Continuing war on pain: a personalized approach to the therapy with nonsteroidal anti-inflammatory drugs and opioids

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Successful pain management requires the delivery of analgesia with minimal risk of adverse drug reactions. Nonsteroidal anti-inflammatory drugs and opioids remain the mainstay of treatment for the majority of patients. Unfortunately, almost 50% of all patients experience inadequate pain relief and serious side effects. Allelic variants in genes coding for target proteins, transporters and enzymes, which govern analgesic drugs action and their fate in the organism, might explain inter-individual variability in pain severity and in drug-induced pain relief and toxicities. Additionally, it seems that epigenetic changes contribute to the highly variable response to pain treatment. Therefore, pharmacogenomic testing might be a valuable tool for personalization of pain treatment, with a multidisciplinary team approach involved.

Chronic pain affects around 27% of the adult European population and represents a huge burden not only for affected individuals, but for health care system, society and economy as well. It has an enormous negative impact on a patient's quality of life, daily functioning, work productivity and interpersonal communication [1,2]. More than 116 million Americans have pain that persists for weeks to years. The total financial costs of this epidemic are $560–635 billion per year, according to Relieving Pain in America [3].

Among the most frequently observed persistent pain conditions in general population are those affecting the musculoskeletal system, like low back pain, temporomandibular joint disorder and chronic widespread pain [4]. Despite different nonpharmacological approaches available nowadays, pharmacotherapy is unavoidable for the majority of patients. According to the data collected by the Agency for Medicinal Products and Medical Devices of Croatia, around 25 million euros were spent on analgesic drugs in 2016; furthermore, those are only the direct costs of pain management [5]. The calculations of indirect costs such as sick leaves or diminished work capability are currently lacking in Croatia.

Two pharmacologically distinct groups of analgesics represent a mainstay for the pain treatment: nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Each group includes various molecules with a common basic mechanism of action; however, with some differences which might favor selection of one drug over another in certain conditions and patient population [1]. Despite a long history of use in different clinical settings and well-established pharmacological profile, these drugs still generate two significant challenges. One is their ineffectiveness in some patients and types of pain and the other equally important is their safety profile. Additionally, long-term
use of opioids is compromised with a high incidence of misuse that leads to the development of addiction and deaths because of overdoses [6].

Complex pathophysiological mechanisms of pain and unpredictable effects of the common analgesics are particularly interesting from the pharmacogenomic point of view [7]. For example, musculoskeletal pain conditions have a genetic basis that is under dynamic influence of different environmental factors (e.g., smoking, physical injury) thus producing specific pain phenotypes [4]. Gene polymorphisms that can affect either pharmacodynamic or pharmacokinetic of the drugs might influence their analgesic effect [8]. Moreover, patient characteristics such as age, sex (chronic pain is more prevalent in female), lifestyle (diet, physical activity, sleep status, smoking, alcohol consuming, obesity and bodyweight), as well as previous illnesses and comorbidities, such as cancer and diabetes, etc., can have a significant impact on pain perception and treatment outcomes. Different environmental, as well as psychological factors (poor mental status associated with chronic pain), ethnocultural differences and socioeconomic background, may additionally increase the chronic pain burden for each individual [9,10].

It can be challenging to identify the extent to which a drug response is influenced solely due to genetic difference [11]. Keeping in mind the pathophysiological complexity of chronic pain and interindividual differences in pain sensitivity and response to analgesics, treatment should be personalized [12].

In this paper, we will critically review the pharmacological properties of commonly used analgesics, in other words, NSAIDs and opioids, with short insight into the possible influence of genes on their effectiveness and safety.

**NSAIDs as a first-line therapy to combat the pain**

NSAIDs, also known as COX inhibitors after their main mechanism of action, represent a heterogeneous group of drugs commonly used for their analgesic, antipyretic and anti-inflammatory effects. They are considered a first-line therapy for managing a pain of low to medium intensity of different localization and etiology [1,8].

They inhibit the catalytic activity of two isoforms of enzyme cyclooxygenase, referred to as COX-1 and COX-2 (Figure 1A). The result of competitive inhibition of either isoform is the inhibition of prostanoid synthesis [1,13]. Both isoenzymes convert arachidonic acid, a phospholipid ester from the cell membranes, into unstable prostaglandin PGG2 followed by the conversion into PGH2, which is a substrate for the synthesis of five prostanooids: PGD2, PGE2, PGF2α, prostacyclin (PGI2) and thromboxane A2 (TxA2). These products regulate numerous biological processes, including inflammation, hemostasis, gastroprotection, renal hemodynamics – among others [1,4].

