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Association Of Opioid Metabolism With Aberrant Drug-Related Behaviors Among Non-Malignant Chronic Pain Patients

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ASSOCIATION OF OPIOID METABOLISM WITH ABERRANT
DRUG-RELATED BEHAVIORS AMONG
NON-MALIGNANT CHRONIC
PAIN PATIENTS

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Eduardo Aguila

2018

Dedication

I wish to dedicate this work to my parents Jaime and Alicia, for without them, I would not have become the person that I am today. I specially dedicate this to my wife, Laurencia, and daughters, Isabela and Paula for providing me with their unconditional support, care and love throughout this whole process, which ultimately enabled me to reach the finish line. Thank you for all your love and understanding.

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by

EDUARDO AGUILA, MBA

DISSERTATION

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The University of Texas at El Paso

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of the Requirements

for the Degree of

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Interdisciplinary Health Sciences Program

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To my wife, Laurencia, and my daughters, Isabela and Paula, I'm especially grateful for putting up with me and for encouraging me on those times when I doubted myself. Thank you for keeping me grounded and for providing me with your unconditional love.

ABSTRACT

An estimated 100 million Americans suffer from some form of chronic pain. Chronic opioid therapy (COT) use in non-malignant chronic pain patients (NMCP) has markedly increased over the past two decades due to growing consensus that COT is suitable for the treatment of moderate-to-severe non-malignant chronic pain. Yet, COT for NMCP has been widely associated with multiple aberrant drug-related behaviors (ADRB) such as misuse, abuse, diversion, addiction, and pseudoaddiction. One reason for the relative high incidence of ADRB among NMCP on COT may be genetics-induced medication response variability, which, can result in pharmacotherapy failure and/or toxicity

The present study evaluated the relationships between opioid metabolizer status (OMS) (caused by inter-personal genetic variability in opioid metabolism) and ADRB such as illicit substance abuse and prescription opioid misuse. Pharmacogenetic testing (PGT) was used to categorize patient OMS, whereas urine drug testing (UDT) identified relevant ADRB. To test the study's hypothesis, retrospective categorical data from an assembled cohort of NMCP on COT was retrieved from a Pain Management Clinic's electronic medical records system (EMR). PGT and UDT results were cross-tabulated and analyzed with the Pearson Chi-square test for difference in proportions. Confounding and effect modification were dealt with by the inclusion of suspect variables Race/Ethnicity and Sex in a logistic regression model.

The results of the study showed that there was no statistically significant association between opioid metabolizer status and aberrant drug-related behaviors nor between the two suspect confounding variables and aberrant drug-related behaviors.

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CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Chronic Pain

An estimated 100 million Americans suffer from some form of chronic pain with a prevalence among adults likely to be as high as 40% (Institute of Medicine, 2011; Webster, L., 2010; Cone et al., 2008). Chronic pain, defined as pain which lasts more than 3-6 months or lasting beyond the normal healing process (Warner, 2012; Institute of Medicine, 2011), is considered the leading cause of disability, the primary reason for physician visits, and a key factor in reduced quality of life and productivity (Webster, L., 2010; Cone et al., 2008). The costs associated with chronic pain, including health care and opportunity costs, amount to an estimated \$560-635 billion annual expenditure in the United States (National Academies of Sciences, Engineering, and Medicine, 2016; Institute of Medicine, 2011).

1.1.2 Treatment for Chronic Pain

Since complete remission of chronic pain is rarely achieved, the focus of treatment therapies consists of attempts at improving quality of life through a multi-modal approach: psychotherapy, physical therapy, alternative medicine, interventional procedures, and pharmacotherapy (Webster, L., 2010; Chou et al., 2009). Chronic opioid pharmacotherapy in non-malignant chronic pain patients (NMCPP) has markedly increased over the past two decades due to growing consensus among medical providers that chronic opioid therapy (COT) is suitable for the treatment of moderate-to-severe chronic pain (Alford, 2009; Chou et al., 2009). Commonly

prescribed drugs in COT include codeine, morphine, hydrocodone, hydromorphone, Oxycodone, Oxymorphone, Fentanyl and Tramadol (Trescot, Datta, Lee, & Hansen, 2008).

1.1.3 Aberrant Drug-Related Behaviors (ADRB)

COT for NMCPD has been widely associated with multiple aberrant drug-related behaviors (ADRB) such as misuse, abuse, diversion, addiction, and pseudoaddiction (Smith et al., 2013; Webster, L., 2010). Misuse is the use of prescription or over-the-counter medications in a manner that contradicts medical advice. Abuse entails an intentional, non-therapeutic use of a drug (both licit and illicit) for the purpose of achieving its psychotropic effects. Diversion is the removal of a drug from legal distribution channels. Addiction refers to the behavioral, cognitive, and physiological phenomena that an individual may develop after exposure to a substance, which may include a strong desire to take the drug, difficulties in controlling its use, persistent use despite harmful consequences, intractable and distracting thoughts about the drug, and placing a higher priority on drug use than on any other activities (Smith et al., 2013).

1.1.4 Adherence Monitoring and Genetic Testing

Responsible prescribing of COT requires that providers commit to the use of available clinical tools and to the application of evidence-based principles to ensure the safety of patients by substantially reducing ADRB risk. Ideally, these clinical tools allow providers to objectively monitor regimen adherence, categorize patients into abuse risk strata, and identify patterns of abuse (Owen, Burton, Schade, & Passik, 2012; Peppin et al., 2012; Chou et al., 2009; Christo et al., 2011; Manchikanti, Boswell, & Singh, 2004;). One of these tools is urine drug testing (UDT), which provides information regarding the presence or absence of prescribed medication, illicit, and adulterants in biological urine specimens. When compared to surveys, clinical history, prescription

drug monitoring program (PDMP) reports and pill counts, UDT is one of the most objective tools for adherence monitoring/risk assessment in pain management as it is biometrically based (Lee & Zhang, 2013; Christo et al., 2011). UDT includes both screening and confirmatory components. The initial qualitative or semi-quantitative screening stage (presumptive) is achieved through immunoassay testing. Yet, due to significant specificity and sensitivity limitations, there is a second quantitative confirmatory stage (definitive) that makes use of a more advanced analytical technique: single or tandem mass spectrometry coupled to liquid or gas chromatography (LC-MS/MS, GC-MS) (Lee & Zhang, 2013; Manchikanti, Malla, Wargo, & Fellows, 2011).

Pharmacogenetic testing (PGT), another pain management tool gives providers personalized patient genetic information like predicted metabolizer status, which enables tailored drug therapy. Most opioid drugs used in pain management are metabolized by polymorphic CYP450 enzymes CYP2D6, CYP3A4 and/or uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7) (Jannetto & Bratanow, 2009). Drug metabolizer status from genetic polymorphisms in the *CYP2D6* gene are categorized into four groups: ultra-rapid metabolizers (UM), presenting with multiple copies of *CYP2D6*; extensive metabolizers (EM) with a single wild-type copy of *CYP2D6*; intermediate metabolizers (IM), exhibiting decreased enzymatic activity; and poor metabolizers (PM), with no detectable enzyme activity (Trescot & Faynboym, 2014; Jannetto & Bratanow, 2009).

1.1.5 Opioid Metabolism and Drug Efficacy: Genetic Testing as a Risk Assessment Biomarker

The relatively high incidence of ADRB among NMCPP on COT may be partly the result of pharmacotherapy failure and/or toxicity from genetic polymorphisms in the CYP2D6 enzyme, which produce a variant or “mutant” metabolizer status for its opioid substrates (i.e. codeine,

hydrocodone, oxycodone, tramadol) (Trescot et al., 2008). NMCCP with genetic polymorphisms could be misusing their prescription medication or supplementing their therapy with illicit substances to mitigate pain when dealing with ineffective opioid drugs. At present, the risk for opioid misuse and aberrant behaviors is largely evaluated with two validated instruments: the Screener and Opioid Assessment for Patients with Pain- Revised (SOAPP-R) questionnaire for COT onset, and the Current Opioid Misuse Measure (COMM) for patients already on COT (Inflexxion, 2015). However, instruments that rely on a patient's individual responses have a risk of erroneously miss-categorizing these same individuals. (Moore, Jones, Browder, Daffron, & Passik, 2009). Genetic testing, as an alternative to these instruments, could serve as a supplementary risk assessment tool for opioid misuse and ADRB. Consequently, the aim of this study was to uncover statistically significant associations between variant opioid metabolism (OMS) and ADRB (i.e. misuse and abuse of licit/illicit substances). Moreover, genetic testing could be substantially more objective than the SOAPP-R and COMM instruments since a genetic biomarker would not be as prone to misrepresentation by determined individuals. The current review of the literature did not conclusively establish an association between variant opioid metabolism and ADRB (although it did establish relationships between opioid metabolism and therapeutic failure/drug toxicity). Therefore, the findings of the present study could significantly contribute to filling in the gaps in the body of knowledge for contributors to COT risk among NMCCP and increasing the likelihood that we are able to mitigate that risk.

1.2 Conceptual Framework

There are three conceptual elements whose relationships were evaluated in this study:

1. Opioid metabolism – Polymorphic *CYP2D6* genotype determines the metabolizer status of an individual and how quickly (UM) or slowly (PM) an opioid prodrug (i.e. hydrocodone) is

biotransformed into its more potent (higher μ -opioid receptor affinity) bioactive metabolite (i.e. hydromorphone) during Phase I of opioid metabolism.

2. Therapeutic failure and toxicity – At standard dosage, a poor opioid metabolizer could either suffer therapy failure from low plasma concentrations of bioactive metabolite, and/or toxicity from the buildup of high concentrations of a bioactive prodrug. The opposite could also be true in ultra-rapid metabolizers; these patients can experience toxicity from rapid plasma buildup of the bioactive metabolite, or therapeutic failure if most of the pain reduction stems from the action of the parent drug.

3. Aberrant drug-related behaviors – NMCCP who are prescribed long-term opioid therapy have a higher risk of misusing these drugs, becoming addicted to them, or abusing illicit substances. Yet, these behaviors could have theoretically originated from efforts to supplement COT when the drugs did not provide adequate pain relief (as would have ensued with therapy failure in PM patients), or attempts to reduce adverse drug reactions (ADR) (as would have taken place with toxicity in UM patients).

The scientific literature already recognizes the link between genetic makeup (opioid metabolizer status) and drug efficacy (therapy failure/toxicity). Yet, there is no clear connection between genetics, specifically OMS, and ADRB incidence. Therefore, I proposed that significant relationships do exist between the conceptual elements presented above. Figure 1 graphically depicts these relationships.

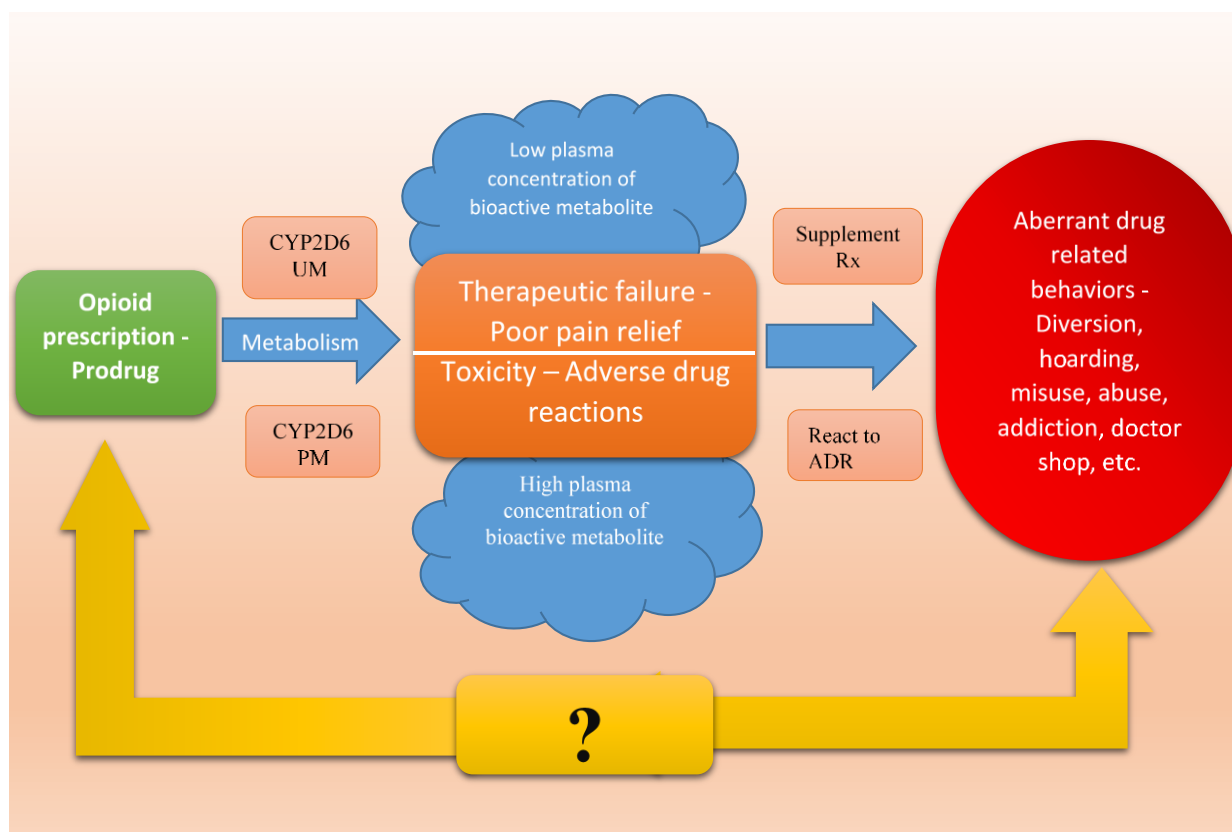


Figure 1. Relationships between opioid metabolism, pain relief/adverse drug reactions (ADR), and ADRB. The figure reveals a potential relationship between opioid metabolism and ADRB.

1.3 Purpose of the Study

The purpose of this study was to assess the relationship between opioid metabolism as determined by phenotypic CYP2D6 expression (OMS) and aberrant drug-related behaviors (ADRB) among non-malignant chronic pain patients (NMCPP). Significant findings could further advance the creation of better ADRB prediction algorithms for at-risk patients on a chronic opioid regimen.

1.4 Definition of Terms

The following is a description of both the conceptual and operational definitions of the variables in the study. They are presented in alphabetical order:

1. Aberrant Drug-Related Behaviors (ADRB)

a. Conceptual definition – Patient misuse, abuse, overuse and diversion of licit and illicit drugs, as evidenced in: urine toxicological confirmatory testing (LC-MS/MS) by a finding of a positive illicit substance (i.e. metabolites of marijuana, cocaine and heroin), positive non-prescribed medication (i.e. hydrocodone/hydromorphone), negative expected prescribed medication, and/or positive adulteration/validity testing (i.e. pH, creatinine, oxidants); inter and intra-state prescription drug monitoring program databases (PDMP), which uncover evidence of doctor shopping; professional psychological evaluation; self-admission, and evidence of dose escalation, amongst other criteria (Substance Abuse and Mental Health Services Administration, 2017; Peppin et al., 2012; Christo et al., 2011; Pergolizzi et al., 2010; Chou, Fanciullo, Fine, Miaskowski et al., 2009; Webster, L. R. & Webster, 2005).

b. Operational definition – In this study, ADRB was treated as a dichotomous outcome (dependent) variable with the following two levels: NEGATIVE for ADRB as determined in objective bioanalytical confirmatory drug testing (NEGATIVE for all four statistics that comprise the level, which are as follows, 1) presence of an illicit (PI), 2) presence of non-prescribed medication (PNP), 3) absence of prescribed medication (AP), and 4) evidence of adulteration (EA)); and POSITIVE, which was deemed as such if at least one of these statistics was positive.

2. Opioid Metabolism (OMS)

a. Conceptual definition – the pharmacokinetic biotransformation or conversion of the more lipophilic opioid parent drug to a more water-soluble metabolite for excretion from the body.

Achieved through oxidation reduction and hydrolysis in phase I metabolism, and conjugation reactions in phase II metabolism (Trescot, 2013; Trescot et al., 2008; Fishbain et al., 2004). For the context of this study, emphasis was placed on the liver super family of microsomal enzymes cytochrome P-450 (CYP450), specifically CYP2D6, which is responsible for catalyzing phase I drug metabolism of important substrate opioids such as codeine, hydrocodone, oxycodone and tramadol (Trescot et al., 2008).

b. Operational definition – Opioid metabolism or opioid metabolizer status (OMS) was initially treated as an independent/predictor categorical variable, which consisted of the following categories: 1) UM – ultra-rapid metabolizers (multiple copies of the *CYP2D6* gene); 2) EM – extensive metabolizers (a single wild-type copy of the *CYP2D6* gene; 3) IM – intermediate metabolizers (1 normal and 1 reduced allele, or 2 partially deficient alleles of the *CYP2D6* gene); and 4) PM – poor metabolizers (2 mutant alleles of the *CYP2D6* gene leading to no detectable enzyme activity). Dichotomization into normal metabolizer (NM) and variant metabolizer (VM) levels was later performed to ensure adequate sample size and sampling ratio.

