Pharmacogenomics in Palliative Medicine

Pain relief is a basic human right.[1,2] Progress in the domain of pain management, particularly in that of cancer, is quite slow and remains as one of the feared aspects of the disease.[3] On an average, one out of three patients is not receiving pain medications appropriate to his/her pain intensity. Poor success rate of the existing pain and adjuvant therapies necessitates the need for pharmacogenomic testing in palliative care for better patient outcomes.[4,5] Newer pharmacogenomic insights in the past two decades have revolutionized the management of many diseases and have paved the way for the induction of precision medicine in the clinical management of diseases.[6] Pharmacogenomics involves the usage of pharmacogenomic testing to guide precision medicine with the ultimate goal of improving the drug efficacy and patient safety. Pharmacogenomic testing could stratify patients into various categories, such as likely responders, likely nonresponders, or likely to experience adverse drug reactions (ADRs) to a drug therapy.[7] Pharmacogenomics has evolved as a potential tool to improve the patient care in pain management.[8] Pain management medications are associated with a significant interindividual variability in the analgesic response. One of the prime reasons for this analgesic response variability is due to single-nucleotide polymorphisms (SNPs) in gene that are involved in the drug metabolism and transport.[9] Some of the genes that have gained a significant clinical interest for pharmacogenomic testing in the pain management of palliative care are cytochrome P450 2D6 (*CYP2D6*), cytochrome P450 2C9 (*CYP2C9*), ATP binding cassette subfamily B member 1 (*ABCB1*), cyclooxygenase-1 (*PTGS1*), cyclooxygenase-2 (*PTGS2*), opioid receptor μ (*OPRM1*), opioid receptor κ (*OPRK1*), opioid receptor δ (*OPRD1*), and catechol-O-methyltransferase (*COMT*).

CYP2D6 enzyme accounts for <5% of all the CYPs expressed in the human body but is responsible for the metabolism for about 20% of all drugs, which includes many drugs employed in pain management.[10] The *CYP2D6* is a highly polymorphic gene with around 109 allelic variants and around 507 SNPs. Significant interethnic differences in allele distribution have been observed globally. Allelic combinations segregate the human populations into four groups of *CYP2D6* phenotypes as poor, intermediate, extensive, and ultrarapid metabolizers. Poor metabolizers are mainly found in Europe, intermediate metabolizers in Asian, and ultrarapid metabolizers in North African population. A lot of medications within the opioid, antidepressant, antipsychotic, and antiemetic categories employed in palliative care settings are substrates for *CYP2D6*.[11,12] *CYP2D6* enzymes are responsible for the metabolism of opioids such as codeine, tramadol, and oxycodone to more potent opioid metabolites. As most of the opioid drugs exhibit narrow therapeutic index, precise dosage regimen design is mandatory for maintaining the delicate balance between therapeutic efficacy and toxicity. *CYP2D6* genotyping becomes a highly relevant decisive dose-determining factor in this scenario.[13] About 85% of antidepressants (amitriptyline, nortriptyline, citalopram, clomipramine, imipramine, desipramine, fluoxetine, fluvoxamine, paroxetine, and venlafaxine) are major substrates of *CYP2D6* enzyme, and 40% of antipsychotics (fluphenazine, haloperidol, aripiprazole, quetiapine, risperidone, and chlorpromazine) are substrates of *CYP2D6* enzymes. Less than 20% of the patients are considered to be effective responders of antipsychotics. Poor metabolizers of *CYP2D6* substrates are more susceptible to develop ADRs than extensive metabolizers, which warrant the need for dosage reductions in these drugs. As ADR to antidepressants mostly occurs during the initial phase of drug treatment, dosage adjustments should be done during the beginning of treatment itself.[14,15]

The *CYP2C9* gene with over 50 variants is also highly polymorphic.[16] Many nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, celecoxib, and naproxen are metabolized by the cytochrome *CYP2C9*.[17] *CYP2C9* polymorphisms are found to be accountable for NSAID toxicity. Poor metabolizers have reduced *CYP2C9* activity compared to wild type, resulting in reduced NSAID clearance, thereby increasing the risk of ADRs, most notably gastrointestinal bleeding.[18]

Another potential target for pharmacogenomic testing in pain management is the *ABCB1* gene that encodes for the efflux transporter P-glycoprotein. A lowered function of the P-glycoprotein transporter permits higher amounts of drug transportation across the blood–brain barrier. Opioids such as fentanyl, morphine, and methadone are P-glycoprotein substrates. Variants of the *ABCB1* gene were associated with a higher frequency of ADRs to oxycodone and fentanyl intake.[19,20] Considerable interest has also been gained on studying the influence of various allelic variants (due to SNPs) of genes such as *PTGS1*, *PTGS2*, *OPRM1*, *OPRK1*, *OPRD1*, and *COMT* in altering the pharmacodynamic responses to pain management drugs.

International consortia such as Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group guidelines, and Canadian Pharmacogenomics Network for Drug Safety guidelines have developed pharmacogenomic-based guidelines for the routine clinical use of opioids, NSAIDs, antidepressants, and antipsychotics.[21-24] The Food and Drug Administration has listed drugs that need to specify pharmacogenomic information in the drug labeling.

Pharmacogenomic information can appear in different sections of the labeling depending on the actions that need to be addressed.[25] Other regulatory agencies can also come up with such drug list that could reveal potential pharmacogenomic information so that specific actions could be taken based on the biomarker information.

Patients who received pharmacogenomic-guided care have reported a better understanding of pharmacogenomics and were more receptive toward the use of their pharmacogenomic information than traditional care patients but have expressed concerns over insurance coverage, employment discrimination, and skepticism about the usage of their pharmacogenomic results. These concerns should be duly addressed by all the stakeholders involved in pharmacogenomic testing.[26] National regulations on pharmacogenomic testing with specific reporting and interpretation templates are required to avoid any ambiguity among patients and health-care professionals.[27] With the advancement of genomic technologies, today genotyping results provide an exciting opportunity for the precise pain management in the palliative care within few hours requiring only short turnaround time for pharmacogenomic analysis with high sensitivity and specificity. Since Indian population has considerable interethnic genomic variations when compared with the Western population due to rich tapestry of cultures and ecologies,[28] pharmacogenomics is an exhilarating field for researchers for establishing reference human genome and identifying novel mutations in the Indian population. Integration of pharmacogenomic and onco-pharmacist expertise into palliative care policy, research, and practice in clinical settings would greatly improve the provision of appropriate pain relief and consequent improvement of the quality of life to patients suffering from cancer and other terminal stage illnesses.

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Mahadev Rao

Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India

Address for correspondence: Dr. Mahadev Rao, Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka, India. E-mail: mahadev.rao@manipal.edu

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