Pharmacological properties of COX inhibitors largely depend on their chemical structure because it governs multiple variables: the affinity of the drug for the respective isoenzyme (selective or nonselective), speed (rapid or slowly-acting) and type (reversible or irreversible) of interaction with the active site of the enzyme. Relative COX selectivity has been described as the ratio of concentration necessary to inhibit the activity of COX-1 or COX-2 by 50% (IC50) in vitro (Figure 1B). Drugs with preferential affinity for COX-2 have selectivity ratios > 1 [1].

According to mechanistic features, NSAIDs can be divided as follows: irreversible COX-1 and COX-2 inhibitor (aspirin), more selective reversible COX-2 inhibitors (celecoxib, etoricoxib, parecoxib; diclofenac and etodolac; meloxicam), nonselective reversible COX inhibitors (paracetamol [acetaminophen]; indomethacin; ibuprofen, ketoprofen, naproxen, dexketoprofen and piroxicam) [12]. However, due to weak anti-inflammatory effect in therapeutic dose range, paracetamol and aspirin are not considered as NSAIDs [17].

COX-1 is constitutively expressed in majority of tissues where it performs important, mostly protective physiological functions. The product of COX-1 in platelets is TxA2, an important mediator of platelet activation and aggregation. The best characterized role of COX-1 is in gastroprotection [1,18]. Strong and repeated inhibition of COX-1 results in hypoproduction of PGE2 and PG12, and consequently decreased secretion of mucus and bicarbonates. Thus, inhibition of COX-1 results in increased secretion of gastrointestinal acid that can have toxic effects in these circumstances, by promoting ulcerations and bleeding of the gastric mucosa. In addition, lower TxA2 production in platelets also contributes to the slower mucosal regeneration due to prolonged bleeding time. The described mechanisms are largely responsible for gastrointestinal side effects of NSAIDs [19].