3. Therapeutic Failure/Toxicity

a. Conceptual definition – Therapeutic failure refers to the failure of chronic opioid therapy to provide patients with meaningful reductions in pain. Often as the result of poor metabolic conversion of a prodrug into its bioactive metabolite (Trescot & Faynboym, 2014; Gaedigk, 2013). Toxicity relates to the group of opioid adverse drug reactions (such as constipation and respiratory depression) that a chronic pain patient manifests from increased bioactive metabolite concentration in the body – the result of increased metabolic enzyme activity.

b. Operational definition – Mediating dichotomous variables with YES/NO levels derived from Likert pain scales (dichotomized) and provider progress notes indicating adverse reactions to prescribed medication.

In addition to the preceding variables, other categorical (race/ethnicity) and dichotomous variables (gender, presence of CYP2D6 inducers/inhibitors) were included in the statistical models to allow for control of confounding and effect modification.

1.5 Research Questions

The main question of the study is the following:

1) Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportions of normal and variant metabolizers on chronic opioid therapy that engage in aberrant drug-related behaviors?

Furthermore, it was of clinical value to seek answers to research questions that included some of the potentially confounding variables (i.e. race, sex). The following two questions illustrate this approach:

1. Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportion of White and Hispanic patients on chronic opioid therapy that engage in aberrant drug-related behaviors?

2. Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportion of men and women on chronic opioid therapy that engage in aberrant drug-related behaviors?

1.6 Significance of the Problem – The Opioid Epidemic

One of the reasons why NMCCP on COT may display aberrant behaviors is the existence of genetic polymorphisms that affect how quickly an opioid substrate is metabolized. The central hypothesis in this study is that those individuals with variant expression of metabolizer enzymes may end up supplementing (misusing, abusing, etc.) their medication with other prescribed drugs and/or illicit substances to counteract the effects of therapeutic failure and/or toxicity. The misuse of opioids is a major public health concern that goes beyond what I suggest here. It is problem of enormous proportions, with profound health, social and financial implications for all Americans. This opioid misuse “crisis” has intensified over the past couple decades. Major contributors to it have been: a) the liberalization of laws governing the prescribing of opioids for the treatment of non-malignant chronic pain by state medical boards, which has led to dramatic increases in opioid use; b) the introduction in 2000 of new pain management standards by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO, now the Joint Commission); c) the increased awareness of the right to pain relief; d) the support from multiple organizations for the use of opioids in large doses; and e) the aggressive marketing by the pharmaceutical industry, which concealed and minimized the addictive characteristics of these drugs (National Institute on Drug Abuse, 2017; Skolnick, 2017; Manchikanti et al., 2012).

According to the 2015 National Survey on Drug Use and Health (NSDUH), there were approximately 91.8 million adults aged 18 or older who had used prescription pain medication; this represents more than one-third (37.8%) of the adult population in the United States (Lipari, Williams, & Van Horn, 2017; SAMHSA: Arthur Hughes, Matthew R. Williams, Rachel N. Lipari, and Jonaki Bose & RTI International: Elizabeth A. P. Copello and Larry A. Kroutil, September 2016; Center for Behavioral Health Statistics and Quality, 2016). Furthermore, the proportion of

those who misused the medication was 12.5 million, 2.1 million misused it for the first time, 2 million had a prescription for opioid use disorder (OUD), and 828,000 abused heroin (SAMHSA, January 25, 2017; SAMHSA, July 25, 2017; Lipari et al., 2017; National Institute on Drug Abuse, 2017; SAMHSA: Arthur Hughes, Matthew R. Williams, Rachel N. Lipari, and Jonaki Bose & RTI International: Elizabeth A. P. Copello and Larry A. Kroutil, September 2016). In the same year (2015) 33,091 died from overdosing on opioids, 9,580 died from overdosing on synthetic opioids such as fentanyl, and 12,989 died from overdosing on heroin; the associated cost to society was \$78.5 billion (Centers for Disease Control and Prevention, 2015; NIDA, 2015; Manchikanti et al., 2012; Leider, Dhaliwal, Sklar, & Kulakodlu, 2010). The United States is in the midst of a significant crisis; 90 Americans die on a daily basis after overdosing on opioids (National Institute on Drug Abuse, 2017), yet, its therapeutic use continues to escalate quadrupling since 1999 (Adams, Bledsoe, & Armstrong, 2016; Manchikanti et al., 2012). It is important to note that there are still situations where patients who suffer from chronic pain legitimately benefit from responsible and conservative prescribing, which integrate adequate monitoring and counseling approaches. Most of the approximately 91.8 million adults who used opioid medication in 2015, did so responsibly. The scale of the problem; product of irresponsible overprescribing, a widespread notion that all you need to do to quickly address an underlying condition is to “pop a pain pill”, and the pharmaceutical industry’s willful dishonesty in the late 90s; suggests that even being a relatively low proportion, by sheer numbers, those who do misuse and abuse opioid medication are still a substantially large number of all Americans (National Institute on Drug Abuse, 2017; Adams et al., 2016). In October of 2017, the federal government finally addressed the opioid epidemic by declaring it a top priority and outlining a comprehensive evidence-based opioid strategy that leverages the expertise and resources of all the agencies from the Department

of Health and Human Services (NIDA, 2018). The aims of this five-point opioid strategy are as follows: 1) Improve access to prevention, treatment, and recovery support services, 2) Target the availability and distribution of overdose-reversing drugs, 3) Strengthen public health data reporting and collection, 4) Support cutting-edge research that advances our understanding of pain and addiction, and 5) Advance the practice of pain management (NIDA, 2018). This dissertation study contributed to these initiatives by presenting novel research data that advances the practice of pain management while providing insight about the assessment of opioid risk and responsible opioid prescribing.

1.7 Significance of the Study

Amid rising public concern for the devastating effects that the opioid epidemic is having all across the United States (i.e. overdose deaths, loss of quality of life, increased cost to society), the significant increase in opioid abuse and misuse over the past couple of decades, and, at the other end of the spectrum, the “opiophobia” displayed by many medical professionals for fear of the very real threat of litigation; there is now a substantial number of chronic pain patients that go untreated, undertreated or poorly managed when they could have benefited from responsibly implemented opioid therapy. Hence, the importance of recognizing that prescription opioid medication continues to play a vital role in the treatment of non-malignant chronic pain. Furthermore, prescribing opioids requires that proper risk assessment procedures be performed on patients that are candidates for COT to substantially reduce the likelihood of opioid-related aberrant behavior. To contribute to the improvement of risk assessment, this study sought to describe whether a statistically significant association existed between OMS and ADRB. If such an association had been significant, it would have supported the theoretical foundation for a new COT ADRB risk assessment tool guided by objective biometric data rather than the more

subjective information currently available from the SOAPP-R and COMM questionnaires. The new tool would have been of considerable clinical value to pain management practitioners since it would have enabled the use of *CYP2D6* genotypic data as a predictor of ADRB. Finally, the data generated in the study could have been feed into protocol algorithms within LIS Decision Support Systems to streamline this patient risk stratification process.

1.8 Assumptions

a. Based on the review of the literature, it was assumed that the independent/exposure variable is comprised of levels from one cytochrome P250 enzyme only (*CYP2D6*), when in fact several enzymes are involved in the metabolism of the same drug. Yet, previous studies justified the approach in the context of this study as the opioids of interest (codeine, hydrocodone, oxycodone & Tramadol) were primarily metabolized by *CYP2D6*.

b. The conceptual framework presented in this dissertation project assumed that variant opioid metabolism dictated whether NMCPD experienced therapeutic failure or significant toxicity, which then potentially lead to ADRB. Yet, opioid therapy failure/toxicity was not necessarily a function of metabolizer status, nor metabolizer status was solely related to the genetic mutations that affect the activity of metabolizing enzymes. Opioid metabolizer status is only one of the reasons (albeit disproportionately significant) as to why patients may experience therapeutic failure and/or toxicity. Some of other reasons include variant expression of transporter proteins, variant expression of opioid receptors sites, genetics-induced variation in signaling for pain perception, etc. Additionally, exogenous compounds (such as some anticonvulsants and some antidepressants) can induce or inhibit the activity of opioid metabolizing enzymes (Trescot et al., 2008).

1.9 Limitations

Metabolism of the drugs of interest in this study undergo metabolic biotransformation by enzymes and substances other than just CYP2D6, the enzyme that was being targeted here. Since retrospective cohort studies are particularly susceptible to confounding (Sullivan, 2012), there might have been other significant confounders that were not accounted for in the study (pain type, pain location, COT duration, age range, and others were proposed as suspect confounding variables for future studies). Use of a non-probability convenience sample in place of true random probability sampling could have prevented adequate population representation and reduced generalizability (Sullivan, 2012; Kaplan & Saccuzzo, 2009). Though, the main variables in the study (OMS and ADRB) were treated as risk/exposure and an outcome variables, which may imply causation, the goal was to only establish a potential association between these variables as there is no experimental intervention. These limitations had the potential to restrict the interpretation and generalizability of the findings in this study.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 The Intersection of COT, ADRBs and Adherence Monitoring (Definitive Testing through LC-MS/MS)

Chronic non-malignant pain management makes use of COT as one of the modalities to relieve pain. Opioid medication adoption has increased dramatically over the past decade as observed between the period from 2000 to 2002 when it increased by more than 200% (Peppin et al., 2012). Peppin and colleagues (2012) indicated that Americans represent 4.6% of global population yet consume 80% of the global opioid supply and two thirds of the world's illicit drugs (Peppin et al., 2012). With the increase in the prescription of opioids, there has been a well-documented increase in its the misuse, abuse and diversion (Christo et al., 2011; L. Webster, 2010; Chou, Fanciullo, Fine, Adler et al., 2009). Furthermore, while clinical experience suggests that opioid medication does improve pain and functional status for some patients, some patients only exhibit minimal improvement, and others will develop conditions such as endocrinopathies, constipation, immunosuppression, sleep-disordered breathing, hyperalgesia, and addiction – ADR and ADRB (L. Webster, 2010; Chou et al., 2009). All these potential behavioral and physiological consequences make the use of opioids somewhat controversial in the treatment of non-malignant chronic pain creating the need for tools to identify and monitor for aberrant drug-related behaviors (Owen et al., 2012; Peppin et al., 2012; Christo et al., 2011; Webster, L., 2010; Chou et al., 2009; Manchikanti et al., 2004). Urine drug testing (UDT) is at present one of the most objective assessment tools in pain management for regimen compliance and detection of illicit drugs. In addition, UDT facilitates the pharmacokinetic assessment of opioid clinical status (accomplished

through the evaluation of relative proportions between parent drugs and their respective metabolites). UDT offers pain practitioners and patients several advantages: it is relatively cost-effective, widely available, and relatively well understood (when compared to other matrices) while providing adequate detection windows. Furthermore, UDT urine specimens are very easily collected, and the testing itself may serve as a deterrent for the abuse-prone patient (Lee & Zhang, 2013; Christo et al., 2011).

Naturally occurring/semi-synthetic opioid/opiate alkaloids such as codeine, hydrocodone, oxycodone and tramadol along with their phase I metabolites (CYP2D6 metabolism), morphine, hydromorphone, oxymorphone and O-Desmethyltramadol, are commonly used (as components of COT) in the treatment of moderate to severe chronic pain due to their activity as μ -opioid receptor agonists. (Christo et al., 2011; Manchikanti et al., 2004) Nevertheless, the benefits of this approach must be weighed against the risk for adverse drug reactions (ADR) and the subsequent potential for ADRB such as misuse and abuse of opioid drugs, and/or illicit. For instance, the prevalence of illicit marijuana abuse among NMCCP is estimated to be around 15%, the highest compared to other illicit. However, it is believed that in some contexts, marijuana use is linked to supplemental pain relief to counteract the effects of therapeutic failure (Reisfield, Wasan, & Jamison, 2009; Cone, Caplan, Black, Robert, & Moser, 2008).

2.2 Opioid Metabolism and Response

Drug metabolism and how it affects drug efficacy have become increasingly relevant in the realm of pain medicine. Genetic polymorphisms may predict how well a drug will help a patient attain pain relief or whether therapeutic failure and/or drug toxicity could occur. Moreover, clinical evidence suggests that genetic differences may explain an estimated 20-95% of the variability in

medication efficacy (Gupta, Hussainzada, & Del Tredici, 2014). This indicates that pharmacotherapy can benefit from a tailored approach through metabolizer status information (pharmacogenetic testing) that results in improved drug effectiveness and a reduction in the potential for ADR. *CYP2D6* gene polymorphism has been significantly implicated in drug response variability, particularly for codeine, hydrocodone, oxycodone and tramadol (Crews et al., 2014; Trescot & Faynboym, 2014). Furthermore, there are more than 100 different *CYP2D6* alleles that may affect enzyme activity and medication response but that still need formal evaluation in clinical trials to ascertain their impact (Crews et al., 2014). Nevertheless, as depicted in Table 1, allele variability does appear to account for metabolizer status differences as demonstrated by a variety of allele diplotypes associated with multiple phenotypes (Crews et al., 2014).

Table 1. Examples of *CYP2D6* genotypes and phenotype classification.

Allele 1	Allele 2	<i>CYP2D6</i> Diplotype	<i>CYP2D6</i> Activity Score	Phenotype
<i>*1</i>	<i>*1xNa</i>	<i>*1/*1xN</i>	≥ 3.0	UM
<i>*2x2b</i>	<i>*41</i>	<i>*2x2/*41</i>	2.5	UM
<i>*1</i>	<i>*2</i>	<i>*1/*2</i>	2.0	EM
<i>*1</i>	<i>*17</i>	<i>*1/*17</i>	1.5	EM
<i>*2</i>	<i>*3</i>	<i>*2/*3</i>	1.0	EM
<i>*1</i>	<i>*4x2</i>	<i>*1/*4x2c</i>	1.0	EM
<i>*10</i>	<i>*10</i>	<i>*10/*10</i>	1.0	EM
<i>*4</i>	<i>*10</i>	<i>*4/*10</i>	0.5	IM
<i>*5</i>	<i>*6</i>	<i>*5/*6d</i>	0	PM

Modified from Crews et al. (2014). Examples of *CYP2D6* genotypes and phenotype classification (Crews et al., 2014). EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra-rapid metabolizer.

