Pharmacogenomics and Personalized Medicine

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REVIEW

Pharmacogenomic considerations in opioid analgesia

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
22 August 2012
Number of times this article has been viewed

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Abstract: Translating pharmacogenetics to clinical practice has been particularly challenging in the context of pain, due to the complexity of this multifaceted phenotype and the overall subjective nature of pain perception and response to analgesia. Overall, numerous genes involved with the pharmacokinetics and dynamics of opioids response are candidate genes in the context of opioid analgesia. The clinical relevance of *CYP2D6* genotyping to predict analgesic outcomes is still relatively unknown; the two extremes in *CYP2D6* genotype (ultrarapid and poor metabolism) seem to predict pain response and/or adverse effects. Overall, the level of evidence linking genetic variability (*CYP2D6* and *CYP3A4)* to oxycodone response and phenotype (altered biotransformation of oxycodone into oxymorphone and overall clearance of oxycodone and oxymorphone) is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy. On the other hand, predicting the analgesic response to morphine based on pharmacogenetic testing is more complex; though there was hope that simple genetic testing would allow tailoring morphine doses to provide optimal analgesia, this is unlikely to occur. A variety of polymorphisms clearly influence pain perception and behavior in response to pain. However, the response to analgesics also differs depending on the pain modality and the potential for repeated noxious stimuli, the opioid prescribed, and even its route of administration.

Keywords: pain perception, opioid analgesia, genetic variation, pharmacogenetics

Introduction

Recent developments in genomic research have opened vast opportunities to expand and improve our understanding of how genetic variability affects response to prescribed medication. The ultimate goal of pharmacogenomic research is to offer "tailored personalized medicine" to improve the efficacy of medication as well as patient safety by helping predict the risk of adverse outcomes. Although numerous hurdles have limited the creation and implementation of pharmacogenetic testing, several pharmacogenetic tests have been recently developed,[1] and the US Food and Drug Administration (FDA)[2] and the European Medicines Agency have approved several drug label modifications to contain pharmacogenetic information.[3] Furthermore, in the last year, the Clinical Pharmacogenetics Implementation Consortium[4] has published guidelines for warfarin,[5] clopidogrel,[6] and thiopurine dosing[7] based on pharmacogenetic testing, and the guidelines for codeine therapy in the context of *CYP2D6* genotype are being published these days.[8]

Pain perception is one of the most complex quantifiable traits because it encompasses several phenotypes involving the peripheral and central nervous systems,

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and as a complex trait it is expected to have a polygenic nature shaped by environmental factors such as trauma, lifestyle, and stress. In addition, an important characteristic in determining the pain phenotype is the wide interindividual pharmacologic range in response to drugs. Therefore, not surprisingly, translating pharmacogenetics to clinical practice has been particularly challenging in the context of pain, due to the complexity of this multifaceted phenotype and the overall subjective nature of pain perception and response to analgesia. Yet with a growing body of evidence demonstrating a strong association between severe acute pain and the risk for persistent pain, identifying individuals with an increased vulnerability to pain, including genetic factors, may allow to substantially improve clinical outcomes.[9] This overview will present an outline of some genetic variants involved in pain and analgesic responses, bearing in mind the interplay between pharmacokinetic (eg, the CYP450 family of enzymes[10]) and pharmacodynamic (eg, the well-studied μ-opioid receptor) effects. It will review patient-specific considerations in the clinical setting of opioids for acute pain, including postoperative pain, opioids for labor analgesia, and the response to opioids for chronic pain. Finally, the clinical utility of pharmacogenomic testing in pain management and the future of personalized medicine in this context will be reviewed.

Interindividual variability in pain sensitivity

Clinicians and pain providers are well aware of the large and unpredictable interindividual variability in pain perception and sensitivity to analgesia.[11,12] Twin and volunteer studies have demonstrated a significant heritability for experimental pain responses,[13,14] and recent genomic and pharmacogenetic research has considered numerous candidate genes as suitable targets for the study of the genetic and inheritable basis of pain and/or response to analgesic drugs.[15]

The "genetic architecture of human pain perception" has been proposed to include rare deleterious genetic variants and more common genetic polymorphisms as mediators of human pain perception and clinical pain phenotypes.[16] An extremely rare pain phenotype characterized by a total absence of pain perception ("congenital insensitivity to pain") with no associated neuropathy has been associated with the mutations in the gene *SCN9A*, encoding the α-subunit of the voltage-gated sodium channel NaV1.7.[17,18] This discovery has already opened directions for novel generations of therapeutic agents blocking NaV1.7,[19,20] with the hope that these drugs may provide selective and safe analgesia/anesthesia. Another clinical phenotype resulting from loss-of-function mutations of NaV1.7 termed "congenital indifference to pain," refers to individuals who actually recognize painful stimuli but lack the affective-motivational component of pain perception, do not show withdrawal responses, and often die in childhood.[21] Along the same line, it has also been proposed from an evolutionary standpoint that individuals experiencing severe pain may in fact not be disfavored, as they are likely to have an increased capacity to sense essentially all environmental stimuli and increase their ability to detect and avoid environmental threats. With that in mind, lower pain threshold is commonly associated with the ability to detect a wide variety of nonnoxious sensory stimuli, and may represent a beneficial adaptive mechanism. This has been suggested as an explanation for sex-dependent differences in pain sensitivity, resulting from evolutionary pain-modulation processes, which afford women a greater sense of awareness of potential environmental threats to offer heightened protection to their offspring.[22]

In the era of opioid therapy, pharmacogenomic studies to guide opioid-based analgesic regimens are flourishing. Among the numerous candidate genes that have been considered important in opioid response, the CYP family of enzymes, the μ-opioid receptor gene (*OPRM1,* p.118 A/G), the catechol-*O*-methyltransferase gene (*COMT,* Val158Met), several variants of the ATP-binding cassette, and subfamily B member 1 gene *(ABCB1)* have been extensively reviewed. However, most drug effects are determined by the interaction of several polymorphisms that influence the pharmacokinetics and pharmacodynamics of medications, including inherited differences in drug targets (eg, receptors) and drug disposition (eg, drug-metabolizing enzymes and transporters). This interplay may result in polygenic determinants that involve numerous potential combinations of drug-metabolism, drug-transporters and drug-receptor genotypes with corresponding drug-response phenotypes yielding a wide-range of therapeutic indexes (efficacy/toxicity ratios) for a given drug.

