Pharmacogenetics of Opioid Use and Implications for Pain Management—Are We Ready?

Gwendolyn A. McMillin[1,2]*

No one can deny the extreme chaos, frustration, and sadness that our families, law enforcement, health-care systems, and our society at large have endured as a consequence of the opioid epidemic in the US. Despite federal guidelines to assist with selection and management of prescription opioid drug and dosing (*1*), along with multiple state guidelines and professional consensus statements on opioid prescribing, selection and optimization of prescription opioid therapy remains largely an exercise of trial and error. Consequences of opioid therapy range from therapeutic failure to intolerable side effects, nonmedical misuse, addiction, overdose, and death. Many individuals who receive prescription opioids or experiment with nonmedical use of prescription opioids transition or augment therapy with illicit and synthetic opioids. The combination of both prescription and nonprescription opioid use has escalated the incidence of opioid overdose, now the most common cause of death among individuals <50 years of age in the US (*2*–*4*). As this epidemic is not specific to sex, level of education, ethnicity, or socioeconomic status, any tool that could help predict opioid response and curb the chaos associated with addiction and untimely death is welcome. I am a strong proponent of pharmacogenetics, and I agree with Nerenz and Tsongalis that the application of pharmacogenetics has great potential to help mitigate risks of drug therapy, but that there is insufficient evidence to promote implementation to all pain and addiction management patients today. Select patients can benefit now, and more will benefit as the evidence becomes stronger. Here I discuss my perspective regarding current understanding of associations between genetics and opioid response, as well as barriers for implementation.

RESEARCH TO SUPPORT IMPLEMENTATION OF PHARMACOGENETICS IN PAIN MANAGEMENT

Application of genetic information to opioid therapy today falls into 3 major categories of impact: pharmacokinetics, pharmacodynamics, and risk of addiction. The evidence for implementation of these 3 categories follows this order, with evidence and consensus for pharmacokinetic-related pharmacogenes greater than pharmacogenes for pharmacodynamics, and evidence for

[1]Department of Pathology, University of Utah, Salt Lake City, UT; [2]ARUP Laboratories, Salt Lake City, UT.
***Address correspondence to the author at:** ARUP Laboratories, MS #115, 500 Chipeta Way, Salt Lake City, UT 84108. Fax 801-584-5207; e-mail Gwen.McMillin@aruplab.com.
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[3] **Human genes:** *CYP2D6*, cytochrome P450 family 2 subfamily D member 6; *ABCB1*, ATP binding cassette subfamily B member 1; *ABCC3*, ATP binding cassette subfamily C member 3; *COMT*, catechol-O-methyltransferase; *CYP3A4*, cytochrome P450 family 3 subfamily A member 4; *CYP3A5*, cytochrome P450 family 3 subfamily A member 5; *SLC22A1*, solute carrier family 22 member 1; *UGT2B7*, UDP glucuronosyltransferase family 2 member B7; *CYP2B6*, cytochrome P450 family 2 subfamily B member 6; *OPRM1*, opioid receptor mu 1; *DRD2*, dopamine receptor D2; *KCNJ6*, potassium voltage-gated channel subfamily J member 6; *OPRD1*, opioid receptor delta 1; *PDYN*, prodynorphin.

pharmacodynamic-related pharmacogenes greater than risk of addiction genetics.

As discussed by Nerenz and Tsongalis, the best studied pharmacogene related to pharmacokinetics of opioids is the gene that codes for a major drug-metabolizing enzyme of the same name, *CYP2D6*[3]. Dosing guidelines and drug labeling reflect the relationship of *CYP2D6* genetic variants to opioid selection (*5*–*7*). It is noteworthy that published guidelines do not recommend widespread testing, nor do they recommend the content of testing for this complex gene. Instead, they help apply what is known to a situation, with caution. The approach to treatment of persons predicted to exhibit extreme metabolic phenotypes (poor metabolizers and ultrarapid metabolizers) is typically to avoid CYP2D6-related opioids rather than dose optimization. Although this strategy avoids the CYP2D6-related concerns, it does not mitigate risk or guide selection of alternative therapeutic options. One criticism lies in the actual penetrance of the CYP2D6-associated phenotype relative to opioid therapy. Although there have been many examples of unintentional toxicity and death in patients who are CYP2D6 ultrarapid metabolizers and receive codeine, not all people with this genetic signature will become toxic in response to codeine in part because of the complex interactions of alternate metabolic pathways, drug–drug interactions (e.g., benzodiazepines), clinical status (e.g., preexisting apnea), and pharmacodynamics. What we do know is that a strong clinical association exists, and that there is sufficient evidence to apply caution and avoid codeine when an extreme CYP2D6 phenotype is predicted. I believe that patients with a personal or family history of toxicity to codeine may benefit from knowing their predicted CYP2D6 phenotype. Or, we all simply avoid codeine. Perhaps when the multigenetic and nongenetic factors contributing to the complex phenotype of opioid response are better understood, and clinically validated, we can confidently recommend *CYP2D6* testing for all pain management patients. Or perhaps codeine and other CYP2D6 substrates with high risk of pharmacogenetic-associated toxicity will simply become obsolete. A recently published "short list" of 10 pharmacogenes that are recommended for implementation in pain management includes *CYP2D6* and 7 other pharmacogenes related to pharmacokinetic processes that affect select opioids: *ABCB1*, *ABCC3*, *COMT*, *CYP3A4*, *CYP3A5*, *SLC22A1*, and *UGT2B7* (*7*). The review by Nerenz and Tsongalis presents overlapping genes *ABCB1*, *COMT*, *CYP2D6*, *CYP3A4*, and an additional gene that codes for another drug-metabolizing enzyme, *CYP2B6*. This difference in selection of the most relevant pharmacogenes by 2 well-respected groups of authors demonstrates that consensus for routine pharmacogenetics in pain management is inconsistent and requires additional study.

