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Medication Exposure Patterns in Primary Care Patients Prescribed Pharmacogenetically Actionable Opioids

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Abstract

Current approaches to assessing medication exposure fail to capture the complexity of the phenomenon and the context in which it occurs. This study's purpose was to develop a typology of subgroups of patients who share common patterns of medication exposure. To create the typology, we used an exemplar sample of 30 patients in a large public healthcare system who had been prescribed the pharmacogenetically actionable opioids codeine or tramadol. Data related to medication exposure were drawn from large data repositories. Using a person-oriented qualitative approach, eight subgroups of patients who shared common patterns of medication exposure were identified. The subgroups had one of five opioid prescription patterns (i.e., singular, episodic, switching, sustained, multiplex), and one of three types of primary foci of medical care (i.e., pain, comorbidities, both). The findings reveal medication exposure patterns that are dynamic, multidimensional, and complex, and the typology offers an innovative approach to assessing medication exposure.

Keywords

Medication Exposure; Pharmacogenomics; Opioid; Pain Management; Person-Oriented Approach

Introduction

The comprehensive assessment of medication exposure is a critical component of health outcomes research and clinical practice. Medication exposure, which includes writing the prescription, dispensing, and ingesting medications, is a multidimensional phenomenon involving many factors—including medication type, dose, frequency, duration, and use over time (Cox et al., 2009; Poole, Bell, Jokanovic, Kirkpatrick, & Dooley, 2015). Despite that medication exposure is an important clinical parameter, there are no universally accepted methods to assess it (Poole et al., 2015). Medication exposure is most often measured dichotomously (e.g., prescribed: yes/no; ingested: yes/no), as a numerical count (e.g.,

number of medications prescribed, and number of tablets ingested) or as an average (e.g., average dose/frequency over a certain duration; Fosbol, 2013; Ross, Anand, Joseph, & Pare, 2012).

Current methods of assessment fail to adequately account for the complexity of medication exposure and the context in which it occurs. Patients often take multiple medications for co-morbid conditions, are prescribed medications that are not dispensed, do not take dispensed medications as prescribed, obtain new prescriptions due to non-response or drug interactions, or seek modifications of their medication regimens from different providers (Svendsen, Skurtveit, Romundstad, Borchgrevink, & Fredheim, 2012). Moreover, medication exposure is influenced by patients' clinical profiles and the healthcare contexts (e.g., clinic, hospital, emergency department) in which the medications are prescribed (Lam, 2013; Ross et al., 2012). We argue that medication exposure can be best understood as a complex process that evolves over time and that is influenced by a variety of factors.

The need for a more comprehensive conceptualization and operationalization of medication exposure is urgent given the increasing implementation of pharmacogenetic testing in healthcare settings (Bruehl et al., 2013; Carpenter et al., 2016). Pharmacogenetic testing, which identifies individual genetic variations influencing drug metabolism and response, promises to address wide interindividual variations in medication responses, improve medication outcomes (e.g., greater pain relief), and mitigate costly adverse drug effects (Xu & Johnson, 2013). Pharmacogenetically actionable medications are those that have strong evidence to guide drug or dosing changes based on pharmacogenetic test results (Crews et al., 2014). To date, however, studies of the efficacy of pharmacogenetic testing on clinical outcomes rely on the oversimplified approaches to the measurement of medication exposure discussed above (Arnaout, Buck, Roulette, & Sukhatme, 2013; Goulding, Dawes, Price, Wilkie, & Dawes, 2015; Schildcrout et al., 2012).

This study was undertaken to explore patterns of medication exposure shared by groups of patients being treated in a large safety-net healthcare system. We believe that identifying and explicating such patterns can eventually contribute to a more comprehensive and contextualized approach to assessing medication exposure. We employed a qualitative person-oriented approach to develop a typology that identifies subgroups of patients that share common patterns of medication exposure (Sterba & Bauer, 2010). Due to the promising role of pharmacogenetic testing in improving outcomes, the high prevalence of acute and chronic pain in all patient populations (National Institutes of Health, 2015), and the importance of pain management in clinical practice (Interagency Pain Research Coordinating Committee, 2016), we chose to use a sample of patients who were newly prescribed the pharmacogenetically actionable opioids codeine and tramadol as exemplar cases to create the typology.

