PHARMACOGENOMICS AND PRECISION MEDICINE IN THE MANAGEMENT OF CHRONIC PAIN

Chronic pain is usually described as pain that lasts longer than three to six months. According to the International Classification of Diseases - Eleventh Revision (ICD-11), Chronic Pain can be classified into seven categories : Chronic primary pain, Chronic cancer pain, Chronic post-traumatic pain, Chronic neuropathic pain, Chronic headache and orofacial pain, Chronic visceral pain, and Chronic musculoskeletal pain. Examples include Migraines and headaches, Endometriosis, Fibromyalgia, Trigeminal neuralgia, Rheumatoid Arthritis, Postoperative pain, Skeletal muscle pain, Multiple Sclerosis, Spinal cord injury, etc. Chronic pain is also categorized as neuropathic pain, mixed pain and nociceptive pain.

There are different types of treatment options available for chronic pain management depending on the type, source/location and severity of pain. Treatment options range from prescription drugs to alternate therapy. Non-opioid analgesic agents like antidepressants, anti-anxiety drugs or sedatives, antiepileptics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, muscle relaxants, and local anesthetics are generally prescribed before treating the patient with opioid agents. Biologics (monoclonal antibodies), cognitive-behavioral therapy, counselling, occupational therapy, physical therapy, acupuncture, aromatherapy, biofeedback, exercises, transcutaneous electrical nerve stimulation (TENS), nerve blocks, spinal cord stimulators, intrathecal pain pumps, deep brain stimulation, etc. are other alternatives that have shown to alleviate the symptoms of chronic pain.

The long term use of NSAIDs and corticosteroids have shown to have adverse effects on the liver and kidney. On the other hand, opioid agents have the potential to manage chronic pain effectively but the biggest risk involved is opioid addiction or opioid use disorder that can cause physical dependence on the drug itself and the individual can establish high tolerance over time which, unfortunately, can lead to serious adverse events like overdose and deaths. It is also known to cause respiratory depression which means the drug has the ability to restrict normal breathing and slow it down if higher doses are taken. Respiratory arrest is another condition that can arise when the patient’s breathing stops completely.

The prescription opioids (legal use) include Buprenorphine, Butorphanol, Codeine, Fentanyl, Hydrocodone, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Tapentadol, and Tramadol. These are available in various dosage forms and routes of administration. Opioids are generally synthetically produced in laboratories or can be naturally sourced from the alkaloids present in the opium poppy plant. Illegally obtained opioid is Heroin (street drug).

Genetics and individual body chemistry play a large role on how these pain-relief drugs are metabolized. Individual biochemical factors such as neurotransmitters, proteins, enzymes, genes, and cytokines can alter how efficiently the drug will perform. Despite completing large clinical trials, gathering safety and efficacy data, and getting approvals from regulatory authorities, not all drugs can be one-size-fits-all. Patients can suffer from multiple conditions which can require co-administration of drugs and checking for drug-drug interactions and drug-food interactions. Patients can also be allergic to certain drugs or active ingredients and that can cause adverse drug reactions or adverse events if not tested prior to beginning the treatment regimen. Precision or personalized medicine is all about the right drug administered at the right dose in the right patient. Thus, performing pharmacogenetic-pharmacogenomic tests can help the medical practitioner assess the risks and benefits accurately before prescribing a drug for chronic conditions.

Pharmacogenetics can be defined as the study of genetic causes that lead to variation in individual drug response whereas, Pharmacogenomics can be defined as the study of the whole genome and all the possible mutations that can alter the individual drug response. These terms are often used interchangeably. The interindividual genetic variants can either be inherited (germ-line variations) or acquired (somatic mutations). Pharmacogenomics is paving the way for personalized medicine as it allows the assessment of these specific interindividual genetic differences. Such genome-wide association studies (GWAS) can help identify important traits and genomic variants that can measure the risk associated with a particular disease. Whole genomes and exomes of a large number of individuals can be mapped for millions of genomic variants to check for associations with a particular disease or a condition. Early detection/prediction, prevention, diagnosis and treatment of a disease, drug safety and toxicity can be analyzed with the help of pharmacogenomics.

