Pharmacogenetics and Pain

Estimated Time To Complete This Activity: 1 hour

Target Audience
This activity has been designed to meet the educational needs of clinicians who treat patients with chronic pain.

Statement of Need
Patients vary widely in their responses to drug therapy due to age, health status, lifestyle, environment, diet, and other factors. In addition, an estimated 20% to 95% of this variability may be related to genetic factors. Pharmacogenomics—the study of how genetic inheritance affects an individual’s response to drugs—is a rapidly growing field. In particular, genomic variations that influence response to analgesics are being investigated, with a focus on candidate genes, such as receptors, transporters, and other molecules, as well as enzymes responsible for drug metabolism, such as cytochrome P450 enzymes, leading to the identification of many polymorphisms.

Although an understanding of the basic science of pharmacogenomics is advancing, the clinical application of this information remains minimal. Currently available pharmacogenetic testing is limited to a few pathways, and no such testing is used clinically in the field of pain management. Comprehension of these concepts can lead to a better understanding of the possible reasons for variability in patient response to analgesics, better clinical decisions about therapy, and ultimately, improved patient care.

Educational Objectives
After completing this activity, the participant should be better prepared to:
- Review current knowledge of genomic variations that influence responses to pharmacotherapy for pain.
- Discuss polymorphisms of drug-metabolizing enzymes that affect various classes of analgesics.
- Review strategies for individualizing analgesic regimens.

Accreditation Statement
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- Jan Hixon, RN, BSN, MA; Trace Hutchison, PharmD; Julia Kirkwood, RN, BSN; Jan Schultz, RN MSN, CCMEP; Rebecca A. Bachmann, PhD; and Lyerka Miller, PhD, hereby state that they or their spouses/life partners do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Method of Participation
There are no fees for participating and receiving CME credit for this activity. During the period April 1, 2010 through April 30, 2011, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) fax the evaluation form with answer key to PIM. The post-test also may be completed online at www.cmeuniversity.com (click on “Find Post-Test/ Evaluation by Course” in the navigation menu and search by Project ID 6181) and www.CMEZone.com (enter Keyword SR0948).

A statement of credit will be issued only upon receipt of a completed activity evaluation form and post-test with a score of 70% or better. Statements of credit will be mailed within 3 weeks.

Media: Journal supplement

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Release Date: April 1, 2010
Expiration Date: April 30, 2011

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Case Example

A 62-year-old Chinese man with no significant past medical history presents with acute herpes zoster in the right S1 dermatome. His symptoms include severe localized pain associated with a vesicular eruption. The rash resolves, but 4 months later he continues to complain of burning pain with signs of allodynia and hyperalgesia, suggesting that he has developed postherpetic neuralgia (PHN). Nor- triptyline, a tricyclic antidepressant (TCA), is prescribed for this neuropathic pain syndrome at an initial dose of 10 mg with the intent of quickly titrating up to a higher dose to achieve pain relief. However, the patient is unable to tolerate even the initial dosing due to adverse events (AEs; sedation, orthostatic hypotension, and dry mouth).1 Tramadol and then hydrocodone/acetaminophen are prescribed, but these also are tolerated poorly. Next, the patient receives gabapentin at an initial dose of 300 mg taken at night, which is titrated to what is considered an effective dose for PHN: 1,800 mg per day in 3 divided doses. The burning pain is lessened but still is not controlled sufficiently, and the patient returns to the physician for further treatment.

Discussion

This case study illustrates a common clinical observation: variability in response to prescribed analgesics. Just as pain responses to an injury or condition are highly individualized, so are responses to pain pharmacotherapies. Although this patient was treated according to current evidence-based guidelines,1-3 he did not obtain adequate analgesic benefit from the prescribed medications. This is not uncommon.4 The response rates in well-designed studies of various analgesic therapies are approximately 50% to 60%; this “success” rate is similar to that achieved in trials of therapies for congestive heart failure and epilepsy.5-7 In fact, many areas of medicine are affected similarly by poor responder rates in clinical trials of diverse drug types. Variability in patient response—whether efficacy or tolerability—can be due to patient nonadherence, interference of other drugs (prescribed, over-the-counter, or other [illegal drugs, nutraceuticals, alternative/plant-based therapies]), mechanisms of pain generation that fail to respond to the analgesic’s mechanism of action, and/or pharmacogenetics.