Researcher Context

This study was conducted when I, Mitchell Knisely, was completing the PhD in Nursing Science program at Indiana University. I am a board-certified pain management nurse and adult health clinical nurse specialist with vast experience caring for individuals with acute and/or persistent pain. I also have extensive experience leading health system initiatives to

improve pain management outcomes. In these roles, I recognized that the “one-size-fits-all” approach that was frequently used to manage pain is not sufficient because there is vast heterogeneity in patients and care environments. Pharmacogentic testing has significant promise in the way we select and dose pain medications, ultimately improving patient outcomes. At the time of this study, there was a large clinical trial that was being implemented within the local safety-net health system which was seeking to evaluate the clinical and economic outcomes of wide-spread implementation of pharmacogenomics testing. Our intention with this project was to highlight the heterogeneity of patients prescribed pharmacogenetically actionable opioids as an initial step in addressing some of the limitations of assessing outcomes of the implementation of pharmacogenetics testing. My co-authors were faculty from various disciplines: nursing (JSC, MEB, DVA, and CBD), health policy and economics (AMH), and pharmacology (TS). The co-authors contributed to the study design, data collection and analysis, and editing of this manuscript.

Materials and Methods

Theoretical Approach

The person-oriented approach is a research method in which persons are considered holistically as the unit of analysis. The approach is based on the assumption that persons’ genetic makeups, histories, behaviors, contextual risks, and protective factors that affect their health and well-being interact synergistically to constitute their experiences (Sterba & Bauer, 2010). The method is also based on the assumption that human functioning is fluid due to developmental processes and constant changes in the person-environment system (Bergman, Magnusson, & El-Khouri, 2003).

In contrast to traditional variable-oriented approaches in which the strength of relationships among variables is ascertained and inferential statistics are used to test causal inferences, the person-oriented approach seeks to uncover common patterns of interacting characteristics and behaviors in heterogeneous samples by identifying subgroups that share common patterns (Bergman & Magnusson, 1997; Bergman & Trost, 2006; Sterba & Bauer, 2010). The subgroups are often presented in a typology to allow for an in-depth description of the characteristic patterns of each group. This approach can use either pattern-based quantitative methods (e.g., latent class analysis or cluster analysis) or qualitative methods (e.g., within-case and cross-case analyses) to identify the subgroups (Draucker & Martsolf, 2010; Miles, Huberman, & Saldaña, 2014; Sterba & Bauer, 2010). Because we were interested in identifying common patterns of medication exposure without prior specification of what person characteristics would be the most salient in determining the subgroups, we used an exploratory person-oriented qualitative approach.

Setting and Databases

The study was conducted in a large public healthcare system where widespread implementation of pharmacogenetic testing was occurring. This healthcare system had robust data repositories which allowed for linkage of patients’ health records to banked DNA samples for genetic analyses. The main data repository accessed was the Indiana Network for Patient Care, which is an information exchange that captures and integrates

varying levels of data from the safety-net healthcare system and from more than 25,000 physicians, 106 hospitals, 110 clinics, and other healthcare providers across Indiana (Indiana Health Information Exchange, n.d.). Other administrative data repositories from the healthcare system directly associated with the managed care program were also accessed. The study was deemed to be non-human subjects research by the Office of Research Compliance at the investigators' university. A trained clinical data analyst accessed all data and used standard procedures to de-identify the data prior to releasing them to the study team.

Sample

A multiple-case sample of patients was obtained through random selection of a subset of de-identified patient electronic health records (EHR) and banked DNA samples from the data repositories. Inclusion criteria for patients were as follows: (a) part of a managed care program for individuals falling at or below 200% of the federal poverty level; (b) had a banked blood sample; (c) were age 21 and older; (d) had no previous documentation of substance abuse. In addition, because we wished to focus on patients who had been newly prescribed codeine or tramadol, we limited the sample to patients who had been prescribed either medication during a primary care visit between January 1, 2010 and December 31, 2014 and whose EHR did not indicate that either medication had been previously prescribed. We obtained a sample of 30 patients based on the recommendation of qualitative researchers using person-oriented methods who found that similar sample sizes provided enough cases to identify meaningful subgroups but did not supply so much data as to become unwieldy to analyze qualitatively (Draucker & Martsolf, 2010; Miles et al., 2014).

