Pharmacogenomics in Pain Management

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KEYWORDS

• Allele • Haplotype • Homozygous • Heterozygous • Genotype
• Pharmacogenomics • Polymorphisms • Single-nucleotide polymorphisms (SNP)
• Pain

KEY POINTS

- Opioid classes have a wide variability in clinical manifestations that can partly be explained by differences in metabolism and receptor molecules.
- There are several cytochrome enzymes involved in ketamine metabolism but strong genetic correlations between metabolism variations and clinical manifestation have yet to be identified.
- Catechol-O-methyltransferase plays an important role in variability of pain sensitivity, and certain alleles may predispose patients to higher opioid requirements for pain control.
- Pharmacogenomics nonsteroidal anti-inflammatory drugs are increasingly better understood and, in some instances, have already led to changes in dosing recommendations.

INTRODUCTION

Pharmacogenomics is a relatively new field that combines pharmacology and genomics to develop effective, safe medications and dosages.[1] This allows for pharmacologic tailoring of treatment to individuals. Much of this field can be applicable to understanding pain management and various responses to drugs seen in the clinical setting. This inter-individual variability is still under review and a better understanding of pharmacogenomics is key to improving patient care.

Pain management is often very costly and time consuming. It is estimated that more than $600 billion is spent annually on managing chronic pain.[2] Some of this cost is attributed to adverse outcomes and lengthened hospital stays. With pharmacogenomics there is potential to improve pain management by predicting outcomes before

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before the medication is even prescribed. According to the US Food and Drug (FDA) administration there are more than 2 million serious adverse drug reactions yearly, with 100,000 resulting in death. Adverse drug reactions are estimated to cost $136 billion annually and are known to increase average length of hospital stay and mortality.[3]

Noninvasive saliva testing, for instance, could someday allow clinicians to determine the most appropriate medication for an individual patient, decreasing the adverse effects and increasing efficacy.[4]

METABOLISM VARIABILITY

There are many enzymes that have been shown to be associated with the metabolism of opioids. This allows room for genetic variability to play a role in both the efficacy and toxicity of these drugs. This variability comes in several forms but can be broadly classified as extensive-metabolism, intermediate-metabolism, poor-metabolism, or ultra-metabolism.[5] An extensive metabolizer would have 2 normal alleles, an intermediate metabolizer would have 1 normal and 1 reduced allele, and a poor metabolizer would have 2 mutant alleles.

One example of opioid metabolism variability is seen when looking at polymorphisms in CYP2D6. Cytochrome enzymes are well-known to be involved in the metabolism of many drugs, including many opioids. There are at least 80 identified CYP2D6 alleles, which leaves much room for enzymatic variability, from 1% to 200% when compared with the wild-type allele.[6]

The CYP2D6 allele is also known to vary among ethnicities. This assembly of allele frequencies may require a larger study for more accurate assessment but also better correlation with clinical responses. The clinical responses may vary significantly as well, given that the nonfunctioning and reduced functioning alleles noted in **Table 1** also may vary in response on a functional gradient.[7]

WEAK OPIOIDS

Codeine

Codeine is considered a weak opioid and is widely used for its analgesic effects. Many practitioners are familiar with CYP2D6 polymorphisms and its effect on codeine metabolism. Plasma codeine and its active metabolites (eg, morphine) have varying pharmacokinetic pathways depending on patient CYP2D6 makeup.[8] Ultrametabolizers of codeine can have high levels of morphine after standard dosing, whereas patients who are poor metabolizers will experience minimal effects.

Table 1
Median frequency of CYP2D6 alleles classified as functional, nonfunctional, and reduced function based on different ethnicities

Ethnicity	Functional Allele (%)	Nonfunctional Allele (%)	Reduced Functioning Allele (%)
Whites	71	26	1–10
Asians	~50	1–10	~40
Africans	50–55	1–10	30–40
African Americans	~50	10–20	30–40

Adapted from Bradford LD. CYP2D6 Allele Frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3(2):230.