A retrospective study to assess abnormal PGT rates by Kirsh and colleagues (2014) (61 men and 41 women from a Louisiana pain clinic – average age of 46.7 years) classified 73.4% of the patients as extensive metabolizers (EM), 11.4% as intermediate metabolizers (IM), 11.4% as ultra-rapid metabolizers (UM), and 3.8% as poor metabolizers (PM) for CYP2D6 cytochrome P450 enzyme. These results provide evidence that substantiates frequently encountered genetic polymorphisms among NMCCP on COT (Kirsh et al., 2014). A study by Gupta et al. (2014) found that CYP2D6 variant metabolizers (PM & UM) tend to exhibit poor clinical outcomes on commonly used opioids such as oxycodone and hydrocodone; and highlighted how this genetic variation increases the risk for opioid dependence. The same study described how CYP2D6 PMs experienced less analgesia than extensive metabolizers with oxycodone and hydrocodone in three out of five well-validated pain tests. Finally, additional results showed that PMs had statistically lower levels of oxycodone's more analgesically potent metabolite oxymorphone (Gupta et al., 2014). Several authors (Gupta et al., 2014; Trescot & Faynboym, 2014; Jannetto & Bratanow, 2009) referencing pharmacokinetic (a patient's capacity for metabolizing drugs) and pharmacodynamic (a patient's ability to respond to a drug at a target or receptor site) principles described how a PM may be unable to activate a prodrug such as codeine into its bioactive morphine metabolite, while a patient with a non-functional mu-opioid receptor (OPRM1) would not respond to that drug regardless of the dosage. These authors implied that polymorphic genes encoding the drug-metabolizing enzymes (such as CYP2D6), drug transporters, drug receptors, and other proteins could serve as useful biomarkers for predicting drug efficacy and potential for ADR in human subjects (Gupta et al., 2014; Trescot & Faynboym, 2014; Jannetto & Bratanow, 2009). In their manuscript, Jannetto and Bratanow (2009) proposed that discrepancies in the metabolism of opioid drugs can lead to therapeutic failure and/or toxicity by changing the

relationship between the dose and plasma concentration of bioactive drug metabolites. They explained that congenital alterations in the metabolism of opioid medication, and inherited polymorphisms in drug receptor targets can have a greater impact on medication response than any of the other clinical and physiological variables. They also indicated that while most individuals are classified as EMs (metabolize affected drugs normally), 5-10% of Caucasians and 1-4% of most other ethnicities have decreased CYP2D6 activity (PMs) and may experience reduced pain relief and/or toxic effects at clinical dosage (Jannetto & Bratanow, 2009). In summary, by influencing the expression of drug metabolizing enzymes, drug transporters, opioid receptors, and structures involved in the perception and processing of pain, genetics have an important effect in the efficacy of opioid analgesics. (Trescot & Faynboym, 2014)

2.3 Pharmacogenetic Testing

Personalized medicine is increasingly becoming an important aspect to consider in the practice of pain management and is now expected that providers tailor their therapy approach to each patient. An example of this growing trend is pharmacogenetic testing (PGT), which helps clinicians modify and optimize medication therapy to a patient's genetic profile. Furthermore, because PGT provides information on medication response, rather than disease risk or vulnerability, it is now considered a more clinically actionable aspect of precision medicine (Gupta et al., 2014). Besides the potential to improve health outcomes through better prediction of medication response, PGT can also have significant economic benefits such as reducing the costs associated with ADR (short term), and through health care savings from targeted drug treatments (long term) (Gupta et al., 2014). Haga and colleagues (2013) described how PGT could have a direct effect on the patient's psyche to positively influence medication regimen adherence. They found that when patients learn about their own genetic likelihood of having a positive therapeutic

response or not experiencing an ADR from their medication, their perceived drug efficacy increased while their level of concern diminished. Additionally, they also make a case for some of the same potential benefits described by Gupta et al. (2014) for using PGT; reduced cost burden associated with less medication trial and error and a significant reduction in the follow-up care required for the management of ADR (Haga & LaPointe, 2013). Ultimately, PGT optimizes the treatment for pain management. For instance, Jannetto & Bratanow (2009) discussed how *CYP2D6* genotyping through PGT could predict initial opioid therapeutic concentrations by patient metabolizer status and identify individuals more likely to experience ADR when started on standard dosage. This genetic knowledge on a patient not initially known to have variant expression of *CYP2D6* (i.e. PM) resulted in revised approaches where prescribers initiate opioid therapy at a lower/higher dose relative to standard dosage to compensate for abnormal metabolism. Furthermore, this patient could now be placed on substitute medication not affected by this particular metabolic pathway (i.e. therapy with fentanyl instead of hydrocodone) (Jannetto & Bratanow, 2009).

2.4 CYP2D6 & Hydrocodone

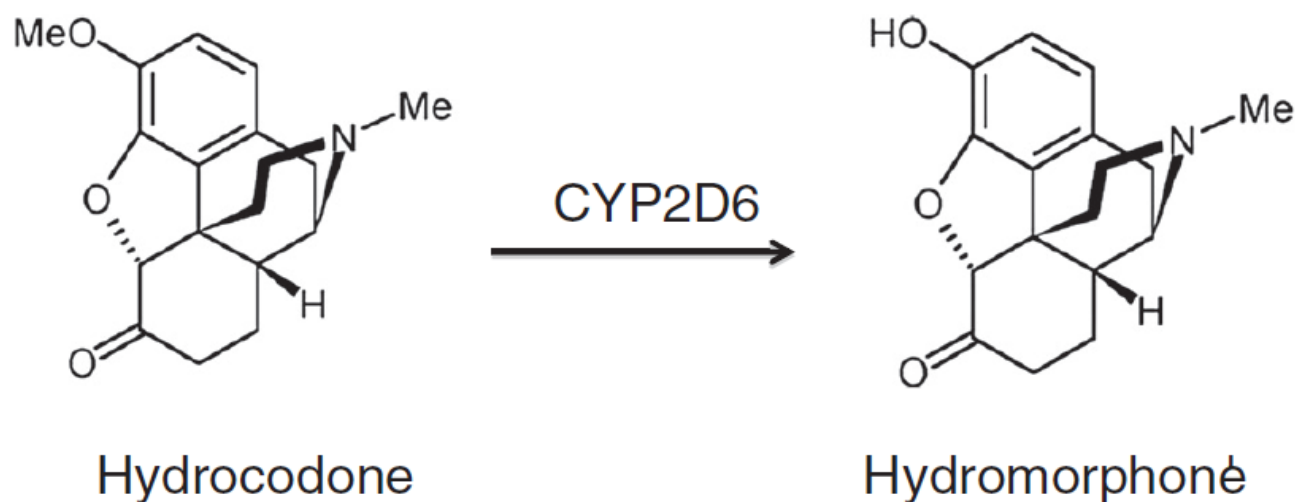


Figure 2. CYP2D6 mediated transformation of hydrocodone to hydromorphone (Stauble et al., 2014). Hydrocodone transformed via *O*-demethylation by CYP2D6 enzyme into bioactive hydromorphone, which has a 10 to 33-fold greater affinity to μ -opioid receptors.

Of interest to the study due to its frequent use in the treatment of moderate-to-severe chronic pain is the semi-synthetic opioid pro-drug hydrocodone. As depicted in figure 2, Hydrocodone is bio-transformed via *O*-demethylation by CYP2D6 into bioactive hydromorphone, an opioid metabolite that has a 10 to 33-fold greater affinity to μ -opioid receptors and significantly higher potency than its parent drug (Crews et al., 2014). A study on pharmacodynamic efficacy by Stauble and colleagues (2014) demonstrated how pain relief is highly correlated to plasma hydromorphone steady-state concentration (C_{ss}). This finding supports the pro-drug/bioactive drug hydrocodone conversion theory in which hydrocodone's metabolite concentration, not hydrocodone dosage, influences therapy effectiveness (Stauble et al., 2014). Moreover, the study emphasized the role that polymorphic *CYP2D6* genotype plays in the efficacy of hydrocodone and

other opioid medication. For instance, PM produce lesser amounts of the bioactive metabolite hydromorphone, irrespective of hydrocodone dose. A separate test in the same study produced a statistically significant inverse association (negative correlation) between plasma hydromorphone C_{ss} and self-reported pain (Stauble et al., 2014). However, there was some evidence of CYP2D6 metabolizer status not affecting response to hydrocodone on PM, and little or no evidence of increased hydrocodone response in CYP2D6 UM. The study concluded that there is insufficient evidence to determine whether PM can be expected to have decreased pain relief, or whether UM have increased risk of toxicity with standard doses of hydrocodone (Stauble et al., 2014). In a case study by Susce et al. (2006), an 85-year-old Caucasian female patient with hip surgery and long-standing intolerance to codeine, oxycodone and tramadol (CYP2D6 substrates) received a second round of opioid therapy with hydrocodone (another CYP2D6 substrate) that yielded a substantially better response even though she had been phenotyped as a CYP2D6 PM (Susce, Murray-Carmichael, & de Leon, 2006). There was, however, no mention of concomitant use of CYP2D6 inducing/inhibiting medication that could have explained the discrepancy. This information seems to similarly contradict the general consensus that variability in *CYP2D6* genotype plays a significant role in the metabolism of several opioid drugs and influences their pain alleviating effects (Trescot & Faynboym, 2014).

While the importance of metabolizer status in the therapeutic effectiveness of hydrocodone and other opioid alkaloids has been well established, it is also important to note that several other genetic factors influence medication response. For instance, Trescot and Faynboym (2014) reported on several well-studied hereditary disorders such as “hereditary insensitivity to pain with anhydrosis”; they described some 200 candidate genes believed to be significantly implicated in pain signal processing (Trescot & Faynboym, 2014). Moreover, certain substances can both inhibit

and promote metabolizer enzyme activity. For example, CYP2D6 inhibitors such as quinidine, paroxetine, fluoxetine and bupropion can affect EM and IM phenotypes making them appear like a PM phenotype at normal dosage levels. (Susce et al., 2006)

2.5 Therapeutic Failure & (Pro-Drug/Metabolite) Toxicity

Several recent studies demonstrated that there is an important relationship between polymorphic CYP2D6 (OMS) and medication response for common opioids such as hydrocodone (Stauble et al., 2014; Jannetto & Bratanow, 2009; Haile, Kosten, & Kosten, 2008; Gan, Ismail, Adnan, & Zulmi, 2007). Most of the research from these studies focused on slower CYP2D6 metabolizers (PM) and on some of the other CYP2D6 substrates (codeine and tramadol), as well as hydrocodone. One study found a statistically significant association between plasma concentrations of bioactive metabolite (hydromorphone) and pain relief, but no association between pain relief and parent drug dosage (hydrocodone), which suggests a lesser role for the CYP2D6 enzyme while it emphasizes the consideration of alternative medications for patients identified as variant metabolizers (Stauble et al., 2014). A similar study that tested the relationship of plasma C_{ss} for hydrocodone, tramadol, codeine and methadone with ADR reported that out of all the patients who experienced ADR, four out of five (80%) had variant *CYP2D6* metabolism based on their predicted *CYP2D6* phenotype (Jannetto & Bratanow, 2009). Another study by Gan and associates (2007) conducted on Asians who had been prescribed tramadol found that IM patients (none of the subjects in the study were PM so IM were used instead as the closest slower metabolizer group) have a statistically higher incidence of ADR when compared to those that metabolize tramadol faster (UM and EM patients). Additionally, *CYP2D6**10 was identified as the allele contributing the most to the incidence of intermediate metabolism among Asians (Gan et al., 2007). Finally, Haile and colleagues (2008) reported on two very interesting findings that

once again highlight the importance for the role of genetics in opioid response; first, that a group of CYP2D6 PM Caucasians appeared to be protected from developing opioid dependence; and second, that UMs tended to do poorly on methadone maintenance, and experienced frequent withdrawal symptoms (Haile et al., 2008).

2.6 Bioanalytical Methodologies

2.6.1 Pharmacogenetic Testing

As previously described, pharmacogenetic testing (PGT) is a type of genetic test that assesses a patient's individual response to a given drug, to include the risk of an adverse reaction, and provides information about optimal drug selection and dosing (Belfer, 2015; Kapur, Lala, & Shaw, 2014; Mills, Voora, Peyser, & Haga, 2013; Stone & Bornhorst, 2012). For tailored opioid therapies, PGT provides information on patient drug metabolizer status, receptor site expression and information on the genetic aspects of pain perception to predict opioid efficacy and/or potential for toxicity (Trescot & Faynboym, 2014). PGT is performed with molecular diagnostic and nucleic acid detection techniques that enable the sequencing of complex genomes (Sawyer, 2015). These techniques involve the selection and amplification of the nucleic acid of interest, the visualization of the amplified nucleic acids, and the identification and quantification of individual nucleic acid species (Sawyer, 2015). These processes are accomplished using the following analytical methodologies:

1.- Polymerase Chain Reaction (PCR): A DNA technique that amplifies a single copy or copies of a segment of DNA across several orders of magnitude to produce thousands to millions of copies of that particular sequence. It makes use of a thermostable DNA polymerase, the deoxynucleotides of each base (collectively referred to as dNTPs), the target sequence (the

sample), and a pair of oligonucleotides (referred to as primers) complementary to opposite strands flanking the sequence to be amplified. The process takes place over repetitive cycles of denaturation, annealing, and extension that are paced by thermal cycling (Sawyer, 2015).

Assay method: First, target duplexes are denatured into single strands by heat. Upon mixture cooling, primers provided in great excess will anneal to specific complementary sequences on the target. After primer annealing, polymerases synthesize two additional DNA strands containing the primers as the 5' ends. The primers are then placed close enough together so that the polymerase extends each strand far enough to include the priming site of the other primer. Temperature cycling occurs as follows: 1) a high temperature to denature the target sequence, 2) a low temperature that allows annealing of the primers to the target, and 3) a third temperature that is optimum for polymerase extension (Sawyer, 2015).

2.- Microarray (also called DNA arrays, DNA chips, or biochips): A solid-phase hybridization multi-plex 2D array assay for high-throughput quantification in which single-stranded nucleic acids form specific double-stranded hybrids. The process requires that both solid-phase probe and target nucleic acids are mixed under conditions that allow for complementary base pairing, and that there is a method to detect any resulting double-stranded nucleic acids. Microarrays can assay large amounts of nucleic acids due the high density of their miniaturized spot sizes (typically less than 200 microns in diameter) and are useful for testing multiple mutations in genetic disease, oncology, and pharmacogenetics. They are also used to monitor the whole genome for single-nucleotide variants (SNVs), gene expression, and copy number variants (CNVs) (Sawyer, 2015).

2.6.1.1 Pharmacogenetic Testing Sample Collection

The following steps describe the proper procedure for the collection of cheek swab samples for pharmacogenetic testing that were carried out on the patients included in this study. This procedure minimizes the risk of contamination with foreign DNA material (Millennium Health, 2017).

1. Open package and remove collector without touching sponge tip.
2. Place sponge as far back in the mouth as comfortable and rub along the lower gums in a back and forth motion.
3. Gently rub the gums at least 10 times. If possible, avoid rubbing the teeth.
4. Gently repeat rubbing motion on the opposite side of the mouth along the lower gums for an additional 10 times.
5. Hold the tube upright to prevent the liquid inside the tube from spilling.
6. Unscrew the cap from the collection tube without touching the sponge.
7. Turn the cap upside down, insert the sponge into the tube and close cap tightly.
8. Invert the capped tube and shake vigorously 10 times to mix fluid completely.

2.6.2 Toxicological Testing (Urine Drug Testing)

UDT is divided into two separate analytical chemistry techniques: enzyme immunoassay (EIA) in the presumptive or screening phase (low specificity and sensitivity), and liquid chromatography tandem mass spectrometry (LC-MS/MS) in the definitive or confirmatory phase (high specificity and sensitivity).

2.6.2.1 Presumptive Testing

Immunoassay testing is an analytical biochemical technique based on the binding reaction of an antibody that is specific to the analyte of interest (i.e. a test drug) and that allows for the detection of its presence and quantitation (A. Pesce et al., 2011). In enzyme-labeled immunoassays (EIA), also called enzyme-linked immunosorbent assay (ELISA), an enzyme is chemically attached (conjugated) to the labeled antibody. Like antibodies, enzymes are proteins that bind to specific targets, but enzymes also catalyze specific reactions. The starting material for an enzyme-catalyzed reaction is called a substrate. Enzyme labels, with the appropriate substrate, can be used to generate color or create fluorescent or luminescent end products, which can be readily measured by optical and electronic equipment. Each molecule of enzyme can convert many molecules of substrate, providing a sensitive signal generation system (Wild, 2013). EMIT or Enzyme multiplied immunoassay technique is a homogeneous immunoassay method for qualitative and quantitative determination of drugs and certain proteins in serum and urine. The most widely used applications for EMIT are for therapeutic drug monitoring (serum) and as a primary screen for abused drugs and their metabolites (urine). Unlike ELISA, EMIT assays were developed in such a way as to not require a separation of bound component. Thus, if a high concentration of sample analyte is present, this sample analyte will bind a large portion of antibodies leaving a large portion of the analyte-bound enzymes free in solution. Conversely, if a low concentration of sample analyte is present, this small concentration will bind only a small portion of the antibodies, leaving a large portion of the antibodies to bind the analyte-bound enzymes and deactivate them (Wild, 2013).

There are important advantages to immunoassay (IA) for drug testing in serum and urine. For testing that takes place within a pain management setting, immunoassay testing exhibits high

levels of agreement for cocaine and other illicit drugs (when compared to results from confirmatory assays), and overall adequate sensitivity but at the expense of decreased specificity. Furthermore, point-of-care (POC) devices provide a quick and inexpensive way to acquire initial patient insight while instrument-based IA affords increased specificity and semi-quantitative data results (Nafziger & Bertino Jr, 2009). However, immunoassays are subject to interference that may produce both false-positive and false-negative results (Dasgupta & Ebooks Corporation, 2012). An example of these limitations can be seen in urine drug testing for chronic pain patients; enzyme immunoassay (EIA) drug profiles do not have proper cutoff levels to allow for detection of small quantities of opioids. Other EIA profiles cannot detect certain parent drugs nor their metabolites (i.e. semi-synthetic and synthetic opioids). In addition, individual drugs within a class may not be identified nor differentiated (McBane & Weigle, 2010). In two separate studies, Pesce & Mikel et al. (2012) reported on the limitations of EIA UDT, first in a diagnostic accuracy (DA) study where they found false negative rates of 28% and 50% for benzodiazepine and cocaine respectively, and on a second DA study for benzodiazepines only, where they reported false negative rates of 20% (Mikel, Pesce, Rosenthal, & West, 2012; A. J. Pesce, Mikel, Rosenthal, & West, 2012).

