacy. Metoprolol: Be alert to adverse drug effects (e.g., bradycardia, cold extremities).

DDI: Drug-drug interaction; PM = Poor Metabolizer; IM = Intermediate Metabolizer
[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.

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CHAPTER 5

The purpose of this dissertation was to advance the sciences of nursing, pain management, and pharmacogenomics through the development of a typology of common patterns of medication exposure to known pharmacogenetically actionable opioids. The dissertation results will be disseminated in three manuscripts. Manuscript 1 (Chapter 2), which has been published in *Nursing Outlook*, is a review of pharmacogenomics in the nursing literature; Manuscript 2 (Chapter 3) is a presentation of the final typology; and Manuscript 3 (Chapter 4) is a discussion of contextual factors to consider when assessing and documenting benefits of pharmacogenetic testing in guiding opioid therapies. This chapter synthesizes key findings from all three manuscripts, the strengths and limitations of the study, and recommendations for future research.

Synthesis of Key Findings

The first key finding was the need for nurses to more fully embrace the burgeoning field of pharmacogenomics. The nursing literature highlights the implications of pharmacogenetic testing for clinical practice in a variety of populations, including individuals seeking care for pain, cardiovascular disease, or psychiatric conditions. However, reports of evidence-based clinical practice guidelines for pharmacogenetic testing and empirical studies of pharmacogenomics are rare in the nursing literature. Some authors recommend: (a) enhanced evaluation of the effectiveness of genetic and genomic technologies, information, interventions, and outcomes; (b) future studies to explore the safety, efficacy, and effectiveness of pharmacogenetic testing and its impact on clinical and economic outcomes; and (c) the elucidation of nursing's roles and responsibilities related to pharmacogenomics.[1] This dissertation was intended to address the need for nurses to lead pharmacogenomic-related research.

The second key finding was that exposure to pharmacogenetically active opioids is dynamic and complex. Previous pharmacogenomic research has over-simplified medication exposure and failed to capture its multifaceted nature.[2] By using a person-oriented approach, this dissertation documented some nuances of exposure to these medications. The final typology uncovered eight groups of patients who had one of five opioid prescription patterns (singular, episodic, switching, sustained, or multiplex) and one of three medical emphases for which care was being sought (pain, comorbidities, or both). The groups had varied patterns of medication exposure that unfolded over a six month period, confirming that medication exposure is a dynamic phenomenon that changes over time. Because the typology revealed meaningful subgroups of individuals with differing patterns of exposure to pharmacogenetically actionable opioid medications, it provides a more complex understanding of medication exposure than prior research.

The third key dissertation finding was that the medical emphasis of care provided a context for opioid exposure and was important in determining exposure patterns. The dissertation sample of 30 persons who were prescribed pharmacogenetically actionable opioids in primary care at the large safety-net health system had complex medical histories, extensive healthcare utilization, and were prescribed numerous medications. On average, the sample had five or more comorbidities, sought care approximately seven times, and had 10 different medications prescribed over the 6-month period of time. In addition, five had potential drug interactions that could affect their CYP2D6 drug metabolizing status. These findings indicate for patients with extensive medical histories, complicated healthcare utilization patterns, and complex medication regimens, multiple factors will need to be considered when assessing and documenting the benefits of implementing pharmacogenetic testing to guide opioid therapies.

Strengths of the Dissertation

This dissertation begins to address important limitations in previous research including oversimplified measures of medication exposure and lack of consideration of contextual factors likely to influence the implementation of pharmacogenetic testing. To my knowledge, this study is the first to employ a qualitative, person-oriented approach to explore patterns of medication exposure with data coming from existing clinical and administrative data repositories. This approach was an alternative to the variable-oriented approach and yielded a new typology of subgroups. The identification of the eight subgroups, clustered on relevant characteristics of medication exposure, captured the complex nature of exposure to pharmacogenetically actionable opioids and accounted for the context in which the exposure to these medications occurred.

These findings contribute new information to the existing sciences of nursing, pain management, and pharmacogenomics. The dissertation manuscripts will add to nursing and healthcare literature by highlighting multiple factors that can influence the use of pharmacogenetic testing in the management of pain and other comorbid conditions in individuals prescribed pharmacogenetically actionable opioids. The dissemination of this work will advance our understanding of patients who have complex medication exposure patterns with numerous comorbidities, concomitant medications and multiple healthcare encounters.

Another strength of this dissertation lies in its implications for nursing practice. These findings underscore that it is important for nurses to routinely monitor the medication responses of patients who are prescribed pharmacogenetically actionable opioids and to assess for factors that can impede their optimal analgesic effects, such as drug interactions that can affect CYP2D6 drug metabolizing activity. Furthermore, nurses should be aware of the multidimensional and complex patterns of medication exposure to pharmacogenetically actionable opioids and the context in which the exposure occurs.

