Genetic Testing in Pain Medicine

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Affiliations

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

—William Ostler (1892)

Clinicians who treat pain have noted that the response to opioids varies widely among patients, with opioid dose requirements varying in the clinical setting by as much as 40-fold.[1]

Differences in the degree of pain stimulation (a fractured femur compared with a splinter in the toe) and pain sensitivity (Figure 1), weight and age differences, prior opioid use and tolerance, and the differences in bioavailability of various opioid formulations have been cited as causes for the wide variability in analgesia seen with opioids. However, even measuring blood levels of opioids does not predict analgesia.[2] Just as there are differences in hair and eye color, there are differences in response to pain and to analgesic medications. We are beginning to recognize that, as is seen in much of medicine in the 21st century, genetics may explain the variability of responses and predict more effective (or less dangerous) medication choices.

By identifying the genetic risks and the most effective analgesic for an individual patient, the clinician (at least theoretically) could improve the efficacy of the pain medication and decrease the risk for iatrogenically induced overdose, addiction, and death.

Genetic versus Environmental Factors

In the classic "nature versus nurture" scenario, investigators use twin pairs, both identical and fraternal, reared together or apart, to evaluate the heritability of a feature or a condition. Several twin studies have looked at pain conditions, and concluded that migraines have a 39% to 58% genetic contribution[3-5]; low back pain carries a 21% to 67% genetic contribution[6-8]; and menstrual pain has a 55% contribution.[9] In general, significant familial effects account for 24% to 32% of the observed variance detected for heat and cold pressor pain thresholds and opioid-mediated elevation in cold pressor pain tolerance.[10]

Genetics of Analgesia

When we give an opioid for pain relief, there is a continuum of responses, from good analgesia and improvement in function, to poor analgesia, tolerance, physical dependence, and addiction.[11] There are several ways that genetics can influence analgesic response, including drug metabolism enzymes, drug transporters,

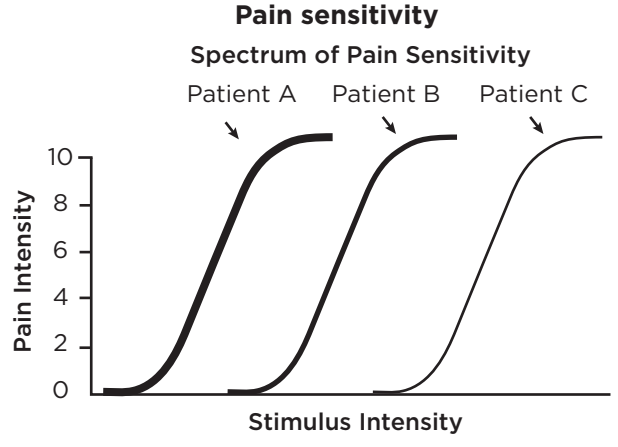
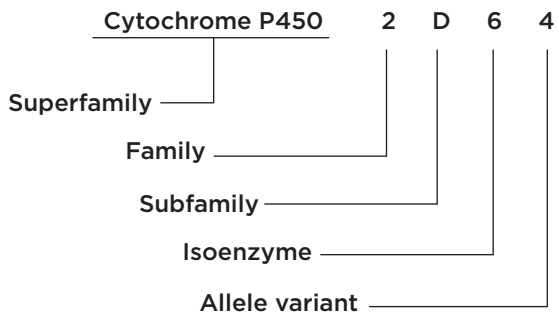


Figure 1. Pain sensitivity graph.[12]



Nomenclaure system for designating enzymes and alleles of cytochrome P450

Figure 3. Cytochrome naming system[56]

opioid or other pain medication receptors, and structures involved in the perception and processing of pain. There are 2 specific genetic issues involving analgesia. The first is the genetic contribution of a variety of different pain types, because if a genetic basis underlies how pain is expressed, including the varying mechanisms of nociceptive, neuropathic, and visceral pain, then the potential exists for new analgesic targets. The second is the genetic influence on drug effectiveness and safety.[12]

Genetic Hypoanalgesia

There are several well-studied hereditary disorders of insensitivity to pain, including "hereditary insensitivity to pain with anhydrosis,"[13] familial dysautonomia (Riley-Day syndrome,[14] Lesch-Nyhan syndrome,[15,16] de Lange syndrome,[17] and Tourette's syndrome[18]). More than 200 candidate genes have been identified that may be involved in pain processing.

Drug Actions

Drug *pharmacokinetics* describes a patient's metabolic status, or the individual's ability to metabolize certain drugs. For example, a patient with impaired metabolism may be unable to activate a prodrug such as codeine into the active morphine metabolite. *Pharmacodynamics* describes a patient's ability to respond to a drug at the level of the drug target or receptor. Here, an example would be a patient who has a nonfunctional receptor for a certain drug who will be unable to respond to that drug regardless of the dosage. *Pharmacogenetics* describes the genetic influence on both the pharmacokinetics and pharmacodynamics (Figure 2). Polymorphic genes that encode the drug-metabolizing enzymes, drug transporters, drug receptors, and other proteins can serve as valuable markers, predictive of the efficacy and adverse responses in human subjects. *Pharmacogenomics* is the science that examines the inherited variations in genes that dictate drug response, predicting whether a patient will have a good or bad response to a drug or no response at all. So, pharmacogenetics refers to the study of inherited differences in drug metabolism and response, whereas pharmacogenomics refers to the general study of the many genes that determine drug behavior. The distinction between the two terms is considered arbitrary and they can be used interchangeably.

Today, many of the complexities of human drug response are sufficiently well understood to transform the field of pharmacogenetics from a descriptive to a predictive science, leading to safer and more effective prescribing and dosing.[12] This kind of testing is being used more frequently in cancer treatment (eg, *BRCA1* in breast cancer) and internal medicine (eg, *VKORC1* for warfarin metabolism), but only very recently in pain medicine.

Tips for Clinicians

- Take a medication history of prior adverse effects or inadequate effects (eg, "What has worked well for you in the past?" "What hasn't helped?" "Are you sensitive to medications or do you need larger than normal doses of medications?"
- Check for common potential interactions with opioids, especially CYP2D6 inhibitors.
- When starting new medications, check the metabolic pathway for activation or excretion issues.
- Be aware of potential drug–drug interactions when adding new medications.
- Use Uniform Data system quantitative metabolite results to evaluate potential drug interactions.
- Consider formal genetic testing to evaluate appropriate opioid choices and potentially to predict opioid risks.

Pain Conditions

Allele-based association studies are expected to shed light on the medical mystery of why pain persists in some patients but not others, despite seemingly identical traumas.

In other words, why do some patients with diabetes develop only numbness as the manifestation of their peripheral neuropathy, whereas others with the same blood sugar fluctuations develop a painful peripheral neuropathy? Why do only some patients with shingles develop postherpetic neuralgia? Why don't all of the victims of a car accident develop the same whiplash pain?

Part of the issue may be "piss poor protoplasm," a term that many young doctors learned as part of their medical training. In a study of Chinese volunteers, investigators found that an allele (COL9A2), which codes for a chain of collagen, was associated with a 4-fold increase in the risk for developing annular tears in individuals aged 30 to 39, and a 2.4-fold increase in the risk for developing degenerative disk disease and endplate herniations in people aged 40 to 49 years old.[19]

Table 1. Common Substrates of CYP Enzymes[23,24]

1A2	2B6	2C19	2D6	3A4
Amitriptyline	Bupropion	Barbiturates	Codeine	Alprazolam
Nabumetone	Methadone	Topiramate	Tramadol	Midazolam
Desipramine	Ketamine	Diazepam	Meperidine	Cyclosporine
Tizanidine	Testosterone	Amitriptyline	Oxycodone	Sildenafil
Imipramine		Imipramine	Hydrocodone	Indinavir
Acetaminophen	2C9	Clomipramine	Dextromethorphan	Verapamil
Cyclobenzaprine	Valproic acid	Sertraline	Amitriptyline	Atorvastatin
Clozapine	Piroxicam	Citalopram	Nortriptyline	Lovastatin
Fluvoxamine	Celecoxib	Phenytoin	Doxepin	Digoxin
Theophylline	Ibuprofen	Carisoprodol	Tamoxifen	Amiodarone
Melatonin	Warfarin	Clopidogrel	Amphetamines	Methadone
Duloxetine			Duloxetine	Erythromyacin
Caffeine			Metoclopramide	Trazodone
Lidocaine			Propranolol	Fentanyl
Warfarin			Venlafaxine	Buprenorphine

CYP, cytochrome p450

Drug Interactions

There are 3 major types of enzyme interactions. A *substrate* is any medication metabolized by that enzyme. An *inhibitor* is a medication that slows the metabolism of another medication, which may result in excessively high blood levels, extended effect, and related toxicity; however, if this is a drug that has to be activated (a *prodrug*), there may be decreased effect. An *inducer* is a medication that boosts the metabolism of another medication, which may result in accelerated breakdown, increased clearance, shortened duration, subtherapeutic levels, or withdrawal; it also may cause increased activity in a prodrug.