Genetic variants of CYP family of enzymes and opioid metabolism

Altogether, 20%–25% of clinically used drugs are influenced by genetic variants of enzymes.[23] Cytochrome P450 enzymes (CYPs) play a major role, as these are responsible for about 80% of phase I metabolism.[24] CYP2D6 metabolizes approximately 25% of frequently used drugs, eg, β-blockers, antiarrhythmics, antidepressants, neuroleptics, and analgesics.[25,26] Four metabolic phenotypes are characterized; poor (PM),

intermediate (IM), extensive (EM), and ultrarapid (UM) metabolizers. Critical base changes or deletions result in more than 80 distinct *CYP2D6* allelic variants, explaining the wide spectrum of metabolic diversity within populations.[27] A comprehensive list of all known cytochrome alleles is displayed at the website of the CYP Allele Nomenclature Committee (http://www.imm.ki.se/CYPalleles). Relevant polymorphisms resulting in nonfunctional alleles are single base exchanges (*CYP2D6*4* [rs3892097], *CYP2D6*7* [rs5030867], *CYP2D6*8* [rs5030865]) or deletions (*CYP2D6*3* [rs35742686], *CYP2D6*6* [rs5030655]) within the cytochrome P450 2D6 gene locus. Deletion of the entire *CYP2D6* gene (*CYP2D6*5*) also results in the absence of CYP2D6 protein production. Subjects with these homozygous PM-associated variants are at increased risk for potentially severe adverse side effects due to drug concentrations exceeding the therapeutic level (ie, tricyclic antidepressants, antiarrhythmics) or for therapeutic failure due to poor metabolism of a prodrug (ie, codeine, tramadol) into its active metabolite. In contrast, duplication or multiduplication of the *CYP2D6* gene is related to the UM phenotype and increased enzyme activity resulting in rapid decline of respective plasmatic drug concentrations. Thus, therapeutic effects cannot be obtained in UM at conventional doses of an active drug.[28]

The distribution of different CYP2D6 phenotypes within specific cohorts varies depending on geographic region and individuals' ethnicity;[13] up to 7%–10% of Caucasians are categorized as PMs. In a study screening 1060 individuals within 52 worldwide-distributed populations,[29] a greater variation of CYP2D6 within populations than between groups thereof was found. When comparing allelic distribution among different ethnicities, the *CYP2D6*4* allele is frequently found in Caucasians (in the order of 20% allelic frequency) and represents more than 75% of the mutant *CYP2D6* alleles, while it is extremely rare among Chinese individuals. Other alleles such as the *CYP2D6*10*, resulting in an IM phenotype, are particularly frequent among Asian individuals, and so are the *CYP2D6*45* and *CYP2D6*46* alleles among individuals of black African origin. In a middle European population, 3%–5% are UMs, whereas in Scandinavia this figure decreases to 1%–2%; however, it increases for subjects from the Mediterranean (10%–12%), Saudi Arabia (21%) and Ethiopia (29%).[23] Of particular clinical relevance, the UM phenotype is the second most common type in North Africa, the Middle East, Oceania, and the EMs being the most common. Prodrugs that rely on CPY2D6 metabolism are likely to reach higher-than-expected plasmatic concentrations of their active metabolite in UMs. Conversely, 7%–10% of Caucasians, those carrying the PM phenotype, are at risk for higher-than-expected drug plasma concentrations of a parent drug, because of delayed or absent CYP2D6 metabolism.

The varied and unpredictable analgesic profiles of codeine, dihydrocodeine, hydrocodone, oxycodone, and tramadol are predominantly explained by CYP2D6 and CYP3A4 metabolism. In recent years, there have been several reports associating *CYP2D6* genotypes and near misses or fatal outcomes after opioid use.[30–33] Adding to the complexity of the metabolic pathway of one drug, adverse outcomes have been noted as a result of multiple drug therapies interacting at the same CYP.[34]

Codeine

Codeine is a prodrug with a low affinity and low intrinsic activity at the μ-opioid receptor (200 times and 50 times less than morphine, respectively).[35] It is classified as a weak opioid (World Health Organization class II), as it is a less potent μ-opioid receptor agonist than morphine. Codeine was initially prescribed because of the belief that this weak opioid is safe and would not result in adverse outcomes. For that reason, codeine has been considered a safe alternative to other opioids for outpatient pain management, and is still available in some countries as an over-the-counter medication, either alone or in combination with paracetamol (acetaminophen). Current use of codeine includes pediatric patients[36] and treatment of postoperative pain, although large-scale evidence on efficacy is sparse and has been challenged by a recent meta-analysis.[37]

Codeine is a prodrug, and requires *O*-demethylation catalyzed by CYP2D6 to be converted into morphine and become analgesic; this metabolic pathway accounts for 10% of codeine clearance (Figure 1). The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation represents approximately 80% of codeine clearance. Morphine is further metabolized into morphine-6-glucuronide (M6G) and morphine-3-glucuronide; both morphine and M6G display opioid activity.

The clinical relevance of *CYP2D6* genotyping to predict analgesic outcomes is still relatively unknown. In a recent pilot study, the relationship between *CYP2D6* genotype, post-cesarean pain scores, codeine consumption, and side effects were evaluated.[38] The two extremes in *CYP2D6* genotype seemed to predict pain response and/or adverse effects.

