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Commentary

Pharmacogenomics-guided policy in opioid use disorder (OUD) management: An ethnically-diverse case-based approach

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ABSTRACT

Introduction: Opioid use disorder (OUD) is characterized by a problematic pattern of opioid use leading to clinically-significant impairment or distress. Opioid agonist treatment is an integral component of OUD management, and buprenorphine is often utilized in OUD management due to strong clinical evidence for efficacy. However, interindividual genetic differences in buprenorphine metabolism may result in variable treatment response, leaving some patients undertreated and at increased risk for relapse. Clinical pharmacogenomics studies the effect that inherited genetic variations have on drug response. Our objective is to demonstrate the impact of pharmacogenetic testing on OUD management outcomes.

Methods: We analyzed a patient who reported discomfort at daily buprenorphine dose of 24 mg, which was a mandated daily maximum by the pharmacy benefits manager. Regular urine screenings were conducted to detect the presence of unauthorized substances, and pharmacogenetic testing was used to determine the appropriate dose of buprenorphine for OUD management.

Results: At the 24 mg buprenorphine daily dose, the patient had multiple relapses with unauthorized substances. Pharmacogenetic testing revealed that the patient exhibited a cytochrome P450 3A4 ultrarapid metabolizer phenotype, which necessitated a higher than recommended daily dose of buprenorphine (32 mg) for adequate OUD management. The patient exhibited a reduction in the number of relapses on the pharmacogenetic-based dose recommendation compared to standard dosing.

Conclusion: Pharmacogenomic testing as clinical decision support helped to individualize OUD management. Collaboration by key stakeholders is essential to establishing pharmacogenetic testing as standard of care in OUD management.

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Abbreviations: OUD, opioid use disorder; SUD, substance use disorder; OAT, opioid agonist treatment; PBM, pharmacy benefits manager; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; NSDUH, National Survey on Drug Use and Health; CDC, Centers for Disease Control and Prevention; ASIPP, American Society of Interventional Pain Physicians; APA, American Psychiatric Association; ASAM, American Society of Addiction Medicine; WHO, World Health Organization; CYP3A4, cytochrome P450 3A4; PK, pharmacokinetics; PD, pharmacodynamics; PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultrarapid metabolizer; CLIA, Clinical Laboratory Improvement Amendments; PHM, Population Health Management

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1. Introduction

1.1. Epidemiology of opioid use disorders

Opioid use disorder (OUD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) as "a problematic pattern of opioid use leading to clinically-significant impairment or distress" characterized by the presence of at least two criteria, such as opioid cravings, tolerance, or withdrawal, over a 12-month period (APA, 2016). OUD constitutes a significant public health crisis that affects 26.4 to 36 million people worldwide (NIDA, 2014). An estimated 2.1 million people in the United States suffered from substance use disorders (SUDs) related to prescription opioids in 2012, and an estimated 467,000 suffered from heroin dependency. The 2014 National Survey on Drug Use and Health (NSDUH) revealed a worsening epidemic, with 4.3 million Americans engaged in non-medical use of prescription painkillers in the last month while 1.4 million people used prescription painkillers non-medically for the first time in the past year (SAMHSA, 2016a). OUD increases the risk of early death, primarily from an accidental overdose, trauma, suicide, or an infectious disease, such as HIV or hepatitis C, by a factor of 20; legal problems associated with criminality and high impulsivity are also prevalent (Schuckit & Longo, 2016). Increasing nonmedical use of prescription opioids has led to a quadrupling of the number of unintentional overdose deaths in the United States since 1999 (NIDA, 2014). According to data from the Centers for Disease Control and Prevention (CDC), there are at least 44 deaths due to nonmedical use of prescription opioid pain relievers daily (SAMHSA, 2016a). There is growing evidence to suggest a relationship between increased non-medical use of opioid analgesics and heroin use in the United States (NIDA, 2014).

1.2. Management of opioid dependence

Several organizations have developed guidelines for the treatment of OUD, including the American Society of Interventional Pain Physicians (ASIPP), the American Psychiatric Association (APA), the American Society of Addiction Medicine (ASAM), and the World Health Organization (WHO). These organizations recommend a combination of pharmacological measures such as opioid agonist treatment (OAT) and psychosocial approaches such as recovery support groups to reduce illicit opioid use and harm related to opioid use while improving quality of life (WHO, 2011). According to the latest survey of opioid treatment providers, more than 300,000 people received some form of OAT for OUD in 2011 (SAMHSA, 2016b). The use of OAT in OUD management is achieved through the administration of methadone, buprenorphine, or extended-release injectable naltrexone by accredited medical professionals (WHO, 2011). These medications exert their action by occupying opioid receptors which alleviates withdrawal symptoms without inducing substantial intoxication. Methadone and buprenorphine are medications with strong clinical evidence for use in OAT because they are sufficiently long-acting for once-daily dosing, can be used in opioid withdrawal, and do not produce the cycles of intoxication and withdrawal seen in shorter-acting opioids, such as heroin (WHO, 2011).