The Impact of Pharmacogenetic Research on Clinical Medicine

Pharmacogenetics is the study of the effect of genetics on therapeutic responses and tolerability. For example, individual unique genetic “blueprints” affect the generation of protein-expression profiles, which can lead to variations in observed clinical responses. Thus, a single drug can be associated with different clinical results in different patients. Awareness of genetic predisposition and receptor subtype expression, as mediated through alternative splicing, potentially can lead to genetically guided, individually tailored prescribing with improved efficacy and safety.4

Ongoing research on the genetic determinants of disease have been derived from the Human Genome Project, and in particular, the The SNP (single-nucleotide polymorphism) Consortium.8 SNPs are the most important contributors to regular variation in the genetic code, which leads to the human population’s diversity of appearance, and at a deeper level, variance in physiology. SNPs are defined as DNA sequence variations resulting from a single nucleotide (adenine [A], thymine [T], cytosine [C], or guanine [G]) change in the genome sequence. The most commonly observed change is the replacement of C with T, as for example, in the sequence ACAGCCTAA modified to ATGGCTAA (Figure).8 Approximately 9 to 10 million common SNPs have been identified.9 In many cases, this miniscule change, amid a background of the of 3.3 billion base pairs of DNA contained in one somatic cell, does not translate into differences at the protein level and thus does not lead to any outwardly observable change in an individual.

Some SNPs, however, do lead to phenotypic differences, and some single base-pair changes do affect a noticeable, clinically relevant change in phenotype. For example, unique SNPs have been identified that lead to lower-activity enzymes, red hair color and fair skin, and lack of or diminished expression of a red blood cell antigen.10,11

The most commonly observed DNA gene sequences are called “wild-type,” and less common sequences are “variants,” as long as they occur in more than 1% of the population. Sequences found in less than 1% of the population are called “mutations.”12 For example, mutations within a specific location in chromosome 9 are responsible for an autosomal dominant neuropathy called hereditary sensory and autonomic neuropathy type I, which causes progressive degeneration of dorsal root ganglia (DRG) and motor neurons.13,14 Individuals with this genetic background cannot sense pain and thus are prone to potentially severe injuries and complications such as chronic skin ulcers and distal amputations. Other DNA changes, such as deletions and insertions, also can affect an individual’s health—sometimes catastrophically.

Since early 2009, large population studies have analyzed hundreds of thousands of SNPs in an attempt to establish the genetic linkages to a diversity of diseases.12 The Wellcome Trust Consortium, for example, published a particularly notable study in the June 2007 issue of Nature. The authors assessed genetic influences on 7 major diseases by comparing SNPs from 14,000 ill patients (2,000 with each disease) with those of 3,000 healthy patients.15 Genomic hotspots (regions of DNA connected to biological functions and/or diseases) were found to be associated with susceptibility to developing bipolar disorder, Crohn’s disease,

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Key Terminology in Pharmacogenetics12

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Genome</td>
<td>The entire collection of genetic information (or genes) that an organism possesses</td>
</tr>
<tr>
<td>Genotype</td>
<td>The genetic constitution of an individual, either overall or at a specific gene</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>The presence of 2 different alleles (1 on the maternal chromosome and 1 on the paternal) at a gene location</td>
</tr>
<tr>
<td>Homozygous</td>
<td>The presence of 2 identical alleles at a gene location</td>
</tr>
<tr>
<td>Isoform</td>
<td>A variant in the amino acid sequence of a protein</td>
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<tr>
<td>Messenger RNA</td>
<td>An RNA-containing single-strand copy of a gene that migrates out of the cell nucleus to the ribosome, where it is translated into a protein</td>
</tr>
<tr>
<td>Mutation</td>
<td>A rare variant in a gene, occurring in less than 1% of a population</td>
</tr>
<tr>
<td>Pedigree</td>
<td>A diagram depicting heritable traits across 2 or more generations of a family</td>
</tr>
<tr>
<td>Phenotype</td>
<td>The observable characteristics of a cell or organism, usually resulting from the product coded by a gene (genotype)</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>The existence of 2 or more variants of a gene in a population, with at least 1% frequency of the less common variant</td>
</tr>
<tr>
<td>Prodrug</td>
<td>A medication that is inactive until it is converted enzymatically to its active metabolite</td>
</tr>
<tr>
<td>Single-nucleotide polymorphism (SNP)</td>
<td>A single base-pair change in a DNA sequence compared with the “common” or “wild-type” sequence</td>
</tr>
</tbody>
</table>

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coronary artery disease, diabetes (types 1 and 2), hypertension, and rheumatoid arthritis.\textsuperscript{15}

The integration of genetic information into clinical practice has far-reaching implications. The oncology field has pioneered the clinical integration of genetic information to guide treatment. Other areas of medicine also are beginning to tailor pharmacotherapies based on individuals’ genetic information (Table 1, page 4), and soon, implementation of genetic testing will be enabled by the identification of markers that affect responses to medicines for treating depression and heart failure, in addition to cancers. Pharmacogenetics already benefits clinical medicine by enhancing risk stratification, having identified groups with higher potentials for AEs or poor efficacy (Table 2, page 5). In the future, pharmacogenetics may improve medication efficacy, decrease rates of AEs,\textsuperscript{16} and reduce health care costs.