Individuals with an UM phenotype carry a risk for respiratory depression with codeine, particularly if CYP3A4 activity is inhibited by concomitant use of antibiotics or in

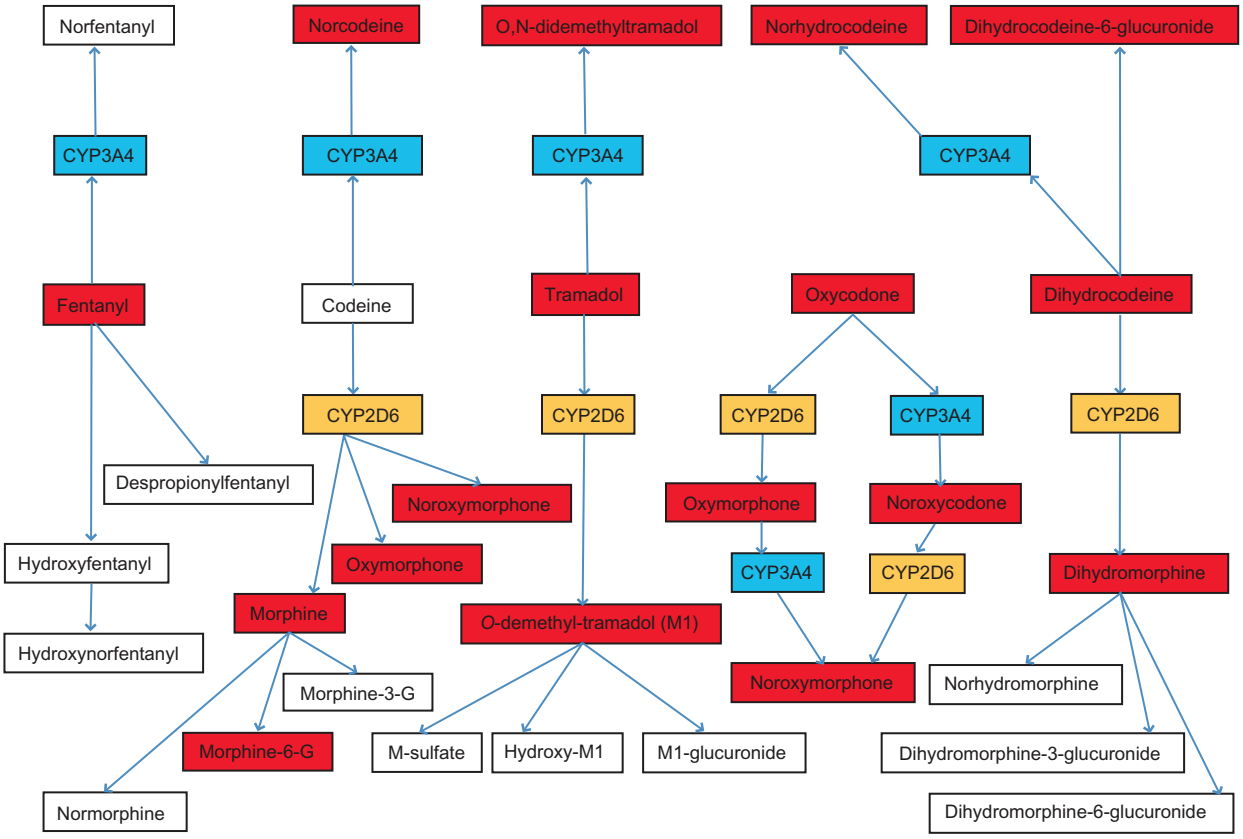

Figure 1 CYP metabolism involved in opioid clearance.

the context of kidney dysfunction.[30] Several reports of fatalities after codeine prescription in pediatric cases with UM have been published in recent years: a 2-year-old boy died due to codeine overdose after a minor surgical procedure,[39] and a 29-month-old child of North African descent suffered major hypoxic brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anesthetic for tonsillectomy.[40] By account of ethnic affiliation, the risk of this child of carrying a *CYP2D6* gene duplication is increased about threefold compared to Caucasian subjects.[40]

Perhaps the most striking report is that of the death of a breast-fed 13-day-old neonate following a morphine overdose because his mother was taking codeine after childbirth. This resulted in a recent FDA warning on codeine use in nursing mothers.[41] Toxic blood levels of morphine or its active metabolite M6G may arise in mothers and neonates that are CYP2D6 ultrarapid or extensive metabolizers. The mother was categorized as a CYP2D6 ultrarapid metabolizer and her breast milk had a morphine concentration of 87 ng/mL, the typical range being 1.9–20.5 ng/mL at doses of 60 mg codeine every 6 hours. The infant was categorized as a CYP2D6 extensive metabolizer (extensively metabolizing the prodrug codeine to morphine), and postmortem toxicology tests using gas-chromatography mass spectrometry revealed blood concentrations of morphine at 70 ng/mL. Sixty mg codeine/day for treatment of postpartum pain normally results in maximum morphine plasma concentrations of 2.2 ng/mL in breast-fed neonates.[42] In contrast, neonates prescribed morphine for analgesia displayed serum morphine concentrations of 10–12 ng/mL.[43] In a quantitative modeling study simulating the risk for neonates according to *CYP2D6* genotypes, repeated codeine administration in a breast-feeding mother demonstrated that toxic plasma levels of morphine could be reached in 4 days.[44] The authors concluded that unmonitored use of codeine for postlabor pain in breast-feeding mothers should not be considered a safe practice.

Codeine and morphine clearance in breast-feeding mothers and their relation to *CYP2D6* genotypes have been extensively commented on and evaluated.[43,45–47] Since 2007, the FDA has required manufacturers of prescription codeine products to state in the "Precautions" section of the drug label the risks of prescribing codeine to breast-feeding mothers.[48]

An FDA-approved genetic test (AmpliChip CYP450: Roche Diagnostics, Palo Alto, CA) is commercially available to test genetic variants of *CYP2D6*.[49] Overall, the level of

evidence linking gene variation (*CYP2D6*) to phenotype (increased biotransformation of codeine into morphine) is significant; however, there is no randomized clinical trial assessing the benefits of genetic testing prior to codeine therapy at large. In addition, while insufficient morphine formation from codeine resulting in failure of analgesia can currently be well predicted, extremely high morphine formation still requires the effort of combining genotyping with phenotyping.[50] Finally, the Clinical Pharmacogenetics Implementation Consortium has just published guidelines based on a focused review and interpretation of the literature by experts in the field (Table 1).[8]

