The Value of CYP2D6 and OPRM1 Pharmacogenetic Testing for Opioid Therapy

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More than 80 million people in the United States suffer annually from serious pain, the vast majority, roughly 85%, suffering from chronic manifestations such as lower back pain, arthritis, and headache [1,2]. The costs associated with pain management are estimated to be over $61 billion annually, primarily because of lost productivity at work [3]. Thus, satisfactory treatment of pain is paramount for patients to return to a productive lifestyle.

In managing pain, clinicians and their patients often face decisions that involve choosing the most appropriate pharmacologic agent, to contemplating nonpharmacologic modalities. If the choice is drug therapy for relieving pain (ie, analgesics), nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are the primary choices. Additional drug types such as the antidepressants and anti-epileptics have also been used to treat neurologic pain. More than 20 years ago, the World Health Organization (WHO) recommended a stepwise and “ladder” approach to management of pain [4]. Administration of non-opioid medications (adjuvants) is considered for mild pain as an initial step. For moderate pain, mild opioids such as codeine, with or without the adjuvants, and non-opioids are considered next. For persistent moderate to severe pain, strong opioids such as morphine, with or without adjuvants, and non-opioids are considered [5]. The effectiveness of this approach has been questioned and studied over the past several years [6].
Regardless, the popularity of the WHO analgesic ladder in various fields of medicine is evident [7].

**Pain management medications**

*Nonsteroidal Anti-Inflammatory Drugs*

NSAIDs are primarily considered in the management of mild to moderate nociceptive pain. They are particularly useful for inflammatory states and pain involving the musculoskeletal system [8]. Several members of this class may cause gastric disturbances, gastrointestinal (GI) bleeding, platelet aggregation inhibition, and nephrotoxicity. Blockade of cyclooxygenase-2 (COX-2) has been a relatively recent alternative to produce analgesia and anti-inflammatory effects without the GI or bleeding side effects; however, COX-2 inhibitors are relatively expensive while being generally equipotent to other NSAIDs. In situations where NSAIDs are required and the risk of GI or bleeding side effects cannot be tolerated, COX-2 inhibitors are considered as great alternatives [9]. Despite these advantages, COX-2 inhibitors increase the risk of myocardial infarction and stroke [10].

*Opioids*

Opioids are a group of narcotic drugs capable of relieving pain, but that can induce sleep, become addictive, and cause stupor, coma, or death in higher doses. There are two major classes of alkaloids in the poppy plant (*Papaver somniferum*) referred to as isoquinolines and phenanthrenes. Morphine, codeine, and thebaine are the major phenanthrenes with binding affinity to the opioid receptors. The term opiate refers to the naturally occurring analogs in the poppy plant as well as their semisynthetic congeners [11]. The word opioid is a broader term and refers to semisynthetic or synthetic substances derived from or resembling the alkaloids in the poppy plant as well as the endogenous neurotransmitters with affinity for the opioid receptors (described in a later section). An alternative definition for opioid is “any directly acting compound whose effects are stereospecifically antagonized by naloxone” [12]. In brief, opioids are all substances, whether natural or synthetic, which have morphinelike properties and bind specifically to opioid receptors.

In addition to analgesia, clinically useful opioids are capable of producing a wide variety of desired results as well as untoward effects pertaining to the respiratory system, gastrointestinal tract, cardiovascular system, mood, and rewarding processes. Depending on their opioid receptor effects, the opioids are divided into pure agonists, antagonists, and mixed agonists/antagonists, also called partial agonists [13]. When an agonist (eg, morphine) binds to the opioid receptor (eg, mu), it causes analgesia, euphoria, respiratory depression, and miosis. The potencies of various agonists differ
and therefore, so too do their doses for maximal therapeutic effect. For example, codeine is considered to be a weak agonist in that it needs to be given at greater doses than morphine to achieve clinically comparable analgesic effects. On the other hand, antagonists such as naloxone are capable of blocking the effects of the agonists by occupying the receptor without activating it. Mixed or partial agonists are capable of stimulating the receptor. However, because of their ability to compete with the full agonists for binding to the opioid receptor, they can actually reduce the final efficacy expected from an agonist. Therefore, the activity of a partial agonist depends on the circumstance and could have mixed agonist and antagonist activity. Interestingly, an opioid can act as agonist for one opioid receptor type and antagonist for the other. Regardless, it is generally recognized that the mu receptors, described in more detail later, are the mediators of various desired and undesired effects generally expected of the opioid therapeutics.