Data Extraction

An extensive review of the literature was conducted to determine what patient characteristics (e.g., demographics, past medical history, pharmacogenetic genotype; Alqudah, Hirsh, Stutts, Scipio, & Robinson, 2010; Rolfs, Johnson, Williams, & Sundwall, 2010; Somogyi, Coller, & Barratt, 2015), medication characteristics (e.g., opioid information, co-prescribed medications, changes in drug regimen, drug interactions; Gustavsson et al., 2012; Lee & Pickard, 2013), clinical responses (e.g., pain intensity and adverse drug effects; Chou et al., 2009), and healthcare utilization factors (Jena, Goldman, Weaver, & Karaca-Mandic, 2014) were most relevant to medication exposure. As a result of this review and consideration of available data, six months of the following data for each individual were extracted starting with the first prescription date of the pharmacogenetically actionable opioid through the following six months: (a) demographic information (i.e., age, gender, race, and ethnicity); (b) age at first prescription for tramadol and codeine; (c) past medical history according to International Classification of Diseases – 9th Revision (ICD-9) codes recorded at each visit; (d) medication information (i.e., names, doses, dose frequencies, routes, supply amounts, administration instructions, prescribers, dates prescribed, and dates dispensed); (e) adverse drug events; (f) pain intensity ratings; (g) location of points of care, categorized as primary care clinics, specialty clinics, emergency departments, or inpatient hospitals; and (h) ICD-9 codes for diagnosis/chief complaint(s) recorded for each visit.

In addition, *CYP2D6* pharmacogenetic genotyping was conducted by the study team on samples from the Indiana Biobank for all 30 cases to determine common variants that influence both codeine and tramadol drug disposition and response (Crews et al., 2014). 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 on samples of extracted DNA for the *CYP2D6* alleles *2, *3, *4, *5, *6, *9, *10, *17, *29, and *41. Based on the *CYP2D6* genotype, an activity score was calculated according to clinical practice guidelines to determine *CYP2D6* drug metabolizing phenotype (e.g., ultra-rapid, normal, intermediated, and poor metabolizer; Crews et al., 2014). Furthermore, potential cytochrome P450 drug-drug-gene interactions that would affect *CYP2D6* metabolism of either codeine or tramadol were identified (Borges et al., 2010; Love et al., 2013).

Data Analysis

Sample characteristics were summarized with descriptive statistics using SPSS™ 23.0 (IBM, Armonk, NY). To develop the typology, a qualitative within-case and cross-case analysis, as described by Miles and colleagues (Miles et al., 2014), was performed by three researchers during regularly scheduled data analysis meetings. Microsoft Excel software (Microsoft, Redmond, WA) was used to visualize the data for the qualitative analytic procedures.

The goal of the within-case analysis is to understand and describe each individual case holistically. The investigators first condensed the data for each case by selecting, simplifying, abstracting, and transforming it into an interpretable format. Data were organized in a case-by-time matrix in which each row lined up on the vertical axis represented a case and each column lined up on the horizontal axis displayed extracted data for case for each of the six months. The case-by-time matrix thus allowed for visualization of factors related to each patient's medication exposure over the 6-month time period and facilitated the development of a detailed narrative description of how the opioid exposure of each patient unfolded over time.

Cross-case analysis was then used to cluster multiple cases into groups that shared patterns of opioid exposure (Miles et al., 2014). 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. Rows from the case-by-time meta-matrix were compared and contrasted, and those with similar patterns were juxtaposed. Through discussion and team consensus, constant revisits with the extracted data, frequent reviews of the narrative descriptions, and multiple acts of repositioning the rows in the matrix, the team clustered cases that exhibited notable similarities in their patterns of exposure into eight subgroups. Each subgroup was labeled and described. The team then reviewed each case to ensure it was placed in the most applicable subgroup.