Specifically, the risks associated with opioid use in chronic pain sufferers can be checked by performing blood and other body fluid tests to detect certain biomarkers. Most commonly found abnormal biomarkers in chronic pain sufferers include elevated levels of quinolinic acid, elevated levels of kynurenic acid, elevated levels of pyroglutamate, elevated levels of xanthurenic acid, elevated levels of methylmalonic acid, elevated levels of acrolein metabolite 3-hydroxypropyl mercapturic acid, low levels of serum glutathione, extremely low levels of neurotransmitter metabolites like 5-hydroxyindoleacetate and vanilmandelate, and depletion of vitamin B6 and Vitamin B12.

Enzymes involved in the opioid metabolic pathway are subfamilies of Cytochrome P450 present in the smooth endoplasmic reticulum of liver hepatocytes, the surface mucosal membranes of intestinal tract, and in the tissues present in the kidney, heart and brain. Insights into CYP450 gene polymorphism have helped understand how variations occur in individual drug response. Important enzymes like CYP2D6 (*cytochrome P450 family 2 subfamily D member 6*) and CYP3A4 (*cytochrome P450 family 3 subfamily A member 4*) are majorly responsible for metabolism of opioids. CYP2D6 enzymes metabolizes 25% of all drugs administered whereas, CYP3A4 metabolizes more than 50% of all drugs. Hence, high risk of drug-drug interactions can happen due to CYP3A4 opioid metabolism even though there are higher genetic polymorphisms of CYP2D6 enzyme. CYP3A4 enzyme metabolizes codeine, dihydrocodeine, oxycodone, hydrocodone, tramadol, methadone, fentanyl, buprenorphine, meperidine, and propoxyphene in part with other CYP enzymes. It follows the N-demethylation pathway to convert the drugs into their active and inactive metabolites. Similarly, CYP2D6 enzyme metabolizes codeine, dihydrocodeine, oxycodone, hydrocodone, and tramadol majorly by following the O-demethylation pathway.

Normorphine <—**CYP3A4**— Morphine <—**CYP2D6**— **Codeine** —**CYP3A4**—> Norcodeine —**CYP2D6**—>

Normorphine

Nordihydromorphine <—**CYP3A4**— Dihydromorphine <—**CYP2D6**— **Dihydrocodeine** —**CYP3A4**—>

Nordihydrocodeine —**CYP2D6**—> Nordihydromorphine

Noroxymorphone <CYP3A4 Oxymorphone <CYP2D6 **Oxycodone** CYP3A4> Noroxycodone CYP2D6> Noroxymorphone

Norhydromorphone <CYP3A4 Hydromorphone <CYP2D6 **Hydrocodone** CYP3A4> Norhydrocodone CYP2D6> Norhydromorphone

O-desmethyltramadol <CYP2D6 **Tramadol** CYP3A4> N-desmethyltramadol

Tapentadol CYP2D6> Hydroxytapentadol

Methadone CYP3A4> EDDP (2-Ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine)

Fentanyl CYP3A4> Norfentanyl

Buprenorphine CYP3A4> Norbuprenorphine

Meperidine CYP3A4> Normeperidine

Propoxyphene CYP3A4> Norpropoxyphene

It is important to check for genetic polymorphisms of phase 1 drug metabolizing enzymes (CYP 450 families) and for genetic variations in drug transporters like *μ-opioid receptor 1* (*OPRM1*), *catechol-O-methyl transferase* (*COMT*), *multidrug resistance 1 gene* (*MDR-1*), and *transient receptor potential vanilloid 2 genes* (*TRPV2*). This will be indicative of drug efficacy and the rate of clearance of drugs in individuals. With the help of pharmacogenomics, these genetic variations can help categorize individuals as different phenotypes of drug metabolizers – poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs)/ extensive metabolizers (EMs), and rapid or ultrarapid metabolizers (UMs).

Poor metabolizers (PMs) will metabolize the drug too slowly, thus indicating the loss of drug efficacy and insufficient pain-relief. The slow rate of clearance of the drug molecule from the body can lead to unwanted side effects due to accumulation of the drug in the plasma overtime (systemic concentration). Intermediate metabolizers (IMs) will have slower rate of drug metabolism but not as slow as PMs and will have minimal analgesic effect whereas, Normal metabolizers (NMs) will have the standard analgesic effect at standard dose. Ultrarapid metabolizers (UMs) will metabolize the drug too fast, thus producing higher levels of the active metabolite and the analgesic effect will be high which could potentially lead to overdose. This means that, at standard recommended dosage, the drug will be harmful for UMs and they will either require a different drug or a modified lower dosage of the same drug. The metabolic action of CYP 450 enzymes (especially CYP2D6) can convert the prodrug codeine to its highly active metabolite morphine and it is necessary to monitor the dosage strictly.