In general, the pharmacologic activity and therapeutic effects of various opioids are compared with morphine. There are also several agonist and antagonist opioid drugs that are structurally related to morphine. A partial list of these includes the agonists codeine, hydrocodone, hydromorphone, and oxycodone; the antagonists naloxone and naltrexone; and the partial agonist buprenorphine. Codeine is the most widely prescribed natural opioid (ie, opiate) and its therapeutic effects are mediated by hepatic conversion to morphine. A synthetic analog of codeine is tramadol, which in addition to its weak opioid action, blocks the reuptake of other neurotransmitters such as serotonin. Hydrocodone is synthesized from codeine and is considered to be more potent. On the other hand, hydromorphone, the active metabolite of hydrocodone, is 7 to 10 times more potent than morphine. Interestingly, hydromorphone can be produced as a minor metabolite of morphine in humans [14]. Both oxycodone and codeine are methylated at position 3. Unlike morphine, there is better oral/parenteral relative analgesic potency ratio for both of these opioids as compared with morphine [15].

Additional mu opioid receptor agonists available clinically include the synthetic analogs including meperidine, fentanyl, methadone, and propoxyphene [11]. Meperidine and propoxyphene have less analgesic potency compared with morphine, while methadone is comparable and fentanyl is 50 to 100 times more potent [16]. There are also several fentanyl analogs, including sufentanil, which have several-fold greater potency than even fentanyl [17]. In addition to the opioid receptor, the synthetic agonists also bind to other types of receptors. Examples include methadone binding to the N-methyl-D-aspartate (NMDA) receptor [18] and fentanyl releasing noradrenaline, a phenomenon that is resistant to the naloxone antagonism [19].

Morphine, tramadol, methadone, oxycodone, hydrocodone, and codeine are all available as oral preparations. Morphine, hydromorphone, oxymorphone, and fentanyl can be administered intravenously. In addition,
fentanyl is frequently prescribed in the form of a patch at various strengths and oxycodone can be administered as a slow-release formulation [20]. As previously mentioned, some of these opioids are clinically available as combination products along with a nonopioid analgesic. Oxycodone combined with aspirin, ibuprofen, or acetaminophen is available in several different formulations and dosages, as are the combinations of codeine with acetaminophen or aspirin, hydrocodone with acetaminophen or ibuprofen, and tramadol with acetaminophen.

Hydrocodone is a semisynthetic opioid that is clinically used for both analgesic and antitussive properties. Hydrocodone elicits its pharmacologic activities through binding to the opioid receptors in the central nervous system. It appears that hydrocodone is a more effective opioid than codeine for relief of musculoskeletal pain [21] having six times the analgesic potency of codeine [22]. Hydrocodone is typically available as a combination product along with many other medications including nonopioid analgesics (eg, ibuprofen and acetaminophen), expectorants (eg, guaifenesin), decongestants (eg, pseudoephedrine), other cough suppressants (homatropine), and antihistamines (chlorpheniramine).

Many analgesic effectiveness studies involving combination drug formulations (an opioid combined with a nonopioid) have been reported. For example, in the treatment of moderate to severe postoperative obstetric or gynecologic pain, 2-tablet dose of hydrocodone 7.5 mg with ibuprofen 200 mg was comparable in efficacy to the 2-tablet dose of oxycodone 5 mg and acetaminophen 325 mg. Obviously both of these treatments were superior to the placebo [23]. In contrast, for treatment of chronic pain, the 2-tablet dose of hydrocodone 7.5 mg and ibuprofen 200 mg was more effective than either the 1-tablet dose of this combination or the 2-tablet dose of codeine 30 mg and acetaminophen 300 mg combination [24]. In a double-blind, randomized controlled trial involving 118 patients with chronic cancer pain, the combination formulation of hydrocodone (25 mg/d) and acetaminophen (2500 mg/d) was effective in relieving pain in 56.5% of the patients [25].