Dihydrocodeine

Dihydrocodeine, a semisynthetic opioid, undergoes similar metabolic pathways as its analog codeine. CYP2D6 catalyses *O*-demethylation to dihydromorphine, an active metabolite with an opioid receptor activity comparable to that of morphine. CYP3A4 catalyzes *N*-demethylation to nordihydrocodeine and nordihydromorphine.[26] Studies to evaluate CYP2D6 metabolism utilize quinidine to inhibit CYP2D6 metabolism, thus resulting in a PM phenotype; plasma concentrations of dihydromorphine were reduced three- to fourfold, and urinary excretion of dihydromorphine was decreased from 0.91% to 0.28% in the first 12 hours in quinidine-induced poor metabolizers.[51] Pain thresholds, however, were not different after a single dose of dihydrocodeine along with quinidine, suggesting that this metabolic pathway and biotransformation of dihydrocodeine into dihydromorphine may not be clinically important for analgesia.[51,52]

Hydrocodone

Hydrocodone is a synthetic opioid analog to dihydrocodeine. The production of the active metabolite hydromorphone from hydrocodone is reduced in CYP2D6 PMs.[53] In vitro studies show that the *O*-demethylation of hydrocodone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low-affinity cytochrome P450 enzyme.[54] Norhydrocodone formation is attributed in part to CYP3A4, and approximately 40% of the clearance of hydrocodone is via non-CYP pathways. In a volunteer trial, CYP2D6 EMs and PMs were equally responsive to oral hydrocodone, and quinidine had no consistent effect on their responses, even though quinidine abolished the preexisting metabolic differences in hydromorphone production, as measured in urine.[55]

A recent case-report of a fatal hydrocodone overdose in a child demonstrated the effect of *CYP2D6* genotype on hydrocodone clearance and highlights the complex interplay between pharmacogenetic factors and drug–drug interactions.[56] The child had a PM CYP2D6 phenotype and was treated with clarithromycin, a potent inhibitor of CYP3A4, for an ear infection. The concomitant medication resulted in a substantial reduction in hydrocodone clearance. The combination of reduced clearance with an inhibited CYP3A4 and a PM phenotype contributed to this fatal overdose. Overall, data regarding pain management and hydrocodone is sparse, and there is no recommendation for pharmacogenetic testing to improve hydrocodone's efficacy and safety profile.

Tramadol

Tramadol, a synthetic analog of codeine and morphine, consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. (+)-Tramadol and the main metabolite (+)-*O*-demethyl-tramadol (M1) are agonists of the μ-opioid receptor. (+)-*O*-demethyl-tramadol's affinity for μ-opioid receptors is approximately 200 times greater

Table 1 Codeine therapy recommendations based on *CYP2D6* phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy
Ultrapid metabolized (CYP2D6 activity score > 2)	Increased morphine formation Higher risk of morphine toxicity	Avoid codeine use (potential for toxicity) Consider alternative such as morphine or a non-opioid Consider avoiding tramadol	Strong
Extensive metabolizer (CYP2D6 activity score = 1-2)	Normal morphine formation	15–60 mg every 4th as needed for pain (label recommendation)	Strong
Intermediate metabolizer (CYP2D6 activity score = 0.5)	Reduced morphine formation	Start at 15–60 mg every 4th as needed for pain If no response, consider alternative analgesics Monitor tramadol use for response	Moderate
Poor metabolizer (CYP2D6 activity score = 0)	Greatly reduced morphine formation Insufficient pain relief	Avoid codeine use (lack of efficacy) Consider alternative such as morphine or a non-opioid. Consider avoiding tramadol	Strong

Adapted from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideliness for Codeine Therapy in the Context of Cytochrome P450 2D6 (*CYP2D6*) Genotype.[8]

than that of the parent compound.[57] (+)-*O*-demethyl-tramadol is metabolized by CYP2D6, therefore the *CYP2D6* genotype will influence the response to tramadol.[58–65] (+)-Tramadol inhibits serotonin reuptake and (–)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord.

Clinical studies have demonstrated that response rates to tramadol are significantly lower in PM compared to EM individuals.[63] In a postoperative study evaluating the efficacy of tramadol, plasma concentrations of the enantiomers tramadol and *O*-demethyl-tramadol were measured 30, 90, and 180 minutes after tramadol was given.[64] Variability of *O*-demethyl-tramadol concentrations was correlated with *CYP2D6* genotype (Figure 2). Concomitant use of CYP2D6 inhibitors further contributed to variability of tramadol metabolism. Poor efficacy of tramadol analgesia with the need for rescue medication was increased fourfold in PMs. Intoxication or adverse effects after tramadol analgesia in individuals with *CYP2D6* duplication have also been reported. Dizziness resulting in hospitalization, respiratory depression requiring naloxone, and a near-fatal cardiotoxicity following tramadol were reported in individuals that were genotyped and found to be UMs.[31,66,67]

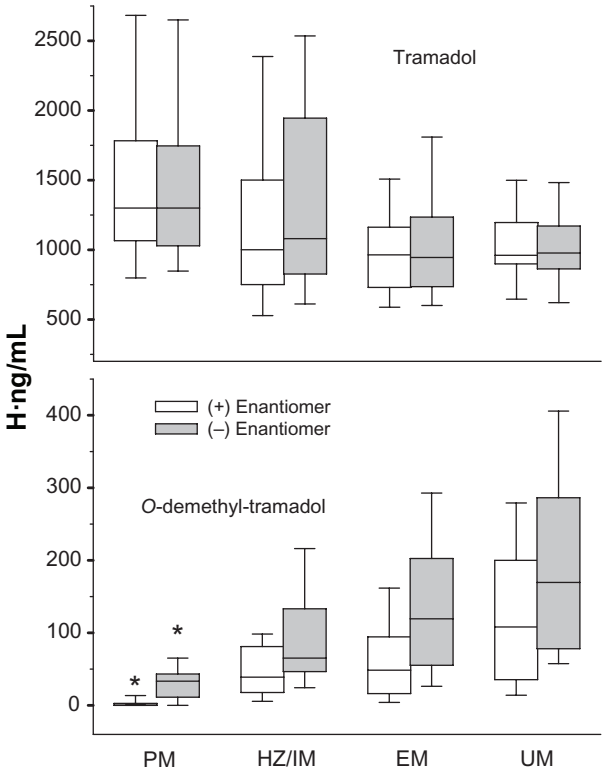

Figure 2 Concentrations of tramadol and enantiomers in different *CYP2D6* genotypes. Adapted with permission from Macmillan Publishers Ltd: Stamer et al. *Clin Pharmacol Ther*. 2007; 82:41–47.[64]

Abbreviations: PM, poor metabolizers; HZ/IM, heterozygous individual/intermediate metabolizer; EM, extensive metabolizer; UM, ultra rapid metabolizer. *$P < 0.001$ (Kruskal-Wallis test).