2.6.2.2 Definitive Testing

There are a number of confirmatory methodologies for the quantification of drugs of abuse including but not limited to: (1) gas chromatography (GC), (2) liquid chromatography (LC), (3) GC/mass spectrometry (GC/MS), (4) LC coupled to MS (LC/MS), (5) GC with tandem MS (GC/MS/MS), and LC with tandem MS (LC/MS/MS) (Center for Substance Abuse Treatment, 2012).

Chromatography is a process by which the components of a mixture are separated by differential distribution between a mobile phase and a stationary phase. Components with greater

distribution into the stationary phase are retained and move through the system more slowly (Burtis, Ashwood, Bruns, & Tietz, 2012). In liquid column chromatography (figure 3) (LC and GC belong to the column chromatography category as opposed to planar chromatography), a sample injected into the mobile phase travels through a column that is packed with a stationary phase composed of irregularly or spherically shaped particles, a porous monolithic layer, or a porous membrane (Burtis et al., 2012).

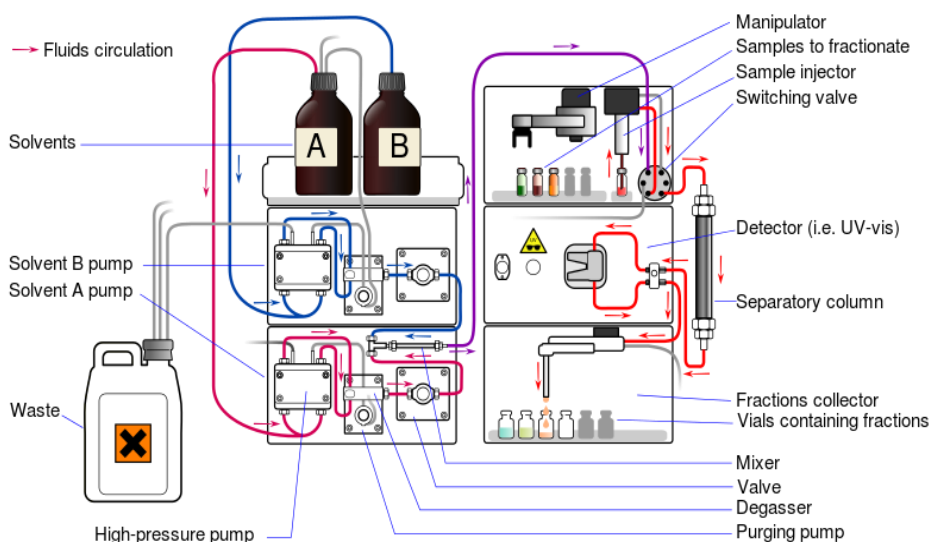


Figure 3. LC setup diagram. File used under the Creative Commons Attribution-Share Alike 3.0.

As the mixture of sample, matrix and solvents (mobile phase) moves forward, compounds with strong interactions with the stationary phase will exhibit longer retention times and therefore will elute in a different order of time (Fanali, Haddad, Lloyd, Poole, & Schoenmakers, 2013; Snyder, Kirkland, & Dolan, 2010; Niessen, 2006). Figure 4 depicts this process.

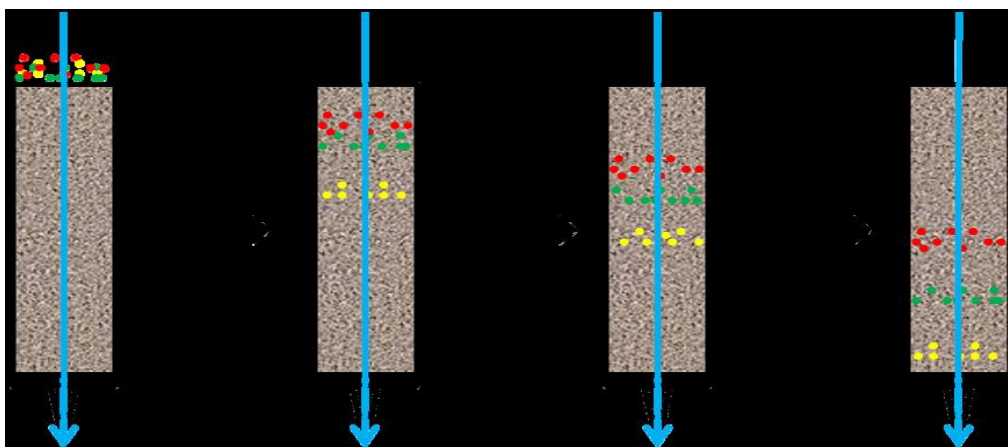


Figure 4. Chromatography column depicting separation of a complex matrix. From left to right, Multiple compounds species (different colored dots) separate by differential affinity to stationary phase (gray) and elute from column by different order of time.

LC employs the following separation techniques: Normal phase LC (polar stationary phase, and a non-polar mobile phase), Reverse phase LC (opposite to normal phase LC, utilizes non-polar stationary phase and polar mobile phase), Ion-pairing LC (performed on both normal and reverse phase LC when analyte is relatively polar and hard to be retained. “counter-ion” used for pairing), and Ion-exchange LC (stationary phase presenting ionizable groups that attract ions with opposite charge through electrostatic interaction) (Fanali et al., 2013; Snyder et al., 2010, Niessen, 2006;).

Mass spectrometry (MS) is a technique that identifies molecules by their mass to charge (m/z) ratio. In MS, the sample containing the analyte is nebulized into an ion source; then, together with the vaporized particles of other species in the sample it is ionized in the gas phase through an ionization mechanism (i.e. electro spray ionization). The ions in the sample then enter an electromagnetic field, the mass analyzer or mass filter, and get separated based on their m/z

ratios. In the final stage, the separated ions are amplified by a detector (electron multiplier) and the collection of their ion signals compose the mass spectrum (Burtis et al., 2012; Mondello, 2011; Niessen, 2006). The most common techniques for MS ion source ionization include: chemical ionization (CI), electron impact (EI), electron spray ionization (ESI), and matrix-assisted laser desorption ionization (MALDI). In tandem mass spectrometry (MS/MS), mass spectra for both precursor (before fractioning by gas induced dissociation) and product ions (after fractioning) is obtained in separate mass filters (Figure 5). m/z data from precursor and product ions create a transition, a set masses specific to an analyte of interest (Hammett-Stabler & Cotten, 2012).

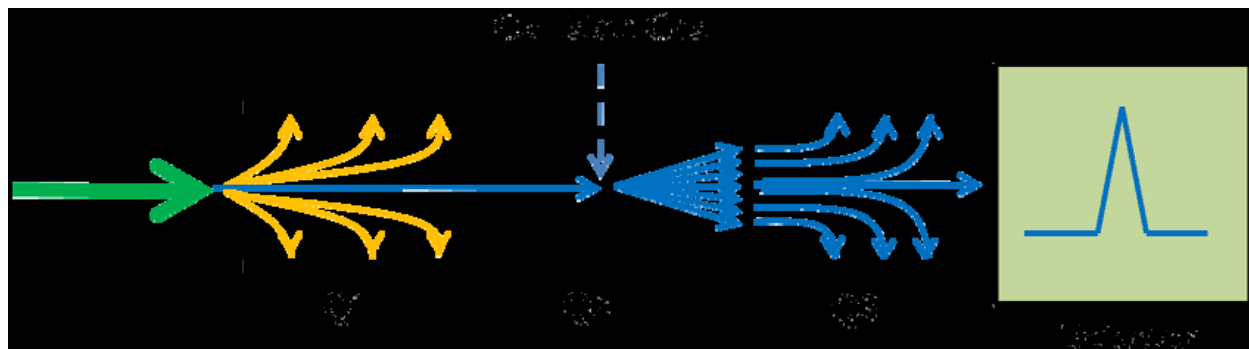


Figure 5. Configuration of triple quadrupole MS. Tandem MS: 2 separate mass filters separated by a gas collision cell. Curved yellow arrows represent filtered compounds in first mass filter. Straight horizontal arrows represent selected precursor and product ions, respectively. Vertical dotted arrow indicates the point where collision-induce dissociation of precursor ion takes place. Curved blue arrows represent filtered compounds in second mass filter.

While both LC-MS/MS and GC-MS provide great capabilities for identification and quantitation of analytes (both offer enhanced selectivity (specificity) and sensitivity compared to

other essays), LC-MS/MS offers advantages that are better suited for drugs of abuse testing (Mikel et al., 2010).

These include:

- The ability to discriminate a larger number of drugs in each test run.
- The requirement of a very small amount of urine specimen (as little as 25 microliters, or one drop).
- The use of samples that are neither derivatized nor extracted.
- The capability to analyze hundreds of urine specimens per day on a single mass spectrometer.
- Through advances automated sample handling and bar coding, allowing for the accurate processing of thousands of samples per day. This method of analysis can provide results more rapidly than GC-MS.
- Can accommodate non-volatile compounds (A. Pesce et al., 2011).
- Can accommodate highly polar, high molecular-weight, or thermally labile compounds (Marquet, 2012).
- May offer improved specificity and lower limits of detection when compared to other chromatographic methods (Dasgupta & Ebooks Corporation, 2012).

2.7 Summary

The purpose of the literature review in this study was to identify and summarize relevant scientific literature that dealt with the topics of genetically-induced opioid metabolism (OMS), its impact on medication effectiveness to relieve pain, and further associations to ADRB. It was also an opportunity to offer more in-depth descriptions of the main bioanalytical methodologies used

to generate the data for the study. The literature search portion focused on identifying available evidence that associated opioid metabolism to adverse drug-related behaviors (misuse, abuse and diversion). The initial alternative hypothesis proposed that an association between variant opioid metabolism and therapeutic failure and/toxicity would lead to the association between variant opioid metabolism and aberrant drug-related behaviors, but the literature review provided no conclusive evidence to support this association. Nevertheless, it did reinforce the link between OMS and medication response by findings of a significant relationship between variant CYP2D6 metabolizer status and response to opioid analgesic medication, which strengthened the resolve to test further associations with ADRB.

The evidence identified in this review made strong correlations between genetic makeup and the way in which different individuals experience pain relief when taking an opioid drug. This connection validated what many patients had been communicating to their providers for many years. It was vindication to them as we now understand that inter-individual variation in the perception of pain and pain mitigation has a legitimate genetic component. In the context of the present study, this finding took the form of a metabolizing enzyme (CYP2D6) whose genetics-dependent variability influences the effectiveness of opioid drugs on pain relief. The evidence presented here made a compelling argument for this association. Several of the reviewed articles further contributed to the argument by reporting that both poor and rapid (variant) opioid metabolism resulted in either low or no pain relief, ADR from toxicity, or both, therapeutic failure and toxicity. However, the literature search produced no evidence linking therapeutic failure/toxicity to ADRB, nor evidence for the association between opioid metabolism (OMS) and ADRB, the main focus of the review. It was therefore appropriate that these potential associations

be explored and tested to increase our understanding of the factors that lead NMCPD on COT to patterns of drug misuse and abuse.

CHAPTER 3

METHODS

3.1 Study Design

A retrospective cohort study design was used to test the association between opioid metabolism and ADRB. Records from an assembled (convenience) cohort of NMCCP on COT were reviewed to retrospectively ascertain opioid metabolizer status and ADRB characteristics. Retrospective categorical data (PGT/UDT and other non-PHI chart information) retrieved from a Pain Management Clinic's electronic medical records system was cross-tabulated and evaluated with the Pearson Chi-square test for difference in proportions. There was no need for the Fisher's Exact test and/or Likelihood Ratio Chi-Square test as all expected cell counts were > 5 . Logistic regression was used to measure the contribution of confounders and to judge the presence of effect modifiers (sex and race/ethnicity).

3.1.1 Design Justification and Applicability

Observational cohort studies involve groups of individuals who usually meet a set of inclusion criteria but that differ by either possessing or not possessing a specific risk factor (Sullivan, 2012). In general, individuals in a cohort study are followed in time to assess whether a risk factor can be associated to an outcome such as a disease or a behavior (Sullivan, 2012). Cohort studies can be further divided into prospective and retrospective studies, that is, by either looking forward in time (ascertaining risk status and outcome prospectively) or looking back in time (ascertaining risk status and outcome retrospectively) (Sullivan, 2012).

Observation of NMCPP on COT in a an El Paso Pain Management Clinic seemed to suggest that some patients experiencing adverse reactions could have been more inclined to misuse their prescribed medication, abuse an illicit or engage in other aberrant behaviors to counter the effects those adverse events. This informed the belief that variant OMS, a significant contributor to therapeutic failure and toxicity, could be associated with incident ADRB. The clinic's protocol for the prescription of opioids included several measures to ensure safe drug administration and to minimize the risk of addiction. Data initially generated as standard of care from two of these measures, drug testing results and genetic testing results, was used to test the hypotheses in this study. Since the data had already been collected on a relatively homogeneous group of patients, a retrospective cohort study design was chosen. The association between risk factor (OMS) and outcome (ADRB) was then evaluated with statistical testing.

Retrospective cohort studies can be affected by confounding and effect modification (Creswell, 2009; Sullivan, 2012). Experience with patient behavior at the pain clinic suggested that race/ethnicity and sex played an important role in ADRB. To counteract these effects, a multivariate method (binary logistic regression) was used to estimate the association between opioid metabolizer status (OMS) and ADRB adjusting for the impact of these confounding variables (Hosmer, Lemeshow, & Sturdivant, 2013; Sullivan, 2012).

3.1.2 Variables

The study included two main variables for its primary hypothesis. There were three others deemed to operate as mediating, confounding, and effect modifying variables. The main variables consisted of opioid metabolizer status (OMS) and aberrant drug-related behaviors (ADRB), which were considered a risk factor variable and an outcome variable, respectively. The potential

mediating and confounding/effect modifying variables consisted of therapeutic failure/toxicity, race/ethnicity, and sex, respectively.

1. OMS – the categorization of a patient’s metabolizing capability to pharmacokinetically biotransform a lipophilic opioid parent drug to a more water-soluble metabolite for excretion from the body. It is achieved through oxidation reduction and hydrolysis in phase I metabolism, and conjugation reactions in phase II metabolism. (Trescot, 2013; Trescot et al., 2008; Fishbain et al., 2004). In this study, emphasis was placed on the liver super family of microsomal enzymes cytochrome P-450 (CYP450), specifically CYP2D6, responsible for catalyzing phase I drug metabolism of substrate opioids such as codeine, hydrocodone, oxycodone and tramadol (Trescot et al., 2008). This categorical variable was treated as a risk factor with the following levels: 1) UM – ultra-rapid metabolizers (multiple copies of the CYP2D6 gene); 2) EM – extensive metabolizers (a single wild-type copy of the CYP2D6 gene); 3) IM – intermediate metabolizers (1 normal and 1 reduced allele, or 2 partially deficient alleles of the CYP2D6 gene); and 4) PM – poor metabolizers (2 mutant alleles of the CYP2D6 gene leading to no detectable enzyme activity).

2. ADRB – Patient misuse, abuse, overuse and diversion of licit and illicit drugs, as evidenced on: urine toxicological testing by a finding of a positive illicit substance (i.e. metabolites of marijuana, cocaine and heroin), positive non-prescribed medication (i.e. hydrocodone/hydromorphone), negative expected prescribed medication, and/or positive adulteration/validity testing (i.e. pH, creatinine, oxidants); inter and intra-state prescription monitoring program databases, which uncover evidence of doctor shopping; professional clinical and psychological evaluation; self-admission, and evidence of dose escalation, amongst other criteria (Peppin et al., 2012; Christo et al., 2011; Pergolizzi et al., 2010; Chou et al., 2009; L. R. Webster & Webster, 2005). In this study, ADRB was treated as a binary outcome variable with

the following levels: NEGATIVE for ADRB as determined in objective bioanalytical confirmatory drug testing (must have been NEGATIVE for all four statistics that comprised each level: 1) presence of an illicit (PI), 2) presence of non-prescribed medication (PNP), 3) absence of prescribed medication (AP), and 4) evidence of adulteration (EA)) and a consistent PDMP; and POSITIVE, which was deemed as such if at least one of these statistics was positive or the PDMP was inconsistent.