Clinical problems of opioid therapy

Adverse drug reactions

Pain management is plagued by two major factors: adverse drug reactions and undertreatment, as both patients and practitioners are fearful of addiction. Common side effects at conventional, therapeutic doses include somnolence, decreased gastric motility, nausea, vomiting, cutaneous flushing, and pruritis [11]. Although not typically life-threatening, these side effects represent quality of life issues for patients, often resulting in additional medications to alleviate the opioid side effects and increase compliance. At higher doses, opioids can cause miosis—pinpoint pupils that are pathognomonic of toxic doses—as well as mental changes, hearing loss [26].
orthostatic hypotension, convulsions, and respiratory depression, the latter being the most common cause of opioid-related death [11]. Most of these adverse reactions, if recognized quickly, can be reversed upon administration of the opioid antagonist naloxone. Chronic opioid therapy can also lead to untoward hormonal effects. Suppression of sex hormones and cortisol can result in male and female infertility, decreased libido, and aggression, which can be reduced with specific hormone replacement therapies [27].

The availability of new routes of administration have led to increased utility and decreased opioid adverse drug reaction risk. Epidural and intrathecal administration through spinal catheters produces adequate regional analgesia at relatively low total doses compared with intravenous or oral routes. As such, spinal administration can thus minimize somnolence, nausea, vomiting, and respiratory depression associated with these medications. Other alternative routes include intranasal administration of butorphanol, and rectal and transdermal administration of fentanyl [28]. Availability of such options provides not only a decreased risk of adverse reactions, but also more comfortable measures for patients who would otherwise require continued intravenous administration, or for those who are unable to receive oral medication [28,29].

Undertreatment and fear of addiction

Physicians tend to prescribe pain medications conservatively, and patients and their families are often just as conservative, choosing to deal with some amount of pain rather than risk addiction. Indeed, the most common error made by physicians in managing severe pain is inadequate dosing of opioids [28]. As a result, many pain patients, including the terminally ill, suffer unnecessarily [28,30]. Lack of understanding of regulatory guidelines regarding the use of controlled substances and a social and legal environment that focuses on prescription drug abuse and a fear of unwanted regulatory scrutiny all contribute to the systemic practice of undertreating pain and the potential for erroneous identification of treatment-resistant patients as noncompliant or addicted [31].

Similar problems plague other therapies, such as warfarin anticoagulation, wherein concern about bleeding events leads to underdosing of that life-saving but potentially dangerous drug [32]. In the case of warfarin, undertreatment produces a high risk of blood clots and stroke [32], whereas the undertreatment of chronic pain decreases patients’ functional status and quality of life, and can lead to loss of work, additional physical problems such as heart disease and obesity, an increased incidence of suicide, and an increased incidence of patients seeking illegal alternatives to alleviate their pain [31]. In both cases, pharmacogenetic diagnostics testing can be used to facilitate better understanding of the individual patient’s risk, thereby freeing practitioners, armed with this knowledge, to practice medicine more effectively.
Fear of addiction leads to both undertreatment and noncompliance among opioid prescribers and patients, and part of this fear is a product of misunderstanding and misinterpretation of the symptoms of physical dependence and tolerance, one or both of which are characteristic effects of chronic opioid therapy (Fig. 1) [20,31]. Addiction is a primary chronic disease influenced by genetic, psychosocial, and environmental factors, and characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving [1,20,31]. Two states of adaptation are physical dependence and tolerance. Physical dependence manifests as drug class–specific withdrawal symptoms as a result of abrupt cessation, rapid dose reduction, decreasing drug blood levels, and/or administration of an antagonist [1,31]. Tolerance is the condition in which exposure to a drug produces physiologic changes that cause the drug’s effectiveness to be diminished over time [1,20,31]. Although the physical symptoms of withdrawal and the behavioral characteristics associated with physiologic tolerance (patients requesting increased drug dosages, complaints of persistent pain in spite of prescription compliance) are often interpreted as signs of addiction, it is important to note that tolerance and dependence are not equivalent with addiction, nor are they predictors of addiction development. The term “pseudoaddiction” has been defined to describe the iatrogenic result of physicians’ misinterpretation of relief-seeking behaviors as the drug-seeking behaviors associated with addiction (see Fig. 1) [20,31]. Compounding the problem is the underappreciated and misunderstood contribution of genetics to the variability in patients’ experience of pain (nociception), as well as their individual dose requirements and risk of experiencing the problems of