**The Impact of Pharmacogenetic Research on Pain Medicine**

Variation in individual levels of pain tolerance and the propensity to develop chronic pain has been demonstrated in in vivo studies.\textsuperscript{17} In 2006, Tegeder and colleagues presented molecular evidence in models of inflammatory and nerve-injury pain, as well as in humans, tracing the predisposition for high pain tolerance to an enzyme cofactor that is upregulated in primary sensory neurons of the DRG following nerve injury.\textsuperscript{18} This cofactor modulates both inflammatory and neuropathic pain. Furthermore, the researchers identified a “pain-protective” polymorphism within the gene for this essential cofactor, present in 15% of the population and associated with reduced pain sensitivity.\textsuperscript{19} Inclusion of individuals with this pain-protective genotype in analgesic trials may confound results unless such subjects are identified and randomized. Polymorphisms in other genes such as the melanocortin-1 receptor gene, have also been linked to pain sensitivity.\textsuperscript{20}

Genetic predisposition also affects individuals’ susceptibility to specific painful conditions. A genome-wide scan identified 2 identified 2 identical polymorphisms in the common type of polymorphism in the human genome.\textsuperscript{12}

**Figure. Common (wild-type) allele and 4 types of genetic polymorphisms.\textsuperscript{12}**

\[A, \text{ adenine}; C, \text{ cytosine}; G, \text{ guanine}; T, \text{ thymine}\]

DNA polymorphisms include deletions, in which a DNA sequence is missing compared with the common allele, and insertions, in which a DNA sequence is added compared with the common allele. Repeats, in which the same sequence repeats multiple times, also may occur. Depending on the size of the repeating unit and the number of repeats, these variants may have different names, such as satellites, microsatellites, minisatellites, or copy number variants. Single-nucleotide polymorphisms, variations at a single base-pair location, are the most common type of polymorphism in the human genome.


