Pharmacogenomic considerations in the opioid management of pain

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Abstract
Physicians continue to struggle with the clinical management of pain, in part because of the large interindividual variability in the efficacy, occurrence of side effects and undesired severe adverse drug reactions from the prescribed analgesics. Pharmacogenomics, the study of how an individual’s genetic inheritance affects the body’s response to medications, has an important role and can explain some of this interindividual variability. Genetic identification of known variant alleles that affect the pharmacokinetics or pharmacodynamics of medications used for pain management can enable physicians to select the appropriate analgesic drug and dosing regimen for an individual patient, instead of empirical selection and dosing escalation. In this article, clinically relevant pharmacogenomic targets for the management of opioid pain, including efflux transporters, proteins that metabolize drugs, enzymes that regulate the neurotransmitters that modulate pain, and opioid receptors, will be reviewed.

Current management of pain
The control of pain, a complex and subjective experience, is critical to clinical success in caring for patients. Opioids such as oxycodone, methadone and morphine are the recommended therapy by the World Health Organization and the European Association for Palliative Care for moderate to severe pain [1,2]. However, the use of opioids in pain management requires careful dose escalation and empirical adjustments based on clinical response and the presence of side effects or adverse drug reactions (ADRs). Unfortunately, successful pain management treatment - defined as adequate analgesia without excessive adverse effects [3] - can be challenging [4]. Unpleasant opioid side effects, such as nausea, vomiting, constipation and sedation, are common and can lead to absence from work, poor performance at work and the resulting risk of job loss, and a diminished quality of life. The most serious issues involve the risk of sedation, depression of respiration and unintentional death due to inability or poor ability to metabolize the medications successfully. An individual’s genetic makeup may predispose the patient to these adverse effects and reduced efficacy. Pharmacogenomic approaches offer insight into the genetic variables that can affect a drug’s uptake, transport, activation of its target, metabolism, interaction with other medications and excretion. The use of pharmacogenomics in patients requiring pain management can lead to more efficient opioid selection, dose optimization and minimization of ADRs to improve patient outcome.

Clinically relevant candidate genes for pain management
Cellular transporters control the uptake, distribution and elimination of drugs. P-glycoprotein is an efflux transporter also called adenosine triphosphate-binding cassette, subfamily B, member 1 (ABCB1) or multidrug resistance 1 (MDR1) [5]. It is expressed in hepatic, intestinal and renal epithelial cells and also on the luminal side of endothelial cells in the blood-brain barrier, and it is a major determinant of the pharmacokinetics and pharmacodynamics of several opioids (such as morphine, methadone and fentanyl) commonly used to treat pain [5]. Genetic variants (such as 3435C>T) in P-glycoprotein have been associated with variability of pain relief in cancer patients treated with morphine [6]. The analgesic effects of morphine are mediated by its interaction at the µ-opioid receptor located in the central nervous system (CNS). P-glycoprotein can limit the concentration of pain management drugs, such as morphine, in the brain because it actively pumps drugs out of the CNS. As a result, homozygous carriers of the 3435C>T variant (TT carriers) experience greater pain relief than heterozygous (CT) or homozygous wild-type (CC) carriers, presumably because higher concentrations...
of morphine can be achieved in the CNS [6]. Table 1 lists the clinically relevant pharmacogenomic targets for pain management.

The cytochrome P450 (CYP) system is responsible for metabolizing a wide range of therapeutic agents used for pain relief. CYP2D6 is especially important for the activation or inactivation of several opioids used to treat pain, including codeine, oxycodone and tramadol [7]. Typically, the genetic variability of CYP can be grouped into four phenotypes: ultrarapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM) and poor metabolizers (PM). UM-classified patients typically contain multiple copies of a gene, which results in an increase in drug metabolism [8]. EM-classified patients are characteristic of the normal population and have a single wild-type copy of the gene, whereas IM-classified patients show decreased enzymatic activity and PM-classified patients have no detectable enzymatic activity [8]. Codeine is a prodrug that requires demethylation to its active metabolite morphine by CYP2D6 before it can exert an analgesic effect. As a result, CYP2D6 PM-classified patients experience ineffective analgesia and increased side effects from the parent drug (codeine) [7]. On the other hand, CYP2D6 UM-classified patients prescribed codeine for pain management generate extensive concentrations of morphine, which can lead to ADRs [9].