This awareness can inform the development of personalized strategies to promote self-management behaviors. Tools and strategies for medication management that are tailored to the complex clinical profiles of patients and the context in which their care is embedded may be more likely to promote optimal pain management outcomes and alert patients and providers to potential medication-related problems. For example, the Singular/Pain subgroup revealed in these findings may benefit from a one-time medication educational intervention about pharmacogenetic testing whereas the Multiplex/Both or Episodic/Both subgroups may require a more in-depth and sustained intervention, such as personalized health coaching, to promote self-management of pain and other comorbid conditions.

Limitations of the Dissertation

The conclusions of this dissertation need to be interpreted in light of some limitations. While this qualitative, person-oriented approach provided a way to identify patterns common to small sets of cases and to describe how medication exposure unfolds over time, the approach does not allow for causative inferences such as how particular factors, such as type of pain or number of comorbidities, influence medication exposure, nor does it allow for conclusions about the frequency with which patients would fall into each group.

Because the data were drawn from one group of patients treated in one healthcare system, the findings may not generalize beyond individuals who are prescribed codeine or tramadol in the primary care setting at a safety-net healthcare system. Furthermore, the retrospective nature and use of existing electronic health records make it difficult to confirm the accuracy of the documentation and determine whether certain data may have been missing. Although electronic health records provide important clinical and administrative information, these sources lack information on patient perspectives.[3] For example, data elements related to the intensity, duration,

distress, and quality of an individual's pain, along with their level of functioning, are not consistently documented or not captured within the electronic health record. Therefore, it was not possible to capture patient perspectives related to their pain and response to the opioid medication.

Summary of Recommendations for Future Research

Several recommendations for future research stem from the findings of this dissertation. First, the subgroups within the existing typology could be used as a sample descriptor variable to ensure equivalence of randomization when comparing pharmacogenetic implementation to usual care. Using the subgroups as a sample descriptor variable allows for capturing an interaction of patterns between medication prescriptions and medical emphasis of care, which is more comprehensive than using individual variables such as age, diagnosis, or other clinical factors. Without assessing or accounting for the patterns identified through the typology, benefits of testing may not be as readily seen in subgroups with more complex patterns, such as Multiplex/Both or Episodic/Both groups, compared to the subgroups with more simple patterns such as the Singular/Pain group. Thus, comparing randomized groups on typology subgroup may provide important information about whether randomized groups are equivalent.

Second, further development and validation of the typology using larger and more diverse samples drawn from a variety of healthcare settings is needed. Future research done prospectively could additionally capture the important information on symptom experience and functioning that was missing in this retrospective review. Such information could add depth to the existing typology. With a more developed typology, researchers could evaluate to what extent group membership may be related to particular clinical or economic outcomes related to the use of pharmacogenetic testing. For example, a more advanced typology could lead to identification of high-risk groups that may benefit from interventions related to medication management and inform the

development of tailored interventions for individuals prescribed pharmacogenetically actionable opioids. Multi-component interventions that include pharmacogenetic testing with additional components such as medication therapy management or care coordination could have a greater impact on improving clinical and economic outcomes.[4, 5]

Third, with further development and validation, the typology could aid in the development of more nuanced medication exposure measures that could then be used in studies evaluating clinical or economic outcomes of pharmacogenetic testing. Failing to account for medication changes over time can lead to exposure misclassification and measurement error.[6] For example, future medication exposure measures must go beyond dichotomous measures and capture the length and pattern of exposure to a pharmacogenetically actionable opioid such as singular, episodic, sustained, switching, or multiplex exposure. Advancing science in this area will depend on further development of research strategies that can capture the heterogeneity of patients who are prescribed pharmacogenetically actionable opioids and the patterns of medical care in which the exposure occurs.

Conclusions

This dissertation aids in understanding the complexity of medication exposure and contextual factors in individuals who were seen in primary care and prescribed a pharmacogenetically actionable opioid. The typology consisted of eight subgroups who shared common patterns of medication exposure. These findings can aid in addressing challenges related to the implementation of pharmacogenetic testing in clinical practice by indicating the need for future studies to develop measures of medication exposure that capture its dynamic nature and interventions to promote optimal implementation of pharmacogenetic testing based on variations in exposure patterns. These initiatives

could provide the foundation for the development of personalized health care strategies to improve pain management outcomes.