Some similarities with codeine were found with regards to lactating mothers and *O*-demethyl-tramadol transfer in breast milk.[68] In women treated with tramadol 50 or 100 mg four to six times daily, the calculated mean *O*-demethyl-tramadol concentration in milk was 1187 nmol/L for EMs and 602 nmol/L for PMs, which are close to measured values reported in a pharmacokinetic modeling study.[69] Mean estimates of relative infant dose of tramadol in EM mothers were 2.16%, in PM mothers 2.6%, and of *O*-demethyl-tramadol 0.93% and 0.47%, respectively.[68] Since none of the infant dose in tramadol equivalents was higher than the generally suggested 10% limit, maternal tramadol administration is considered safe, although the authors did recommend caution in individual infants.[68]

In addition to CYP2D6, the organic cation transporter OCT1 also contributes to the pharmacokinetics of *O*-demethyl-tramadol. OCT1 is most abundantly expressed in the liver and mediates the cellular uptake of this active tramadol metabolite.[70] The *O*-demethyl-tramadol uptake in vitro is 2.4-fold higher in OCT1-overexpressing cells than in control cells. In vivo common genetic polymorphisms of this transporter resulting in reduced or absent OCT1 activity were correlated with higher plasma concentrations of *O*-demethyl-tramadol and a prolonged opioid-induced miosis. These data suggest that OCT1 activity is related to hepatic reuptake of *O*-demethyl-tramadol before glucuronidation and elimination.[70,71] More work has to be done in this field to understand the complex interplay between *CYP2D6* genotypes, the influence of OCT1, and other candidate genes.

Oxycodone

Oxycodone is a semisynthetic opioid agonist and is widely used as an analgesic for both acute and chronic pain. Both oxycodone and oxymorphone, one of its metabolites, are potent analgesics used for chronic pain. Since the introduction of controlled-release oxycodone in 1995, annual prescriptions of oxycodone have steadily increased several-fold.[72] Oxycodone undergoes metabolism in the liver through four different metabolic pathways catalyzed by CYP3A4 and CYP2D6 (Figure 1). *N*-demethylation of oxycodone by CYP3A4 into noroxycodone is quantitatively the most important metabolic route (45% ± 21%), while a smaller fraction (11% ± 6%) of oxycodone is *O*-demethylated to oxymorphone by CYP2D6.[73] The resulting metabolites, when compared to morphine, have different affinities for the μ-opioid receptor,[74] from highest to lowest: oxymorphone > morphine > noroxymorphone > oxycodone > noroxycodone. The importance of an intact CYP3A4 pathway for oxycodone clearance has been

emphasized in numerous pharmacokinetic studies.[73,75–80] Many drugs,[79–86] as well as grapefruit juice intake,[87] have been shown to interfere with this pathway. Noroxymorphone is a metabolite of noroxycodone and oxymorphone that is a potent μ-agonist when administered intrathecally, but that lacks analgesic activity after systemic administration, probably because of an a priori poor blood–brain barrier penetration.[88] Early studies describing the impact of CYP2D6 metabolism (phenotype) on clinical outcomes of oxycodone (analgesia and side effects) have demonstrated a weaker effect in PMs.[89,90] Anecdotic cases of adverse effects after oxycodone in CYP2D6 PMs have been reported.[91]

Despite its widespread and increasing use for pain management and postoperative analgesia, evidence related to the pharmacogenetic influence of *CYP3A4* and *CYP2D6* on the clinical response (analgesic and side-effect profile) of oxycodone or oxymorphone is particularly scarce. Oxycodone analgesia and side effects were evaluated in ten healthy Caucasian volunteers (all men) phenotyped and genotyped for CYP2D6.[92] Experimental pain tests were performed in a five-arm crossover, randomized, double-blinded, placebo-controlled manner, with oral oxycodone 0.2 mg/kg. Differences in analgesia were found with increased analgesic effects in UMs; conversely, PMs had a two- to twentyfold reduction of analgesia compared to EMs. Notable differences in the incidence of spontaneously reported adverse reactions after oxycodone were reported by 2/2 UM, in comparison to only 1/6 EM and no toxicity reported in IM and PM (0/2). Importantly, CYP3A4 blockade, such as that which occurs with itraconazole, increased the analgesic efficacy of oxycodone as well as the toxicity of oxycodone, especially in CYP2D6 UMs. These findings are consistent with reports of life-threatening events in ultrarapid metabolizers receiving codeine.[30,39,41]

The effects of itraconazole, an inhibitor of the CYP3A4-mediated *N*-demethylation of oxycodone, were evaluated after administration of oxycodone (0.1 mg IV and 10 mg orally) in eleven healthy Caucasian subjects.[86] Itraconazole affected the metabolism of oxycodone to a greater extent when oxycodone was given orally. As a result, dose adjustments of oral oxycodone may be necessary in CYP3A4 poor metabolizers to avoid opioid-related adverse effects.

Another report on the effect of oxycodone analgesia according to *CYP2D6* genotype evaluated 33 healthy Caucasian volunteers undergoing nociceptive tests (five experimental modalities) in a placebo-controlled double-blinded study.[93] All subjects were evaluated after receiving either placebo or 20 mg oxycodone orally during two separate study sessions in a randomized fashion. Subjects were classified into two groups (rather than the four possible genotypic groups based on allelic function): intermediate, extensive, and ultrarapid metabolizers were pooled into a composite group (called "EM"); and poor metabolizers (PM) were analyzed separately according to *CYP2D6* genotype and pharmacokinetic assays. Oxycodone resulted in marked analgesia to all pain modalities in all subjects, with a difference in the extent of analgesia depending on the pain modality. The analgesic effect of oxycodone was less pronounced in the 16 PM subjects, mainly due to a marked increase in analgesia in EM subjects occurring 1–2 hours after the oxycodone dose. The results indicate that oxycodone metabolism to oxymorphone contributes to the analgesic effect but is not responsible for all of its effect.