Clinical Potential for Disaster

There are potentially many drug interactions, and the risk increases with increased numbers of medications being used. Glintborg et al[20] looked at 200 patients discharged from the hospital; the average age of the patients was 75, and the median number of drugs used was 8 (with a range of 1-24). They calculated a potential of 476 drug interactions in 63% of the patients. In another study, patients who were taking 3 to 5 drugs had a 29% risk for interactions, whereas patients who were taking 11 or more drugs had a 96% risk for interactions. Only 1% of patients were aware of the potential for drug–drug interactions.[21]

Cytochrome p450 Enzymes

The cytochrome p450 (CYP) enzyme system is a heme-containing, microsomal drug-metabolism superfamily involved in biosynthesis and degradation of endogenous compounds, chemicals, toxins, and medications. There have been 57 enzymes identified in humans, and they are divided into family, subfamily, isoenzymes, and allele variants (Figure 3).[22] Metabolism of most currently used drugs occurs by about 7 clinically relevant enzymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, all of which have different (but partially overlapping) catalytic activities (Figure 4). Many of the medicines commonly used are substrates (Table 1), inhibitors (Table 2), or inducers (Table 3) of medicines used in pain treatments.

There also are multiple potential interactions between herbs, supplements, or foods and prescription medications. For instance, St. John's wort, commonly taken for depression, induces CYP1A2, 2C9, and 3A4 enzymes. The induction of CYP1A2 and CYP2C9 can increase warfarin metabolism, leading to lower blood levels and, therefore, an increase in the risk for clotting. St. John's wort can decrease verapamil, statins, methadone, digoxin, and HIV medication levels (via CYP3A4), tricyclic antidepressant and tizanidine levels (via CYP1A2), as well as potentially causing a

Table 2. Common Inducers of CYP Enzymes[23,24]

1A2	2C9	2C19	2D6	3A4
Carbamazepine	Rifampin	Carbamazepine	Carbamazepine	Carbamazepine
Griseofulvin	Ritonavir	Rifampin	Phenobarbital	Phenytoin
Lansprazole	Barbiturates	Ginko	Phenytoin	Nevirapine
Omeprazole	St. John's wort		Rifampin	Modafinil
Ritonavir			Dexamethasone	Topiramate
Tobacco				Butabutal
St. John's wort				St. John's wort

CYP, cytochrome p450

Table 3. Common Inhibitors of CYP Enzymes[23,24]

1A2	2C9	2C19	2D6	3A4
Fluvoxamine	Fluvoxamine	Fluoxetine	Duloxine	Ketoconazole
Ciprofloxin	Paroxetine	Fluvoxamine	Cimetidine	Erythromycin
Mexiletine	Amiodarone	Paroxetine	Sertraline	Mifepristone
Verapamil	Modafinil	Topiramate	Fluoxetine	Nefazodone
Caffeine	Tamoxifen	Modafinil	Haloperidol	Grapefruit
Grapefruit juice		Oral contraceptives	Methadone	Indinavir
			Paroxetine	Ritonavir
			Quinidine	Verapamil
			Celecoxib	Diltiazem
			Bupropion	
			Ritonavir	
			Amiodarone	
			Metoclopramide	
			Chlorpromazine	

CYP, cytochrome p450

serotonin syndrome with serotonin reuptake inhibitors. Intestinal CYP3A4 concentration can be decreased by 47% within 4 hours of grapefruit consumption.[25] Smoking is a potent inducer of CYP1A2, leading to decreased caffeine levels (which may be the cause of the increased agitation seen with smoking cessation, as caffeine levels increase when the induction stops). In a study comparing smokers with nonsmokers, the smokers had higher pain scores, and took larger doses of hydrocodone, but had significantly lower serum levels of hydrocodone.[26]

Why Consider Genetic Testing?

There are several potential reasons to consider genetic testing. Drugs are metabolized slowly in individuals carrying a genetic polymorphism that causes absent or decreased enzyme activity, and these individuals are at an increased risk for adverse drug reactions (ADRs) or therapeutic failure. However, drug therapy could be ineffective if the drug is metabolized too quickly because of a genetic polymorphism. Knowledge of these polymorphisms before beginning a drug therapy could help in choosing the right agent at a safe dosage,

especially those drugs with a narrow therapeutic index and a high risk for the development of ADRs.[27] In a literature review of ADRs from 1995 to 2000, more than 50% of the drugs cited are metabolized by at least one enzyme with known poor-functioning alleles.[28]

Types of Metabolizers

Patients can be classified by how effectively they metabolize a medication, which is based on how many copies of normal or abnormal alleles they inherited (Table 4). An *extensive metabolizer* (EM) has 2 normal, or "wild-type," alleles and is considered "normal." An *intermediate metabolizer* (IM) has 1 normal and 1 reduced allele or 2 partially deficient alleles. A *poor metabolizer* (PM) has 2 mutant alleles leading to a very limited or complete loss of activity, whereas the *ultra-rapid metabolizer* (UM) has multiple copies of functional alleles leading to excess activity.

There also is an ethnic distribution of this polymorphism. Approximately 7% to 10% of whites are *CYP2D6* deficient (PM), but only 1% to 2% of Asians and 2% to 4% of blacks are PMs. However, approximately 30% of Asians and blacks have intermediate metabolism of CYP2D6. On the other hand, approximately 29% of Ethiopians, 10% of Southern Europeans, and 1% to 2% of Northern Europeans are UMs.[29] In psychiatry, 52% of the psychiatric and 62% antidepressant or antipsychotic drugs are metabolized by CYP2D6.[30] A prospective 1-year clinical study of 100 psychiatric inpatients suggested a trend toward longer hospital stays and higher treatment costs for UMs and PMs of CYP2D6.[31] Tamoxifen must be metabolized via CYP2D6 to endoxifen to be effective; therefore, a PM might be at risk for failure of breast cancer treatment.[32] And, as is seen shortly, CYP2D6 activity can have substantial influence on the opioids that are commonly used in pain management.

These alternate genes, known as single-nucleotide polymorphisms (SNPs), are identified by letters or numbers. For example, normal functional activity alleles of the *CYP2D6* gene are designated CYP2D6*1 and CYP2D6*2. The four most common mutant alleles are CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6 and account for 93% to 97% of the PM phenotypes in the white population.