COX-2 is the enzyme isoform expressed constitutively in some tissues, for example, vascular endothelium and kidneys where it catalyzes the production of PGE2 and PG12 with significant role in the regulation of platelet aggregation, vasodilation and renal hemodynamics [8,20]. During inflammation or tissue damage, expression of COX-2 is induced by inflammatory mediators such as the TNF-α or interleukins produced by monocytes and macrophages [1,20]. Drugs with high-degree selectivity for COX-2 enzyme, like celecoxib and etoricoxib, exert strong anti-inflammatory effect with better gastrointestinal tolerability in comparison to nonselective counterparts. However, they carry a risk for cardiovascular (CV) adverse events because of the impaired vasodilation, increased
Figure 1. COX enzymes and selectivity of NSAIDs. (A) Schematic representation of structural differences between COX-1 (green; left) and COX-2 (red; right) enzyme. The amino acids Tyr385 and Ser530 (purple) are important for the activity of both enzymes. COX-2 has a wider binding site pocket in comparison to COX-1 because of substitution of Ile434, His 513 and Ile523 (lighter green) in COX-1 with less bulky amino acid residues in COX-2, Val434, Arg513 and Val523 (orange). Larger molecules like coxibs cannot enter the narrower hydrophobic entrance channel of COX-1 and do not fit into the COX-1 smaller active site [15]. (B) Selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs) for COX-1/2 was determined using a whole blood assay. This chart represents the log (IC₅₀ of COX-1 relative to the IC₅₀ of COX-2) for NSAIDs and clearly demonstrates their affinity towards either COX-1 or COX-2 [16].
Table 1. Pharmacokinetic properties of different COX-inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>Half-life (h)</th>
<th>Binding to plasma proteins (%)</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>70–90</td>
<td>9.85</td>
<td>1</td>
<td>1.9–2.5</td>
<td>10–20</td>
<td>Glucuronidation (main pathway), CYP2E1 (minor contribution)</td>
<td>Mostly urine</td>
<td>[24,25]</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>80–100</td>
<td>3–7</td>
<td>1</td>
<td>0.4–0.6</td>
<td>88–93</td>
<td>Hydrolysis to salicylates, conjugation with glycine and glucuronic acid</td>
<td>Mostly urine</td>
<td>[24,26]</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>100</td>
<td>0.4–1.3</td>
<td>1.25</td>
<td>1.1</td>
<td>99.7</td>
<td>CYP2C9 (hydroxylation), glucuronidation</td>
<td>65% urine, 35% feces</td>
<td>[24,27,28]</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>100</td>
<td>0.5–3</td>
<td>1–1.5</td>
<td>1</td>
<td>90</td>
<td>CYP2C9 (O-demethylation, deacetylation)</td>
<td>60% urine, 40% feces</td>
<td>[29]</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>≈85</td>
<td>2.5–4</td>
<td>1.3</td>
<td>1.1–2.5</td>
<td>99.2</td>
<td>Glucuronidation</td>
<td>Mostly urine</td>
<td>[24,30]</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>≈85</td>
<td>2.5</td>
<td>0.25–0.75</td>
<td>≈2</td>
<td>99.2</td>
<td>Glucuronidation</td>
<td>Mostly urine</td>
<td>[31]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>74–99</td>
<td>37.2</td>
<td>0.5–3</td>
<td>12–15</td>
<td>99.7</td>
<td>CYP2C9; CYP1A2 (dealkylation), acyl glucuronidation committee</td>
<td>Mostly urine</td>
<td>[24,32]</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>89</td>
<td>≈1.5</td>
<td>9–11</td>
<td>22–24</td>
<td>99</td>
<td>CYP2C9; CYP3A4 (oxidation)</td>
<td>≈50% urine, ≈50% feces</td>
<td>[33]</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>100</td>
<td>2.63</td>
<td>2.4</td>
<td>50</td>
<td>99</td>
<td>CYP2C9 (hydroxylation), conjugation</td>
<td>Mostly urine</td>
<td>[34–37]</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>–</td>
<td>0.71</td>
<td>2.8</td>
<td>11.2</td>
<td>97</td>
<td>CYP2C9 (hydroxidation), glucuronidation</td>
<td>Urine and feces</td>
<td>[38]</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>100</td>
<td>0.095–2.2</td>
<td>1</td>
<td>22</td>
<td>91.9</td>
<td>CYP3A4; CYP2D6; CYP2C9; CYP1A2; CYP2C19 (methyl hydroxylation, N-oxidation)</td>
<td>70% urine, 20% feces</td>
<td>[39,40]</td>
</tr>
</tbody>
</table>

platelet reactivity and disturbed renal blood flow [14]. Since all NSAIDs inhibit both COX isoenzymes, cardiotoxicity is a class effect. Among COX inhibitors, naproxen has shown a better CV safety profile, which is probably due to its prolonged and significant inhibition of COX-1 in platelets [21]. According to several meta-analyses, risks for gastrointestinal and CV side effects as well as risk for renal failure are dependent on the applied doses and the duration of treatment. It is generally recommended that NSAIDs should be taken in the lowest effective dose and for the shortest period possible [17].

The goal of pain treatment is to achieve and maintain effective drug concentration in the site of injury as quickly as possible, and at the same time to minimize its systemic concentration. Thus, pharmacokinetic properties of NSAIDs (rate of absorption, the time to maximal plasma concentration, half-life, tissue versus plasma distribution, elimination) and the type of pharmaceutical formulations (immediate- or extended-release tablets, oral solutions, suppositories and parenteral solutions) can significantly influence their efficacy and tolerability [1]. After repeated administration, acidic NSAIDs such as diclofenac and ibuprofen, achieve higher and more sustainable concentrations in inflamed tissues. Despite their short plasma half-lives, this testifies their long-term effect. Moreover, this feature allows rapid recuperation of prostanoid production in the endothelium, kidneys and platelets, thus making these drugs safer and more tolerable in comparison to drugs with longer plasma half-lives, like meloxicam and piroxicam [1,22]. Unfortunately, this benefit is sustained only with lower doses and immediate-release formulations, as extended-release formulations carry an increased risk of adverse effects [20].

Hepatic biotransformation via cytochrome P450 (CYP450) enzyme system, mostly subfamily 2D6 and 2C9, and renal excretion are the principal routes of metabolism and elimination of the majority of NSAIDs. Accordingly, NSAIDs are not recommended for patients with severe renal and/or hepatic impairment [23]. Furthermore, due to a quite strong plasma protein binding, NSAIDs cannot be efficiently removed by hemodialysis (Table 1) [13].