The best studied pharmacogene associated with pharmacodynamics of opioids is *OPRM1*, which codes for the primary receptor target of most opioids and is recognized by both the Nerenz and Tsongalis review and the short-list review (*7*). The former review also included a dopamine receptor gene (*DRD2*), and the latter review included a voltage-gated potassium channel gene (*KCNJ6*), again introducing inconsistency and uncertainty about what pharmacogenes are most relevant to opioid therapy. Despite extensive study, the data remain controversial and inconclusive, and no dosing or consensus guidelines have been published regarding implementation of pharmacogenes that predict pharmacodynamics.

In the category of addiction risk tools, a recently published study suggested that a gene panel and associated software algorithm exhibited 88% positive predictive value and 97% negative predictive value for identifying risk of opioid addiction (*8*). However, the algorithm represents a small cohort, being developed with data from 37 patients, and tested with an additional 138 patients. There are 4 genes that overlap with those proposed in the 2 reviews mentioned previously above (*ABCB1, COMT, DRD2*, *OPRM1*) and 12 others. Another study

evaluating genetics of opioid addiction risk in a much larger cohort found strong association with *OPRD1* and *PDYN* variants (*9*). Regardless of these pharmacogenetics associations, there are numerous studies that demonstrate changes in gene expression, and epigenetic modifications are important to the pathogenesis and persistence of addiction (*10*). In my opinion, a comprehensive evaluation of addiction risk will involve far more than targeted genotyping, and much more research is required to understand critical variables and biomarkers of risk.

BARRIERS TO IMPLEMENTATION OF PHARMACOGENETICS IN PAIN MANAGEMENT

What will drive uptake of routine pharmacogenetics in pain management? Certainly, government mandates with assurance of payment would help, but there are few examples of laboratory testing that fall into that category of implementation. One of the most widely accepted tools for monitoring opioid use and mitigating risk of misuse in pain management clinics today is urine drug testing (*1*). Urine drug testing is widely available through point-of-collection devices, physician office laboratories, hospital laboratories, and specialized reference laboratories and is recommended by federal, state, and professional guidelines. However, routine urine drug testing remains underutilized for treatment of chronic pain management patients. Use of urine drug testing by physicians was estimated at 15% for a pretreatment screening tool and 26% for monitoring opioid treatment (*3*). Several studies also demonstrate poor competency among physicians for interpretation of urine drug testing results. Implementation of pharmacogenetics is far less defined than urine drug testing, so I am pessimistic that genetic testing will be either adopted or appropriately interpreted in the setting of pain management for some time.

Additional barriers to implementation include lack of standardization in pharmacogenetics testing content, who to test and when, clinically appropriate time to result, lack of standardization among proprietary algorithms used for interpretation and clinical decision support, portability of results from one health-care system to another, and concerns about payment for testing.

APPLICATION OF PHARMACOGENETICS TO FUTURE OPIOID AND NONOPIOID THERAPIES

Perhaps one of the best outcomes of pharmacogenetics in medicine will be to assist with development of drugs that do not have pharmacogenetic variability, or for which the pharmacogenetics variability is well characterized as part of the drug development process. The opportunity for companion diagnostics to guide selection of medications has been successful in many areas of oncology, such as colorectal cancer (*10*). I am optimistic that pharmacogenetics will contribute substantially to the development and characterization of future opioid and nonopioid therapies that are efficacious and safe, with low potential for addiction and drug–drug interactions. With all this said, if I needed pharmacotherapy today, for which pharmacogenetic testing may be relevant, I would request it.

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