CYP2D6 Influence on Opioids

Codeine is an inactive compound (prodrug), metabolized by CYP2D6 into its active form, *morphine*. It only has a weak affinity for the μ-receptor, 300 times less than morphine.[33] Therefore, CYP2D6 PM patients and patients taking CYP2D6 inhibitors (see Table 3) who are given Tylenol # 3 (codeine/acetaminophen) are really being given only acetaminophen, whereas UM patients may have dangerously high levels of morphine after standard doses.[34] Tramadol is metabolized by CYP2D6 to its M1 metabolite, which is at least 6 times more potent than the parent compound.[35] *Hydrocodone* displays weak binding capacity for the μ-receptor, but the CYP2D6 enzyme demethylates it into *hydromorphone*, which has much stronger μ binding than hydrocodone.[36] Otton et al found that individuals identified as EM reported more "good opiate effects" and fewer "bad opiate effects" than PM or EM patients pretreated with quinidine (a potent CYP2D6 inhibitor). They concluded that activity of CYP2D6 might limit the abuse liability of hydrocodone.[37] A study looking at 25,200 urine samples from patients taking only hydrocodone showed a 60-fold variability in hydrocodone/hydromorphone ratios. They identified 0.6% UM and 4% PM, with a 134-fold between-subject variability.[38] *Oxycodone* is metabolized by glucuronidation to noroxycodone (which has less than 1% of the analgesia potency of oxycodone), and by 2D6 to *oxymorphone*. Oxycodone is an analgesic, not a prodrug; however, oxymorphone is an active metabolite of oxycodone, and may have significant effects on analgesia.

Because oxycodone is dependent on the 2D6 pathway for clearance, it is possible that toxicity and overdose can occur with 2D6 inhibitors.[39]

Drugs of abuse also are metabolized by CYP2D6. Methamphetamine acts as both a substrate and a competitive inhibitor of *CYP2D6*, whereas methylenedioxy-*N*-methylamphetamine (MDMA) acts as a high-affinity substrate and potent inhibitor of the enzyme, so that methamphetamine and MDMA users, regardless of their genotype, act as poor metabolizers of CYP2D6.[40]

CYP3A4 also is involved in opioid metabolism. Fentanyl and buprenorphine are excreted via CYP3A4, and blood levels would be expected to rise in PM patients or those receiving CYP3A4 inhibitors.[41] Methadone has been widely reported to be metabolized by CYP3A4,[42,43] although some evidence suggests that it is primarily metabolized by CYP2B6[44] and patients who are homozygous for the variant *CYP3B6*6* gene required lower doses of methadone than the heterozyotes or noncarriers.[45]

Genotype-Based Dose Adjustments

Standard dose adjustments look at the differences in pharmacokinetic parameters, such as clearance and area under the curve (AUC). Genotype-based dose adjustments would suggest a standard dose

Table 4. Population Distribution of Isoenzymes

Gene	PM	IM	EM	UM
CYP2C9	2%-4%	>35%	60%	NA
CYP2C19	2%-20%	24%-36%	14%-44%	30%
CYP2D6	10%	35%	48%	7%

EM, extensive metabolizers, **IM,** intermediate metabolizers, **PM,** poor metabolizers, **UM,** ultra-rapid metabolizers

Test	Test Method	Test Outcome	Measured Reults	Creatinine normalize	Cutoff
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	Pos	530	640	50.00
Norhydrocodone	LC-MS/MS	Pos	494	595	50.00
Hydromorphone	LC-MS/MS	Pos	78	95	50.00
Oxycodone	LC-MS/MS	Pos	8,388	10,119	50.00
Noroxycodone	LC-MS/MS	Pos	2,358	2,845	50.00
Oxymorphone	LC-MS/MS	Pos	899	1,085	50.00

Figure 5. Urine drug screen showing poor conversion of hydrocodone to hydromorphone and oxycodone to oxymorphone

(image courtesy of Andrea Trescot, MD).

(eg, 2 tablets of medication X) for an EM; however, a PM might need only 1 tablet, an IM might need 1.5 tablets, and an UM might need 3 or more tablets of the same medication to get the same effect.[46] In a study of antidepressant drugs, it was calculated that, for a CYP2D6 PM patient taking nortriptyline, the therapeutic dose would be 50 mg, whereas a UM patient would need a dose of 500 mg.[46]

As another example, amitriptyline is metabolized by CYP2C19 to nortriptyline, which is then metabolized and excreted by CYP2D6. Genetic testing of CYP2D6 and CYP2C19 can identify patients at low or high risk for side effects of amitriptyline therapy. Carriers of 2 functional CYP2D6 alleles had a significantly lower risk for side effects than carriers of only 1 functional allele, with the lowest risk seen for carriers of 2 functional CYP2D6 alleles combined with only 1 functional CYP2C19 allele.[47] The authors noted that 65% of patients (normal CYP2D6 and normal to poor CYP2C19) could receive standard doses of amitriptyline (which is very inexpensive) with little or no side effects, but those patients with normal CP2C19 and poor CYP2D6 were at very high risk for anticholinergic and mental side effects, and should be treated with newer (and more expensive) medications.

Urine Drug Screening

Many urine drug screens (UDS), especially office "point-of-service" dipsticks, give a simple "positive" or "negative" result. But some quantitative UDS report opioid metabolites (Figure 5), which can give clues as to the genetic makeup of a patient. In this example, there is poor conversion of hydrocodone to hydromorphone, as well as poor conversion of oxycodone to oxymorphone, suggesting a CYP2D6 deficiency or inhibition. If this patient had complaints of poor analgesia, changing to hydromorphone or oxymorphone would be expected to bypass the CYP2D6 enzyme and provide better pain relief. Most normetabolites (such as norhydrocodone and noroxycodone) have longer elimination half-lives than the parent drugs, so that urine samples that test negative for the parent compound still can be positive for the normetabolite.[48] Checking for metabolites in the urine also can uncover adulterations such as those seen in Figure 6, where the dipstick was positive for hydrocodone and methadone, as was prescribed, but the UDS showed a complete lack of metabolites, consistent with scraping the pills into the urine (which this patient admitted to when confronted by the results).

DNA Testing

The use of oral samples or buccal swabs for specific genetic testing recently ha become economically feasible, given a dramatic decrease in pricing. Several SNPs are readily available, providing information on CYP enzymes 2D6, 2C9, 2C19 as well as VKORC1 (reflecting the metabolism of warfarin; Figure 7). Additional testing for CYP3A4 also is available (Figure 8). However, intriguing information regarding potential risk for addiction and misuse also may be available through genetic testing (Figure 9).

How Do We Use Genetic Testing?

Genetic testing can be used to explain and confirm ineffective or high opioid use. For example, patients with CYP2D6 deficiencies would be expected to have poor (or relatively poor) relief from tramadol, codeine, hydrocodone, and oxycodone, whereas patients with CYP2D6 UM might be at risk for unexpectedly high levels of morphine from codeine.[49] Switching to an opioid not metabolized by that enzyme (such fentanyl or morphine) might be much more effective or less risky. Patients with poor opioid efficacy from an inactive OPRM1 allele might benefit from a κ-agonist such as buprenorphine instead of a μ-agonist such as morphine.

There is less evidence for (but a great deal of interest in) the predictive value of genetic testing. Can it be used to predict those patients who are likely to participate in risky behaviors or those patients more likely to abuse opioids? Can it predict the patients more likely to develop post-traumatic stress disorder after a motor vehicle collision or more likely to fail antidepressants?

Test	Test method	Test outcome	Measured Results	Creatinine normalized	Cutoff
Natural and Semi-synthetic Opioids					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	Pos	16,077	29,718	50.00
Norhydrocodone	LC-MS/MS	Neg		-	50.00
Hydromorphone	LC-MS/MS	Neg		-	50.00
Oxycodone	LC-MS/MS	Neg		-	50.00
Noroxycodone	LC-MS/MS	Neg		-	50.00
Oxymorphone	LC-MS/MS	Neg		-	50.00
Synthetic Opioids					
Fentanyl	LC-MS/MS	Neg		-	2.00
Norfentany;	LC-MS/MS	Neg		-	8.00
Methadone	LC-MS/MS	Pos	16,502	30, 503	100.00
EDDP (methadone metabolite)	LC-MS/MS	Neg		-	100.00

Figure 6. Lack of urine metabolites, consistent with adulteration

(image courtesy of Andrea Trescot, MD).