Tricyclic Antidepressants

In the case described here, the TCA produced intolerable AEs. TCAs are metabolized in the liver by the cytochrome P450 (CYP) system, a group of enzymes responsible for the breakdown of 40% to 50% of all medications,\textsuperscript{22} including some antidepressants. CYP is the most intensely studied gene family,\textsuperscript{23} and polymorphisms within this class of enzymes can lead to reduced or accelerated metabolism of specific medications (Table 2, page 5). As such, 2 individuals having the same weight and given the same drug dosage can exhibit a greater than 1,000-fold difference in plasma drug levels.\textsuperscript{4} In studies, individuals have been grouped by their phenotype: poor metabolizers (PMs) have 2 nonfunctional enzyme alleles; intermediate metabolizers (IMs) have at least 1 reduced-function enzyme allele; extensive metabolizers (EMs) have at least 1 functional allele; and ultra-rapid metabolizers (UMs) have multiple copies of a functional allele and/or an allele with a promoter mutation that confers increased transcription of that gene.\textsuperscript{22} EMs obtain the expected therapeutic benefit from standard doses of a drug, whereas PMs are at risk for poor efficacy of a prodrug or AEs from an active drug, as they are metabolized incompletely as a result of genetic differences in their liver enzyme systems. (A prodrug is a medication that is inactive until it is converted enzymatically to its active metabolite.) Conversely, UMs are prone to AEs due to higher-than-expected drug concentrations resulting from enhanced metabolism of a prodrug, as well as peak-and-troughs in plasma drug concentrations when administered standard doses of active drugs that are rendered inactive more quickly than expected. The plasma drug concentrations in individuals given the same dose of antidepressants have been found to vary—primarily based on the polymorphisms in the CYP2D6 enzyme (as well as CYP1A2, CYP2C19, and CYP3A4/5).\textsuperscript{24,25} Like the patient in the case example, PMs of TCAs (approximately 7% of the Caucasian population) tend to accumulate drug concentrations outside the narrow therapeutic range for this drug class, leading to AEs at lower-than-expected doses.\textsuperscript{22,24} In contrast, CYP2D6 UMs may require higher doses to achieve analgesia.\textsuperscript{22,24,25} Potentially, the patient presented is a CYP2D6 PM.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Label Context</th>
<th>Examples of Drugs Associated With This Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Drugs posing ↑ risk for bleeding in the presence of CYP2C9<em>2 or CYP2C9</em>3 alleles</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Drugs affected by ↓ liver enzyme activity, thus associated with ↑ plasma drug concentrations</td>
<td>Atorvastatin, maleate, risperidone, tamoxifen, timolol, tiotropium bromide inhalation, verlafaxine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Drugs that inhibit the activity of CYP2D6: Patients with ↓ activity of this isoenzyme have relatively narrow therapeutic index for other drugs metabolized primarily by this enzyme</td>
<td>Aripiprazole, carvedilol, cevimeline hydrochloride, clozapine, fluoxetine HCl, metoprolol, olanzapine, propafenone, propranolol, protoplyline HCl, terbutaline, tetrabenazine, thioridazine, tolterodine, tramadol + acetaminophen</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Drugs affected by polymorphisms, thus leading to ↓ metabolic capacity and ↑ plasma drug concentration</td>
<td>Diazepam, esomeprazole, nefinavir, omeprazole, pantoprazole, rabeprazole, voriconazole</td>
</tr>
<tr>
<td>Glucose-phosphate dehydrogenase deficiency</td>
<td>Drugs that may induce moderate to severe hemolytic reactions in patients with this deficiency</td>
<td>Chloroquine, primaqmine</td>
</tr>
<tr>
<td>Human leukocyte antigen-B*1502 allele</td>
<td>Drugs that may induce serious dermatologic reactions in patients with this allele</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>N-acetyltransferase</td>
<td>Drugs that can lead to slower acetylation and potentially ↑ plasma drug concentrations, thus ↑ risk for a toxic reaction in patients with variants of this enzyme</td>
<td>Hydralazine hydrochloride, isoniazid, isosorbide dinitrate, pyrazinamide, rifampin</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Drugs that pose ↑ risk for tissue necrosis following administration in patients with deficiency in protein C or its cofactor, protein S</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Thiopurine methyltransferase deficiency</td>
<td>Drugs that pose ↑ risk for myelotoxicity in patients with ↓ activity or deficiency in this enzyme</td>
<td>Azathioprine, mercaptopurine, thioguanine</td>
</tr>
<tr>
<td>UCD deficiency (mutations in one of several genes, including ornithine transcarbamylase deficiency and carbamoyl-phosphate synthetase 1 deficiency)</td>
<td>Drugs contraindicated in patients with UCD deficiency due to risk for fatal hyperammonomnic encephalopathy</td>
<td>Sodium benzoate, sodium phenylacetate, sodium phenylbutyrate, valproic acid</td>
</tr>
<tr>
<td>Vitamin K epoxide reductase variants</td>
<td>Drug that requires ↓ doses in patients with certain polymorphisms within this enzyme (eg, -1639G)</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

Table 1. Valid Biomarkers in the Labels of FDA-Approved Medications

The value of genotyping prior to prescribing antidepressants was considered in a large population-based study of 1,198 elderly Dutch patients. Perhaps not surprisingly, PMs of TCAs required either lower maintenance doses or discontinuation of TCAs altogether relative to EMs. Although current research does not yet support routine liver enzyme genotyping before analgesic treatment, a growing number of companies are developing the capabilities to perform such assays. Clinically, the recognition that a patient might be a PM, even without genotyping data, can lead the provider to consider medication adjustment or discontinuation in cases of poor efficacy or AEs. Recognizing the susceptibility of specific racial or ethnic groups also may prove helpful in the assessment of medication response.

Nonsteroidal Anti-Inflammatory Drugs

Pharmacogenetic research in pain management has identified wide interindividual variation in the analgesic efficacy of both nonspecific nonsteroidal anti-inflammatories (NSAIDs) and selective inhibitors of cyclooxygenase (COX)-2 due to SNPs within the COX genes (Table 2). A SNP in the promoter for the gene encoding COX-2 (-1195G>A) has a prevalence of more than 10% and has been associated with mild asthmatic reactions. Indeed, another functional effect of the increased expression of COX-2, potentially mediated by several SNPs, include hypersensitivity to standard doses of aspirin and other NSAIDs that inhibit COX-2—otherwise known as aspirin-intolerant asthma. A large genotyping study further determined that individuals with specific variants of the COX-1 and COX-2 genes have an increased risk for cardiovascular disease when taking aspirin. In addition, investigations have identified an increased risk for gastroduodenal bleeding in patients who have specific genotypes of the CYP enzyme CYP2C9 and take NSAIDs metabolized by that enzyme.

