Could a Personalized Approach to Therapy End the War on Pain?

The authors provide their view, based on a recent publication, on the potential that genes and pharmacogenomics may have when added to the armamentarium of NSAIDs and opioids.

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Chronic pain affects around 20% of the adult population worldwide and represents a huge burden for the affected individuals, with a significant negative impact on their quality of life, daily functioning, and work productivity. Consequently, the financial direct and indirect cost of chronic pain on an annual basis is enormous, ranging from $560 to 635 billion. Chronic pain denotes one of the greatest challenges in contemporary medicine, both from the aspect of basic researchers seeking an explanation of complex pain mechanisms, to clinicians trying to find an optimal therapeutic strategy for their patients. Although findings from laboratories often contribute to the clarification of complex pain pathophysiology and suggest novel molecular targets, pain treatment is still grounded on two classes of analgesic drugs: NSAIDs and opioids. Responses to these “pain-killers” vary to a great degree (~40-fold), with nearly 50% of all patients experiencing inadequate pain relief as well as various disturbing or even unbearable side effects.
BACKGROUND

Current Pharmacological Treatment of Mild to Moderate Pain

NSAIDs, Aspirin, and Acetaminophen/Paracetamol

NSAIDs, aspirin, and acetaminophen/paracetamol represent the mainstay for treating mild to moderate pain pharmacologically. These medications’ common mechanism of action is attributed to non-selective cyclooxygenase (COX) inhibition; growing research is widening its potential molecular targets and spectrum of actions. NSAIDs represent a heterogeneous group of drugs, with some important differences in pharmacological properties that may favor selection of one medication over another when treating certain conditions and patient populations.

Thus, a chemical structure largely influences the affinity of the drug for the respective COX isoenzyme (selective or non-selective), speed (rapid or slowly-acting), and type (reversible or irreversible) of interaction with the active site of the enzyme. Furthermore, some pharmacokinetic properties of NSAIDs (eg, rate of absorption, the time to maximal plasma concentration, half-life, tissue versus plasma distribution, elimination) and the pharmaceutical formulations (eg, immediate- or extended-release tablets, oral solutions, suppositories, and parenteral solutions) may significantly influence their efficacy and tolerability.

These highly available analgesic drugs have several drawbacks that need to be considered. Among them, gastro and cardiotoxicity, as well as a risk for renal failure are the most prevalent and typically originate from the COX inhibition. Although characterized mostly with mild to moderate symptoms, these toxicities may be associated with serious life-threatening consequences, such as ulcer perforation or myocardial infarction in a percentage of high-risk patients. According to several meta-analyses, these risks are dependent on the applied doses and the duration of treatment, so it is generally recommended that NSAIDs be taken in the lowest effective dose and for the shortest period possible.

Opioids

Opioids share common sites and mechanism of action on pain, however, some dissimilarities in pharmacodynamics (eg, affinity toward opioid receptor subtypes, intrinsic activity, dissociation rate from the receptor, the fate of drug-receptor complex on the neuronal membrane), as well as considerable differences in pharmacokinetic characteristics might influence their therapeutic effect as well as safety profile. Drugs differ in their half-life, biotransformation pathways, and activity of metabolites (these parameters influence the duration of analgesic action).

Because of wide distribution of opioid receptors in the peripheral tissues and through the central nervous system, opioid medications produce analgesia and mood-altering effects. They also regulate the gastrointestinal, neurohormonal, respiratory and cardiovascular functions, thereby producing various side effects, such as nausea and vomiting, sedation, dizziness, paradoxical hyperalgesia, myosis, suppression of cough reflex, pruritus, and modulation of the immune system. Continuous use of opioids may cause the development of tolerance, physical dependence, and addiction.

Antidepressants, Anticonvulsants, and Other Options

Empirically, it has been shown that drugs from different therapeutic classes, such as antidepressants (venlafaxine, duloxetine, as well as older tricyclics like imipramine, amitriptyline), some anticonvulsants (carbamazepine, gabapentin, pregabalin), anesthetics (local, such as lidocaine, or systemic such as ketamine and propofol), and different molecules of natural origin (capsaicin from chili peppers, ziconotide – a derivative of conotoxin from cone snail) may effectively reduce certain types of pain syndromes in some patients. These drugs are now considered to be adjuvant analgesics and deserve special attention in clinical practice. Belonging to diverse chemical and therapeutic classes, they differ in molecular targets related to pain treatment, from sodium and calcium channels, serotonin and noradrenaline reuptake transporters, to glutamate and GABA receptors. Except in pharmacodynamic profile, significant differences exist regarding their pharmacokinetic profile, especially biotransformation pathways. Side-effect and tolerability profile influence their applicability in unique chronic pain states.