3. Therapeutic Failure/Toxicity – Therapeutic failure referred to the failure of chronic opioid therapy to provide patients with meaningful reductions in pain. Often as the result of poor metabolic conversion of a prodrug into its bioactive metabolite (Trescot & Faynboym, 2014; Gaedigk, 2013). Toxicity related to the group of opioid adverse drug reactions (such as constipation and respiratory depression) that chronic pain patients experienced when the concentration of a bioactive metabolite exceeded therapeutic levels – the result of increased metabolic enzyme activity. This mediating dichotomous variable was to be accounted for in a logistic regression model but was instead removed due to the very few records in our collected sample that included the Likert scale and ADR information.

4. Race/ethnicity – categories included: Asian, Black, Hispanic, and White (National Institutes of Health, 2015). Based on the observations of patients at the pain clinic, it was reasonable to suggest that race/ethnicity was a potential confounder and/or effect modifier, and thus, had to be accounted for in a logistic regression model.

5. Sex – consisted of two levels: Male and Female. As with race/ethnicity, empirical observations pointed to a confounder and/or effect modifier role in the relationship between the main study variables. Therefore, Sex was also be accounted for in a logistic regression model.

3.2 Setting, Population and Sample

The setting for the study was a pain management clinic located in El Paso, Texas. Being one of the largest in the region, the clinic saw an annual volume of approximately 15,000 patients with non-malignant chronic pain. The main two treatment modalities offered at this clinic were pharmacotherapy with adjuvant analgesics/opioid therapy; and interventional pain management procedures such as epidural steroid injections, nerve blocks, facet joint injections, radiofrequency nerve ablations, kyphoplasty, and spinal cord stimulators. Some of the conditions treated here included the following: low back pain, radiating leg pain, knee pain, extremity pain, pelvic pain, facial pain, acute or chronic back pain, back pain secondary to spondylosis/osteoarthritis, pain from compression fractures, as well as acute/chronic musculoskeletal injuries (EPOSG, 2017).

The study population consisted of all the adult patients from an El Paso, Texas Pain Management Clinic suffering from any kind of chronic pain of non-malignant origin (as indicated in the ICD-10 diagnosis code (World Health Organization, 2015) or the provider's progress note in the patient's chart), and who had, as treatment modality, been prescribed any opioid substrate of the CYP2D6 metabolizing enzyme (i.e. morphine, hydrocodone, etc.) on a chronic basis (as indicated on the provider's progress note in the patient's chart). This patient population encompassed individuals of different race/ethnicities and sex.

The sample subset of the preceding population used in the study consisted of a non-probability convenience sample of NMCP on COT who meet the following inclusion criteria:

- Patients of the clinic, male or female, of any race/ethnicity who are at least 18 years of age, and;
- had been diagnosed with any kind of non-malignant chronic pain,

- had been prescribed COT with one or several substrates of the CYP2D6 metabolizing enzyme,
- had signed an opioid treatment agreement,
- had Texas PDMP (Texas State Board of Pharmacy, 2017) data retrieved recently,
- had risk assessment/stratification performed with the SOAPP-R (Inflexxion, 2015), and;
- have had UDT/PGT performed in association with the COT regimen.

3.3 Sampling Procedures

The process to identify medical records that met inclusion criteria turned out to be unexpectedly challenging and required a revision of strategy. Upon consultation with the clinic's pain physicians, Effect Size (ES) was revised to 0.13-0.15 (expected difference in proportions), which allowed for a reduction in sample size to a target of 70 to 110 patient records for each cohort while retaining critical values for significance and power ($\alpha = 0.05$, $1-\beta = 0.80$). One hundred and eighty-six total patient records met all stipulated requirements ($n = 186$). However, due to the extraordinary variability encountered in time elapsed to follow up office visits and drug testing (7 days to 3+ years), the initial protocol for identification of patient records with cohort matching inter-visit times was eliminated. Furthermore, only the first visit (baseline) ended up having enough collected data to competently evaluate incident ADRB and correlate it to the risk factors included in the study. The second visit dataset had a considerable amount of missing UDT paired values ($n = 69$); this eliminated the possibility of evaluating the study's proposed associations for the specified effect sizes at the second visit and was not used for any of the inferences drawn. However, second visit statistical testing results, though suboptimal, were still compared to those

of the initial visit to subjectively assess differences in patterns of opioid misuse, or changes in the number of ADRB between these two visits.

3.4 Instrumentation

The biometric data included in the UDT and PGT reports was analyzed by highly specific and sensitive validated analytical methods. Testing results to determine ADRB (positive/negative for PI, PNP, AP & EA) were produced by analyzing a biological matrix (urine) in specialized instrumentation at the toxicology laboratory of the clinic in the study, and at the laboratory of Alere Toxicology, a partner of the pain clinic (Alere, 2017). For this study, an Agilent Technologies 6420 Triple Quad Liquid Chromatography Tandem Mass Spectrometry instrument or LC-MS/MS (Agilent Technologies, 2013) was used to test for the presence of parent compounds and metabolites of opioid medication and illicit substances, as well as for evidence of specimen adulteration. Testing to evaluate OMS was conducted by several partner laboratories on cheek swabs collected at the pain clinic. DNA testing methodologies, such as DNA extraction, polymerase chain reaction (PCR), real-time PCR, PCR arrays, and PCR product electrophoresis were used in instrumentation from various manufacturers to isolate genomic DNA, amplify it, and analyze for deletions, duplications, and polymorphisms in the CYP2D6 cytochrome gene (AltheaDx, 2017; AssureX Health, 2017; Millennium Health, 2017; PinPoint Molecular, 2017; Proove Biosciences, 2017; Vantari Genetics, 2017; Dasgupta, 2007).

As advanced laboratory-developed methods (LDT), UDT and PGT methodologies underwent extensive validation procedures that verify analytical performance and ensure that testing quality is up to par for clinical testing in human subjects (CLSI, 2014; U.S. Food and Drug Administration (FDA) & Center for Drug Evaluation and Research (CDER)). LDTs must be reliable, valid and robust. A detailed multi-study method development and validation protocol was

implemented to achieve these characteristics in the LC-MS/MS instrument that was used in the study. This protocol involved studies that evaluated internal standard selection, sample preparation and extraction; development and optimization of ion transitions; determination of mobile phases and chromatography columns; verification of specificity, linearity, accuracy, precision (reproducibility), reportable range, quantitation limits, and detection limits; evaluation of interfering substances, matrix effects, ion suppression, and carryover; specimen stability; hydrolysis optimization of glucuronide conjugates; and assessment of quality control material (CLSI, 2014; U.S. Department of Health and Human Services U.S. Food and Drug Administration (FDA) & Center for Drug Evaluation and Research (CDER)). There was no validation protocol available for the methodologies from partner laboratories since LDTs are proprietary. However, they all had to meet CLIA 88' stringent criteria for LDTs in a high-complexity CLIA laboratory setting, which, upholds their testing methods' validity and reliability (COLA Accreditation Program, 2016).

3.5 Data Collection

Patient medical record retrieval began on July 20 of 2018 and ended in July 27 of 2018. All records corresponded to dates of service extending from January 2016 through March 2018. The retrieval process entailed the collection of basic, non-PHI, demographic information (such as Age, Sex and Race/Ethnicity) supplemented with a special study identifier ("Study ID"); initial visit information (baseline pain scale, treatment agreement/informed consent for COT, baseline risk assessment, baseline PMP, PGT, baseline UDT, and baseline CYP2D6 drug substrates and inhibitors), subsequent visit information (most items from initial visit but no PGT and treatment agreement/informed consent); and if available, information from a third visit (same information as previous visit). There was a two-fold rationale for collecting data on initial and subsequent visits:

1) the patient would have had to have received a prescription for opioid medication on their initial office visit in order to detect a legitimate positive opioid drug test results at these subsequent visits. This was required to inform ADRB assessments. However, upon review of the data, it was made clear that almost all patients coming in to their first visit were already on COT; and 2) there was evidence that repeated drug testing served as a deterrent for abuse-prone patients (A. J. Pesce et al., 2011). A deterrent-induced reduction in UDT positivity rates had the potential to confound the relationship between incident ADRB and OMS and merited further exploration across separate office visits. Additionally, attempts were made to retrieve only those patient records that had, for both OMS cohorts (normal and variant), similar time periods elapsed in-between office visits to control for artificial confounding of UDT positivity rates. Yet, significantly high variability in these inter-visit times made that approach extremely impractical.

3.5.1 Collection of Patient Urine Drug Testing Results

The Principal Investigator (PI) and his professional assistant (took CITI training for the protection of human participants) retrieved approximately 70-100 individual drug testing patient records for each cohort (n = 186) from either the clinic's EMR: Prime Suite (Greenway Health, 2017), the clinic's toxicology laboratory cloud-based information system (LIS): AxisLabsDX (Alternative Biomedical Solutions, 2017), and/or the Alere Toxicology web portal: Alere Datalink (Alere, 2017). Only pertinent variable data (opioid, illicit and adulterant results indicating PI, PNP, AP & EA) along a non-PHI unifying identifier was extracted to an excel database.

3.5.2 Collection of Patient Pharmacogenetic Testing Results

The same procedure was applied to the retrieval of genetic testing data. However, in addition to the sources mentioned above, data was also retrieved from the Millennium Health,

AltheaDx, AssureX, Vantari Genetics, PinPoint Molecular and Proove Biosciences web portals (AltheaDx, 2017; AssureX Health, 2017; Millennium Health, 2017; PinPoint Molecular, 2017; Proove Biosciences, 2017; Vantari Genetics, 2017). Pertinent variable data (CYP2D6 metabolizer status indicative of PM, IM, EM and UM) along non-PHI unifying identifier was extracted to an excel database.

3.5.3 Collection of Patient Medication History and Demographic Information

Patient demographics to include age, sex, race/ethnicity; and other non-PHI relevant data, such as date of service, diagnosis codes, and relevant instances of opioid medication prescription were retrieved from the clinic's own EMR: Prime Suite (Greenway Health, 2017), and extracted to an excel database.

3.6 Data Analysis

3.6.1 Data Preparation

The PI was responsible for manipulating the data extracted to the excel database. Patient data from various sources was consolidated for each patient record with the aid of unifying identifiers. To ensure confidentiality, no protected health information (PHI) identifying individual patients (i.e. name, date of birth) was retrieved and added to the study's database spreadsheet. After subsequent cleaning of variable data, secondary variables derived from primary data were created to properly address the research questions and to further conceal personal identifiable information. Such variables include: Outcome dichotomous variable: ADRB, with levels NEGATIVE/POSITIVE; derived from confirmatory drug testing statistics PI, PNP, AP and EA, that were themselves derived from individual drug/adulterant testing result reports; and PDMP reports. Categorical risk variable: OMS, with four initial categories: UM, EM, IM and PM;

transformed to a dichotomous risk variable, with levels NORMAL/VARIANT. EM phenotype classified as normal OMS, and UM/PM/IM phenotypes classified as variant OMS. Transformation was made to ensure adequate sample size and sampling ratio.

3.6.2 Statistical Analyses

The PI conducted all the statistical analyses required to address the research questions of the study. In the first analysis, summary statistics were calculated on all the relevant variables of the study and presented in frequency distribution tables (Sullivan, 2012). Next, hypothesis testing was used to evaluate associations between variables and answer the study's research questions.

I. The primary hypotheses tested whether a statistically significant difference existed in the proportions of normal and variant metabolizers that engage in ADRB in a group of NMCCP on COT from an El Paso, Texas pain management clinic (Sullivan, 2012), where:

H₀: There is no statistically significant difference in the proportion of normal and variant metabolizers that engage in ADRB.

H₁: There is a statistically significant difference in the proportion of normal and variant metabolizers that engage in ADRB.

The test statistic used was χ^2 (Chi-squared) test for difference in proportions at $\alpha = .05$ (Sullivan, 2012). The cross-tabulation of risk and outcome variables, calculation of expected frequencies, and computation of test statistic and odds ratios were performed in SPSS Statistics, Version 24 (IBM Corp., 2016).

II. The secondary hypotheses with race/ethnicity as the risk variable tested whether a statistically significant difference existed in the proportions of White and Hispanic patients that

engage in ADRB in a group of NMCPD on COT from an El Paso, Texas pain management clinic (Sullivan, 2012), where:

H₀: There is no statistically significant difference in the proportion of White and Hispanic patients that engage in ADRB.

H₁: There is a statistically significant difference in the proportion of White and Hispanic patients that engage in ADRB.

The test statistic used was χ^2 (Chi-squared) *test for difference in proportions* at $\alpha = .05$ (Sullivan, 2012). The cross-tabulation of risk and outcome variables, calculation of expected frequencies, and computation of test statistic and odds ratios were performed in SPSS Statistics, Version 24 (IBM Corp., 2016).

III. The last set of secondary hypotheses with sex as the risk variable tested whether a statistically significant difference existed in the proportions of Males and Females that engage in ADRB in a group of NMCPD on COT from an El Paso, Texas pain management clinic (Sullivan, 2012), where:

H₀: There is no statistically significant difference in the proportion of Males and Females that engage in ADRB.

H₁: There is a statistically significant difference in the proportion of Males and Females that engage in ADRB.

The test statistic used was χ^2 (Chi-squared) *test for difference in proportions* at $\alpha = .05$ (Sullivan, 2012). The cross-tabulation of risk and outcome variables, calculation of expected frequencies, and computation of test statistic and odds ratios were performed in SPSS Statistics, Version 24 (IBM Corp., 2016).

IV. Stepwise binary logistic regression analyses were conducted to account for confounding and effect modification of the relationship between primary variables OMS and ADRB by suspect variables “Sex” and “Race/Ethnicity”. Suspect mediating variable “Therapeutic failure/Toxicity” was ultimately excluded from the study due to insufficient Likert pain scale records and inconsistent provider progress notes indicative of adverse drug reactions. The computation of regression statistics, odds ratios and confidence intervals was performed in SPSS Statistics, Version 24 (IBM Corp., 201612).

3.7 Protection of Research Subjects

As a retrospective cohort study with no human participants/subjects, the risk of adverse events was significantly low. Indeed, in its policy for protection of human research subjects, the department of Health and Human Services stipulates that “unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects includes the collection or study of existing data, documents and records are exempt from requiring internal review board (IRB) approval” (U.S. Department of Health & Human Services, 2009). However, an IRB exemption request application was submitted to UTEP’s IRB office to certify exempt status and obtain explicit authorization to conduct the study. In addition, written authorization from the clinic’s chief medical officer was obtained in order to access and retrieve patient record data from the EMR. Even if exempt from IRB approval, patient confidentiality was rigorously maintained throughout all phases of data collection and data analysis. All non-PHI patient record data retrieved was “manually deidentified” by elimination of identifiers that in conjunction with other information could be traced back to an patient, and, “statistically de-identified” by only presenting aggregate data and summary/inferential statistics. Only the PI and his professional assistant had access to the dataset. Data manipulation and statistical analyses were only performed on password-

protected devices (PPD). Aside from the PI's secured portable device, data also resided on PPDs at the clinic's toxicology laboratory where access is highly restricted.

CHAPTER 4

RESULTS

The purpose of this study was to lay the scientific foundation for the creation of a novel biometric tool based on genetic information about the polymorphic expression of CYP2D6 for the prediction of ADRB among NMCPP on COT. More specifically, the study's objective was to address the question of whether a statistically significant association existed between opioid metabolism, as determined by phenotypic CYP2D6 expression (OMS), and aberrant drug-related behaviors among non-malignant chronic pain patients. It also sought to address other research questions evaluating the association of sex and race/ethnicity with ADRB. To test the study's hypotheses, retrospective categorical data from an assembled cohort of NMCPP on COT was cross-tabulated and analyzed with the Pearson Chi-square test for difference in proportions. Confounding and effect modification were dealt with by the inclusion of suspect variables in a logistic regression model.

4.1 Descriptive Statistics

The median age in the sample population was 54 years old with an age range from 20 to 87 years old. Age data appears to be slightly skewed towards older age. Table 2 shows Age descriptive statistics.

Table 2. Descriptive statistics for Age.

Age	
N	186
Mean	53.39
Median	54.00
Std. Deviation	14.143
Range	67
Minimum	20
Maximum	87

N = total sample size.

There were 104 (55.9%) females and 82 (44.1%) males from four race/ethnicity categories: 4 (2.2%) Asian, 10 (5.4%) Black, 103 (55.4%) Hispanic and 69 (37.1%) White. There were more Hispanics than all other race/ethnicities combined (55% vs. 44.6%, respectively). Due to very low representation (and to prevent bias) Asian and Black patient records were excluded from inferential statistics. Tables 3 and 4 present frequency distributions and percents for Sex and Race/Ethnicity.