Future Therapies

Knowledge of genetic issues is allowing more effective screening of drugs for inflammatory and neuropathic pain treatment.[50] Currently, each patient is given a trial-and-error analgesic trial. However, in the near future, pharmacogenetic approaches may be implemented to best predict which medicine may be most appropriate for an individual, providing the therapy with the most sustained efficacy and the best side-effect profile.[51] Droney and colleagues maintain that, "integration of genetic analysis in clinical studies with carefully defined outcome measures will increase the likelihood of identifying clinical and genetic factors which can be used to predict opioid response."[52]

Conclusion

Patient care may be improved by genotyping and following drug concentration levels.[53] Pharmacogenetics and therapeutic drug monitoring can potentially minimize adverse events, while maximizing efficacy.[54] Integration of genetic analysis in clinical studies will increase the likelihood of identifying clinical and genetic factors that can be used to predict opioid responses.[52] With knowledge of a patient's potential for beneficial response to a given opioid, a physician is armed with critical information that can guide therapeutic decisions. Incorporation of such biomarkers are occurring on the forefront of personalized medicine, and have the potential to dramatically improve the utility and efficacy of both current and future pain management strategies.

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REVIEW ARTICLE

Genetic Testing for Enzymes of Drug Metabolism: Does It Have Clinical Utility for Pain Medicine at the Present Time? A Structured Review

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ABSTRACT

Study Design. This is a structured review of genomic (genetic) testing for enzymes of drug metabolism.

Objectives. Recently, industry began offering genomic testing for enzymes of drug metabolism. As such, the objective of this review was to determine if genomic testing for enzymes of drug metabolism has any imminent clinical relevance for the practice of pain medicine.

Methods. Relevant references relating to pharmacogenetics, pharmacogenomics, and the metabolizing of drugs used in pain medicine by cytochrome P-450 enzymes were located and reviewed in detail. The P-450 enzymes that metabolize each drug and whether that drug had been identified as being subject to a clinical consequence of a genetic polymorphism of the P-450 enzyme involved in its metabolism were placed into tabular form.

Results of Data Synthesis. 1) For a large number of drugs, we do not yet know which cytochrome P-450 enzymes are involved in their metabolism; 2) For a large number of drugs, the consequences of a P-450 genetic polymorphism have yet to be determined; 3) Genetic polymorphism can lead to important potential clinical consequences for some opioids, anticonvulsants (phenytoin), benzodiazepines (diazepam), muscle relaxants (succinylcholine), antidepressants (imipramine, nortriptyline, venlafaxine), typical neuroleptics, alcohol, antihypertensives (propranolol, timolol), local anesthetics (procainamide), L-dopa, nicotine, and warfarin. Based on these results, factors for and against using genomic testing were reviewed.

Conclusions/Recommendations. It was concluded that genomic testing for enzymes of drug metabolism has significant potential for improving the efficacy of drug treatment and reducing adverse drug reactions. Recommendations for when such testing would be useful are outlined.

Key Words. Drug Metabolism; Cytochrome P-450 Enzymes; Genomic Testing; Pharmacogenetics; Pharmacogenomics; Genetic Polymorphism

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Introduction

There has recently been an explosion in knowledge relating to the genetics of drug metabolism. Because of the technical nature of this information, there has been some difficulty in disseminating this information to the clinician. The purposes of this review are: A) To review the current status of the genetics of drug metabolism; B) To determine if this information has any imminent clinical relevance for the practicing pain physician; and C) To conclude if newly available genetic testing has any current clinical value to the practice of pain medicine. This review uses genetic terms. Definitions for those terms can be found in Appendix 1.

Drug Metabolism and Phenotypic Variation

Interpatient variability in response to drug therapy is the rule, not the exception for almost all medications [1]. It is rare for a drug to be safe or effective for everyone [2]. Thus, drug efficacy varies unduly. For example, the highest percentage of patients responding to a drug is 80%, for the COX-2 inhibitors, and the lowest is 25%, for cancer chemotherapy, while depression treatment with selective serotonin reuptake inhibitors has a 62% response rate [2]. Twin studies on drug metabolism have shown clear hereditability in the rate of drug metabolism [3]. As such, drug levels in plasma can vary more than 1000-fold between two individuals having the same weight and given the same drug dosage [4]. It is thought that phenotypic variation accounts for 20–40% of the interindividual differences in drug metabolism and response [4].

Phenotypic variation is also the likely cause of a rough percentage of adverse drug reactions [5]. In a study in a major hospital, Classen et al. identified 2,227 instances of adverse drug reactions among hospitalized patients [6]. Of those, 42% were attributed to misdosing; however, 50% had no preventable cause and were likely related to phenotypic variation. In another study, a systemic review of 27 drugs frequently cited in adverse drug reactions, 59% of those drugs were metabolized by at least one enzyme with a variant allele known to cause poor metabolism [7]. Thus, phenotypic variation has been implicated in both drug efficacy problems and adverse drug reactions.

Genetic Polymorphisms

Genes are considered functionally "polymorphic" when allelic variants exist stably in the population, one or more of which alters the activity of the encoded protein in relation to the wild-type sequence [5]. Genetic polymorphisms in drug metabolism are common occurrences [9]. Mutations in the genes for numerous drug-metabolizing enzymes cause enzyme variants with higher or lower activities or lead to the partial or total absence of an enzyme [9]. This understanding and the clinical identification of patients who appear to be hypersensitive or insensitive to drug effects have enabled researchers to classify individuals into poor, intermediate, extensive, and ultrarapid metabolizers of antidepressant drugs [10]. This classification has been shown to be dependent on or proportional to the number of allele copies of the gene carried. For example, for clearance of nortriptyline, poor metabolizers have zero copies of the cytochrome P-450 enzyme CYP2D6, intermediate metabolizers have one copy, extensive metabolizers have two copies, and ultrarapid metabolizers have more than two copies [4]. Knowledge of the phenotypic status of the patient for CYP2D6 thus becomes important, as it translates into metabolizer status. This has clinical significance for response. For example, it has been calculated that, to reach a therapeutic level of nortriptyline, the dosage has to be adjusted in relationship to the number of gene copies. Thus, among patients homozygous for a null CYP2D6 allele (poor metabolizers), the dosage should be 50 mg/day. For patients with multiple gene copies (extensive and ultrarapid metabolizers), the dosage should be 500 mg/day [11]. These polymorphic differences reflected in different metabolizer statuses vary among racial groupings. It has long been known that many polymorphic drug-metabolizing enzymes exhibit qualitative and quantitative differences among racial groups [1]. Some of these racial differences are outlined in Table 1.

There are also polymorphisms in drug transporter genes. It is now believed that membrane transporters may be extremely important in: absorption of oral medications across the gastrointestinal tract; excretion into bile and urine; distribution into "therapeutic sanctuaries" such as brain and testis; and transport into sites of action such as cardiovascular tissues, tumor cells, and infectious microorganisms [5]. However, at the present time, the clinical relevance of polymorphisms in drug transporter genes has not been fully elucidated [5]. Some examples of genetic polymorphisms relevant to drug transporters for some drugs important to pain medicine and their clinical relevance are presented in Table 2.

Drug targets are also subject to genetic polymorphisms. Molecular studies have revealed that many of the genes encoding these drug targets

Table 1 Differences in metabolizer status among racial (ethnic) groups [7,8]

Gene or enzyme	Phenotype	Frequencies for different ethnic groups
CYP1A2	PM	Caucasians 12%
CYP2C9	PM	Caucasians 2–6%
CYP2C19	PM	Caucasians 2–6% Chinese 15–17% Japanese 18–23%
CYP2D6	PM	Caucasians 3–10% Chinese/Japanese/African Americans <<2%
	UR	Ethiopians 20% Hispanics 7% Scandinavians 1.5%
N-acetyl transferase (NAT_2) (acetylation)	PM	Caucasians 60% African Americans 41% Chinese 20% Japanese 8–10% Egyptians 92% Inuits 5%
Thiopurine methyltransferase (S-methylation)	PM	Caucasians 1%

Abbreviations: PM = poor metabolizer; UR = ultrarapid metabolizer.

exhibit genetic polymorphisms, which, in many cases, alter their sensitivity to specific medications [5]. Some examples of genetic polymorphisms relevant to receptors for some drugs important to pain medicine and the resultant clinical relevance are presented in Table 3.