LOOKING AHEAD

Genes and Pain

While searching for an explanation of the inter-individual variability in pain perception and drug-induced pain relief, scientists have tried to find the answers in the genes. As of this publication, researchers have identified at least six genes or gene clusters (mostly associated with opioid, adrenergic, and catecholamine pathways) that may have a connection with pain development.

The action and safety profile of opioids may also be influenced by polymorphisms of the Opioid Receptor Mu 1 gene (OPRM1) encoding for the mu opioid receptor (MOR), as well as by some functional single nucleotide polymorphism (SNP) of the gene encoding for Catechol-O-methyltransferase (COMT), an enzyme that degrades catecholamines. For example, SNP A118G in the OPRM1 gene may impact dose requirements of opioids: individuals with the AA genotype may have improved response to OPIOIDS and require lower doses to achieve analgesic effect, in contrast to those with AG...
and GG genotypes who may experience decreased response to opioids and for whom the higher doses are needed. However, there are no clear clinical guidelines about the analgesic dosage adjustments relevant to this or any other polymorphism of gene coding for specific drug targets. Further investigations into the correlation between analgesic therapeutic dose range and specific gene polymorphisms are warranted before drawing any specific dosing conclusion.

Even more than genes involved in pharmacodynamics, highly polymorphic genes encoding for enzymes responsible for drug metabolism (especially CYP2D6 and CYP2C9) may significantly change their effects and fate in the organism. In individuals who are poor metabolizers of opioids, which are either prodrugs (eg, codeine) or have an active metabolite (eg, tramadol), the analgesic effect might be compromised. In contrast, patients who are ultra-rapid metabolizers of these drugs may have a higher risk of toxicity/side effects as compared to patients with normal enzyme function.

For example, it is estimated that codeine therapy due to the CYP2D6 polymorphisms pose a risk of either lack of effect or adverse drug reactions for approximately 1 out of 7 Caucasians due to extremely low or high morphine formation.

Epigenetic changes may further alter the genes involved in pain perception and drug action, which is a matter of continuous research, and for now, the community can only speculate about the contribution of epigenetics to the pain treatment.

A recent study confirmed changes in total plasma N-glycosylation pattern in patients with chronic low back pain (CLBP) compared to healthy controls suggesting a connection between inflammatory response and total plasma N-glycosylation. Interestingly, observed changes in CLBP on the plasma N-glycome level are consistent with N-glycosylation changes usually seen in chronic inflammation. To our knowledge, this study was a first large clinical study on CLBP patients and plasma N-glycome providing a new glycomics perspective on potential disease pathology. The study was supported by an EU FP7-funded project called PAIN OMICS: “Multi-dimensional omics approach to stratification of patients with low back pain” aiming to discover and validate new “omics biomarkers” for the stratification of patients. To summarize: the use of omic approach will be critical in gaining additional knowledge necessary in understanding molecular mechanism of pain and consequently to use that knowledge in facilitating diagnosis and more accurate categorization as well as the treatment of chronic pain subphenotypes.

**Pharmacogenomics in Pain Medicine**

Many clinicians are already witnessing the significant benefit of implementing pharmacogenomics into their everyday practice. Dosage adjustments according to a patient’s genotype in order to optimize drug therapy have been implemented into relevant clinical guidelines and in summaries of products characteristics (SmPC) for certain drugs and drug classes (eg, clopidogrel, phenytoin, antidepressants). Accordingly, translating genomic data into clinical practice is becoming particularly important in understanding differences in the effect of medications during the treatment of pain.

The authors strongly believe that genotype-guided drug therapy for pain will play a crucial role in clinical practice. At present, the following medications indicated for pain management contain pharmacogenomics (PGx) information in the FDA label.

- **opioids:** codeine, oxycodone, tramadol
- **non-opioid, anti-inflammatory and neuropathic pain drugs:** celecoxib, amitriptyline, desipramine, clomipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, venlafaxine.

Considering challenges in individual pain treatment, pharmacogenomic studies may clarify interindividually differences in analgesic efficacy and tolerability. At St. Catherine’s Hospital, in Croatia, in collaboration with OneOme, co-founded by the Mayo Clinic, clinicians are routinely using PGx tests (RightMed) “covering” CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, OPRM1, and COMT genes in order to design a successful pain management protocol. The risk of adverse drug reactions are minimized while patient outcomes are optimized.

Due to multiple factors involved in this type of decision-making, which integrates not only knowledge about pharmacogenetics and epigenetics, but also of individual medication’s pharmacological characteristics and their interactions with other drugs and xenobiotics, a multidisciplinary team approach is necessary. This practice works to enable optimal, timely, evidence-based, and cost-effective pain management. Going forward, the authors strongly believe that to meet current challenges in individual pain treatment, clinicians should place crucial importance on additional pharmacogenomic to help clarify interindividual differences in analgesic effect and tolerability of the drugs before engaging in a full treatment plan.

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References