Tramadol, another opioid commonly used for pain management, produces analgesia by the synergistic action of its two enantiomers and their metabolites [7]. Tramadol undergoes metabolism by CYP2D6 to an active metabolite (O-desmethyl tramadol), which has greater affinity for the µ-opioid receptor than does the parent compound [7]. Genetic variations in CYP2D6 have been shown to account for some of the variable pain response in the post-operative period because the CYP2D6 activity has a clinically relevant impact on the level of analgesia mediated by the µ-opioid receptor [10].

Another important genetic target is uridine diphosphate-glucuronosyltransferase 2B7 (UGT2B7), which metabolizes morphine to morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). The latter has a higher analgesic potency than the parent compound [11]. Morphine is commonly used to control moderate and severe pain associated with sickle cell disease. Darbari et al. [12] showed that the presence of the UGT2B7*802C>T polymorphism (802C>T) was associated with lower M3G:morphine and M6G:morphine ratios than AA genotypes. As a result, genetic polymorphisms in UGT2B7 have been shown to decrease the hepatic clearance of morphine, which translates into lower dosage requirements of morphine [12]. In another study [13], the UGT2B7*2 polymorphism (802C>T) was also shown to be associated with the frequency of morphine-induced ADRs (nausea) in cancer patients. The authors showed that the frequency of nausea was higher in patients without the UGT2B7*2 allele [13].

Furthermore, the efficacy of opioid analgesia can be enhanced by the co-administration of catecholamines, which are involved in the modulation of pain [14]. Catechol-O-methyltransferase (COMT) is responsible for the inactivation of catecholamines (dopamine, adrenaline and norepinephrine). As a result, genetic variability in the COMT gene can contribute to differences in pain sensitivity and response to analgesics. It has been shown that a common variant allele (1947G>A; Rs4680) results in a three- to fourfold reduction in COMT enzyme activity [15]. Homozygous wild-type (GG) cancer patients required higher doses of morphine to control pain than heterozygous or homozygous variant (AA) alleles [16,17].

Finally, the µ-opioid receptor encoded by the opioid-receptor-like 1 (OPRM1) gene is the primary site of action for most of the commonly used opioids. The 118A>G polymorphism in this gene results in less effective opioid analgesia, as reported with cancer patients with homozygous variant alleles (GG) who required higher morphine doses for pain relief than homozygous wild-type (AA) participants [18]. In another study [19], Chou et al. investigated the correlation between the 118A>G polymorphism and patient-controlled morphine consumption in patients undergoing

| Table 1. Clinically relevant pharmacogenomic targets for pain management |
|-------------|-------------|-------------|-------------|
| Gene       | Variant     | Analgesics affected | Consequence of genetic variation                |
| ABCB1      | 3435C>T     | Morphine          | Homozygous variants cause increased efficacy    |
| CYP2D6     | 1846G>A, 2549A>del | Codeine, oxycodone, tramadol | Poor metabolizers (PM; variants) have more adverse drug reactions and less efficacy |
| UGT2B7     | -840G>A, 802C>T, *2 | Morphine          | Homozygous variants require lower doses of morphine for efficacy; UGT2B7*2 variants have less side effects (nausea) with morphine |
| COMT       | 1947G>A, (Rs4680) | Morphine          | Homozygous variants have a three- to fourfold decrease in COMT activity; wild-type patients require higher doses of morphine for efficacy than variant patients |
| OPRM1      | 118A>G     | Morphine, M6G     | Homozygous variants cause decreased effectiveness and increased dose requirements |
to best select the appropriate analgesic from the onset to provide sustained efficacy with the lowest side effect profile.

**Abbreviations**
ADR, adverse drug reaction; CNS, central nervous system; COMT, catechol-O-methyltransferase; EM, extensive metabolizer; IM, intermediate metabolizer; M3G, morphine 3-glucuronide; M6G, morphine 6-glucuronide; PM, poor metabolizer; UGT2B7, uridine diphosphate-glucuronosyltransferase 2B7; UM, ultra-rapid metabolizer.

**Competing interests**
PJJ has no competing interests to declare. NCB serves on the Speakers Bureau and Advisory Board of King Pharmaceuticals, Pfizer Inc. and Forest Pharmaceuticals.

**Authors’ contributions**
PJJ and NCB drafted, read and approved the final manuscript.

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