Opioids

SNPs

In properly selected patients, opioids can be effective treatments for moderate to severe acute or chronic pain. Like TCAs, most opioids are metabolized by the CYP enzyme class (Table 2); thus, their clinical analgesic and AE response profiles are affected by SNPs within the CYPs. In particular, codeine has been associated with variable individual clinical responses. Codeine is a prodrug. It must be converted to morphine by CYP2D6 to provide analgesia. As with codeine, CYP2D6 PMs also may experience inadequate effectiveness from standard doses of the prodrug tramadol. While the metabolism of almost all opioids can be affected by SNPs within the CYP450s, there are 3 opioid analgesics that are not metabolized by the CYP enzymes: morphine, hydromorphone, and oxymorphone. Hence, if an individual has an SNP that changes the enzymatic activity of a CYP, possibly indicated by a poor initial response to an opioid metabolized by the CYP family, an opioid metabolized by a different liver enzyme system might elicit a better response. Pharmacogenetic data can play a role in stratification of risk for poor response to opioids and can guide prescribing decisions. Relevant to the...
case presented, between 41% and 51% of individuals of Asian origin express an unstable CYP2D6 enzyme, another 12% to 21% of Caucasian people express an inactive CYP2D6 enzyme. In contrast, 10% to 29% of people of Ethiopian or Saudi Arabian descent have heightened CYP2D6 activity. This pharmacogenetic information can provide clues about how a specific patient may respond to codeine or other opioids metabolized by CYP2D6 and thereby, offer prescribing guidance (Table 3, page 6). Perhaps the Chinese patient in the case example is predisposed genetically to low CYP2D6 activity, with insufficient enzymatic capacity to obtain an expected analgesic response to hydrocodone; hydrocodone has an active metabolite, hydromorphone, that may contribute to its overall analgesic effects. Pharmacogenetic information may provide the connection between the opioid prescribed and the lack of efficacy or the presence of unexpected AEs. Opioid responsiveness is a highly individualized phenomenon, and pharmacogenetics can have an important impact on clinical responses, along with the pain etiology, opioid tolerance level, and other psychophysiologic determinants.

Genetic determinants beyond metabolic enzymes also affect individual responses to opioids. These include drug transporters and drug targets such as the µ-opioid receptor gene OPRM1. The specific combination of SNPs within genes that code for the targets of analgesics (such as OPRM1) in an individual may have an additive effect and knowledge of these SNPs could help guide effective opioid prescribing practices in the future. For example, Lotsch and colleagues analyzed the combined effects of SNPs within genes encoding the µ-opioid receptor MOR1 and 2 other genes relevant to opioid responsiveness, and then recommended dose adjustments for prescribing morphine.

**Alternative Splicing**

Although most studies of opioid-response variability have focused on SNPs, others are investigating cellular mechanisms that contribute to interindividual variability in response to opioids. Evidence gathered during the last several decades have identified multiple µ-opioid receptor subtypes (so-called “splice variants”) with distinct properties that influence the pharmacodynamics of opioids. To explain the source of diversity in these receptors, a review of the central dogma of biology is required. Genetic material, DNA, is transcribed into RNA and then translated into proteins with cellular structural, enzymatic, and receptor functions. SNPs are sources of variation in the DNA, while diversity also is introduced during the transcription of RNA, during which alternative splice variants are produced. This idea, proposed 30 years ago by Nobel Prize winner Walter Gilbert, has been well characterized and is recognized as the major source of proteome diversity enabling the complexity of human traits.

Alternative splice variants of the µ-opioid receptor have been identified and correlated with the clinical phenomenon of incomplete cross-tolerance, by which tolerance of one opioid does not translate to tolerance of others. Furthermore, although most clinically used opioids are selective for the µ-opioid receptor, their ability to activate the receptor can vary, leading to widely different efficacy and AE profiles among individuals. Indeed, the minimal effective analgesic concentration of morphine can fluctuate among patients by as much as 10-fold. Further response variation within an individual is related to changing gene expression patterns over time and even diverging across organ systems and tissues, based on this individual’s state of health, degree or type of physiologic or emotional stress present.