Fig. 1. Continuum of pain relief outcomes.
tolerance or addiction. Indeed, naïve patients whose genetics make them resistant to opioid therapy will experience little to no pain relief, and may quickly be judged noncompliant when in fact they are physiologically incapable of experiencing therapeutic benefit from the given drug.

A study from the American Pain Society estimates that 9% of the US adult population suffer from moderate to severe noncancer-related chronic pain [33]. More than half (57%) of these patients report severe to very severe pain, which is more likely to be constant than “flare-up,” and less likely to be caused by arthritis [33]. In spite of reporting substantial pain, almost 40% are not currently seeing a physician for their pain, and those who are being treated by a physician are those who report experiencing severe (72%) and moderate (51%) pain [33]. Chronic pain sufferers who report moderate to severe pain are more likely to visit the emergency room, require hospitalization, or receive counseling for their pain [33]. As an indicator of the difficulty patients experience in obtaining effective pain relief, it is interesting to note that 47% of all chronic pain sufferers find it necessary to change doctors several times and their reasons for doing so include insufficient pain relief (42%), perceived lack of physician’s knowledge or willingness to treat pain (27%–31%), and a perceived lack of sympathy (29%) [33]. Also telling is the fact that, although 55% of chronic pain sufferers report their pain as “under control,” the vast majority of these (70%) are those reporting only moderate pain. The more severe a sufferer’s pain, the less likely they are to consider their pain “under control” (51% severe, 39% very severe). When pain is under control, there are significant positive improvements in the sufferer’s quality of life and emotional health, except in the case of very severe pain.

From a physician’s standpoint, effective pain management is complicated by several factors, including (1) strict regulatory requirements and concerns about addiction or diversion, and (2) the fact that both the experience and treatment of pain are subject to a broad degree of interindividual variability. The House of Delegates of the Federation of State Medical Boards of the United States cites several major contributors to the problem of pain undertreatment [31]. Topping the list is a lack of knowledge among practitioners regarding medical standards, the latest research, and clinical guidelines for administering appropriate pain treatment; this lack of knowledge contributes to a misunderstanding of the disparate concepts of dependence and addiction. Many practitioners, unfamiliar with regulatory processes and policies, are also unsettled by the perception that prescribing adequate amounts of controlled substances to effect pain relief will trigger regulatory scrutiny [31]. Although pain policies and procedures are being put in place by state medical boards, the implementation and adoption of such policies is not uniform and can vary substantially between jurisdictions. Setting such policy and procedural issues aside, the very subjective nature of pain is at the heart of the problem for practitioners. Research has found that the experience of pain and patients’ response to therapy (with regard to adverse
reactions and therapeutic benefit), are subject to wide interindividual variability caused by a number of factors, including patient age, organ function, comedication, underlying disease, and genetics.