In order to improve the pharmacokinetic profile of available drugs, different pharmaceutical approaches can be employed. One such example is dexketoprofen – an active S(+)- enantiomer of ketoprofen, which achieves faster onset of analgesic effect with lower doses and better tolerability profile compared with racemic (S,R) ketoprofen [41].
In conclusion, pharmacological differences between drugs and patient history must be taken into consideration when selecting an optimal drug for pain management. As for all medicines, positive and negative aspects of treatment should be evaluated with caution for each individual.

Opioid agonists as the most powerful weapon to conquer the pain
Even nowadays, opioids are the most effective drugs for pain management. They relieve moderate to severe acute and chronic pain in cancer patients and patients experiencing nonmalignant pain [8,42]. Drugs can be applied via different routes, like oral (most drugs, except fentanyl and congeners, buprenorphine), buccal, transdermal, intravenous, intramuscular and intraspinal.

Morphine, once described as a golden standard in pain therapy, is still considered as the representative drug of the opioid group. Its popularity is grounded on natural origin, longevity in pain management, well-known pharmacological properties, established therapeutic and adverse effects profile. Opioid drugs can be classified according to their origin, as natural, semi synthetic and pure synthetic; an intensity of action, from moderate to extremely potent; duration of action, from short-acting to long-acting – among others [43].

Opioids, either endogenous or exogenous, activate opioid receptors. Three major classes of opioid receptors have been identified: mu (μ) opioid receptor (MOR), kappa (κ) opioid receptor (KOR) and delta (δ) opioid receptor (DOR). They are widely distributed in the peripheral tissues and through the central nervous system, thus mediating different physiological effects, like gastrointestinal motility and smooth muscle tone, nociception, motivation and hormonal processes. Accordingly, opioid drugs produce analgesia and mood altering effect; regulate the gastrointestinal, neurohormonal, respiratory and CV function [44].

Although endogenous opioid peptides exert affinity toward all three types of opioid receptors, drugs have preferential affinity toward MOR, while buprenorphine and pentazocine have additional activity on KOR, acting either as antagonist or agonist, respectively [43]. Drugs can be classified according to their mode of action on opioid receptors either as full agonists (morphine, codeine, methadone, tramadol, tapentadol, oxycodone, fentanyl, sufentanil, hidromorphone), partial agonists with high affinity but low intrinsic activity (buprenorphine) or mixed agonists–antagonists (pentazocine) [42,43].

Opioid receptors belong to a family of G-protein coupled receptors. Upon activation by an agonist, receptor protein undergoes conformational change, resulting in a various downstream intracellular events, that might include the following: inhibition of the adenyl cyclase (AC) and consequently reduced cellular cyclic adenosine 3',5'-monophosphate (cAMP) concentration and protein kinase A (PKA) activity; reduced postsynaptic neuronal excitability due to the membrane hyperpolarization and opening of potassium channels; and inhibition of calcium influx into the presynaptic nerve terminals with resulting reduced neurotransmitter release [43]. Opioid drugs differentially activate postreceptor signaling pathways and influence MOR desensitization, resensitization, endocytosis or recycling [45]. Complex pharmacology of opioid system might explain observed clinically significant differences between various opioid drugs in their effectiveness, risk of adverse effects, including development of tolerance and addiction.

Except for dissimilarities in pharmacodynamics (affinity toward opioid receptor subtypes, intrinsic activity, dissociation rate from the receptor, the fate of drug-receptor complex on the neuronal membrane), there are some considerable differences in pharmacokinetic parameters between opioid drugs which might influence their therapeutic effect as well as safety profile (Table 2). Thus, lipophilic drugs (fentanyl, hydromorphone, buprenorphine) exert rapid onset of the analgesic effect due to the faster transport through the blood–brain barrier, unlike more hydrophilic drugs, such as morphine. Duration of action is largely dependent on drug half-life, degree of biotransformation and activity of metabolites. Lipophilic drugs are gradually accumulated in tissues (muscles and fat) and clearance mechanisms become saturated after repeated administration. Thus short-acting fentanyl becomes longer-acting after prolonged use [43]. Codeine is a prodrug of morphine, therefore its analgesic activity as well as safety depends on the degree of biotransformation and activity of metabolic enzyme CYP2D6. Some opioids, like oxycodone and methadone, undergo extensive metabolic reactions by the CYP450 enzyme systems in the liver to metabolites that are inactive, partially active or even more active in comparison to the parent drug. Morphine, on the other hand primarily undergoes glucuronidation by 5’-diphospho-glucuronosyltransferase-2B7 (UGT2B7) to inactive morphine-3-glucuronide and active morphine-6-glucuronide metabolites [46]. Opioids and its metabolites are eliminated primarily in urine; consequently, dose adjustments are required in patients with renal impairment and in elderly patients because of decline in renal function and smaller volume of distribution [43].
Table 2. Pharmacokinetic characteristics of different opioid agonists.