Clinically significant response variation in both the efficacy and AEs of opioids has been observed for decades. Evidence-based pain management guidelines published in 2009 by the American Pain Society and the American Academy of Pain Medicine recommended opioid rotation or “switching from one opioid to another opioid” when the initial opioid is not well tolerated or is not suitably effective after a trial of reasonable duration. Grilo and colleagues conducted a study of 67 patients with recalcitrant chronic rheumatologic pain, and in most cases, rotated the participants from morphine to either oral hydromorphone or transdermal fentanyl. This strategy resulted in a mean pain reduction of 30 mm on a visual analog scale (P<0.001), indicating a clinically important difference in pain intensity, and leading the authors to conclude that opioid rotation may reduce pain not controlled with previously prescribed opioids. Studies of opioid rotation indicate that when it is necessary to change the opioid because of ineffectiveness or intolerable AEs, each new opioid tested increases the cumulative percentage of efficacy that can be achieved.

### Table 2. Metabolizer Status by Racial/Ethnic Group

<table>
<thead>
<tr>
<th>Gene or Enzyme</th>
<th>Phenotype and Frequency by Groups</th>
<th>Clinical Effect</th>
<th>Examples of Drugs Metabolized by This Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>PM: Caucasian, 12%</td>
<td>Weak metabolism of enzyme substrates</td>
<td>Anticonvulsants: phenytoin, carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antidepressants: clomipramine, fluoxetine, fluvoxamine, imipramine, maprotiline, nortriptyline</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle relaxant: cyclobenzaprine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NSAIDs: acetaminophen, naproxen</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>PM: Caucasian, 2%-6%</td>
<td>Weak metabolism of enzyme substrates</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Angiotensin II blockers: irbesartan, losartan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSAIDs: celecoxib, diclofenac, ibuprofen, meloxicam, naproxen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral anti-diabetics: glipizide, tolbutamide</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>PM: Caucasian, 2%-6%; Chinese, 15%-17%; Japanese 16%-23%</td>
<td>Weak metabolism of enzyme substrates</td>
<td>Anticonvulsants: diazepam, phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proton pump inhibitors: omeprazole, pantoprazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>PM: Caucasian, 3%-10%; Chinese/Japanese/African-American, &lt;2%</td>
<td>Weak metabolism of enzyme substrates</td>
<td>Analgesics: codeine, dextromethorphan, oxycodone, tramadol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antiarrhythmic drugs: ajmaline, flecaïnine, mexiletine, propafenone</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Antimetabolites: metoclopramide</td>
</tr>
<tr>
<td></td>
<td>UR: Ethiopian, 20%; Hispanic, 7%; Scandinavian, 1.5%</td>
<td>Enhanced metabolism of enzyme substrates</td>
<td>Antipsychotics + SSRIs: fluoxetine, haloperidol, paroxetine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>β-blockers: metoprolol, propranolol, timolol</td>
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<td></td>
<td></td>
<td></td>
<td>5-HT3 antagonists: ondansetron, tropisetron</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TCAs: amitriptyline, clomipramine, desipramine, imipramine</td>
</tr>
</tbody>
</table>

5-HT<sub>3</sub>, serotonin; NSAID, nonsteroidal anti-inflammatory drug; PM, poor metabolizer; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UR, ultra-rapid metabolizer
**Table 3. Enzymes Involved in Opioid Metabolism**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opium alkaloids</td>
<td>Codeine</td>
<td>10% CYP3A4 (to norcodeine); 5% CYP2D6 (to morphine); 80% UGT2B7 CYP2D6 (to hydromorphone) and CYP3A4 (to norhydrocodone); other minor non-CYP oxidative enzymes; UGTs (CYP-metabolized products)</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>Hepatic glucuronide by UGT1A3 and UGT2B7 CYP2D6 (to oxymorphone) and CYP3A4 (to noroxycodone); CYP-metabolized product(s) by UGTs</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>CYP2D6 (to hydromorphone) and CYP3A4 (to norhydrocodone); other minor non-CYP oxidative enzymes; UGTs (CYP-metabolized products)</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td>CYP2D6 (to hydromorphone) and CYP3A4 (to noroxycodone); CYP-metabolized product(s) by UGTs</td>
</tr>
<tr>
<td>Semisynthetic derivatives</td>
<td>Dihydrocodeine</td>
<td>5%-10% CYP2D6 (to dihydromorphone) and CYP3A4 (to nordihydrocodeine); 85% UGT2B7</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>Hepatic glucuronide conjugation via UGT1A3, UGT2B7; dihydromorphine ketone reductase UGT1A3 and UGT2B7, with UGT2B7 being the predominant enzyme</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone</td>
<td>Conjugation with glucuronic acid via UGTs, mainly UGT2B7</td>
</tr>
<tr>
<td>Phenytoylethylamine</td>
<td>Methadone</td>
<td>N-demethylation by CYP3A4</td>
</tr>
<tr>
<td>Oripavine derivatives</td>
<td>Buprenorphine</td>
<td>CYP3A4 (65%), CYP2C8 (30%), CYP3A5, CYP3A7, CYP2C9, CYP2C19, and CYP2C18; CYP-metabolized product(s) further cleared by UGTs</td>
</tr>
<tr>
<td>Phenylpiperidines</td>
<td>Fentanyl</td>
<td>N-dealkylation by CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Meperidine</td>
<td>CYP3A4, CYP2B6, and CYP2C19</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>Nonspecific blood and tissue esterases to remifentanil acid</td>
</tr>
<tr>
<td></td>
<td>Sufentanil</td>
<td>N-dealkylation by CYP3A4</td>
</tr>
<tr>
<td>Diphenylpropylamine derivatives</td>
<td>Loperamide</td>
<td>N-demethylation by CYP2B6, CYP2C8, CYP2D6, and CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Propoxyphene</td>
<td>N-demethylation by CYP3A4</td>
</tr>
<tr>
<td>Others</td>
<td>Naloxone</td>
<td>Aldo-keto reductase (dihydropinol dehydrogenase); glucuronidation via UGTs</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td>O-demethylation by CYP2D6; N-demethylation by CYP2B6 and CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>Conjugation with glucuronic acid via UGTs, mainly UGT2B7</td>
</tr>
</tbody>
</table>