Current chronic pain management guidelines suggest a multidisciplinary, or biopsychosocial, model that incorporates pharmacologic and psychologic approaches to treating pain. Even acute pain management guidelines, such as those for postsurgical patients, incorporate various psychosocial elements in addition to general pharmacologic approaches. Although guidelines may call for titration protocols and pharmacovigilance for such adverse reactions as excessive sedation and respiratory depression, they are all based on a general “try it and see” approach; patient therapy is generally initiated using a standard drug and dosage that is typically based on a patient’s reported pain level as measured on a standardized pain scale. Although these methods are meant to assist physicians in tailoring pain management to the needs of the individual patient, these are all based on inherently subjective measures. Not only do these subjective approaches create a lack of clarity for physicians as they approach patient management, they also can lead to misunderstandings when standard therapeutic protocols appear to fail. Adverse reactions are events to which physicians currently must respond after the fact, as they have no tools available to them to avoid or alleviate the risk. Patients who report no pain relief can also present a confounding element to physicians, in the absence of any evidence as to the cause for the therapeutic failure. In many such cases, the patient’s particular genetic profile may present some explanation.

**Pharmacogenetic effects on opioid sensitivity**

The genetic effects on patient drug sensitivity (ie, therapeutic response and relative risk of experiencing adverse effects) can be separated into two mechanistic categories: pharmacokinetics and pharmacodynamics. A patient’s metabolic status, or their ability to metabolize certain drugs, affects the drug pharmacokinetics. For example, a patient with impaired metabolism may be unable to activate a prodrug such as codeine into the active morphine metabolite. Such patients will report little to no pain relief in response to codeine therapy, and may not receive therapeutic benefit even from greater dosages. In other cases, a patient may metabolize the prodrug excessively quickly, and is thus at greater risk for toxicity. A patient’s ability to respond to a drug is also determined at the level of the drug target, or receptor, also referred to as pharmacodynamics. Patients exhibit genetic variability in the number and functional status of their receptors, which leads to interindividual variability in therapeutic response to certain drug therapies. For example, a patient who has a nonfunctional receptor for a certain drug will be unable to respond to that drug regardless of the dosage. Patients with varying degrees of receptor functionality may require different dosages than patients exhibiting no such variable.
In the case of opioid analgesic therapies, several pharmacokinetic and pharmacodynamic players have been identified as reliable indicators of therapeutic efficacy with regard to certain drugs. The cytochrome P450 metabolic enzymes have been implicated in the metabolism of opioid drugs, and variants in these enzymes, specifically the CYP2D6 and CYP2C19, have been linked to toxicity and therapeutic efficacy of opioids. In addition, opioid receptors, specifically the mu and kappa opioid receptors, have been implicated both in the therapeutic efficacy and the risk of experiencing adverse effects. Of these biomarkers, CYP2D6 and OPRM1 (the mu opioid receptor) have been thus far identified as having the greatest relevance to determining a patient’s relative risk of experiencing adverse effects and the potential therapeutic efficacy of opioid therapies (Table 1). These are discussed further in the following sections.

**Opioid Metabolism by CYP2D6**

CYP2D6 catalyzes the biotransformation of several opioid prodrugs into their active metabolites. These include codeine, dihydrocodeine, oxycodone, hydrocodone, tramadol, dextropropoxyphene, ethylmorphine, and to some extent, methadone. For example, approximately 90% of a codeine dose is metabolized to inactive metabolites by CYP3A4, which undergo subsequent conjugation and renal elimination. The other 10% of a codeine dose undergoes O-demethylation by CYP2D6 and accounts for the analgesic activity of the medication (Fig. 2) [34]. Glucuronidation of morphine to morphine-6-glucuronide produces an additional active metabolite. Hydrocodone is also metabolized to the more potent hydromorphone by CYP2D6 O-demethylation, in addition to other pathways including N-de- methylation to norhydrocodone and 6-keto reduction to the corresponding hydroxy-metabolites (hydrocodol) and hydromorphol [22].