Table 3. Frequency distribution for Sex

Sex				
	Frequency	Percent	Valid Percent	Cumulative Percent
Female	104	55.9	55.9	55.9
Male	82	44.1	44.1	100.0
Total	186	100.0	100.0	

Table 4. Frequency distribution for Race/Ethnicity

Race/Ethnicity				
	Frequency	Percent	Valid Percent	Cumulative Percent
Asian	4	2.2	2.2	2.2
Black	10	5.4	5.4	7.5
Hispanic	103	55.4	55.4	62.9
White	69	37.1	37.1	100.0
Total	186	100.0	100.0	

Sample frequency distribution for CYP2D6 phenotype categories was as follows: 101 (54.3%) EM's, 42 (22.6%) IM's, 24 (12.9%) PM's and 19 (10.2%) UM's. As a convenience sample, frequency distributions for variant OMS (PM, IM & UM) were much higher than in the patient population where the sample was draw from (See Table 5).

Table 5. Frequency distribution for CYP2D6 Phenotype

CYP2D6 Phenotype				
	Frequency	Percent	Valid Percent	Cumulative Percent
Extensive Metabolizer	101	54.3	54.3	54.3
Intermediate Metabolizer	42	22.6	22.6	76.9
Poor Metabolizer	24	12.9	12.9	89.8
Ultrarapid Metabolizer	19	10.2	10.2	100.0
Total	186	100.0	100.0	

4.2 Inferential Statistics

4.2.1 Opioid Metabolizer Status and Aberrant Drug Related Behaviors

A χ^2 (Pearson Chi-squared) test for difference in proportions at $\alpha = 0.05$ was conducted to ascertain whether differences in proportions between OMS category levels predicted ADRB incidence (H_1). To address discrepancies in sample size for each of the CYP2D6 metabolizer categories, OMS was dichotomized into Normal Metabolizer (NM = 54.3%), which included the EM phenotype, and Variant Metabolizer (VM = 45.7%), which included the other three phenotypes: PM, IM and UM. Table 6 shows the frequency distribution of the 2 independent samples with a sampling ratio (κ) that is closer to 1 after OMS was dichotomized.

Table 6. Reorganization of CYP2D6 Phenotype (OMS) from categorical to binary.

CYP2D6 Phenotype				
	Frequency	Percent	Valid Percent	Cumulative Percent
Normal Metabolizer (EM)	101	54.3	54.3	54.3
Variant Metabolizer (PM, IM or UM)	85	45.7	45.7	100.0
Total	186	100.0	100.0	

The crosstabulation of OMS and baseline ADRB revealed very little discrepancy in incident ADRB by level of OMS variable (NM = 32.7% vs. VM = 35.3%). Total ADRB incidence was 33.9%. (Table 7 depicts this and other crosstab data).

Table 7. Crosstabulation of OMS and ADRB (baseline)

CYP2D6 Phenotype (OMS) * ADRB (baseline)					
			ADRB (baseline)		
			Not Present	Present	Total
CYP2D6 Phenotype (OMS)	Normal Metabolizer (EM)	Count	68	33	101
		Expected Count	66.8	34.2	101.0
		% within CYP2D6 NM	67.3%	32.7%	100.0%
	Variant Metabolizer (PM, IM or UM)	Count	55	30	85
		Expected Count	56.2	28.8	85.0
		% within CYP2D6 VM	64.7%	35.3%	100.0%
Total		Count	123	63	186
		Expected Count	123.0	63.0	186.0
		% within CYP2D6 EM & VM	66.1%	33.9%	100.0%

There was no statistically significant difference in proportions of incident ADRB (baseline) between normal and variant opioid metabolizers [$\chi^2 = 0.142$, $p = 0.707$, $\alpha = 0.05$]. Further substantiation of this finding was offered by a 95% confidence interval for the odds of ADRB in NM vs. that of VM which includes 1 [OR = 0.926, 95% CI (.620, 1.383)]. (Please see Table 8 for Chi-squared statistics).

Table 8. Chi-squared statistics for OMS *ADRB (baseline)

CYP2D6 Phenotype (OMS) * ADRB (baseline)					
	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	0.142^a	1	0.707		
Continuity Correction ^b	0.049	1	0.825		
Likelihood Ratio	0.141	1	0.707		
Fisher's Exact Test				0.757	0.412
Linear-by-Linear Association	0.141	1	0.708		
N of Valid Cases	186				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 28.79.

b. Computed only for a 2x2 table

Figure 6 below conveys the similarities of the relative proportions of incident ABDR between NM and VM.

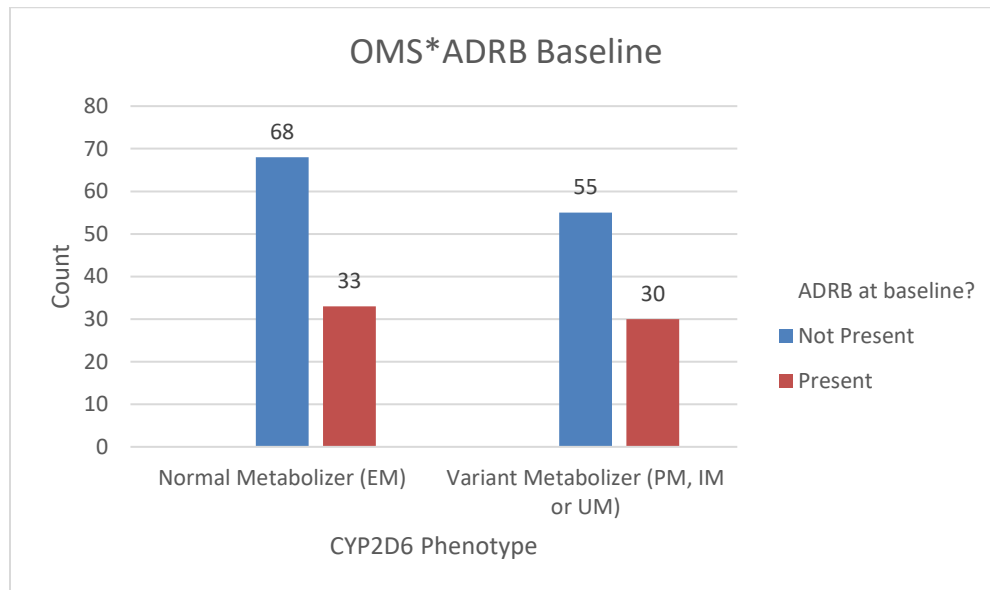


Figure 6. Bar chart depicting relative proportions of incident ABDR between NM and VM. Normal metabolizer (NM) category is comprised of extensive metabolizers (EM), whereas, variant metabolizer (VM) includes poor metabolizers (PM), intermediate metabolizers (IM), and ultra-rapid metabolizers (UM).

The information gathered from the second office visit was missing a substantial amount of UDT data points, which rendered many patient records unusable. Sample size went down to $n = 69$. The sampling ratio (κ) remained close to 1 with each independent sample containing approximately 35 patient records. Retaining critical values for significance and power ($\alpha = 0.05$, $1-\beta = 0.80$) made the model significantly less sensitive to smaller ES and less suitable for robust statistical evaluation. Second visit distribution for incident ADRB by level of OMS was NM = 43.8% vs. VM = 45.9%. There was no statistically significant difference in proportions of incident ADRB (second visit) between normal and variant opioid metabolizers [$\chi^2 = 0.33$, $p = 0.855$, $\alpha = 0.05$]. Further substantiation of this finding would have been offered by a 95% confidence interval for the odds of ADRB in NM vs. VM that includes 1 [OR = 0.952, 95% CI (0.563, 1.611)]. Tables 9 and 10 show Chi-squared and Odds Ratio statistics.

Table 9. Chi-squared statistics for OMS *ADRB (second visit)

CYP2D6 Phenotype (OMS) * ADRB (Second visit)				
	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)
Pearson Chi-Square	0.033^a	1	0.855	
Continuity Correction ^b	0.000	1	1.000	
Likelihood Ratio	0.033	1	0.855	
Fisher's Exact Test				1.000
Linear-by-Linear Association	0.033	1	0.856	
N of Valid Cases	69			

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 14.38.

b. Computed only for a 2x2 table

Table 10. Odds ratio and 95% confidence intervals for OMS *ADRB (second visit)

OR and 95% CI for CYP2D6 Phenotype (OMS) * ADRB (Second visit)			
	Value	95% Confidence Interval	
		Lower	Upper
OR ADRB (2nd visit) = Present	0.952	0.563	1.611

The total percentage of incident ADRB (both OMS levels) increased significantly from first visit to the second visit, 33.9% vs 44.9%, respectively.

4.2.2 Sex and Aberrant Drug Related Behaviors

Crosstabs of Sex and ADRB (assessed on first and second patient visits) revealed patterns like those of OMS first and second visit data – slight incidence discrepancies between OMS categories and an incidence jump in ADRB from first to second visit. Incidences for ADRB, first and second visits, were as follows: (Male = 37.8% vs. Female = 30.8%) and (Male = 41.7% vs. Female = 48.5%), respectively. There was no statistically significant difference in proportions of incident ADRB (baseline and second visits) between males and Females [$\chi^2 = 1.013$, $p = 0.314$, $\alpha = 0.05$] [$\chi^2 = 0.323$, $p = 0.570$, $\alpha = 0.05$]. The 95% confidence interval for the odds of ADRB in Male vs. Female included 1 [OR = 1.229, 95% CI (0.823, 1.833)] and [OR = 0.859, 95% CI (0.510, 1.449)] for baseline and subsequent visits, respectively.

4.2.3 Race/Ethnicity and Aberrant Drug Related Behaviors

The Race/Ethnicity variable was dichotomized for inferential statistics by dropping two low representation levels: Asians and Blacks. The crosstabulation of Race/Ethnicity and ADRB (assessed on baseline and subsequent visits) followed previous ADRB incidence patterns. Incidence for ADRB, first and second visits, were as follows: (White = 36.2% vs. Hispanic = 33.0%) and (White = 44.0% vs. Hispanic = 45.0%), respectively. There was no statistically significant difference in proportions of incident ADRB (baseline and second visits) between Whites and Hispanics [$\chi^2 = 0.190, p = 0.663, \alpha = 0.05$] [$\chi^2 = 0.006, p = 0.937, \alpha = 0.05$]. The 95% confidence interval for the odds of ADRB in Whites vs. Hispanics included 1 [OR = 1.098, 95% CI (0.724, 1.665)] and [OR = 0.978, 95% CI (0.559, 1.711)] in baseline and subsequent visits, respectively.

4.2.4 Binary Logistic Regression for Confounding and Effect Modification

Stepwise binary logistic regression analyses were conducted to evaluate the relationship between OMS and ADRB while adjusting for suspect variables “Sex” and “Race/Ethnicity” individually and in combination. There was no statistically significant difference in the proportions of incident ADRB (baseline) between normal and variant opioid metabolizers after adjusting for Sex [(Sig.) $p = 0.682, \alpha = 0.05, \text{OR}[\text{Exp}(B)] = 0.880, 95\% \text{ CI } (0.478, 1.621)$]. There was no statistically significant difference in the proportions of incident ADRB (baseline) between normal and variant opioid metabolizers after adjusting for Race/Ethnicity [(Sig.) $p = 0.485, \alpha = 0.05, \text{OR}[\text{Exp}(B)] = 0.797, 95\% \text{ CI } (0.422, 1.506)$]. There was no statistically significant difference in the proportions of incident ADRB (baseline) between normal and variant opioid metabolizers after adjusting for both Sex and Race/Ethnicity [(Sig.) $p = 0.773, \alpha = 0.05, \text{OR}[\text{Exp}(B)] = 0.938, 95\%$

CI (0.608, 1.447)]. Table 11 presents the logistic regression statistics for the formal evaluation of confounding and effect modification.

Tables 11. Logistic regression coefficients and statistics.

Logistic Regression Statistics*ADRB (baseline)						
Step	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
OMS/SEX*ADRB (baseline)	-0.128	0.312	0.682	0.880	0.478	1.621
OMS/RACE*ADRB (baseline)	-0.227	0.325	0.485	0.797	0.422	1.506
OMS/RACE/SEX*ADRB (baseline)	-0.064	0.221	0.773	0.938	0.608	1.447

CHAPTER 5

DISCUSSION

Amid intensifying public concern for the devastating and very real effects that the misuse and abuse of opioids are having in our communities across the country; the so called “Opioid Crisis”, it is important to recognize that these are legitimate medications that help many people when prescribed and taken responsibly. Widespread “opiophobia”, though justified, may in some ways be contributing to the growing number of chronic pain patients who go untreated or undertreated as medical professionals stop making the option of these drugs available to them. Sometimes even out of fear for the very real threat of litigation associated with prescribing narcotics. Prescription opioid medication continues to play a crucial role in the treatment of non-malignant chronic pain. Reducing the likelihood of patients engaging in aberrant drug-related behaviors such as opioid misuse requires the implementation of proper risk assessment procedures for the safe and effective administration of these medications to those individuals who really need them most.

The aim of this study was to test for statistically significant associations between opioid metabolism and aberrant drug-related behaviors among non-malignant chronic pain patients. The information gathered from the study would have served as the theoretical foundation of a new tool for risk assessment that relies on objective biometric data. Currently, we largely base these assessments on information drawn from survey instruments such as the SOAPP-R and COMM (Inflexxion, 2015), which have the potential to be manipulated. This “improved” biometric tool would have allowed pain practitioners to make use of genotypic data to better predict which patients are at a greater risk of engaging in aberrant drug-related behaviors. Moreover, the data

generated by the study could also be feed into protocol algorithms, such as patient risk stratification, and incorporated into LIS Decision Support Systems.

The approach selected to meet the objectives of the study consisted of an evaluation of the relationship between opioid metabolism, as determined by phenotypic CYP2D6 expression (OMS), and aberrant drug-related behaviors (ADRB), in the population of interest. The specific research questions to be answered were the following:

1. Among non-malignant chronic pain patients on COT from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportions of normal and variant metabolizers that engage in aberrant drug-related behaviors?

This was the central question of the study. Previous experience at a pain clinic and discussions with providers informed the hypothesis that patients who are variant opioid metabolizers, in particular poor metabolizers, seemed more inclined and willing to misuse their medication or supplement with an illicit substance, when compared to normal metabolizers. Statistical analysis revealed there is no statistically significant association between OMS and ADRB. This answers the question, but not necessarily in the manner that was expected. In her review on the role that genetics play in opioid metabolism, Trescot and colleagues (2014) pointed out that the prevalence of variant CYP2D6 metabolism at its fringes (PM & UM) is around 17% in the general population (Trescot & Faynboym, 2014). That is almost a fifth of all Americans who could conceivably deal with therapeutic failure and/or toxicity at some point in their lifetime, and whom you could have expected to be at a higher risk of misusing narcotic substrates of CYP2D6. Yet, study data showed that this is clearly not the case with the clinic's variant metabolizers as they don't appear to misuse medication at comparably higher rates. The pain clinic where this study was performed has a similar prevalence of variant CYP2D6 metabolizers, 15% – 20%. We

frequently encounter patients who experience adverse drug reactions (who later test as variant metabolizers) that appear to misuse their opioid medication more often to counter those adverse events. However, the results from this study seem to again suggest that if that was in fact true (VMs misusing opioids more often), it happens just as often with normal metabolizers. An interesting finding of the study was that the incidence of ADRB was a lot higher than expected, 33.9% at baseline visit. This would mean that, irrespective of 2D6 metabolizer status, 1 out of every 3 patients in our sample population engaged in some kind of aberrant behavior. Perhaps the inclusion as ADRB of inconsistencies with prescribed medications, non-prescribed licit medications, and doctor shopping, in addition to positive illicit (all are just as clinically relevant in pain medicine), revealed a more accurate picture of the incidence of these undesirable behaviors among NMCPP, which may merit further exploration. Total ADRB incidence for the second visit was even higher than that of the first, however, the sample size on the second visit was very small ($n = 69$) due to missed UDT paired data. This makes inference from that data set highly unreliable and was not used in the study's conclusions even though the statistics are included in the results chapter. The data collected on both the first (baseline) and subsequent visits showed a similar ADRB incidence pattern for both cohorts, with slightly higher incidence in the VM cohorts (NM = 32.7% vs. VM = 35.3%, and NM = 43.8% vs. VM = 45.9%; for first and subsequent visits, respectively). While these findings appear to support the alternative hypothesis in the direction we would have expected it to sway towards (high ADRB on VMs), first, the incidence difference was shown to be statistically insignificant by sample data drawn from the first office visit, and second, it could not have been corroborated by the statistically sub-optimal data from the second visit. The assessment of confounding from the deterrent-induced reduction in UDT positivity rates for subsequent visits [as described by Pesce et al. (2011)] was not performed due to the lack of paired

UDT data in the second office visit and wild variation in inter-visit time frames, which is itself a potential source of confounding. Future studies could aim at assessing confounding from this phenomenon.