Single Nucleotide Polymorphism

Single nucleotide polymorphisms (SNPs) are single base differences in DNA sequences that can be observed between individuals in the population [21]. SNPs are present throughout the human genome, with an average frequency of approximately 1 per 1000 base pairs [22]. The SNP Consortium is currently producing an ordered high-density SNP map of the human genome [23]. When alleles are physically close, they are more likely to be inherited together than alleles that are farther apart. Therefore, variations of several ordered SNP markers that are close to or within a particular gene variant are more likely to be inherited together with the gene variant. As such, recent data have indicated that SNP mapping can be an inexpensive and fast method of identifying disease-susceptibility genes [23]. SNP mapping is predicted to be a tool for personalized genetic profiling [23]. SNPs will, thus, be useful for identifying patients who are likely to benefit from a specific agent or those likely to experience unacceptable toxicities [1]. In addition, SNP mapping will be used in the selection of patient groups enriched for efficacy in phase III studies [23]. Finally, SNPs may provide the necessary huge number of markers sequenced for association studies. These studies correlate the presence of a chromosomal region and a trait (disease or drug response) in unrelated individuals of a population rather than related individuals as in linkage genetic studies [24].

Pharmacogenomics and Pharmacogenetics

SNP research is now being incorporated into the research area of pharmacogenomics. The ultimate goal of pharmacogenomics is to define the contributions of genetic differences in drug disposition and drug targets to drug response, thereby improving the safety and efficacy of drug therapy through use of genetically guided, individualized treatments [20]. Although the principles of pharmacogenomics have been around for decades, this field has recently undergone rapid development because of a number of technological advances: High throughput DNA and mRNA analyses; the introduction of microarrays for the simultaneous assessment of multiple genes (64,000 gene clones on a single slide); automated multiplex assays that can analyze 100,000 genotypes per day; the

Table 2 Clinically relevant genetic polymorphisms affecting drug transporters and their effects on drug efficacy [12,13,29]

Drug	Transporter gene	Altered drug effect
Lithium	Serotonin transporter gene (5-HTTPLPR = serotonin transporter promoter-linked polymorphic region)	Prophylactic efficacy in mood disorders (bipolar disorder and major depression) affected by 5-HTTPLPR variant. Patients with S/S variant have worse response to Lithium than L/S and L/L variants (S = short, L = long)
Clomipramine Fluoxetine Paroxetine Fluvoxamine	Serotonin transporter gene (5-HTTLPR)	Antidepressant efficacy
Not applicable	Serotonin transporter promoter gene moderates the effect of stressful life events on depression as follows: Individuals with two copies of the short allele (s/s) have more depressive symptoms in relationship to stress than those homozygous for the long allele (L/L)	Not applicable

Table 3 Clinically relevant genetic polymorphisms affecting receptors and their altered drug effects [4,13,15–20]

Drug	Receptor	Altered Drug Effect
Enarapril Captopril	Angiotensin-converting enzyme (ACE)	Blood pressure, cardiac effects, renoprotective effects
Clozapine and other neuroleptics	5-hydroxytryptamine 2A receptor	Response in schizophrenia
Heroin and other opioids	μ–opioid receptor, variation in binding the opioid	May be implicated in response to painful stimuli and pioid addiction
Mexiletine	SCN5A	SCN5A gene mutation predisposes to long QT syndrome with mexiletine
Halogenated inhalational anesthetics, suxamethonium	Ryanodine receptor (RYR1)	Drug-induced malignant hyperthermia
Benzodiazepines Alcohol	GABAA26	Pro385/Ser385 heterozygotes are more resistant to the effects of alcohol than Pro 385/Pro385 homozygotes
Neuroleptics	Dopamine D_3 receptor gene (DRD3)	Tardive dyskinesia and akathisia (acute) significantly associated with DRD3 genotype (homozygous at greater risk than heterozygous glycine allele)
Lithium	Inositol PEP	Response to lithium in manic depressive illness
Haloperidol Clozapine	Dopamine receptors, D_2, D_3, D_4	Response to antipsychotics

completion of the human genome project, which sequenced the entire human genome; and the development of computational biology or bioinformatics, which has provided special software to analyze genotypic data and compare it with existing genome databases using pattern recognition, leading to the rapid interpretation and implementation of data [1,23]. These advances have enabled genomic researchers to identify genes and families of genes for tractable or screenable targets that are not known to be genetically related to disease [23].

The term pharmacogenomics has been used interchangeably with pharmacogenetics. The genetically determined variability in the drug responses of individuals defines the research area known as pharmacogenetics. The goal of pharmacogenetics is to predict a patient's genetic response to a specific drug as a means of delivering the best possible medical treatment. As such, the field covers the area of the genetic basis of pharmacokinetics and pharmacodynamics, basic drug development, patient genetic testing, and clinical patient drug trials [2]. The purposes of a clinical pharmacogenetic assay are twofold: 1) To distinguish between those patients who are more and those who are less likely to respond to a drug; and 2) To distinguish between those who are more and those who are less likely to be at risk for adverse events from that drug [2]. Potential applications of pharmacogenomic research are presented in Table 4. It is to be noted that potential application #7 is similar to the major goal of pharmacogenetics as described above.

Pharmacogenetics and the Drug-Metabolizing Systems of the Liver

An example of a recent success in pharmacogenetics has been the work performed with drug-metabolizing enzyme systems of the liver. These enzyme systems usually convert drugs to metabolites that are more water soluble and, thus, more easily excreted. Pathways of drug metabolism are classified as either phase I or phase II (Appendix 1). Both types of reactions convert lipid-soluble drugs into more water-soluble forms [25]. The cytochrome P-450 (CYP) enzymes are a superfamily of microsomal enzymes in the liver that are the most important enzymes for catalyzing phase I drug metabolism. There are more than 20 CYP enzymes; however, there are only six that play significant roles in the metabolism of clinical medications. These are CYP1A2, CYP2D6, CYP2C9, CYP3A4, CYP3A5, and cypocia [25].

Sequencing of the human genome has revealed 58 different human *CYP* genes. This enzyme system is extremely polymorphic. For example, more than 80 different allele forms of *CYP2D6* have been described [4]. This polymorphism is extremely important, as CYP2C9, CYP2D6, and CYP3A4 together account for 60-70% of all phase I dependent metabolism of clinically important drugs [4]. The potential consequences of genetic polymorphisms relevant to drug metabolism are presented in Table 5.

Table 4 Applications of pharmacogenomics [1]

1. Identification of novel drug targets
2. Prediction of efficacy in drug development
3. Prediction of drug toxicity in drug development
4. Improved efficiency drug development by decreasing the numbers of patients required to show drug efficacy in early clinical trials
5. Definition of the mechanisms of action of new compounds
6. Screening for the direct influence of an agent on a specific pathway
7. Identification of drug responders, drug nonresponders, and drug toxic responders in a population (individualized therapy)

Table 5 Potential consequences of polymorphisms relevant to drug metabolism [8]

1. Drug toxicity
2. Adverse drug reactions
3. Extended pharmacological effects
4. Decreased effective dose
5. Exacerbation of drug-drug interactions
6. Metabolism by alternative deleterious pathways
7. Lack of drug efficacy
8. Requirement for higher dose to be efficacious
9. Lack of prodrug activation

It is believed that, at the present time, the available pharmacogenetic information is substantial enough to provide patients with information that could facilitate individualized therapy both with respect to the choice of drug and to the dose of a specific drug [4]. Although pharmacogenetic knowledge about drug metabolism is extensive, knowledge of drug transport systems and receptor sensitivity is scarce [4]. Thus, the rest of this review focuses on drug-metabolizing systems.