Systematic procedures for ensuring the quality of this research included techniques outlined by Lincoln and Guba (1985). The team maintained an extensive audit trail of all methodological and analytic decision, provided an extensive description of sample characteristics to enhance the transferability of the findings, used systematic peer debriefing

processes during team meetings to ensure all members of the analysis team had extensive input into the findings, and presented the results to experts in nursing science, health services research, and clinical pharmacology for consideration and comment.

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). The majority of patients were White (*n*=18), with the other patients being Black (*n*=11) or Biracial (*n*=1). Most patients were *CYP2D6* normal metabolizers (*n*=25), whereas the others were poor metabolizers (*n*=2), intermediate metabolizers (*n*=1), or ultra-rapid metabolizers (*n*=2).

Typology of Exposure Patterns to Pharmacogentically Actionable Opioids

After extensive review of the within-case data for the 30 patients, the analysis team determined that the cases varied most notably on two dimensions. The first dimension was the prescription pattern for the pharmacogenetically actionable opioids occurring during the 6-month period. The patterns were based primarily on variations in medication doses, timing of fills/refills, and supply amounts. Five patterns were identified and labeled as follows: (a) singular (i.e., one time-limited prescription); (b) episodic (i.e., intermittent or discontinuous prescriptions); (c) switching (i.e., a short-term prescription followed by a prescription for new/different opioid); (d) sustained (i.e., uninterrupted prescriptions for an extended period of time); (e) multiplex (i.e., a combination of several of the other patterns). The second dimension was the primary focus of medical care over the six-month period. This dimension was based primarily on the patients' medication histories, type/indication for all medications prescribed, clinical responses, and type/reasons for healthcare encounters. The three foci of medical care were (a) pain; (b) comorbidities (i.e., non-pain related conditions); (c) both pain and comorbidities. We developed a conceptually clustered matrix (Miles et al., 2014) with the prescription patterns on the horizontal axis and the foci of medical care on the vertical axis, which created cells within which each case could be placed. All cases were placed in one of eight cells based on agreement of the three research team members, thereby creating eight subgroups reflecting distinct medication exposure patterns. The eight subgroups are displayed in Table 1 and described below with a case exemplar from each subgroup. Table 2 displays the characteristics of the members of each subgroup.

Singular/Pain.—Patients (*n*=2) placed in this subgroup received a one time-limited (30 days or less) prescription for the pharmacogenetically actionable opioid. The focus of their medical care was on controlling a pain-related condition such as cervicalgia, paresthesia, and carpal tunnel syndrome, and their medical histories were otherwise unremarkable. They had one to three health care visits during the six-month period.

Patient 26 is an example of a patient who belongs to the singular/pain subgroup. Patient 26 was a 61-year-old White male who was a *CYP2D6* normal metabolizer. He had a history of cervicalgia, sought care at the primary care clinic for this condition, and was prescribed tramadol 50 mg to be taken at night for severe pain. At this visit, his pain intensity rating

was five out of 10. He was also prescribed naproxen and cyclobenzaprine and had all three prescriptions filled. He had no further healthcare visits or prescriptions.

Singular/Comorbidities.—Patients (n=4) placed in this group received one time-limited (10 to 30 days) prescription for a pharmacogenetically actionable opioid. However, the primary focus of their medical care was on non-pain related comorbidities such as diabetes or hypertension, and some were treated for several conditions affecting multiple body systems. The patients in this group had between five and 10 healthcare visits during the 6-month period and were prescribed six to 10 different medications.

Patient 19 is an example of a patient who belongs to the singular/comorbidities subgroup. Patient 19 was a 34-year-old Black male who was a *CYP2D6* normal metabolizer. At a primary care visit, he was prescribed a 30-day supply of codeine/acetaminophen to be taken as needed for back and shoulder pain. His pain intensity rating at this visit was 10 out of 10. He also had a number of comorbidities, including HIV/AIDS, Hepatitis B and C, seborrheic dermatitis, and constipation. During the visit, he was also prescribed bupropion and conjugated estrogen; he had all three of the medications filled. He received no further pain medications, although he had nine other medications that were regularly filled. He had two more primary care visits and three 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.