**CYP**, cytochrome P450; **UGT**, uridine diphosphate glycosyltransferase

Note. If patient has poor initial response (eg, lack of therapeutic effect, adverse events) to an opioid metabolized by CYP, an opioid metabolized by a different enzyme system may elicit a better response. Knowledge of metabolic pathways drug is important to safe polypharmacologic prescribing.


References


for the treatment of chronic noncancer pain, Quang-Cantagrel and colleagues reported that the first long-acting opioid prescribed was effective for 36% of patients. However, the original opioid had to be discontinued due to AEs or ineffectiveness in 30% and 34% of those studied, respectively. Eventually, a clinical response was obtained by changing to a second (31% responded), third (40% of the remainder responded), fourth (56% of the remainder responded), or fifth (14% of the remainder responded) opioid.46 Furthermore, it is important to note that the failure of one opioid does not predict response to another.47 Safe and effective opioid rotation requires specific clinical knowledge on the part of the health care provider. In the case where opioid rotation is determined to be the most appropriate approach to managing opioid nonresponsiveness, guidelines for the calculation of equianalgesic equivalency and other steps in this process should be referenced.45

**Future Outlook and Conclusions**

The future promise of pharmacogenetics is individually tailored, rational drug therapy that maximizes efficacy and minimizes AEs. At this stage, recognition of the role that pharmacogenetics may play in therapeutic response is an important first step toward the application of such important translational research. In pain management, the expression of genes that encode analgesic targets, the enzymes involved in metabolizing analgesic agents, and the proteins that transport them vary considerably, leading to extraordinary variation in the ability to achieve pain relief safely and effectively across individuals.34 Pharmacogenetic data can help clinicians select and optimize analgesic therapy.
CME Post-Test

Choose the single-letter response that best answers the question or completes the sentence, and record your response on the post-test answer key on the evaluation form.

1. Variability in the efficacy or tolerability reported by a patient can be due to ___.
   a. nonadherence to a prescribed drug regimen
   b. drug-drug interactions
   c. pharmacogenetics
   d. all of the above

2. A single-nucleotide polymorphism (SNP) is defined as ___.
   a. a change from adenine to thymine in a protein
   b. a change from adenine to thymine caused by alternative splicing
   c. a single-nucleotide change from wild-type in the genome sequence
   d. a change from adenine to thymine in the genome sequence

3. Recent evidence suggests that there are approximately ___.
   a. 1,000 to 14,000
   b. 14,000 to 100,000
   c. 1 to 2 million
   d. 9 to 10 million

4. Specific genotypes or SNPs have been linked to ___.
   a. susceptibility to diabetic peripheral neuropathy
   b. sensitivity to pain
   c. susceptibility to rheumatoid arthritis
   d. all of the above

5. Who would be expected to obtain the least therapeutic effect?
   a. A poor metabolizer of a prodrug
   b. An intermediate metabolizer of a prodrug
   c. An extensive metabolizer of a prodrug
   d. An ultra-rapid metabolizer of a prodrug

6. An ultra-rapid metabolizer may be prone to ___.
   a. a lack of drug efficacy
   b. low blood concentrations of a prodrug
   c. increased rate of adverse events (AEs) commonly associated with high doses of a drug
   d. the need for higher doses of a drug to avoid AEs