Genomic Analysis

The availability of significant knowledge on the genetics of drug-metabolizing systems plus the parallel development of efficient automated methods (described above) to perform genetic analyses to determine an individual's genotype for polymorphic genes known to be involved in drug metabolism has very recently led to the ability of industry to offer clinical individual genomic analysis to patients. Thus, there has been considerable growth in the number of companies offering patient genomic analysis of drug-metabolizing systems to physicians [19]. The intended purpose of such genomic analyses is to identify individual patients as poor, intermediate, extensive, or ultrarapid metabolizers of a specific drug in order to predict drug response and/or drug toxicity [18]. However, because this area is so new and so complex, the average physician does not, at the present time, have the knowledge base to determine if such analyses would help him/her clinically to be more effective in treating patients.

The objectives of the main body of this review are: 1) To present an overview of the drugs that are currently known to be targets of metabolism of CYP enzymes that are determined by polymorphic genes; 2) To present the clinical consequences of these polymorphisms; and 3) Based on this information, to make some recommendations as to whether pain physicians should or should not consider patient genomic analyses for their pain patients.

Methods

Relevant references were located by the following procedure. The MEDLINE, Science Citation Index, and National Library of Medicine Physician Data Query (PDQ) databases were searched using the following subject headings: cytochrome P-450 enzymes; pharmacogenetics; and pharmacogenomics. Each of these terms was exploded with each type of drug subgroup (e.g., nonsteroidal anti-inflammatories) as a medical subject heading (MESH). Each term was exploded for all subheadings in MESH and all retrieved references were reviewed. The searches were not restricted to the English language only and were conducted back to 1966, except for that of the Science Citation Index, which was conducted back to 1974. The most recent year of each search was 2003. Any research article reporting on a drug and its metabolism by a CYP enzyme, or another enzyme (e.g., alcohol dehydrogenase), was isolated. Reports relating to drugs used in pain medicine were isolated. A table was then constructed, in which each drug on which there was a report was placed into a drug group. In addition, the specific CYP enzymes metabolizing those drugs were added to the table. Finally, whether each drug had been identified as being subject to a clinical consequence of a genetic polymorphism of the enzyme involved was included in the table.

Results

Results of the search and review are presented in Table 6. This table lists the individual drug groups, drugs within those groups, CYP enzymes and other enzymes metabolizing the drugs, and most importantly, the clinical consequences of genetic polymorphism of the enzyme involved in metabolizing the drug. Closer examination of Table 6 reveals the following observations: 1) We do not, as yet, know the cytochrome P-450 metabolism of a large number of drugs; 2) For a large number of drugs, the consequences of genetic polymorphism have yet to be clarified; 3) Genetic polymorphism can lead to important clinical consequences for some opioids, some anticonvulsants (phenytoin), some benzodiazepines (diazepam), some muscle relaxants (succinylcholine), some antidepressants (imipramine, nortriptyline, venlafaxine), some typical neuroleptics, alcohol, some antihypertensives (beta-blockers, propranolol, timolol), some local anesthetics (procainamide), L-dopa, nicotine, and warfarin.

Table 6 Drugs and their CYP metabolizing enzymes and associated clinical consequences of gene polymorphisms

Drug group and drug	Metabolizing enzyme	Clinical consequence of polymorphism affecting drug metabolism
I. Nonsteroidal anti-inflammatory analgesics (COX-1, mainly)		
Ibuprofen	+CYP2C9 [5]	▲
Diclofenac	CYP2C9 [5]	▲
Piroxicam	+CYP2C9 [5]	▲
Tenoxicam	CYP2C9 [5]	▲
Mefenamic acid	CYP2C9 [5]	▲
Naproxen	CYP1A2 [7]	▲
II. Nonsteroidal anti-inflammatory analgesics (COX-2)		
Celecoxib	CYP2C9 [27]	▲
III. Steroidal anti-inflammatory analgesics		
Cortisol	CYP3A4 [27]	▲
Budesonide	CYP3A4 [27]	▲
Dexamethasone	CYP3A4 [27]	▲
Hydrocortisone	CYP3A4 [27]	▲
Methylprednisolone	CYP3A4 [27]	▲
IV. Opioids		
Codeine	CYP2D6 [15,28,29]	Poor metabolizers are unable to convert codeine to morphine (no pain effect from codeine). Rifampin induces increased metabolization to morphine in extensive metabolizers but not in poor metabolizers.
Morphine	Uridine diphosphate glycosyl transferase (UGT2Bs)	▲
Dihyrocodeine	CYP2D6 [30]	These opioids are structurally similar to codeine and, as such, their metabolism could be under genetic control leading to variability of clinical response (side effects, efficacy, and dependence) in poor metabolizers [20,31].
Hydrocodone	CYP2D6 [30]	
Oxycodone	CYP2D6 [30]	
Thebaine	CYP2D6 [30]	
Methadone	CYP2D6 [30]	
Tramadol	CYP2D6 [5]	
Alfentanyl	CYP3A4 [5]	▲
Fentanyl	CYP3A4 [5]	▲
Sufentanil	CYP3A4 [5]	▲
V. Nonopioid nonanti-inflammatory analgesics		
Acetaminophen	CYP1A2 [32], CYP2E1 [20]	▲
Phenacetin	CYP2D6 [20], CYP1A1 [7]	▲
VI. Anticonvulsants		
Phenytoin	CYP1A2 [7], CYP2C9 [33,19], CYP2C19 [35]	Phenytoin toxicity for poor metabolizers; low levels of drug for ultrarapid metabolizers at therapeutic doses [33,19,35].
Carbamazepine	CYP3A4 [33], CYP1A2 [7]	▲
Barbiturates	CYP2C19 [5]	▲
Gabapentin	CYP3A4 [36]	▲
Lamotrigine	CYP3A4 [36]	▲
Hexobarbital	CYP2C19 [20]	▲
Mephobarbital	CYP2C19 [20]	▲
VII. Antianxiety agents (benzodiazepines)		
Diazepam	CYP2C19 [5], CYP3A4 [5]	Unacceptable prolonged sedation in poor metabolizers, unconsciousness noted more frequently in Asian populations [5]
Alprazolam	CYP3A4 [36]	▲
Clonazepam	CYP3A4 [36]	▲
Midazolam	CYP3A4 [36]	▲
VIII. Antianxiety agents (nonbenzodiazepines)		
Buspirone	CYP3A4 [37]	▲
IX. Sedatives (benzodiazepines)		
Triazolam	CYP3A4 [36]	▲
Temazepam	CYP3A4 [5]	▲
X. Sedatives (nonbenzodiazepines)		
Zolpidem	CYP3A4 [36]	▲