Singular/Both.—Patients (n=3) placed in this group received one time-limited (six to 15 days) prescription for a pharmacogenetically actionable opioid. The primary focus of their medical care was on both their pain and other comorbidities such as depression, thyroid disease, or allergies. These patients had four to 10 visits during the six-month period and were prescribed nine to 12 different medications.

Patient 30 is an example of a patient who belongs to the singular/both subgroup. Patient 30 was a 61-year-old White female who was a *CYP2D6* normal metabolizer. At a primary care visit for esophageal reflux, H. pylori infection, headache, and neuralgia, she was given a prescription for 15-day supply of tramadol. She had a number of pain conditions, including headache, neuralgia, and abdominal pain, and multiple comorbidities, including coronary artery disease, asthma, esophageal reflux, and depression. At the visit, she was prescribed eight additional medications including prednisone, amitriptyline, esomeprazole, two asthma medications, and two anti-infective medications. All the prescriptions were filled the day after the visit. She had three more visits to the primary care clinic, five visits to specialty care clinics, and one emergency department visit for pain and non-pain-related conditions. Despite these frequent healthcare visits, she received only one additional prescription for esomeprazole and no new prescriptions for tramadol or other pain medications.

Episodic/Pain.—Patients (n=3) placed in this group received intermittent or discontinuous prescriptions for pharmacogenetically actionable opioids. They also received an anti-inflammatory medication such as naproxen, ibuprofen, or piroxicam to treat their pain. The primary focus of their medical care was on a pain-related condition, especially shoulder or

leg/knee pain. The patients in this group had two to five healthcare visits over the six-month period and were prescribed five to eight different medications.

Patient 29 is an example of a patient who belongs to the episodic/pain subgroup. Patient 29 was a 44-year-old White male who was a *CYP2D6* normal metabolizer. He sought care at the primary care clinic for joint pain in his left leg. He had a history of knee pain and hypertension. At this visit his pain intensity rating as eight out of 10, and he was prescribed a short-term (seven-day) supply of tramadol to be taken every six hours as needed for pain. Additionally, he was prescribed naproxen to be taken twice a day. Both of these prescriptions were filled, along with a prescription for lisinopril. He had three more primary care visits and one specialty clinic visit for joint pain/osteoarthritis. His pain intensity ratings at these visits ranged from seven to 10 out of 10. Three months following the original tramadol prescription, he received a new prescription for a 15-day supply of tramadol to be taken every six hours as needed for pain. The naproxen prescription was refilled at this time as well.

Episodic/Both.—Patients (n=10) placed in this group received intermittent or discontinuous prescriptions for pharmacogenetically actionable opioids. Each received at least two separate prescriptions for tramadol (n=8) or codeine (n=2), which were prescribed or refilled several months apart. The opioids were often prescribed for joint or lower back pain. Most were also prescribed anti-inflammatory medications such as ibuprofen, piroxicam, or naproxen. The primary focus of their medical care was also on other comorbidities, such as hypertension, diabetes, and depression. They had between one to 11 visits during the six-month period and were prescribed four to 19 different medications. The non-pain related medications were prescribed most commonly for hyperlipidemia and hypertension.

Patient 04 is an example of a patient who belongs to episodic/both subgroup. Patient 04 was a 57-year-old Black female who was a *CYP2D6* normal metabolizer. At a primary care visit for depressive disorder, hypertension, and joint pain, she was prescribed codeine/acetaminophen. Her pain intensity rating was seven out of 10. She was also prescribed one antihypertensive medication (hydrochlorothiazide) and two psychiatric medications (desvenlafaxine and risperidone). All her medications were filled, and a 10-day supply of codeine was dispensed. Approximately one month following this visit, she had another primary care visit during which her pain intensity rating was six out of 10, a specialty clinic visit for venereal disease, and two inpatient hospitalizations for cervicalgia that lasted longer than one month. One month following discharge from the hospital, she had a primary care visit for Herpes Zoster during which her pain intensity rating was 10 out of 10. Subsequently, she received a prescription for a 10-day supply of codeine, along with an antiviral medication, both of which were filled. In total, she received eight different medications and had a total of six healthcare encounters.