7. Increased risk for gastroduodenal bleeding has been associated with a variant of CYP2C9 and taking some___.
   a. nonsteroidal anti-inflammatory drugs
   b. tricyclic antidepressants (TCAs)
   c. anticonvulsants
   d. opioids

8. Which of the following is not a prodrug metabolized by the cytochrome P450 liver enzymes?
   a. Tramadol
   b. Codeine
   c. Hydromorphone
   d. Hydrocodone

9. Alternative splice variants ___.
   a. are defined as different single nucleotides within a protein
   b. are defined as different alleles present in different species
   c. have been identified in the μ-opioid receptor and have been correlated with the clinical phenomenon of incomplete cross-tolerance
   d. have not been established as a mechanism for creating diversity

10. Opioid rotation may be useful when ___.
    a. a TCA is not effective
    b. the first opioid tried is not tolerated
    c. a longer duration of effect is needed (eg, switching from an immediate-release to an extended-release agent)
    d. a patient’s pain etiology is resolved

Disclaimers: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients’ conditions, possible contraindications, dangers with use, review of applicable manufacturer’s product information, and comparison with recommendations of other authorities.

The content of this activity was provided and factual accuracy confirmed by PIM. Applied Clinical Education (ACE) is responsible for review of the educational format and design only. Although the information included in this activity is believed to be true and accurate at the date of publication, ACE accepts no legal responsibility for any errors or omissions that may have been made. ACE makes no warranty, expressed or implied, with respect to the material contained herein.
Evaluation Form
Pharmacogenetics and Pain  Project ID: 6181 ES 29

Postgraduate Institute for Medicine is committed to excellence in continuing education, and your opinions are critical in this effort. To assist in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate ratings:

1 = Strongly disagree  2 = Disagree  3 = Neutral  4 = Agree  5 = Strongly agree

Educational Objectives

After participating in this activity, I am better able to:

• Review current knowledge of genomic variations that influence responses to pharmacotherapy for pain.  1  2  3  4  5
• Discuss polymorphisms of drug-metabolizing enzymes that affect various classes of analgesics.  1  2  3  4  5
• Review strategies for individualizing analgesic regimens.  1  2  3  4  5

Based on your participation in this activity, choose the statement(s) that apply:

❑ I gained new strategies/skills/information that I can apply to my area of practice.
❑ I plan to implement new strategies/skills/information in my practice.

What strategies/skills/information do you plan to implement in your practice? ______________________________________________________

Which of the following best describes the impact of this activity on your performance?

❑ I will implement the information in my area of practice.
❑ I need more information before I can change my practice behavior.
❑ This activity will not change my practice, as my current practice is consistent with the information presented.
❑ This activity will not change my practice, as I do not agree with the information presented.

What barriers do you see to making a change in your practice? __________________________________________________________________

Please rate your level of agreement by circling the appropriate ratings:

1 = Strongly disagree  2 = Disagree  3 = Neutral  4 = Agree  5 = Strongly agree

The content presented:

Enhanced my current knowledge base  1  2  3  4  5
Addressed my most pressing questions  1  2  3  4  5
Promoted improvements or quality in health care  1  2  3  4  5
Was scientifically rigorous and evidence-based  1  2  3  4  5
Avoided commercial bias or influence  1  2  3  4  5
Are you willing to participate in a post-activity follow-up survey?  ❑ Yes  ❑ No

CME Credit (for physicians only)

I certify my actual time spent to complete this educational activity to be: _____

❑ I participated in the entire activity and claim 1.0 credit.
❑ I participated in only part of the activity and claim _____ credit.

Post-Test Answer Key

Enhanced my current knowledge base  1  2  3  4  5
Addressed my most pressing questions  1  2  3  4  5
Promoted improvements or quality in health care  1  2  3  4  5
Was scientifically rigorous and evidence-based  1  2  3  4  5
Avoided commercial bias or influence  1  2  3  4  5
Are you willing to participate in a post-activity follow-up survey?  ❑ Yes  ❑ No

Please list any topics you would like to see addressed in future educational activities:

__________________________________________________________________________________________________________________

To receive acknowledgment for completing this activity, please complete the post-test answer key by selecting the best answer to each question, completing this evaluation form, and faxing it to (303) 790-4876. Online participation is available at www.cmeuniversity.com (click on “Find Post-Test/Evaluation by Course” in the navigation menu and search by Project ID 6181) and www.CMEZone.com (enter Keyword SR0948).

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