Race/Ethnicity and Sex were not just only important from the perspective of the impact they might have had on the interaction between the primary risk variable (OMS) and the outcome variable (ADRB) but were themselves of significant clinical value and merited individual evaluation of a potential associations with ADRB. However, as initially hinted by the χ^2 statistics in Chi-squared testing, and confirmed in formal logistic regression analysis, Race/Ethnicity and Sex do not confound or modify the association between OMS and ADRB.

2. Among non-malignant chronic pain patients on COT from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportions of White and Hispanic patients that engage in aberrant drug-related behaviors?

While the actual study conducted in this dissertation did not answer our original question, it did evaluate the incidence of ADRB in the two cohorts with the greatest number of patient records: White and Hispanic. These two groups account for most of the patients at the pain clinic, which makes them relevant to the analysis. The results showed that there is no statistically significant difference in the proportion of incident ADRB between White and Hispanic patients. As in the analysis of OMS, this was true for both the first (baseline) and subsequent visits. However, only the first visit had enough patient records for a sample size suitable for inferential statistics ($n = 172$). ADRB (baseline) incidence rates between cohorts were (White = 36.2% vs. Hispanic = 33.0%), which are statistically identical ($p = 0.663$).

3. Among non-malignant chronic pain patients on COT from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportions of men and women that engage in aberrant drug-related behaviors?

There was no statistically significant difference in the proportions of incident ADRB (baseline) between males and females ($p = 0.314$). ADRB incidence rates for first visit were as follows: (Male = 37.8% vs. Female = 30.8%). Out of the three risk variables, Sex was the one that got closer to attaining statistical significance. ADRB rates were most discrepant between Males and Females than between any of the other cohort pairs. Although this discrepancy can be merely due to chance (failed to reject the H_0), it may warrant further inquiry in future studies.

Overall, none of the risk variables tested showed statistically significant associations to incident ADRB, the outcome variable. The implication of these results is that the data clearly showed (very small χ^2 statistic numbers) that we should not expect for a patient with variant metabolism of CYP2D6 substrates to be more predisposed to abuse or misuse of medication and/or illicit drugs, or at least, not at a higher rate than what we would expect to see in a patient with normal CYP2D6 metabolism. The same was true (no statistically significant incident discrepancies) for White patients versus Hispanic patients and Males versus Females. Although with the later comparison and based on incidence statistics alone, one might be forgiven for being inclined to believe that Males were more likely than Females to engage in ADRB. However, as pointed before, the difference could have been the result of chance alone. It is important to note that the conclusions reached here are the result of statistical analyses conducted on the first (baseline) visit sample only. Of the two samples collected, only the first visit sample had the size and sampling ratio (κ) that allowed for the detection of smaller differences in

proportions (small ES) while keeping $\alpha = 0.05$ (minimizing type I error) and $1 - \beta = 0.80$ (minimizing type II error).

The initial data collection protocol called for at least a second set of data to be retrieved on the same patient for a subsequent office visit. There were a couple of reasons for this. First, we needed to ensure there would be something to detect (i.e. a positive consistent opioid result, negative inconsistent opioid result) as it was initially assumed that most patients would not be taking any opioid medication on their first visit to the clinic. This would have been the case (per pain clinic policy) if not for the fact that the first visit was assumed to be the one when the PGT collection took place. This meant that most patients (>80%) were already taking at least one opioid by the time they came to that office visit. This also meant that, contrary to what was initially thought, a complete assessment of aberrant drug related behaviors was in fact possible and appropriate at this time. The second reason was to assess the potential for confounding from repeated drug testing events (decrease in positivity rates) (A. J. Pesce et al., 2011). This required inter-visit time periods to be approximately equal between cohorts. However, as detailed in methods, significant variability in inter-visit times (7 days to 3+ years) made this impossible to achieve. Furthermore, second visit data was not used on any of the analyses due to the large amount of missing paired UDT data values ($n = 69$).

5.1 Implications of Study Results

An important implication of what was found is that the data did not support the main hypothesis. This means that it could not have been used for the creation of biometric tool for risk assessment as initially conceived, nor that data from the study could have been feed into automated decision support systems. This also means that the risk assessment process will for now continue to rely on current methods. An interesting finding was that the data showed unexpectedly high

total ABDR incidence rates (> 30%). While this is only true of NMCPD on COT at this clinic and not generalizable to the public at large, it can have important implications for our approach to curtailing these behaviors in this patient population. At the very least, it shows that we need to do a better job at attempts to reduce ADRB in NMCPD. Finally, it is important to note that what the data from the study really showed is that presuppositions we might have had about expecting to see higher ADRB incidence rates for individual categories in our risk variables were in fact incorrect. In other words, the data showed that we should not allow preconceived notions about who we would have expected to be more likely to misuse medication or abuse an illicit substance to dictate the quality of care a patient receives, absent any other objective assessment.

5.2 Limitations

There were some factors that limited the interpretation and generalizability of the findings in this study. These include the following:

Although (based on the literature review) it was appropriate to assume that the main genetic risk/exposure variable for outcome ABDR was one cytochrome P250 metabolizing enzyme only (CYP2D6), there are in fact several other enzymes, opioid receptors (pharmacodynamic influencers), transporter proteins and other substances implicated in pain perception that also play a role on the biotransformation and effectiveness of the opioid drugs of interest to this study (Codeine, Hydrocodone, Oxycodone and Tramadol). Not including these biomarkers in the analysis could have had an effect on the interpretation of results. As a retrospective cohort study, there is always a risk that there might have been significant confounders (other than Race and Sex) that were not accounted for in the analysis. As an association study, there was no expectation that a causal relationship could have been established between OMS and ADRB, had the association been statistically significant. The dichotomization of categorical variables OMS (PM, IM, EM &

UM transformed into NM and VM) and Race/Ethnicity (dropped Black and Asian categories due to low representation), although necessary to achieve a sampling ratio that was closer to one (as in the case of OMS) and to avoid bias from low representation (Race), might have masked important individual category associations with ADRB, therefore affecting the interpretation of results. The designation of ADRB as a binary outcome variable encompassing several statistics (UDT results, PMP results, drug adulteration testing (DAT) results) might have oversimplified the nature of the potential relationships between these individual statistics and the risk variables. A non-probability convenience sample was used in this study to ensure that there were enough patient records for each of the risk variable's categories to meet significance and power requirements. However, the use of this type of sampling approach might have hindered adequate representation, which reduces generalizability. Finally, a restrictive sample inclusion criteria was used in order to minimize the effect of additional potential confounders (a legitimate concern in retrospective cohort studies). Beyond the issue of generalizability, the resulting reduced sample size might have had a detrimental effect on the detection of even smaller effect sizes ($ES < 10\%$), this was certainly true with data collected on the second visit.

5.3 Future Directions

It is conceivable that study design choices might have partially contributed to the lack of statistically significant associations between the study's variables. However, the significant lack of strength in the associations between the study's variables (high p -values, low χ^2 values) for our sample size ($n = 186$, total for both cohorts) might indicate that even with larger sample sizes, and accounting for additional confounders, there is still a good chance the same conclusion would have been reached. Of course, this does not preclude the fact that improvements can be made to future studies. For instance, future research could benefit from adequate sample sizes for each of the

category levels of the dichotomized variables so that all are properly represented. Future studies could also focus on evaluating the individual components of the outcome variable (ADRB), or on accounting for all the genetic contribution to opioid medication effectiveness (not just CYP2D6 metabolizer status). Finally, future studies could limit the impact that an over-restrictive inclusion criteria can have on determinations of sample size.

5.4 Conclusion

The purpose of this dissertation study was to assess the relationship between opioid metabolism, as determined by phenotypic CYP2D6 expression, and aberrant drug-related behaviors, such as opioid misuse, in a population of non-malignant chronic pain patients within an El Paso, Texas pain management clinic. Significant data gathered in this study would have informed the conception of a risk assessment tool that relied on objective biometric information. However, the results of the study showed that there was no statistically significant association between opioid metabolizer status and aberrant drug-related behaviors. In addition, the results also showed that there was no statistically significant association between two suspect confounding variables, race and gender, and aberrant drug-related behaviors. Although, no statistically significant associations were found, a closer look at the data revealed interesting findings that merit further exploration in studies that expand sample size and reconfigure the study's variables for more granular assessments.

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TITLE OF APPENDIX

Appendix A. SOAPP-R



EL PASO ORTHOPAEDIC SURGERY GROUP
SPINE CENTER OF EL PASO AND EL PASO PAIN MANAGEMENT CENTER
 1755 CURIE, STE. C, EL PASO, TEXAS 79902 PHONE (915) 533-7465 · FAX (915) 534-1246
www.eposg.com

SOAPP®-R

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. How often do you have mood swings?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. How often have you felt a need for higher doses of medication to treat your pain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. How often have you felt impatient with your doctors?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. How often have you felt that things are just too overwhelming that you can't handle them?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. How often is there tension in the home?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. How often have you counted pain pills to see how many are remaining?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. How often have you been concerned that people will judge you for taking pain medication?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. How often do you feel bored?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. How often have you taken more pain medication than you were supposed to?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. How often have you worried about being left alone?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. How often have you felt a craving for medication?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. How often have others expressed concern over your use of medication?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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EL PASO ORTHOPAEDIC SURGERY GROUP

SPINE CENTER OF EL PASO AND EL PASO PAIN MANAGEMENT CENTER
1755 CURIE, STE. C, EL PASO, TEXAS 79902 PHONE (915) 533-7465 · FAX (915) 534-1246
www.eposg.com

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
13. How often have any of your close friends had a problem with alcohol or drugs?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. How often have others told you that you had a bad temper?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. How often have you felt consumed by the need to get pain medication?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. How often have you run out of pain medication early?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. How often have others kept you from getting what you deserve?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

18. How often, in your lifetime, have you had legal problems or been arrested?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. How often have you attended an AA or NA meeting?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. How often have you been in an argument that was so out of control that someone got hurt?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21. How often have you been sexually abused?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22. How often have others suggested that you have a drug or alcohol problem?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
23. How often have you had to borrow pain medications from your family or friends?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24. How often have you been treated for an alcohol or drug problem?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please include any additional information you wish about the above answers. Thank you.

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COMM™

Please answer each question as honestly as possible. Keep in mind that we are only asking about the **past 30 days**. There are no right or wrong answers. If you are unsure about how to answer the question, please give the best answer you can.

	Never	Seldom	Sometimes	Often	Very Often
Please answer the questions using the following scale:					
	0	1	2	3	4
1. In the past 30 days, how often have you had trouble with thinking clearly or had memory problems?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. In the past 30 days, how often do people complain that you are not completing necessary tasks? (i.e., doing things that need to be done, such as going to class, work or appointments)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. In the past 30 days, how often have you had to go to someone other than your prescribing physician to get sufficient pain relief from medications? (i.e., another doctor, the Emergency Room, friends, street sources)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. In the past 30 days, how often have you taken your medications differently from how they are prescribed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. In the past 30 days, how often have you seriously thought about hurting yourself?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. In the past 30 days, how much of your time was spent thinking about opioid	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

medications (having enough, taking them, dosing schedule, etc.)?	
--	--

	Never	Seldom	Sometimes	Often	Very Often
Please answer the questions using the following scale:					
	0	1	2	3	4
7. In the past 30 days, how often have you been in an argument?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. In the past 30 days, how often have you had trouble controlling your anger (e.g., road rage, screaming, etc.)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. In the past 30 days, how often have you needed to take pain medications belonging to someone else?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. In the past 30 days, how often have you been worried about how you're handling your medications?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. In the past 30 days, how often have others been worried about how you're handling your medications?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. In the past 30 days, how often have you had to make an emergency phone call or show up at the clinic without an appointment?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. In the past 30 days, how often have you gotten angry with people?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. In the past 30 days, how often have you had to take more of your medication than prescribed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. In the past 30 days, how often have you borrowed pain medication from someone else?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

16. In the past 30 days, how often have you used your pain medicine for symptoms other than for pain (e.g., to help you sleep, improve your mood, or relieve stress)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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	Never	Seldom	Sometimes	Often	Very Often
Please answer the questions using the following scale:					
	0	1	2	3	4
17. In the past 30 days, how often have you had to visit the Emergency Room?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



Institutional Review Board Office

The University of Texas at El Paso

Office of Research and Sponsored Projects

Exemption Request Application

Instructions: This form must be reviewed and completed in its entirety. This form is to be submitted to the IRB only when an investigator is contemplating the initiation of a research or capstone project, which, in the investigator's judgment, may be exempt from full IRB review. Please type and submit this form along with finalized copies of all project related materials via [IRBNet](#). Study information sheets can be used in lieu of consent forms for exempt research projects. See forms section for more information.

Attention to these elements will facilitate the IRB's review of your project. The IRB will then determine whether the activity is covered by the allowable Exempt regulations. Research activities are exempt from regulations for the protection of human research subjects when they are considered minimal risk (the probability or magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (as defined by 45 CFR 46.101), and the ONLY involvement of human subjects falls within one or more of the exempt categories.

The Federal Office for Human Research Protections (OHRP) has allowed for **six exempt categories**.

The **exempt categories** outlined below are based solely on methods of research, and do not take the level of risk into consideration. Although most exempt research requires no further oversight to be conducted ethically, some exempt research raises ethical concerns or requires measure to protect participants. As such, the IRB will not consider any research exempt that does not fulfill ethical principles reflected in the Belmont Report. These three basic ethical principles are:

Respect for Persons (autonomy)- individuals should be treated as autonomous agents and persons with diminished autonomy are entitled to protection.

Beneficence- human participants should not be harmed and the research should maximize possible benefits and minimize possible harms.

Justice- the benefits and risks of research must be fairly distributed.

Research that otherwise would be exempt by federal regulations that raises ethical concerns or requires measures to protect participants may be denied and/or moved to a higher level of review.

For further guidance or assistance, please contact the IRB office at (915) 747-7693 or by email at irb.orsp@utep.edu.

Project Information			
Project Title	ASSOCIATION OF OPIOID METABOLISM WITH ABERRANT DRUG-RELATED BEHAVIORS AMONG NON-MALIGNANT CHRONIC PAIN PATIENTS		
Principal Investigator (Last Name, First Name)	Eduardo Aguila		
University Title	<input type="checkbox"/> Faculty/Staff <input checked="" type="checkbox"/> Student		
Department	Interdisciplinary Health Sciences		
Co-Investigator (Last Name, First Name)			
University Title	<input type="checkbox"/> Faculty/Staff <input type="checkbox"/> Student		
Protocol Title:	ASSOCIATION OF OPIOID METABOLISM WITH ABERRANT DRUG-RELATED BEHAVIORS AMONG NON-MALIGNANT CHRONIC PAIN PATIENTS		
E-mail Address	lalord78@gmail.com	Phone Number	(915) 490-6530
Human Subjects Research Training Completed:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		Anticipated Start Date Anticipated End Date: Summer semester of 2018 upon IRB approval with retrieval of data from Jan 2016 through March 2018 (retrospective collection of existing data. Initially generated as part of standard of care)

If the **Principal Investigator is a student**, the faculty advisor must indicate knowledge and approval of this submission. By electronically signing the package in IRBNet, the faculty advisor certifies that the study is under their direct supervision and that the faculty advisor is responsible for ensuring that all provisions of the IRB approval are complied with by the investigator.

A. Type of Project*Check all that apply*

<input type="checkbox"/> Faculty Research	<input type="checkbox"/> Thesis	<input checked="" type="checkbox"/> Dissertation
<input type="checkbox"/> Presentation/Conference	<input type="checkbox"/> Capstone	<input type="checkbox"/> Internal Evaluation/Non-Publishing
<input type="checkbox"/> Funded-Source:	<input type="checkbox"/> Publication:	<input type="checkbox"/> Other:

B. Applicability

C1. Does the study protocol include children as research subjects? (see 45 CFR 46.101(b)(2))	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
C2. Does the study protocol include prisoners, fetuses, pregnant women, or human in vitro fertilization?	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
C3. Does the protocol involve more than minimal risk?	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
C4. Does the protocol involve deception?	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
C5. Does the protocol include cognitively impaired participants as research subjects?	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>

If you answered yes to any of the above, the submission does not qualify for exemption. Please fill out a full study protocol.