Switching/Both.—Patients (n=3) placed in this group received one time-limited (less than 10 days) prescription for a pharmacogenetically actionable opioid that was followed shortly after (less than 30 days) with a prescription for a different opioid. Two of the patients received a prescription for oxycodone/acetaminophen, and one received a prescription for

hydrocodone/acetaminophen. The primary focus of their medical care was on both their pain and other comorbidities. They had four to six health care visits over the 6-month period and received at least 10 medications for multiple indications.

Patient 03 is an example of a patient who belongs to the switching/both subgroup. Patient 03 was a 44-year-old Black male who was a *CYP2D6* normal metabolizer. At a primary care visit for gout and hypertension, he was prescribed codeine/acetaminophen to be taken as needed for pain. At this visit, his pain intensity rating was 10 out of 10. The codeine prescription was filled with a three-day supply. Less than a week later, he sought care in the emergency department for foot pain and was prescribed a five-day supply of oxycodone/acetaminophen. Three weeks later, he returned to the primary care clinic during which his pain intensity rating was eight out of 10, and he was prescribed a five-day supply of oxycodone/acetaminophen which was filled. In addition to these opioids, he was prescribed eight different medications for hypertension, heart failure, and gout. He consistently filled these medications.

Sustained/Both.—Patients (n=2) placed in this group received pharmacogenetically actionable opioids for extended or continuous periods. They were given 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. Patients in this group were prescribed few other pain medications, with a maximum of two additional medications for pain over the six-month period. The primary focus of their medical care was on both their pain and other comorbidities. They had six to 10 healthcare encounters for pain-related conditions such as fibromyalgia, carpal tunnel syndrome, joint pain, and for non-pain related conditions such as diabetes, depression, and hypertension. They received between seven and 20 medications for multiple indications.

Patient 23 is an example of a patient who belongs to the sustained/both subgroup. Patient 23 was a 52-year-old White male who was a *CYP2D6* normal metabolizer. At a primary care visit for coronary atherosclerosis, he was prescribed tramadol 50 mg to be taken as needed for pain. He had a history of fibromyalgia, depression, hypertension, and coronary artery disease. In addition, he was prescribed nine other medications. The 20-day supply of tramadol was filled/refilled a total of four times. He had two more primary care visits and seven specialty clinic visits for abdominal pain, neuralgia, major depression, anxiety, and hypertension. Overall, he was prescribed a total of 20 different medications for multiple chronic conditions over the six-month period. There were also four different potential cytochrome P450 drug-drug interactions, one of which was between duloxetine (moderate inhibitor) and tramadol. Other P450 drug-drug interactions were between duloxetine (inhibitor) and metoprolol, omeprazole (inhibitor) and clopidogrel, and esomeprazole (inhibitor) and clopidogrel.

Multiplex/Both.—Patients (n=3) placed in this group received a complex regimen of pharmacogenetically actionable opioids. Their opioid prescriptions included some combination of the episodic or sustained patterns with incremental dose adjustments. They received six to eight different prescriptions for pain, including the pharmacogenetically actionable opioids, other opioids (e.g., hydrocodone, oxycodone, fentanyl, or hydromorphone), acetaminophen, anti-inflammatory medications (e.g., naproxen or

ibuprofen), and other adjuvant medications (e.g., cyclobenzaprine or capsaicin). The primary focus of medical emphasis care was on both their pain and other comorbidities. They were treated for pain-related conditions such as cervicalgia, lumbago, myalgia, and abdominal pain. All were also 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 they had between 12 to 21 visits over the six-month time period. Overall, these patients received prescriptions for between 11 to 15 different medications.