Buprenorphine/naloxone is an opioid partial agonist/opioid antagonist combination medication indicated in the treatment of opioid dependence. Naloxone is included to discourage parenteral use. The dosing range as published in the package insert for buprenorphine/naloxone is from 4 mg/1 mg to 24 mg/6 mg, with a recommended dose of 16 mg/4 mg; doses exceeding 24 mg/6 mg are not considered to garner an additional clinical benefit (Indivior, 2015). Buprenorphine is metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. CYP3A4 is encoded by a polymorphic gene and is responsible for the metabolism of approximately 50–60% of currently prescribed medications (Rendic & Di Carlo, 1997; Westlind-Johnsson et al., 2006). Variation in CYP3A4 correlates to differences in metabolism rates of medications like buprenorphine. Genetic differences in genes involved in drug metabolism and response can complicate the OAT process. Novel approaches to treatment selection and dosing are warranted to overcome the challenges presented by these genetic differences. Current pharmacogenomic testing strategies can accurately identify clinically actionable variants in all related genes is one solution for optimizing drug selection and dosing for each patient.

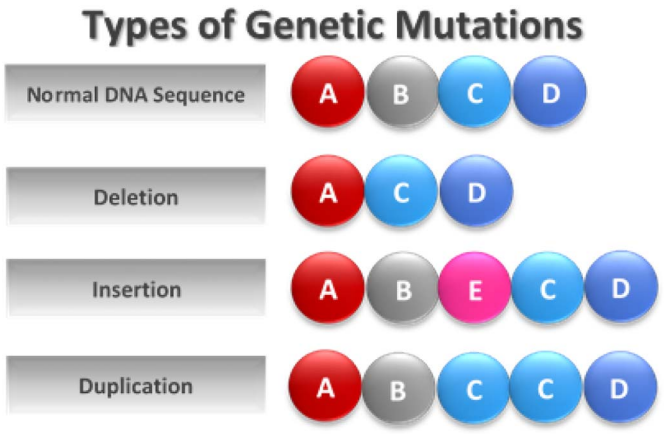

Fig. 1. Types of genetic mutations.This figure depicts a comparison of a normal DNA sequence compared to DNA sequences that became mutated during DNA replication. Each circle represents a DNA nucleotide.

1.3. Pharmacogenomics: individualizing OAT dosing in OUD management

Clinical pharmacogenomics is the study of effects of inherited genetic variation on an individual's medication response and combines pharmacology (the science of drug kinetics and dynamics of response) and genomics (the study of the entire genome) to optimize medication therapy (NIH, 2016a). Fig. 1 shows examples of the types of genetic mutations that may give rise to functional phenotypes. Polymorphisms in pharmacodynamic (PD) genes can affect drug action at its target, such as a receptor, and polymorphisms in pharmacokinetic (PK) genes, such as the cytochrome P450 (CYP450) family of metabolic enzymes, can affect blood and tissue drug levels. Functional variants in the CYP3A4 gene impact the rate at which drugs are metabolized and correlate to four basic phenotypes: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs) (Fig. 2). These pharmacogenetic variants have direct clinical application in the OAT of OUD, as buprenorphine is metabolized primarily by CYP3A4. The patient's CYP3A4 metabolizer phenotype can impact treatment outcomes with buprenorphine. Patients that are CYP3A4 PMs may have higher than normal plasma levels of buprenorphine, putting the patient at risk for untoward side effects. Conversely, patients that are CYP3A4 UMs may have lower than normal serum levels of buprenorphine, which may manifest as opioid cravings and/or withdrawal symptoms. Pharmacogenetic testing conducted at the onset of treatment can guide medical practitioners, a priori, to the optimal dose for the patient by determining their metabolizer phenotype. Table 1 below explains common terminology used when describing pharmacogenomics testing results.

The successful implementation of pharmacogenomics in clinical practice is dependent on a number of different processes, including (1) a priori knowledge of functional variants and their impact on drug metabolism and therapeutic effects, (2) the ability to accurately test a patient for known functional variants involved in drug disposition and dynamics and determine metabolizer phenotype, and (3) the ability to use this information to improve the standard of care by prescribing the right drug at the right dose.