A follow-up study by the same authors investigated the pharmacogenetic effect of *CYP2D6* on oxycodone for postoperative analgesia.[94] A total of 270 Caucasian patients undergoing surgery received postoperative analgesia with intravenous oxycodone via IV patient-controlled analgesia (PCA) for 24 hours. There was no difference in overall oxycodone consumption, pain ratings, or side effects between genotype groups despite a significant difference in plasma concentrations. The mean oxymorphone/oxycodone ratio was substantially higher in EM compared to PM subjects. One of the shortcomings of this study is that no genetic test for the UM status was performed, and possibly individuals might have been misclassified to the EM group. Furthermore, pain scores and analgesic consumption were low, and a differentiation of genotypes might not have been possible due to overall low analgesic needs. In another recent study in Caucasian cancer patients managed with oral oxycodone, oxymorphone/oxycodone ratios differed between genotypes. However, this did not translate into any measurable difference in clinical outcomes (pain intensity, nausea, tiredness, or cognitive function).[95]

Overall, the level of evidence linking genetic variability (*CYP2D6* and *CYP3A4)* to phenotype (altered biotransformation of oxycodone into oxymorphone and overall clearance of oxycodone and oxymorphone) is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy. There is also no warning on the oxycodone label cautioning against prescription of oxycodone in CYP2D6 UMs or in patients taking CYP3A4 inhibitors concomitantly. Given the widespread use and potential abuse of oxycodone prescription, further studies should certainly investigate this phenotype/genotype association.

Methadone

Methadone is a synthetic opioid best known for its use in the treatment of opioid dependence and is considered a second-line option in the setting of neuropathic pain in cancer patients.[96,97] Methadone occurs in *R*- and *S*-enantiomeric forms, with essentially all of its activity due to *R*-methadone. Both enantiomers bind to the noncompetitive site of the *N*-methyl-D-aspartate receptor;[26] however, *R*-methadone (levomethadone) is a tenfold stronger μ-opioid receptor agonist than *S*-methadone.[98] *S*-methadone on the other hand seems to be related to side effects (eg, increased QTc intervals in the electrocardiogram).[99] The *N*-methyl-D-aspartate antagonistic effect explains the popularity of methadone as second-line opioid, and its place in opioid switching when conventional opioids fail to provide satisfactory pain relief.[100] With regard to methadone metabolism, a great variation in plasma concentration of the different enantiomers has been shown. CYP3A4 and CYP2B6 are the major CYP isoforms involved in methadone metabolism, with CYP2D6 only contributing in a negligible manner, with close to no impact on methadone dosage requirements.[101–104] *ABCB1* genetic polymorphisms do contribute slightly to the interindividual variability of methadone kinetics.[102,103,105,106] CYP2B6 activity is clearly associated with altered pharmacokinetics, clinical outcome and adverse effects.[107–110] Methadone should be carefully administered in patients using CYP3A inhibitors[104] or drugs inhibiting CYP2B6.[110]

OPRM1 polymorphism, pain perception, and opioid analgesia

Among the numerous candidate genes that have been considered important in opioid response, the μ-opioid receptor gene (*OPRM1*) is probably the best studied. A common polymorphism of *OPRM1* is a single nucleotide substitution at position 118, with an adenine substitution by a guanine (A118G) reported to occur with an allelic frequency of 10%–30% among Caucasians,[111] a higher prevalence among Asians,[112] and a lower one in African–Americans.[113] The major interest for this particular polymorphism is due to its pharmacological and physiological consequences; however, the exact mechanism by which the altered receptor influences opioid analgesia is still unresolved. In vitro studies have suggested that A118G polymorphism affects receptor binding characteristics[114,115] or messenger RNA expression levels;[116] however, under some experimental conditions, there was no effect on function[117] or expression levels.[118] In a recent humanized mouse model exploring signal transduction pathways that mediate opioid pharmacology, sensory neurons expressing the *118GG* gene displayed reduced morphine (but not fentanyl) potency and efficacy compared with the *118AA* version. This suggests that the genetic effect is at least at the level of the sensory neurons.[119]

Experimental pain

Individuals carrying the variant receptor gene (*G118*) could show differences in some of the functions mediated by β-endorphin action and exogenous opioids. Human volunteers (male and female) carrying a *G118* allele exhibited lower sensitivity to pressure pain (ie, higher tolerance threshold to pressure pain) compared with A118 homozygotes.[120] However, the association between genotype and pain perception is not that simple; a significant interaction between sex and genotype for heat-pain ratings at 49°C was identified, indicating that the variant *G118* allele was associated with lower pain ratings among men but higher pain ratings among women. A study in a Han Chinese cohort of healthy female volunteers demonstrated that pressure-pain threshold is influenced by another polymorphism of *OPRM1* (IVS2 + A31G) but not the A118G polymorphism.[121] Other studies assessing the influence of genetic variants on experimental pain demonstrated no effect of *OPRM1* A118G genotype on pain processing[122] or lower pain-tolerance thresholds to single electrical nerve stimulation in individuals carrying the *G118* allele.[123] It has been determined that the effect size of various determinants for experimental pain perception is greatest for heat sensitization by capsaicin, followed by gender (higher pain sensitivity in women) and a more modest effect size for genetic determinants.[33] Therefore, cautious interpretation of experimental pain tests should take into account ethnicity (population admixture), the noxious stimulus, and gender, as well as possible linkage disequilibrium with other polymorphisms that may represent the true functional genetic variant.