Table 6 Continued

Drug group and drug	Metabolizing enzyme	Clinical consequence of polymorphism affecting drug metabolism
XI. Muscle relaxants		
Cyclobenzaprine	CYP1A2 [10]	▲
Succinylcholine	Butyryl cholinesterase (pseudocholine esterase)	Poor metabolizers have enhanced drug effect
XII. Antidepressants (dual action)		
Imipramine	CYP2C19 [5,10], CYP2D6 [10], CYP1A2 [7]	Imipramine dose requirement varies according to metabolizer status
Amitriptyline	CYP2D6 [10]	▲
Clomipramine	CYP2D6, CYP1A2 [10]	▲
Maprotiline	CYP2D6 [10]	▲
Venlafaxine	CYP2D6 [10]	Venlafaxine metabolism slower in those lacking a functional *CYP2D6* gene [38]
Trimipramine	CYP2D6 [10], CYP2C19 [10]	▲
Maprotiline	CYP2D6 [8], CYP1A2 [8]	▲
XIII. Antidepressants (adrenergic)		
Desipramine	CYP2D6 [10]	▲
Nortriptyline	CYP2D6 [10], CYP1A2 [7]	Ultrarapid metabolizers require up to 500 mg/day to reach therapeutic dose [37]
Bupropion	CYP2B6 [10]	▲
Mirtazapine	CYP3A4 [10], CYP1A2 [10]	▲
Nefazodone	CYP3A4 [16]	▲
XIV. Antidepressants (serotonergic)		
Paroxetine	CYP2D6 [15,10]	▲
Citalopram	CYP2D6 [10], CYP3A4 [37]	▲
Fluoxetine	CYP2D6 [10], CYP1A2 [7]	▲
Sertraline	CYP2D6 [10]	▲
Trazodone	CYP2D6 [10,34]	▲
Fluvoxamine	CYP2D6 [10], CYP1A2 [32]	▲
XV. Neuroleptics (typicals)		
Chlorpromazine	CYP2D6 [36], CYP3A4 [39], CYP1A2 [39]	Oversedation and possible Parkinsonian symptoms are more likely to develop in CYP2D6 poor metabolizers of typical neuroleptics [40]
Thioridazine	CYP2D6 [36], CYP3A4 [36], CYP1A2 [39]	▲
Perphenazine	CYP2D6 [36]	▲
Haloperidol	CYP2D6 [36], CYP3A4 [36], CYP1A2 [40]	▲
Fluphenazine	CYP2D6 [39], CYP1A2 [40]	▲
Molindone	CYP2D6 [39]	▲
Pimozide	CYP3A4 [39]	▲
Thiothixene	CYP1A2 [39]	▲
Trifluoperazine	CYP1A2 [39]	▲
XVI. Neuroleptics (atypicals)		
Risperidone	CYP2D6 [36], CYP3A4 [36]	▲
Clozapine	CYP2D6 [36], CYP3A4 [36], CYP1A2 [39], CYP2E1 [39]	▲
Sertindole	CYP2D6 [36], CYP3A4 [36]	▲
Quetiapine	CYP3A4 [36]	▲
Ziprasidone	CYP3A4 [36]	▲
Olanzapine	CYP1A2 [39], CYP3A4 [40]	▲
Aripiprazole	CYP2D6, CYP3A4 [39]	▲
XVII. Alcohol	CYP2E1 [20]	Possible effect on alcohol consumption [20] greater alcohol consumption and dependence [20]
	Alcohol dehydrogenase [20]	
	Acetyaldehyde dehydrogenase [20]	Alcohol dehydrogenase polymorphism; poor metabolizers flush reactions and abuse side effects with alcohol leading to lower alcoholism in this group versus extensive metabolizers [4]
	Dihydropyrimidine dehydrogenase (DPD) [20]	▲
XVII. Antihistamines		
Chlorpheniramine	CYP2D6 [41]	▲

Table 6 Continued

Drug group and drug	Metabolizing enzyme	Clinical consequence of polymorphism affecting drug metabolism
XIX. Antihypertensives (ACE inhibitors)		
Losartan	CYP2C9 [41]	▲
Irbesartan	CYP2C9 [41]	▲
XX. Antihypertensives (calcium channel blockers)		
Diltiazem	CYP3A4 [36]	▲
Nifedipine	CYP3A4 [36]	▲
Nimodipine	CYP3A4 [36]	▲
Verapamil	CYP3A4 [36], CYP1A2 [7]	▲
Felodipine	CYP3A4 [41]	
Nisoldipine	CYP3A4 [41]	▲
XXI. Antihypertensives (beta blockers)		
Propranolol	CYP2D6 [15], CYP1A2 [20], CYP2C19 [20]	Altered beta-blocker effect
Timolol	CYP2D6 [8,15]	Altered beta-blocker effect
Metoprolol	CYP2D6 [41]	▲
XXII. N-methyl-D-aspartate antagonists		
Dextromethorphan	CYP2D6 [15,42]	▲
XXIII. Local anesthetics		
Procainamide	N-Acetyl transferase [27]	Enhanced drug effect in poor metabolizers [27]
Lidocaine	CYP3A4 [20]	▲
Mexiletine	CYP2D6 [20], CYP1A2 [20]	▲
XXIV. Antimigraine triptans		
Eletriptan	CYP3A4 [41]	▲
Almotriptan	CYP3A4 [41]	▲
Frovatriptan	CYP1A2 [41]	▲
Naratriptan	CYP1A2 [41]	▲
Zolmitriptan	CYP1A2 [41]	▲
XXV. Antiparkinsonian agents		
L-dopa	Catechol-O-methyltranferase [25]	Poor metabolizers have enhanced drug effects [25]
XXVI. Psychostimulants		
Modafinil	CYP1A2 [10]	▲
Amphetamine	CYP2D6 [5]	▲
Methoxyamphetamine	CYP2D6 [5]	▲
Theophylline	CYP1A2 [41,7]	▲
Caffeine	CYP1A2 [41], N-acetyl transferase (NAT2) [20]	▲
Nicotine	CYP2A6 [32]	Nicotine addiction [44]
XXVI. Anti-impotence agents		
Sildenafil	CYP2C9 [10]	▲
XXVIII. Antiemetics		
Ondansetron	CYP2D6 [5]	▲
XXVIIII. Anticoagulants		
Warfarin	CYP2C9 [32,20]	Increased or decreased anticoagulant effect [32,20]
XXX. Drugs of abuse		
△′—Tetrahydrocannabinal	CYP2C9 [5]	▲
Cocaine	CYP3A4 [5]	▲

▲ indicates a drug for which the clinical consequences of gene polymorphisms have not yet been determined.
Cytochrome P-450 enzymes are designated by CYP followed by a number-letter-number combination. The first number indicates the family of the enzyme, the letter indicates the subfamily, and the final number identifies the specific enzyme.

Discussion

Until now, genotyping for enzymes of drug metabolism has only been available in a limited number of academic centers [7]. Thus, the average physician has had to use an empirical treatment approach for many diseases, with factors such as clinical familiarity with available medications and knowledge of dosing schedules influencing choice of medications. This crude method reflects the lack of a single optimal treatment strategy for most diseases and the large number of medications available for most illnesses. Very recently, industry began offering individual patient genome profile testing, which includes genes coding for the following enzymes: CYP1A2, CYP2A6, CYP2C19, CYP2D6, and N-acetyl transferase 2. Of these, the CYP2D6 and CYP2C19 enzymes are the ones most commonly involved in psychotropic drug metabolism, with CYP2D6 being involved in the metabolism of almost all psychotropic drugs [38]. *CYP3A4* is not offered for analysis because it has not yet been shown to demonstrate functional drug polymorphism [9,13]. It is, however, involved in the metabolism of a large number of psychotropic drugs and as such, there is reason to include this gene in the genetic profile [9,13]. The above genomic analysis profile could potentially offer an optimal targeted treatment strategy to physicians. It was the objective of this review, based on the available literature (Table 6), to determine if pain physicians should consider genomic analysis for inclusion in their practices. The discussion of this issue is broken down (below) into three areas: Factors that speak to the need to include genomic testing; factors that speak to the possibility that genomic testing is not necessary; and recommendations.