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2010 – 2012	Member, Indiana Society of Perianesthesia Nurses
2009 – 2012	Member, American Association of Critical Care Nurses

SERVICE & PROFESSIONAL CONTRIBUTIONS

2015 – 2016	Member, *PhD Student Advisory Board*, Indiana University School of Nursing
03/2016	Abstract Reviewer, *2016 ISONG World Congress*, International Society of Nurses in Genetics
11/2015	Manuscript Reviewer, Journal of Pain Management Nursing
05/2015	Abstract Reviewer, *2015 ISONG World Congress*, International Society of Nurses in Genetics
11/2014	Abstract Reviewer, *2015 NACNS Annual Conference*, National Association of Clinical Nurse Specialists
2014 – 2015	Panelist/Mentor, *Career Connections*, Indiana University School of Nursing
2014 – 2015	Member, *Graduate Student Technology Committee*, Indiana University School of Nursing
2012 – present	Content Expert, *Content Expert Registry – Pain Management*, American Nurses Credentialing Center
2012 – 2013	Faculty/Content Expert, *Total Joint Replacement Pain Management Multi-Site Collaborative*, Indiana University Health
2011 – 2013	Chair, *Pain Management Committee*, Indiana University Health North Hospital
2011 – 2013	Co-developer & Lecturer, *Pain Resource Nurse (PRN) Training Program*, Indiana University Health North Hospital
2011 -2012	Member, *Publication Committee*, Indiana Society of Perianesthesia Nursing
10/2010	Super User, *Perioperative Computerized Order Entry*, Indiana University Health University Hospital
2010	Member, *Nursing Research Collaborative,* Indiana University Health University Hospital
2009 – 2010	Member, *Medical ICU RN Satisfaction Committee,* Houston Methodist Hospital
2008 – 2009	Member, *Search Committee for the Head of the School of Nursing and Associate Dean for the College of Pharmacy, Nursing, & Health Sciences*, Purdue University

ACADEMIC & PROFESSIONAL HONORS

04/2016 *Elite 50 Award* and *Best in School Recognition*, IUPUI Graduate & Professional Student Government
06/2015 *Intramural Research Training Award (IRTA),* National Institute of Nursing Research, National Institutes of Health
04/2015 *Elite 50 Award*, IUPUI Graduate & Professional Student Government
10/2014 *Graduate Travel Fellowship*, Indiana University School of Nursing
09/2014 *Jan Bingle Scholarship*, Clinical Nurse Specialists Foundation, Inc.
04/2014 *Mary Hise Scholarship*, Indiana University School of Nursing
03/2014 *Golden Graduate Award*, Purdue University School of Nursing
05/2013 – 12/2015 *100th Anniversary Scholar*, Indiana University School of Nursing
04/2013 *Dayhoff-Lyon Outstanding Clinical Nurse Specialist Student Award*, Indiana University School of Nursing
04/2013 *MSN Academic Achievement Award*, Indiana University School of Nursing
2012, 2013 *Salute to Nursing Nominee*, Indianapolis Star
05/2009 *Ethel Crocket Epple Outstanding Student Nurse Award*, Purdue University School of Nursing
05/2009 *Student Speaker at May 2009 Pinning Ceremony*, Purdue University School of Nursing
2008 – 2009 *Order of the Iron Key*, Purdue University
2005 – 2009 *Dean's List*, Purdue University

PUBLICATIONS

Peer Reviewed (articles)

Shieh, C., **Knisely, M.**, Clark, D., & Carpenter, J.S. (in press). Self-weighing in weight management interventions: A systematic review. *Obesity Research & Clinical Practice.* [Epub 02/2016]. PMID: 26896865.

Carpenter, J.S., Rosenman, M.B., **Knisely, M.**, Decker, B.S., Levy, K., & Flockhart, D.A. (2016). Pharmacogenomically actionable medications in a safety net health care system. *SAGE Open Medicine,* eCollection 2016*.* PMID: 26835014.

Knisely, M., & Draucker, C.B. (2016). Using a person-oriented approach in nursing research. *Western Journal of Nursing Research, 38*(4), 508-520*.* PMID: 26333302.

Knisely, M., Ellis, R., & Carpenter, J. (2015). Complexities of medication management across care transitions: A case report. *Clinical Nurse Specialist: The Journal for Advanced Nursing Practice, 29*(5), E1-E7. PMID: 26258840.

Knisely, M., Fulton, J., & Friesth, B. (2015). Perceived importance of teaching characteristics in clinical nurse specialist preceptors. *Journal of Professional Nursing, 31*(3), 208-214*.* PMID: 25999193.

Knisely, M., Carpenter, J., & Von Ah, D. (2014). Pharmacogenomics in the nursing literature: An integrative review. *Nursing Outlook, 62*(4), 285-294. PMID: 24863878.

Peer Reviewed (abstracts)

Knisely, M. (2013). Using the triadic partnership model to achieve clinical competency for clinical nurse specialist students: Student role. *Clinical Nurse Specialist: The Journal of Advanced Nursing Practice, 27*(2), E58.

Knisely, M., Haley, B., Grey, B., Fourroux, E., Cumberland, H., & Sullivan-Wright, D. (2012). Exploring characteristics of an advanced nursing assessment. *Clinical Nurse Specialist: The Journal of Advanced Nursing Practice, 26*(3), E7.