Neuraxial opioids for labor analgesia

Using the up–down sequential allocation model to identify differences in analgesic requirement according to *OPRM1* genotype in women requesting neuraxial analgesia early in labor, women carrying the *G118* allele required substantially lower doses of spinal fentanyl, with a 1.5-fold difference compared to wild types.[124] This finding was replicated with a different pharmacological study design using random-dose allocation, with a twofold difference between genetic groups.[124] Of note, cervical dilatation at the time of analgesia request was significantly less in 118 AA women than that in women carrying one or two variant

alleles (118 AG or 118 GG). The finding of lower analgesic requirements at a more advanced stage in labor is consistent with the principle that women carrying the *G118* allele may have higher pain tolerance that allows them to wait longer before requesting epidural analgesia. Therefore, according to our findings, genotyping may help in improving labor analgesia, because 30% of Caucasian women (and probably a vast majority of Asian women) may in fact require significantly lower doses of spinal fentanyl during labor. On the other hand, the duration of spinal fentanyl analgesia does not appear to be influenced by A118G genotype,[125] suggesting that this SNP may influence spinal fentanyl potency without affecting the duration of analgesic action. Using the same methodology, a recent study demonstrated a similar pharmacogenetic association, although with a more modest effect, with lower dose requirement for epidural sufentanil in women carrying the variant G allele.[126]

Spinal and systemic morphine for postoperative analgesia

The effect of the A118G polymorphism of *OPRM1* on postcesarean analgesia after spinal and IV morphine was also evaluated in three recent studies with variable outcomes.[125,127,128] One study found no differences in the duration of spinal morphine analgesia, the need for analgesic supplementation or the incidence of nausea according to A118G genotype; however, pruritus was less frequent in carriers of the *G118* allele during the first 24 hours.[125] In Asian women, however, with a slightly different analgesic regimen, *G118* carriers exhibited increased 24-hour postoperative consumption of morphine via IV PCA.[127] In a multiple regression analysis, the most important factor contributing to morphine usage was maximum pain score, followed by ethnicity and A118G polymorphism.[129] After correction for genotype, ethnicity was still a significant contributing factor, with Indian women reporting higher pain scores and using higher doses of IV morphine.

Although the analysis and interpretation of specific allelic combination of multiple SNPs is often challenging,[130,131] morphine consumption via IV PCA for management of acute postoperative pain, in the nonobstetric context, has been shown to be higher in patients carrying the *G118* allele.[132–135] The effect may be modest and not clinically relevant.

Overall, inconsistent findings across studies investigating opioid analgesia according to *OPRM1* genotype may be due to the fact that spinal and systemic opioid pharmacokinetics and pharmacodynamics may be different; enhanced analgesia in response to spinal fentanyl in the presence of the *G118* allele may not exist in response to IV fentanyl or other opioids via the IV route. Or one could speculate that human spinal cord receptor function and signal transduction is selectively more altered by the *G118* variant than supraspinal receptors. Another potential explanation and factor to bear in mind is the different nature of the nociceptive stimulus in labor (predominantly a visceral component in early labor) versus other painful syndromes.

Systemic fentanyl for postoperative analgesia

Recent studies evaluating postoperative IV consumption of fentanyl according to A118G polymorphism of *OPRM1* after surgery in various Asian cohorts revealed lower fentanyl requirements in A118G-homozygous individuals (Table 2).[136–139] Potential explanations for these varying findings are that labor pain is different from that tested by experimental models of pain or that experienced in other clinical settings (postoperative or chronic pain), or that the response to systemic administration of fentanyl, rather than spinal, is affected differently by *OPRM1* genotype. Alternatively, it may be that other factors, including ethnicity, influence the effect of genetic variants of *OPRM1*.

In a Japanese cohort of healthy individuals undergoing surgery, a baseline preoperative cold pressor test was better tolerated in 118 AA individuals, and the response to fentanyl was enhanced in these subjects; however, there was no difference in pain ratings or fentanyl consumption during the first 24 hours after surgery.[138] Women, on the other hand, required more fentanyl postoperatively than men. Another polymorphism of the *OPRM1* gene (IVS3 + A8449G SNP in intron 3), present in 22% of individuals in this cohort, did alter the clinical effect of fentanyl, with a modest reduction of total postoperative IV PCA use of fentanyl in carriers of the minor G allele of this SNP. A study in Han Chinese patients undergoing laparoscopic abdominal surgery concluded that individuals carrying the *G118* allele have a shorter time to awakening and extubation, and experience reduced analgesic efficacy of fentanyl with no clinically significant changes in respiratory depression.[139] In another study in a Han Chinese cohort of women undergoing elective hysterectomies, pain thresholds after electric stimulation did not differ between genotypic groups; however, there was a difference for pain tolerance with this experimental model of pain. Pain-tolerance threshold was lower in women carrying the minor *G118* allele, and there was no difference in postoperative pain scores; however, IV PCA fentanyl consumption was higher in women carrying the *G118* allele.[136] The same authors did

Table 2 *OPRM1* genotype and fentanyl requirement

Subjects [n]	Study cohort	Route of administration	Measured outcomes	Observed associations in *G118* carriers
223 [124]	Nulliparous women in early labor	Spinal (up–down sequential and randomized doses)	ED_{50} (median effective dose providing 60 minutes of early labor analgesia)	Analgesia requested at later stage (greater cervical dilatation) Lower spinal fentanyl dose (ED_{50})
147 [125]	Nulliparous women in early labor	Spinal (25 mcg)	Duration of effective analgesia in early labor	No difference in duration of analgesia
280 [137]	Healthy Japanese, orodental surgery	• Preop IV test (2 mcg/kg) • Postop IV PCA (40 mcg/10 minutes)	• Cold-pressor test before vs after IV dose • 24-hour postop IV PCA consumption	Pre-IV test: increased sensitivity Post-IV test: reduced analgesic effect Reduced fentanyl sensitivity in women vs men No difference in VAS scores and 24-hae postop fentanyl consumption
189 [139]	Han Chinese, laparoscopic abdominal surgery	• Preop IV (5 mcg/kg) • Intraop IV (1 mcg/kg/30 minutes) • Postop IV (1 mcg/kg)	• Postop pain scores (15, 30, 45, 60 minutes) • Time to awakening • Respiratory depression • $PaCO_2$	Higher pain scores (at 15 and 30 minutes) Shorter time for awakening Lower $PaCO_2$
174 [136]	Han Chinese, hysterectomy	• Preextubation (1 mcg/kg) • Postop IV PCA (continuous 5 mcg/hour, bolus 20 mcg/5 minutes)	• Preop electrical pain threshold • 24-hour postop VAS scores • 24-hour postop IV PCA consumption	No difference in pain threshold Lower electrical pain tolerance threshold (gene-dose-dependent effect) No difference of initial postop or averaged 24-hour pain scores Higher consumption of postop fentanyl Trend for lower incidence PONV