C. Exempt Research Categories*Check the applicable category below. Only answer questions related to the applicable category.*☐ **Category 1 EDUCATIONAL**

- a. Will the researchers use their current students or trainees as participants?
YES ☐ NO ☐

Please explain what additional measures will be taken to ensure participants do not feel pressured or coerced during recruitment for or participation in the research:

☐ **Category 2 SURVEYS, INTERVIEWS, EDUCATIONAL TESTS, AND OBSERVATION OF PUBLIC BEHAVIOR**

- a. Will the researchers use their current students or trainees as participants?
YES ☐ NO ☐
- b. Will the research involve children in survey procedures, interview procedures, or observation of public behavior when the investigator(s) participate in the activities being observed?
YES ☐ NO ☐

If yes, this study does not meet the criteria for exemption.

- c. Will you record information in a way that human subjects can be identified, directly or through identifiers (coded) linked to the subjects?

YES ☐ NO ☐

- d. Could any disclosure of the subjects' responses outside the research reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, or reputation?

YES ☐ NO ☐

☐ **Category 3 ELECTED OR APPOINTED PUBLIC OFFICIALS OR CANDIDATES FOR PUBLIC OFFICE**

☒ **Category 4 EXISTING DATA**

- a. What is the source of the data?

☐ Publicly available database

☐ Student Records

Include Link:

CIERP will be providing dataset: YES ☐ NO ☐

☒ Medical or Private Records

☐ Another PI/Researcher collected it in the

past

Do you have permission to use this data? NO ☐ YES ☒

If yes, describe how and attach documentation indicating permission.

Granted by the covered entity's chief medical officer after a review of the study's

protocol.

- b. Will this data be stripped of any identifiers?

YES ☒ NO ☐

- c. Will you be using a data collection form? Attach documentation and/or list data points.

YES ☐ NO ☒

Please note that HIPAA prohibits the collection of specified identifiers such as name, street address, telephone/fax numbers, e-mail address, URLs & IP addresses, social security numbers, certificate/license number, vehicle/serial identifiers and full face photos.

☐ **Category 5 ONLY USED BY OR WITH THE APPROVAL OF GOVERNMENT AGENCIES**

☐ **Category 6 TASTE/FOOD QUALITY EVALUATION & CONSUMER ACCEPTANCE**

D. Project Site(s): <i>Check all that apply</i> <i>This includes subject recruitment, subject enrollment, data collection, and data analysis</i>	
<input type="checkbox"/>	Project will be conducted entirely at UTEP.
<input type="checkbox"/>	Research will be conducted at another institution.* Project will be reviewed by another IRB and/or Ethics Committee Provide the institution name and contact person:
<input checked="" type="checkbox"/>	Other*: Study to be conducted at the El Paso Orthopaedic Surgery Group Toxicology Laboratory. Approved by Medical Director/Medical Chief of Staff (Authorization attestation attached).
*Please include applicable Authorization Letter(s) indicating permission to conduct project in the submission package	

E. Ethical Considerations:	
<p>E1. Does this project include inclusion and exclusion criteria? IF yes, please describe:</p> <p>The records to be used in the study will originate from a subset of the chronic pain patient population who meet the following inclusion criteria:</p> <ul style="list-style-type: none"> • non-malignant chronic pain patients (NMCPP) on chronic opioid therapy (COT) who visit our pain clinic; • male or female, of any race/ethnicity who are at least 18 years of age, and; • had been diagnosed with any kind of chronic pain of non-cancerous origin, • had been prescribed COT with one or several substrates of the CYP2D6 metabolizing enzyme, • had signed an opioid treatment agreement, • have had Texas Prescription Drug Monitoring Program (PMP) data retrieved recently, • have had risk assessment/stratification performed with The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) and/or The Current Opioid Misuse Measure (COMM) instruments, and; • have had urine drug testing/pharmacogenetic testing performed in association with the COT regimen. 	<p>YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> N/A <input type="checkbox"/></p>
<p>E2. Will you be audio or video recording during any portion of this project? IF yes, please describe:</p>	<p>YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/></p>

E3. Does the project pose any risk to the individual(s)? IF yes, please describe how the risk/benefit ratio has been weighed and explain how you will address this concern:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
E4. Will subjects benefit from participating in the research? (compensation is not a benefit) Describe and assess potential benefits to be gained by participants (if any) and the benefits that may accrue to society in general: <p>The aim of the proposed study is to describe whether a statistically significant association exists between opioid metabolism and aberrant drug-related behaviors among non-malignant chronic pain patients. If such an association is proven to be significant, it would become the theoretical underpinnings of a new tool for COT aberrant drug-related behaviors (ADRB) risk assessment, which would be guided by objective biometric data rather than more subjective information, as in the case of the tools that are currently available (i.e. SOAPP-R and COMM). This new tool could be of substantial clinical value to pain management practitioners since it would enable them to make use of genotypic data to better predict which patients are at a greater risk of engaging in aberrant drug-related behaviors. Moreover, the data generated could be feed into algorithms for protocol creation, and be incorporated into a laboratory's information system (LIS) decision support modules. Finally, the insight gathered by the tool would streamline patient risk stratification, which in turn would enable better care.</p>	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> N/A <input type="checkbox"/>
E4. Is there a possibility of coercion or undue influence? IF yes, please describe how you will address this concern:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
E5. Will subjects be compensated (payment, incentives, extra credit, etc.)? IF yes, please describe:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
E6. Will this project use social media, internet websites, or any other web based software? IF yes, please describe and include link(s):	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
E7. Will identifiable data be made available to anyone other than the Principal Investigator and approved study staff? IF yes, explain who and why they will have access to the identifiable data:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
E7. Will the results of the project be disseminated? Check all that apply. Results are to become part of a dissertation study, which will be both, published and orally presented. <input checked="" type="checkbox"/> Publication <input checked="" type="checkbox"/> Presentation	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> N/A <input type="checkbox"/>

F. Literature Review:

In this section describe the significance of the proposed project. Provide appropriate references.

An estimated 100 million Americans suffer from some form of chronic pain (Cone, Caplan, Black, Robert, & Moser, 2008; Institute of Medicine, 2011; Webster, 2010). Chronic opioid therapy (COT) use in non-malignant chronic pain patients (NMCP) has markedly increased over the past two decades due to growing consensus that COT is suitable for the treatment of moderate-to-severe non-malignant chronic pain (Chou et al., 2009). Yet, COT for NMCP has been widely associated with multiple aberrant drug-related behaviors (ADRB) such as misuse, abuse, diversion, addiction, and pseudoaddiction (Webster, 2010). One reason for the relative high incidence of ADRB among NMCP on COT may be genetics-induced medication response variability, which, can result in pharmacotherapy failure and/or toxicity

The present study will aim at uncovering potential relationships between opioid metabolizer status (OMS) (caused by inter-personal genetic variability in opioid metabolism) and ADRB such as illicit substance abuse and prescription opioid misuse. Pharmacogenetic testing (PGT) will be used to categorize patient OMS, whereas urine drug testing (UDT) will identify relevant ADRB. The findings of the study could contribute to the creation of better prediction algorithms that make use of genetic biomarkers for reducing the likelihood of at-risk NMCP on COT, those who may be variant opioid drug metabolizers, of engaging in ADRB.

To test the study's hypothesis, unidentified retrospective categorical data from an assembled cohort of NMCP on COT retrieved from a Pain Management Clinic's electronic medical records system (EMR) – PGT and UDT results – will be cross-tabulated and analyzed with the Pearson Chi-square test for difference in proportions and test of independence. However, the Fisher's Exact test or Likelihood Ratio Chi-Square will be used if expected cell count is low. Confounding and effect modification will be dealt with by the inclusion of suspect variables in a logistic regression model and, if necessary, by reporting findings separately for different variable levels.

References

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., . . . Fudin, J. (2009).

Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain*, 10(2), 113-130. e22.

Cone, E. J., Caplan, Y. H., Black, D. L., Robert, T., & Moser, F. (2008). Urine drug testing of chronic pain patients: Licit and illicit drug patterns. *Journal of Analytical Toxicology*, 32(8), 530-543.

doi:10.1093/jat/32.8.530

Webster, L. (2010). Current state of chronic pain management: Current and emerging long-acting opioids. *University of Tennessee Advanced Studies in Pharmacy*, 7(2), 36-40. Retrieved from

<http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=65095813&site=ehost-live&scope=site>

G. Summary of Project Activity:

Briefly state the purpose of this research project and your research question(s):

The purpose of this study is to assess the relationship between opioid metabolism and aberrant drug-related behaviors among non-malignant chronic pain patients. Significant findings could further advance the creation of better ADRB prediction algorithms for at-risk patients on a chronic opioid regimen.

The main questions of the study are the following:

- 2) Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, are opioid metabolizer status and aberrant drug-related behaviors independent?
3. Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, are race/ethnicity of patients on chronic opioid therapy and aberrant drug-related behaviors independent?
4. Among non-malignant chronic pain patients from an El Paso, Texas pain management clinic, is there a statistically significant difference in the proportion of men and women on chronic opioid therapy that engage in aberrant drug-related behaviors?

What is the project goal(s)? Please include the specific population geared to benefit from this project:

The main goal of this project is to uncover statistically significant associations between opioid metabolism and aberrant drug related behaviors to advance the creation of better and more accurate ABDR prediction tools for at-risk non-malignant chronic pain patients on chronic opioid regimens.

Describe the informed consent process plan. How will participants be fully informed of this research prior to their participation and how will their voluntary consent be documented. * Note: Please SUBMIT a copy of the form(s).

No informed consent process plan is required as the study will only make use of properly de-identified existing data initially collected as standard of care.

Describe how the project will be implemented. Describe the task(s) subjects will be asked to perform. List what procedures you will follow and what the study participants will be exposed to. *Please provide details (# of subjects, procedures, duration, etc.). Alternately, describe the study plan for a project working with existing data (# of files, specimens, time frame, etc.)*

The Principal Investigator (PI) and his professional assistant (all will undergo CITI training for the protection of human participants and certificates are to be forwarded to the IRB office) will retrieve approximately 100-110 individual drug testing patient records for each cohort ($n = 200-220$) from either the clinic's own EMR: Prime Suite (Greenway Health, 2017), the clinic's toxicology laboratory cloud-based information system (LIS): AxisLabsDX (Alternative Biomedical Solutions, 2017), and/or Alere Toxicology

web portal: Alere Datalink (Alere, 2017). Only pertinent variable data (opioid, illicit substance and adulterant results) along a non-PHI unifying identifier will be extracted on to an excel database.

The same procedure will be applied to the retrieval of genetic testing, gender and race/ethnicity data.

However, in addition to the sources mentioned above, data will also be retrieved from the Millennium Health, AltheaDx, AssureX, Vantari Genetics, PinPoint Molecular and Proove Biosciences web portals (AltheaDx, 2017; AssureX Health, 2017; Millennium Health, 2017; PinPoint Molecular, 2017; Proove Biosciences, 2017; Vantari Genetics, 2017). Pertinent variable data will be extracted along the aforementioned unifying identifier (i.e. Study ID #).

Anticipated collection of this existing record data (initially collected as standard of care from January 2016 through March of 2018) will take place in the summer of 2018 upon obtaining explicit IRB approval. The PI will then be responsible for analyzing the collected data.

Describe how the project team will protect the privacy of study participants:

There are no study participants in this project.

Could the information obtained or recorded about subjects place them at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, insurability, or reputation?

YES ☐ NO ☒ N/A ☐

If yes, please explain:

Describe how the project team will collect, manage, and analyze data.

Describe provisions that will be taken to maintain confidentiality of the data. Will it contain subject names or images? (e.g surveys, video, audio tapes, database) The PI will be responsible for manipulating the data extracted on to the excel database. Patient data from various sources will be consolidated for each patient record with the aid of a unifying identifier. To ensure confidentiality, no protected health information (PHI) identifying individual patients (i.e. name, date of birth) is to be retrieved and added to the study's database spreadsheet. After subsequent cleaning of data, secondary variables will be created to properly address the

study's research questions. Secondary data variables used in the study's analyses will also be devoid of any PHI.

Describe the security plan for data, including where data will be stored, and for how long, noting that you may not keep identifiable data indefinitely (i.e., password protection, encrypted, locked filing cabinet, etc.):

Safeguarding patient information (even if not PHI) and ensuring confidentiality is of paramount importance.

All patient record data will be further manually deidentified (by elimination/transformation of any non-PHI variables or variable relationships that in conjunction could be traced back to an individual), and statistically de-identified (by presenting aggregate data and summary statistics only). Only the PI and his professional assistant at the EL Paso Orthopaedic Surgery Group's (EPOSG) Toxicology Laboratory will have access to the patient data. Data manipulation and statistical analyses will only be performed on the PI's password-protected device. The study's data will be stored in the PI's password-protected device and at one of the password-protected devices of the aforementioned facility where access is highly restricted.

ASSURANCES – Conflict of Interest and Fiscal Responsibility

All UTEP researchers (faculty, staff, and students) and outside collaborators who will be conducting human subjects' research (intervention and/or interaction) must complete human subject research ethics training in order to conduct research with human participants.

Do you or any person responsible for the design, conduct, or reporting of this project have an economic interest in, or act as an officer or director of any outside entity whose financial interests may reasonably appear to be affected by this project? If yes, please explain any potential conflict of interest	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Do you or any person responsible for this project have existing financial holdings or relationships with the sponsor of this study? If yes, please explain any potential conflict of interest	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A <input type="checkbox"/>

Principal Investigator Certifications:

With this submission I certify that:

- ☒ I agree to fully comply with the ethical principles and regulation regarding the protection of human subjects in research.
- ☒ I agree that the information provided in this form and all other supporting documents are accurate and complete.
- ☒ I accept responsibility for making sure all study personnel involved in the project have been appropriately trained. PI affirms responsibility for keeping training records on file for all study personnel.
- ☒ I understand that any changes in procedure with affect to participants must be submitted to the IRB for written approval prior to their implementation. Furthermore, I understand that any adverse events and significant changes

in risk for participants must be immediately reported in writing to the UTEP IRB.

Copies of all required documentation of consent (if applicable) and any related to this research are securely stored as outlined above.

Appendix D. Abbreviation List

ADR – Adverse drug reactions

ADRB – Aberrant drug-related behaviors (abuse, misuse, diversion, addiction & pseudoaddiction)

AP – Absence of prescribed medication

COMM – Common opioid misuse measure

COT – Chronic Opioid Therapy

EA – Evidence of adulteration

EM – Extensive metabolizer

EMR – Electronic medical records

ES – Effect size

GC-MS – Gas chromatography mass spectrometry

IM – Intermediate metabolizer

IRB – Internal review board

LC-MS – Liquid chromatography mass spectrometry

LC-MS/MS – Liquid chromatography tandem mass spectrometry

LIS – Laboratory information system

NM – Normal metabolizer

NMCP – Non-malignant chronic pain patients

OMS – Opioid metabolizer status (CYP2D6 enzyme)

OD – Opioid use disorder

PDMP – Prescription drug monitoring program

PGT – Pharmacogenetic testing

PHI – Protected health information

PI – Presence of an illicit

PM – Poor metabolizer

PNP – Presence of non-prescribed medication

SOAPP-R – Screener and opioid assessment for patients with pain-revised

UDT – Urine drug testing

UM – Ultra-rapid metabolizer

VM – Variant metabolizer

CURRICULUM VITA

Eduardo Aguila was born in Chihuahua, Chihuahua, Mexico. The eldest of five children, he was raised in Mexico and completed his primary and secondary education there. He earned his Bachelor of Science degree in Clinical Laboratory Science from UTEP in 2001 and a Master of Business Administration with a concentration in finance from SUNY Albany in 2008. He joined UTEP's doctoral program in Interdisciplinary Health Sciences in 2011.

Dr. Aguila has for over a decade worked in multiple leadership positions at different clinical laboratories where he guided their strategic vision, managed their operations and implemented laboratory-developed methodologies.

Dr. Aguila has presented his research at several meetings and symposiums where he talked about the potential use and benefits of genetic biomarkers to curtail the risk of opioid abuse and misuse for patients on chronic opioid therapy, and the implementation of chromatographic-spectrometric techniques for definitive drug testing in adherence monitoring programs.

While perusing his degree, Dr. Aguila directed the operations of a clinical toxicology laboratory in a large orthopaedic/pain management group, worked as the technical director for a hospital based clinical laboratory and consulted for other clinical toxicology laboratories.

Dr. Aguila's dissertation, "Association of Opioid Metabolism with Aberrant Drug-Related Behaviors among Non-Malignant Chronic Pain Patients", was supervised by Dr. Delfina C. Domínguez.

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This dissertation was typed by Eduardo Aguila.