PRESENTATIONS

Peer Reviewed

Knisely, M., Draucker, C., & Carpenter, J. (Apr. 2016). "Using a Qualitative Person-Oriented Approach to Identify Meaningful Subgroups within Heterogeneous Population," poster presentation, *Midwest Nursing Research Society's Annual Research Conference, Milwaukee, WI.*

Shieh, C., **Knisely, M.**, Clark, D., & Carpenter, J. (Apr. 2016). "Self-weighing in weight management: A systematic review of literature," poster presentation, *Midwest Nursing Research Society's Annual Research Conference, Milwaukee, WI.*

Knisely, M., & Von Ah, D. (Apr. 2015). "Evaluation of Nursing Faculty's Perceived Knowledge & Comfort Related to Genetics/Genomics Content," poster presentation, *Midwest Nursing Research Society's Annual Research Conference, Indianapolis, IN.*

Knisely, M., Carpenter, J., & Von Ah, D. (Sept. 2014). "State of the Science: Evaluating the Complexity of Pharmacogenomics in the Nursing Literature," podium presentation, *Council for the Advancement of Nursing Science 2014 State of the Science Congress, Washington, D.C.*

Knisely, M. (Mar. 2013). "Using the Triadic Partnership Model to Achieve Clinical Competency for Clinical Nurse Specialist Students: Student role," podium presentation, *National Association of Clinical Nurse Specialist Annual Conference, San Antonio, TX.*

Knisely, M., Haley, B., Grey, B., Fourroux, E., Cumberland, H., & Sullivan-Wright, D. (Mar. 2012). "Exploring Characteristics of an Advanced Nursing Assessment," poster presentation, *National Association of Clinical Nurse Specialist Annual Conference, Chicago, IL.*

Invited

Knisely, M. (Nov. 2015). "From Bench to Bedside: Clinical Application of Pharmacogenomic Information in Managing Pain," podium presentation, *Central Indiana Organization of Clinical Nurse Specialist Annual Conference, Indianapolis, IN.*

Knisely, M. (Apr. 2015). "Alumni Panel – Preparing for Your Future Role as a Nurse Leader," panelist, *Helen R. Johnson Leadership Conference – Purdue University School of Nursing, West Lafayette, IN.*

Knisely, M. (Feb. 2015). "The Basics of Pharmacogenomics," guest lecturer, *Indiana University School of Nursing, Bloomington, IN.*

Knisely, M. (Apr. 2014). "Leadership in Nursing," panelist, *Purdue University School of Nursing, West Lafayette, IN.*

Knisely, M. (Jan. 2013). "Interdisciplinary Approach to Excellence in Pain Management," podium presentation, *Pain Management Symposium – Indiana University Health, Indianapolis, IN.*

Knisely, M. (Jan. 2013). "Multimodal Pain Management in the Surgical Patient: The Effects on Medication Safety and Patient Outcomes," podium presentation, *Indiana University Health Medication Safety Grand Rounds, Indianapolis, IN.*

Knisely, M. (Oct. 2012). "Multimodal Pain Management in the Surgical Patient," podium presentation, *Indiana Society of Perianesthesia Nurses' Fall Meeting, Carmel, IN.*

Knisely, M. (Jul. 2008). "Prevention of Ventilator Associated Pneumonia in the ICU," poster presentation, *The Methodist Hospital Advancement into Professional Practice, Houston, TX.*

FUNDING

Grant/Fellowship	Conferring Organization	Amount	Dates
Predoctoral Fellow, IU: Training in Behavioral Nursing Research	National Institute of Nursing Research, NIH	$28,218	2016
Research Incentive Funding	IU School of Nursing	$10,000	2016
William & Doris Rodie IUSON Dissertation Award	IU School of Nursing	$2,000	2015 – 2016
Graduate Travel Fellowship Grant	IU School of Nursing	$700	2014
100th Anniversary Scholars Fellowship	IU School of Nursing	$112,322	2013 – 2015

COMMUNITY INVOLVEMENT

2014 – present	Board Member, Alumni Board of Directors, Purdue University College of Health & Human Sciences
2014 – 2016	Wish Granter, Make-A-Wish Foundation, Ohio, Kentucky, & Indiana Chapter
07/2014	Volunteer, National Down Syndrome Congress
09/2013	Volunteer, Health Screening, American Indian Center of Indiana, Inc.
2011 – 2014	Member, 50th Anniversary Planning Committee, Purdue University School of Nursing
2009 – present	Member, Griffin Society, Purdue University
2009 – 2012	Member, President's Council, Purdue University
2009 – 2010	Wish Granter, Make-A-Wish Foundation, Gulf Coast Chapter