Phenotypic differences in CYP2D6 metabolizer status, as a function of genotype, are categorized as poor, intermediate, extensive, and ultra-rapid. These phenotypic categories and the most common pharmacogenetic polymorphisms associated with the designations are more broadly described in other articles in this issue (see the articles by de Leon and colleagues and Algeciras-Schimnich and colleagues) [35–37]. Briefly, CYP2D6 poor metabolizers (PM) are those who have two deficient alleles, found in approximately 7% to 10% of white populations and 1% to 2% in African Americans. They are unable to metabolize most opioids, antidepressants, and antipsychotics, and are therefore prone to experiencing elevated blood concentrations of those medications. In addition, because of the lack of CYP2D6 activity, PMs are also unable to convert certain prodrugs into their active metabolites, e.g., codeine to morphine or tamoxifen to endoxifen, resulting in therapeutic failure from administration of the inactive parent compound [37,38]. For example, PMs administered hydrocodone will produce little to no active hydromorphone and are at risk of analgesic failure...
Table 1
Clinical effects of CYP2D6 and OPRM1 variants on opioid toxicity and efficacy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene variants</th>
<th>Opioid</th>
<th>Effect</th>
<th>Clinical consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic variants</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CYP2D6</td>
<td>Inactive alleles: *3–*7, and others</td>
<td>Codeine</td>
<td>Decreased morphine production via O-demethylation</td>
<td>Loss of opioid analgesia</td>
</tr>
<tr>
<td></td>
<td>Partially active alleles: *9, *10,</td>
<td>Tramadol</td>
<td>Decreased O-desmethyl tramadol production</td>
<td>Slightly decreased analgesia and increased side effects</td>
</tr>
<tr>
<td></td>
<td>*17, *41</td>
<td>Oxycodone</td>
<td>Decreased oxymorphone production</td>
<td>Decreased analgesia and increased side effects</td>
</tr>
<tr>
<td></td>
<td>Ultra-rapid alleles: *1xN, *2xN</td>
<td>Hydrocodone</td>
<td>Decreased hydromorphone production</td>
<td>Unclear; no significant effects</td>
</tr>
<tr>
<td></td>
<td>(active allele duplication)</td>
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<td></td>
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<tr>
<td></td>
<td>Codeine</td>
<td>Oxycodone</td>
<td>Increased oxymorphone production</td>
<td>Increased risk of ADRs</td>
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<td>(active allele duplication)</td>
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<tr>
<td><strong>Pharmacodynamic variants</strong></td>
<td></td>
<td>Morphine and Alfentanil</td>
<td>Unclear; impaired receptor affinity, and possibly decreased expression</td>
<td>Decreased effectiveness, increased dose requirement</td>
</tr>
</tbody>
</table>

*Abbreviations: CYP2D6, cytochrome P450 2D6; OPRM1, mu opioid receptor 1; ADR, adverse drug reaction.

Data from Refs [53,60–62].
Previous pharmacokinetic studies have shown after taking a single oral dose of 10 mg hydrocodone, extensive metabolizers (EMs) display peak serum hydromorphone concentrations roughly five times that of the PMs [39]. Further, the mean peak serum concentrations in PMs are consistent with serum hydromorphone concentrations in patients who received the same 10-mg hydrocodone dose together with the strong CYP2D6 inhibitor quinidine, thus demonstrating how CYP2D6 metabolic capacity is the determinant for therapeutic hydromorphone concentrations. By leveraging these single-dose peak serum hydromorphone concentration data, the effect of PM status on chronic hydrocodone dosing can be modeled (Fig. 3). Using standard pharmacokinetic calculations for the concentration maximum at steady state (Cmaxss) following 10-mg hydrocodone dosing every 6 hours, it is clear that PMs consistently produce no appreciable hydromorphone concentrations as compared with EMs (see Fig. 3). Whether the difference in serum drug concentrations results in differential analgesic efficacy remains to be determined.