Patient 08 is an example of a patient who belongs to the multiplex/both subgroup. Patient 08 was a 61-year-old Black female who was a *CYP2D6* normal metabolizer. At a primary care visit for hyperparathyroid, hypertension, and osteoarthritis, she was prescribed tramadol 50 mg as needed for pain. At this visit, her pain intensity rating was eight out of 10. She was also prescribed lorazepam and cyclobenzaprine, and all three medications were filled. The tramadol prescription was refilled with a 17-day supply approximately one month after the original fill date. Ten days after the refill, she had a visit to a specialty clinic for polyarthritis and was given a new prescription for a 28-day supply of hydrocodone. Less than a week later, she returned to the primary clinic for osteoarthritis and was prescribed a seven-day supply of hydromorphone for fibromyalgia. She received two more prescriptions for 15-day supplies of hydromorphone a month apart in the following two months. Less than a month after the third prescription for hydromorphone, and approximately three months following the last tramadol refill, she was given a new prescription for tramadol. This prescription was filled and then refilled three weeks later. In addition to the opioids, she received prescriptions for an anti-inflammatory (indomethacin), a muscle relaxant (cyclobenzaprine), an antirheumatic (leflunomide), and a benzodiazepine (lorazepam)—all of which were filled over the six months. Overall, she was prescribed 11 different medications, six of which were for pain. She had 12 healthcare visits: six visits to the primary care clinic, all for pain-related conditions, and six visits to specialty clinics, of which only three were related to pain. During four of the visits, there were documented pain intensity ratings ranging from eight to nine out of 10.

Discussion

The purpose of this study was to develop a typology of subgroups of patients who share common patterns of medication exposure. We used an exemplar sample of patients from a large public healthcare system who were prescribed tramadol and codeine to develop the typology. Using a person-oriented qualitative approach, we were able to extract relevant data for each patient from large repositories and organize it chronologically to construct robust patient narratives related to the unfolding of medication exposure. We identified eight subgroups of patients with different exposure patterns which varied on two major dimensions: pharmacogenetically actionable opioid prescription patterns and primary medical focus of care. Our approach is responsive to national calls for addressing heterogeneity among patients who use opioids and identifying meaningful subgroups that may respond differently to pain treatments (National Institutes of Health, 2015). Our study represents one approach for obtaining a more complex and dynamic understanding of opioid exposure in the context of patients' overall healthcare experiences.

The variations in opioid prescription patterns represented in our sample indicate that discrete numerical measures of medication exposure (e.g., numerical counts or average doses) are not adequate as they do not capture discontinuations and interruptions of opioid therapies and the sequential use of different types of pain medications (Arnaout et al., 2013; Goulding et al., 2015; Lee & Pickard, 2013; Schildcrout et al., 2012). Moreover, the variations in the primary focus for medical care represented in our sample suggest that factors such as polypharmacy and potential drug interactions, healthcare utilization practices, and complicated treatment regimens need to be considered when assessing medication exposure. In most of our subgroups, and consistent with previous studies, pain was just one small part of a complex medical picture (Deyo et al., 2011; Giummarra, Gibson, Allen, Pichler, & Arnold, 2015).

Our findings need to be interpreted in light of several limitations. First, a larger sample would be needed to refine, modify, and validate the typology. For example, only a much larger sample could be used to predict the prevalence of patients likely to fall in each subgroup in any given patient population or to determine if there are patients who would belong to subgroups not present in our sample (e.g., Switching/Pain or Sustained/Comorbidities). Second, our findings have limited generalizability beyond individuals who are prescribed either tramadol or codeine in the primary care setting at a safety-net healthcare system. We do believe, however, that the methods we used to develop our typology could be used with other patient populations taking other types of medications. Third, while the retrospective nature of the study design and the use of existing electronic health records provided important clinical and administrative information, it did not always include complete data on all factors of interest (e.g., medication side effects), nor did it allow incorporation of patient self-report data on medication exposure experiences (Wu, Kharrazi, Boulware, & Snyder, 2013).