If the patient has more than 2 copies of normal-function alleles, then they are at a risk of potential serious toxicity. These patients are PMs and have increased activity of the CYP2D6 enzyme which leads to increased conversion of codeine to higher levels of morphine. If the patient is NM then the CYP2D6 enzyme activity will be normal and expected levels of morphine will be produced due to 2 copies of normal-function alleles, or a combination of one normal and one decreased-function allele. Patients in the IM category will have reduced morphine production due to intermediate CYP2D6 enzyme activity. This is because these patients have 2 decreased-function alleles, or one normal-function alleles and one no-function, or one decreased-function allele and one no-function allele. PMs have 2 copies of no-function alleles, which means absence of CYP2D6 enzyme activity. This leads to highly reduced production of morphine. Co-administration with drugs that are metabolized by CYP3A4 enzyme can also lead to unwanted side effects with potential for toxicity or overdose. Patients who require opioid therapy are at a higher risk of opioid addiction and drugs that are not metabolized by CYP2D6 enzyme should be prescribed. It is of utmost importance that pharmacogenomic tests for drug-gene interactions be conducted prior to opioid therapy to minimize side-effects and increase drug efficacy without changing the treatment regimen multiple times and experimenting with different drugs.

Opioid overdose epidemic also known as opioid crisis has left North America and parts of Europe with millions of deaths each year. Illegally obtained opioids like heroin or other synthetically produced drugs can be laced with other drugs. Fentanyl which is more potent than morphine has caused several deaths due to fatal overdose in the last few years. Governing authorities are taking action against this crisis by making Naloxone freely available and more accessible. Naloxone is considered to be a miracle life saving drug that can reverse the toxic and fatal effects of opioid overdose if administered in time. It is a competitive opioid antagonist as it binds with the μ-opioid receptors present in the central nervous system to inhibit and reverse the effects of the opioid drugs.

Safer alternatives to opioids are biologics like monoclonal antibodies (mAbs). They are relatively new and considered highly effective as they act against certain targeted molecules which are identified to be involved in pain pathways. Scientists are currently working on producing more mAbs for pain management and in order to decrease opioid usage. Several mAbs have cleared preclinical and clinical trials and are awaiting approval from regulatory authorities. Monoclonal antibody infusions/injections need to be taken less frequently as they have longer half-life as compared to standard oral medications, have high potency and low off-target effects. mAbs need to be taken less frequently as the antibodies stay in the systemic circulation for weeks after administration and hence have the potential for sustained pain-relief.

Migraine (type of chronic headache) prevention and management has become possible due to these mAbs. Erenumab, Galcanezumab, Fremanezumab, and Epitenezumab are the currently available mAbs for chronic pain management in patient suffering from migraines. These mAbs target CGRP (Calcitonin gene-related peptide) and its receptor. Tanezumab, Fulranumab, and Fasinumab are used in patients suffering from osteoarthritis and target NGF (Nerve growth factor). Tanezumab targets NGF and Infliximab targets TNF (Tumor necrosis factor) for chronic lower back pain management. Tanezumab is also used for the reduction of neuropathic pain. For patients suffering from rheumatoid arthritis, mAbs targeting IL-6 (interleukin 6), TNF, and CD20 in B cells are available. Sarilumab and Tocilizumab (targeting IL-6); Adalimumab, Golimumab, Certolizumab, and Infliximab (targeting TNF); and Rituximab (targeting CD20 in B cells).

There are over hundred mAbs available for the treatment or management of cancer, neurogenerative diseases and other diseases. Further research is currently being conducted to find novel mAbs delivery methods to enable their entry into CNS and across the BBB from blood. mAbs can also be used in combination with NSAIDs and DMARDs to manage chronic pain. The future of precision medicine relies on the novel therapeutics discovered, designed and modified with the help of pharmacogenomic testing. Pharmacogenomics will thus play a major role in chronic pain management and developing new monoclonal antibodies. It will help identify prognostic and predictive biomarkers.