Intermediate metabolizers (IMs) are typically defined as those who carry one deficient allele and one active allele, or two partially deficient alleles [36,40,41]. These individuals retain some residual capacity to metabolize drugs, but are still at risk of experiencing somewhat elevated blood levels and associated side effects at standard dosages [36,40,41]. EMs are considered “normal,” and are homozygous for the wild-type or common allele. These individuals retain full metabolic capacity, and in general, receive benefit from standard dosages of medications that are CYP2D6 substrates.
In contrast, ultra-rapid metabolizers (UMs) carry three or more functional alleles, and are present in 1% to 2% of whites and up to 29% of Northern African populations. These patients metabolize drugs much more quickly, and may see little or no therapeutic benefit from standard dosages, as they eliminate the drug too quickly to allow therapeutic drug concentrations to be achieved. Or, in the case of a prodrug such as codeine, UM s may achieve higher than normal blood concentrations of the active metabolite morphine, thus putting these patients at risk of toxic side effects [33,42]. A recent case report detailed the fatal morphine overdose of a breastfeeding neonate whose mother, a CYP2D6 UM, had been taking low-dose codeine for episiotomy pain. Postmortem analysis of the baby’s blood and mother’s stored breast milk showed morphine levels well over 10 times higher than would have been expected in both fluids [43]. This case report led to the Food and Drug Administration (FDA) public health advisory issued in August 2007 informing health care professionals about the safety of codeine-based products given to breastfeeding mothers who are CYP2D6 UM s [44]. In the advisory, the FDA warned that higher levels of morphine in the breast milk of UM mothers prescribed codeine can lead to life-threatening or fatal side effects in nursing babies, and that doctors should educate their nursing patients how to recognize signs of morphine overdose. The FDA subsequently asked makers of codeine-based pharmaceuticals to include information about metabolic differences and breastfeeding concerns.

Fig. 3. Modeled hydromorphone accumulation following repeated hydrocodone dosing as a function of CYP2D6 metabolizer status. Hydromorphone concentrations calculated are approximately five times higher in EMs compared with PMs following 10-mg hydrocodone dosing every 6 hours, based on genotype-specific peak hydromorphone serum concentrations [39]. EM, extensive metabolizer; PM, poor metabolizer.
in the drug labels. Although this situation has been reported only with codeine, the FDA notes that it has the potential to affect other narcotics with active metabolites produced by CYP2D6, and, thus, cause the same serious side effects in nursing infants if the breast milk drug levels are high [44].

**Opioid response via μ-opioid receptor**

**Opioid receptors**

Opioid receptors are members of the G-protein–coupled transmembrane protein class [45]. They are present throughout both central and peripheral nervous systems and are linked to various neurotransmitter systems. In the mid-1970s, Martin and colleagues [46] proposed the idea of multiple opioid receptor subtypes with ligands having agonist, antagonist, or mixed agonist activity. The list of opioid receptor subtypes has been growing in part because of the identification of their endogenous ligands such as enkephalins, endorphins, and dynorphin [45] as well as the availability of selective agonists and antagonists.

There are nomenclature schemes for various subtypes of opioid receptors. One very traditional and popular approach has been the use of Greek letters to refer to the drug that was used in the study of that particular receptor subtype [12]. For example, mu (μ) stands for morphine, kappa (κ) for ketocyclazocine, sigma (σ) for SKF-10,047, also known as N-allylnormetazocine, and delta (δ) for deferens. The sigma was later shown to be nonopioid in nature; therefore, the mu, kappa, and delta are the pharmacologically defined opioid receptors [12,47]. Additional receptors including epsilon (ε), zeta (ζ), and lambda (λ) have also been described [12]. An alternative approach to naming opioid receptors is the use of the OP series starting from that which was described first (ie, delta), OP1. This was followed by OP2 and OP3 for kappa and mu receptors, respectively. Molecular biologists have also used their own nomenclature referring to delta, kappa, and mu as DOR, KOR, and MOR receptors, respectively. For most clinicians, the original Greek alphabet system is the most familiar.