With further development and testing, however, a typology such as presented here could advance research on the relationships between medication exposure and health outcomes. For example, researchers could investigate the relationship between subgroup membership and variables such as clinical response, adverse outcomes, and efficacy of pharmacogenetic testing. For example, Jonzon and Lindblad (2006) employed a person-oriented approach to identify subgroups of women who had experienced sexual abuse during childhood and found subgroup membership (e.g., scarce resources or good coping) to be significantly associated with psychological and psychosomatic symptoms and healthcare utilization in adulthood. Similarly, in our population of interest, it might be that patients in the Singular/Pain subgroup may benefit most directly from pharmacogenetic testing, whereas the outcomes of pharmacogenetic testing for persons in our Multiplex/Both subgroup may be attenuated by a host of confounding factors. Moreover, different subgroups may require tailored strategies to ensure that the benefits of the testing are fully realized. For example, patients in the Singular/Pain subgroup may require a medication educational intervention following pharmacogenetic testing, but patients in the Multiplex/Both subgroup may require personalized health coaching or coordinated pain management approaches across multiple providers.

Novel approaches to the assessment of medication exposure are necessary, especially in light of the anticipation of wide scale uptake of pharmacogenetic testing. The typology we present here is a beginning attempt to conceptualize and operationalize medication exposure in a way that captures its dynamism and complexity. Identifying distinct patterns of medication exposure has the potential to advance research related to the outcomes of medication therapies and suggest tailored approaches to medication management.

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Table 1.

Typology of Exposure to Pharmacogenetically Actionable Opioids

		Pharmacogenetically Actionable Opioid Prescription Pattern[1]				
		Singular	**Episodic**	**Switching**	**Sustained**	**Multiplex**
Primary Focus of Medical Care[2]	Pain	One time-limited prescription for the PGxA opioid and primary focus of medical care on pain-related condition(s). *(n = 2)*[3]	Intermittent or discontinuous prescriptions for PGxA opioids and primary focus of medical care on pain-related condition(s). *(n = 3)*			
	Comorbidities	One time-limited prescription for the PGxA opioid and primary focus of medical care on non-pain related comorbidities. *(n = 4)*				
	Both	One time-limited prescription for a PGxA opioid and primary focus of medical care on both pain-related conditions and non-pain related comorbidities *(n = 3)*	Intermittent or discontinuous prescriptions for PGxA opioids and primary focus of medical care on both pain-related conditions and non-pain related comorbidities *(n = 10)*	Short-term prescription for PGxA opioid followed by a new/different prescription for an opioid and primary focus of medical care on both pain-related conditions and non-pain related comorbidities *(n = 3)*	Extended periods of uninterrupted prescriptions or refills of the PGxA opioid and primary focus of medical care on both pain-related conditions and non-pain related comorbidities *(n = 2)*	Combination of PGxA opioid patterns and primary focus of medical care on both pain-related conditions and non-pain related comorbidities *(n = 3)*

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] Primary Focus of Medical 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.

[3] n = number of patients in each subgroup

Table 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 (SD)	57.5 (4.9)	52.8 (12.8)	47 (12.1)	47 (3.6)	51 (11.9)	49.3 (4.7)	58.5 (9.2)	48.3 (16.3)	50.9 (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)
CYP2D6 Drug Metabolizing Phenotype									
UM	---	---	---	1 (33.3)	---	---	---	1 (33.3)	2 (6.7)
NM	1 (50)	4 (100)	3 (100)	2 (66.7)	8 (80)	3 (100)	2 (100)	2 (66.7)	25 (83.3)
IM	1 (50)	---	---	---	---	---	---	---	1 (3.3)
PM	---	---	---	---	2 (20)	---	---	---	2 (6.7)
Potential cytochrome P450 DDGI									
n (%)[1]	---	---	1 (25)	1 (33.3)	2 (20)	2 (66.7)	1 (50)	---	7 (23.3)

SD = standard deviation; PGxA = Pharmacogenetically Actionable; UM = Ultra-rapid Metabolizer (CYP2D6 activity score: >2); NM = Normal Metabolizer (CYP2D6 activity score: 1–2); IM = Intermediate Metabolizer (CYP2D6 activity score: 0.5); PM = Poor Metabolizer (CYP2D6 activity score: 0); DDGI = drug-drug-gene interaction

[1]Number and percentage of patients with at least 1 potential DDGI identified.