Abbreviations: IV, intravenous; PCA, patient-controlled analgesia; VAS, visual analog scale; PONV, postoperative nausea and vomiting.

not find an association between *A118G* genotype and the incidence of nausea and vomiting caused by fentanyl for postoperative pain.[140]

Finally, subjects carrying the *G118* allele complained of more severe pain during shock-wave lithotripsy, despite self-administration of higher doses of alfentanil, reaching higher plasma alfentanil concentrations. This indicates that carriers of the minor *G118* allele may experience impaired analgesia in response to alfentanil.[141] The advantage of this model of clinical pain and anesthetic protocol resides in the fact that patients received only alfentanil, and therefore pharmacokinetic/dynamic interactions resulting from concomitant medications are unlikely to have confounded the findings.

Morphine for cancer pain

Screening for A118G genotype in a cohort of cancer patients on oral morphine initially revealed that individuals homozygous for the *G118* allele required higher morphine doses for adequate pain control.[142] In addition, combining this genotype with other gene variants (*ABCB1* or *COMT*) seemed to confirm an association of these polymorphisms with morphine requirements.[143,144] However, subsequent larger trials did not confirm that oral morphine consumption for chronic pain (eg, cancer pain) could be reliably predicted by A118G genotype.[145,146] In particular, a large European multicenter study found no association between 112 SNPs in 25 candidate genes, including *OPRM1* and *COMT*, and opioid dose (morphine, oxycodone, or fentanyl primarily) in a cohort of 2294 cancer patients.[145] While no joint combined allelic combination was evaluated, this trial does fail to validate associations related to opioid efficacy reported in several previous association studies, and with the current body of knowledge argues against including pharmacogenetic testing for improvements in clinical decision-making for opioid prescription.

COMT gene, pain and opioid analgesia

Among the usual candidate genes proposed, the *Val158Met* polymorphism of the catechol-*O*-methyltransferase (*COMT*) gene that regulates the metabolism of dopamine and noradrenaline may be identified as potentially inferring an increased risk for the development of chronic pain disorders,[147] acute postoperative pain,[36,135] chronic postsurgical pain,[148] and opioid-induced hyperalgesia.[149] High COMT activity, as found with the *Val158* allele, is associated with improved dopaminergic transmission and has been suggested

to confer an advantage in the processing of aversive stimuli or stressful conditions (warrior strategy), while *Met158* alleles may be associated with an advantage in memory and attention tasks (worrier strategy).[150] Individuals homozygous for the *Met158* allele display increased pain sensitivity, and there are findings of lower μ-opioid system activation during sustained pain.[151–153] The interplay between COMT inhibition and pain sensitivity mediated by β2 and β3 adrenergic receptor modulation has been highlighted,[154] and response to propranolol for management of temporomandibular pain has been shown to be predicted by *COMT* haplotype.[155] In a recent study evaluating repeated thermal-pain stimulation before and after a single opiate dose in a Caucasian cohort, the Val158Met genotype did not influence the reaction to the initial noxious stimulus or the analgesic response to intravenous remifentanil administration.[149] However, after repeated heat stimulation and post-remifentanil administration, pain ratings in *Met158* individuals were significantly higher, suggesting that initial pain response is not influenced by *COMT* and that differences may become apparent only after endogenous pain modulation is challenged. The increased pain sensitivity in *Met158* individuals following remifentanil could result from reduced efficacy of endogenous pain modulation and/or increased susceptibility to opioid-induced hyperalgesia. The suggestion that the effect of *COMT* genotype on pain processing becomes apparent only when the pain modulation is challenged, such as occurs after repeated pain stimulation, was confirmed in a functional magnetic resonance imaging study investigating brain responses to thermal pain stimuli.[156]

The future of personalized medicine

Contrasting results in human genetic studies of pain sensitivity have been shown to occur with each of the usual polymorphisms assessed.[157,158] This illustrates the challenges in evaluating a genotype–phenotype association when the underlying genetic susceptibility is clearly polygenic, and genotyping of allelic combinations should be done concomitantly.[48] The phenotype is indeed complex in itself, representing subjective and multifactorial pain perception experiences and/or responses to pain-modulating drugs. Numerous candidate genes as well as elaborate models have been suggested for the study of the genetic component of pain. Nonetheless, due to the inherent complexity in the study of pain, involving different nociceptive modalities, gender differences, limitations in extrapolating data from animal models to human perception, interethnic and environmental differences in addition to the obvious polygenic nature of pain, it is the design and execution of large clinical studies analyzing multiple haplotypes simultaneously that remains the true challenge to date. Meanwhile, genome-wide association studies in the context of acute postoperative pain are being published,[159] and researchers are already actively working on gene therapies for chronic pain.[160–162]

Conclusion

To improve clinical outcomes based on pharmacogenetic testing in the context of pain therapies, genotyping of CYP isozymes is likely to become strongly recommended. The individual pharmacokinetic profile and possible drug–drug interactions with potentially devastating outcomes for opioids relying on CYP2D6 and CYP3A4 metabolism are well-recognized major variables influencing the pharmacotherapy of pain. On the other hand, predicting the analgesic response to morphine based on pharmacogenetic testing is more complex; though there was hope that simple genetic testing would allow tailoring morphine doses to provide optimal analgesia, this is unlikely to occur. Different polymorphisms clearly influence pain perception and behavior in response to pain. However, the response to analgesics also differs depending on the pain modality and the potential for repeated noxious stimuli, the opioid prescribed, and even its route of administration.

Acknowledgments

Ruth Landau is the recipient of Swiss National Foundation Research grant SNF 3200B0-114129 that funded in part the *OPRM1* genetic research conducted in Switzerland. Pascal H Vuilleumier is the recipient of Swiss National Foundation Research grant SPUM 33CM30-1241117.

Disclosure

The authors declare no conflicts of interest.

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