Regardless of the nomenclature used, it is evident that opioid receptors have structural similarity, but each has distinct clinical effects and tissue distribution. In addition to the classical opioid receptors, a new G-protein–coupled receptor signaling system referred to as the opioid-receptor-like 1 (ORL1) receptor has been cloned [48]. Significant structural-functional homology as well as positive cooperativity between the two systems has been described [48]. Nociceptin, an endogenous ligand for ORL1, is a nonopioid peptide able to modulate pain response [49]. However, it is evident that most of the currently available opioid therapeutic analgesics exert their analgesic and adverse effects primarily through the classical mu receptors [50]. The agonists of the mu opioid receptor share many pharmacologic characteristics that now are known to be mediated through the subtypes of this receptor.
Cloning experiments of MOR-1 have suggested that there are at least seven splice variants of this gene leading to the variability in analgesic effects of opioids with mu receptor affinity [51]. Interestingly, each of these variants selectively binds morphine and other drugs that act at the MOR receptor (currently referred to as mu opioid peptide or MOP). For example, naloxonazine antagonizes the mu-1 whereas morphine-6-beta-glurucoside affects the mu-2 subtype. The other opioid receptors including delta and kappa also have various subtypes, which will not be discussed here.

\[ \mu \text{-opioid receptor genotyping} \]

Opioid agonists, such as morphine, hydromorphone, and fentanyl, exert their analgesic properties via stimulation of the mu receptors. Their analgesic effects increase in a log-linear fashion with the dose, although this theoretically unlimited effect is tempered by the occurrence of increasingly intolerable side effects, which are also mediated by the mu receptors. Analgesic efficacy of mu-acting drugs has been linked to the 118A > G single nucleotide polymorphism (SNP) of \textit{OPRM1}, the gene encoding the mu-1 receptor. The frequency of the variant G allele varies from 10% to 48% depending on the population studied [52]. The base substitution creates a missense mutation in the N-terminus of the protein, changing an asparagine to aspartic acid. This results in the loss of a site (one of five) for receptor N-glycosylation. The polymorphism in \textit{OPRM1} has also been reported to affect the expression of the mu receptor [53]. Early reports that the variant affects receptor binding potential have not been confirmed, leaving the precise mechanism for the variant’s effect a mystery [54,55]. The polymorphism has been found to affect both nociception and the therapeutic efficacy of opioid drugs [56,57].

Studies show that patients carrying the GG (homozygous variant) genotype require much higher opioid doses to achieve pain relief [58,59]. In one study, \textit{OPRM1} AA patients required an average dose of 112 mg morphine/24 hrs, AG patients required 132 mg morphine/24 hrs, and GG patients required 216 mg morphine/24 hrs [58]. The difference between these groups’ pain scores was not statistically significant during therapy, indicating that pain relief was consistent across the variable dose ranges and genotype groups. Another study of cancer patients found a similar difference between the morphine dose requirements of AA (97 mg/24 hrs) and GG (225 mg/24 hrs) patients, but did not see the same intermediate dose requirement for the heterozygous group (66 mg/24 hrs) [59]. In this study, however, the median pain score for this group was significantly different from the others.

When one considers such drastically different dose requirements for patients carrying the GG genotype and the frequency of the genotype, it is not surprising that many patients receiving standard dosing regimens frequently complain of insufficient opioid pain relief. Thus, the use of the \textit{OPRM1} 118A > G variant as a diagnostic marker could facilitate the identification of patients who may be less sensitive (or, more resistant) to
standard opioid therapeutic regimens, and may help guide individualized
dosing and therapeutic choices.

Summary

Adequate pain management in the United States represents a significant
ongoing problem facing physicians, patients, and regulatory agencies. The
use of opioids continues to be a mainstay of pain management strategies, de-
spite their risks of toxicity and addiction; thus, more effective means by
which to provide adequate pain relief while balancing the potential negative
aspects is paramount. Integration of novel diagnostics, such as the pharma-
cogenetic biomarkers CYP2D6 and OPRM1, hold promise as a means by
which to assess a patient’s risk of adverse events or likelihood of efficacy.
With a priori 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 in real time. Incorporation of such biomarkers are
emerging 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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