Factors That Speak to the Need to Include Genomic Testing

These factors are the following. First, although no data are available, it is the opinion of the senior author (D.F.) that the clinical outcome of the psychopharmacological treatment of chronic pain, both in terms of pain and depression, is often unsatisfactory. A close review of Table 6 shows that both opioids and antidepressants are subject to significant functional polymorphisms. As such, genomic testing could potentially improve treatment outcomes in terms of both pain and depression. Second, both depression and pain are central nervous system (CNS) phenomena. It has recently become clear that CYP2D6 not only occurs in the liver but also in the CNS [42]. Its role in the brain is unknown, but the presence of CYP2D6 there could be of great functional significance. This could account for the large interpatient variability in the psychodynamic effects of psychotropic drugs [42]. As such, genomic testing for CYP2D6 could be important, especially in patients who do not respond to treatment. Third, genomic testing could complement phenotyping and therapeutic drug monitoring. Phenotyping with probe substrates can be used to assess the activity of specific drug-metabolizing enzymes in vivo. In reference to the cytochrome P-450, system, this can be done using a cocktail of noninteracting substrates (caffeine for CYP1A2, tolbutamide for CYP2C9, mephenytoin for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, midazolam for CYP3A4) [45]. Unfortunately, in clinical practice, phenotyping methods to predict dosage requirements or to understand mechanisms involved in extremely low or high drug levels determined by therapeutic drug monitoring (TDM) have inherent clinical problems. Phenotyping tests require the patient to be drug free. Thus, genotyping methods, which can be used during active drug therapy, have great potential as a complement to traditional TDM [37]. Fourth, traditional TDM is not available for most drugs. As such, genomic testing could serve the purpose of an alternate test to TDM when TDM is not available. Fifth, genomic analyses could help physicians to avoid drug reactions when drugs that are inhibitors of the cytochrome P-450 system have to be used. This review did not address drugs that can be inhibitors of the cytochrome P-450 system; for example, some neuroleptics, some antidepressants, etc. [45]. It is obvious that patients with a genetic polymorphism are of concern, for example, poor metabolizers would be at greater risk for drug reactions if a drug that was an inhibitor was used with these patients in association with other drugs. As such, there have been a number of case reports of massive increases in plasma concentrations of tricyclic antidepressants and severe cardiotoxicity when these drugs were used with the CYP2D6 inhibitor fluoxetine [46]. These kinds of interactions are predictable with genotyping [45]. Sixth, some drugs relevant to pain medicine (e.g., beta-blockers, antidepressants, warfarin, and opioids) that are the subjects of genetic polymorphism are widely used. As such, more population subgroups are affected [5]. This speaks to the need for genomic testing.

Factors That Speak to the Possibility That Genomic Testing Is not Necessary

These factors are the following. First, a review of Table 6 indicates that, at the present time, only a

few genetic polymorphisms in drug metabolism have clinical drug relevance. For the vast majority of drugs, the clinical consequences of gene polymorphisms have not yet been determined. Thus, genomic testing may not be cost effective at the present time, if one is not using or planning to use a drug previously determined to be the subject of drug polymorphism. Second, genotyping information does not necessarily translate into treatment outcome. As an example, to date, it has not been possible to demonstrate convincingly for antidepressants that the higher plasma levels of active drug in CYP2D6 poor metabolizers are associated with a greater amelioration of depression [47]. However, data on polymorphisms and adverse effects are more impressive. Chen et al. [48] found twice as many alleles associated with deficient CYP2D6 activity in depressed patients with adverse reactions as in those without such reactions and in normal controls. Third, polymorphisms only have clinical relevance when they result in large differences between poor metabolizers and extensive metabolizers [5]. Fourth, differences only become extremely relevant when a drug has a small therapeutic index (i.e., the ratio of the therapeutic effect to its adverse effects) [26]. Such is the case with neuroleptics. Fifth, in clinical practice, in most disease states (e.g., hypertension), the dosage is adjusted based on the therapeutic effect. In such a case the difference between poor metabolizers and extensive metabolizers is automatically corrected for [5]. Sixth, Kirchheiner et al. [10] have argued that genotyping cannot be of significant clinical use unless it provides precise dose recommendations according to the genotype status of the patient. As such, they provided precise dose recommendations for antidepressants based on CYP2C19 genotyping for ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. This is not available for other drug groups. However, the knowledge of whether someone is or is not an ultrarapid metabolizer or poor metabolizer is clinically helpful, as these patients can be titrated appropriately. Thus, exact dosing guidelines may not be necessary. Seventh, CYP3A4 is involved in the metabolism of 80-90% of the currently available drugs [38]. Yet, as pointed out above, it has not yet been found to demonstrate a functional polymorphism that significantly impacts drug metabolism [9,13]. However, Asian patients have higher plasma levels of alprazolam (a metabolite of CYP3A4) than Caucasians on intravenous and oral administrations of the same dose of that drug [49]. Thus, *CYP3A4* may demonstrate a functional polymorphism that has yet to be discovered. The situation with this gene demonstrates the major issue with this research area: At the present time, a significant number of genetic polymorphisms translating into functional polymorphisms have been discovered, but it is likely that future research will discover a significant number of other functional polymorphisms relating to drug metabolism. Eighth, at the present time, the above genomic testing profile is extremely expensive and is not covered by insurance. Thus, only a few patients would be able to afford such a service. Yet, Wedlund et al. [50] estimated that the total cost for the United States for 1 year related to CYP2D6 poor metabolizers' drug reactions to antidepressants alone is $420,000,000. As such, the high cost of genomic testing may turn out to be cost effective. Ninth, for the above reasons, some researchers have advised that the routine use of genomic information to make treatment decisions in the field of psychopharmacology is not an immediate prospect at the present time [10].

Recommendations

From the above discussion, it is clear that genomic testing for enzymes of drug metabolism has significant potential for improving the efficacy of drug treatments and reducing adverse drug reactions. Yet, as pointed out above, at the present time, this technology may be premature for routine use with every patient pretreatment. As such, the following approach is recommended for the pain physician who wishes to include genomic testing in his practice. First, check to see whether the drug you wish to use is metabolized by a polymorphic drug-metabolizing enzyme (Table 6). Second, check what the clinical consequence of this polymorphism *is*. Third, check on the prevalence of the polymorphic alleles of the relevant drug-metabolizing enzyme in the patient population to which the patient belongs (Table 1). Fourth, if genetic variability could be a significant problem, consider an alternate drug that may not be subject to known polymorphic drug-metabolizing enzymes. Fifth, if a drug that is subject to known drug-metabolizing polymorphic enzymes is used, advise the patient to carefully monitor adverse effects. Sixth, be careful not to prescribe drug inhibitors of the polymorphic enzymes in question, as this may compound adverse drug reactions. Seventh, if an adverse drug reaction occurs, and no alternate drug is available, con-

sider genotyping to determine that a polymorphism is the cause. This may provide a rough guideline for dosage reduction [11]; however, as clinicians would likely reduce a dosage in reference to toxicity anyway, this recommendation may not have any practical utility. Eighth, in cases of no response to treatment, that is, efficacy issues, consider performing TDM. This would help to identify the ultrarapid metabolizer. For example, if you have a patient on a significant dose of a drug known to be therapeutic in most cases and yet the blood levels are very low or negligible, that patient may be an ultrarapid metabolizer. Note that the issue described here is not testing to see if a patient is in a therapeutic blood level but to simply define if that patient may be an ultrarapid metabolizer. Ninth, if TDM is not available or indicates that a drug plasma level is low or high at an alleged therapeutic dose of the drug, and if the patient is compliant, consider genomic testing, as the patient could be an ultrarapid metabolizer or a poor metabolizer, respectively. For the case of the ultrarapid metabolizer, this knowledge would indicate to the clinician that this patient will require doses of medications that may be much larger than the usual therapeutic dose. For the case of the poor metabolizer this knowledge would indicate that this patient may have side effects at usual therapeutic doses.

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Appendix 1 Definitions for genetic terms used in text [1,2,4,9,20,25,41]

Allele	An alternate form of a gene
Genotype	A person's genetic makeup as reflected by his or her DNA sequence
Homozygous	Having two identical alleles at a specific autosomal (or X chromosome in a female) gene locus
Heterozygous	Having two different alleles at a specific autosomal (or X chromosome in a female) gene locus
Phenotype	The clinical presentation or expression of a specific gene or genes, environmental factors, or both
Single nucleotide polymorphism (SNP)	A common variant in the genome sequence; the human genome contains about 10 million SNPs
Genetic polymorphisms	A monogenic trait that exists in the normal population in at least two phenotypes, neither of which is rare
Pharmacogenetics	The study of genetic variations that cause variable drug responses; includes the study of genetic polymorphisms of drug transporters, drug-metabolizing enzymes, and drug receptors
Genomics	The study of the functions and interactions of all genes in the genome, including their interactions with environmental factors; it rests on direct experimental access to the entire genome
Pharmacogenomics	A genome-wide approach to identifying a network of genes that govern an individual's response to drugs, both drug toxicity and drug efficacy
Phase I reactions	The metabolism of drugs by oxidation reduction and hydrolysis
Phase II reactions	The metabolism of drugs by conjugation reactions, e.g., acetylation, glucuronidation, sulfation, and methylation