<table>
<thead>
<tr>
<th>Drug (route of administration)</th>
<th>Bioavailability (%)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>Half-life (h)</th>
<th>Binding to plasma proteins (%)</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine-sulfate (PO-IR)</td>
<td>30</td>
<td>10</td>
<td>0.5–1.5</td>
<td>2–3.5</td>
<td>20–35</td>
<td>Glucuronidation, N-demethylation</td>
<td>Mostly urine</td>
<td>[46-48]</td>
</tr>
<tr>
<td>Hydromorphone (PO)</td>
<td>50</td>
<td>1–1.3</td>
<td>0.5–1</td>
<td>2–3</td>
<td>7.1</td>
<td>Glucuronidation</td>
<td>Mostly urine</td>
<td>[46,49]</td>
</tr>
<tr>
<td>Codeine (PO)</td>
<td>50</td>
<td>149</td>
<td>1</td>
<td>2.9</td>
<td>7</td>
<td>CYP2D6 (N-demetylation to morphine), CYP3A4 (O-demetylation), glucuronidation</td>
<td>Mostly urine</td>
<td>[46,50]</td>
</tr>
<tr>
<td>Oxycodone (PO)</td>
<td>60–87</td>
<td>15.5</td>
<td>1.6</td>
<td>3–5</td>
<td>45</td>
<td>CYP3A4 (N-demethylation), CYP2D6 (O-demethylation)</td>
<td>Mostly urine</td>
<td>[46,51]</td>
</tr>
<tr>
<td>Tramadol (PO)</td>
<td>68–84</td>
<td>592</td>
<td>1–2</td>
<td>6</td>
<td>20</td>
<td>CYP2D6; CYP3A4 (O-demethylation)</td>
<td>Mostly urine</td>
<td>[46,52]</td>
</tr>
<tr>
<td>Tapentadol (PO)</td>
<td>32</td>
<td>64.2</td>
<td>1–1.5</td>
<td>4</td>
<td>20</td>
<td>Glucuronidation</td>
<td>Mostly urine</td>
<td>[46,53]</td>
</tr>
<tr>
<td>Buprenorfine (SL)</td>
<td>51</td>
<td>2.7</td>
<td>1.2</td>
<td>16.2</td>
<td>96</td>
<td>CYP3A4 (N-dealkylation), glucuronidation</td>
<td>Mostly feaces</td>
<td>[46,54]</td>
</tr>
<tr>
<td>Fentanyl (transmucosal, SL)</td>
<td>50</td>
<td>0.8</td>
<td>0.4</td>
<td>3.7</td>
<td>84</td>
<td>CYP3A4 (N-dealkylation)</td>
<td>Mostly urine</td>
<td>[46,55]</td>
</tr>
<tr>
<td>Pentazocine (PO)</td>
<td>18.4</td>
<td>50</td>
<td>1.74</td>
<td>3.4</td>
<td>56–66</td>
<td>Glucuronidation</td>
<td>Mostly urine</td>
<td>[56,57]</td>
</tr>
</tbody>
</table>

IR: Immediate release; PO: Per os; SL: Sublingual.

Tramadol and tapentadol are synthetic opioids with a typical mechanism of action. Tramadol is used as racemic mixture where S(+) enantiomer binds and inhibits serotonin reuptake but also activates MOR, while R(-) enantiomer selectively inhibits noradrenaline (NA) reuptake and activates $\alpha_2$-adrenergic receptors. According to the published studies, tramadol exerts better effect on neuropathic pain than morphine due to the modulation of monoaminergic pathways in the dorsal horn of the spinal cord. In contrast to tramadol, tapentadol is a stronger MOR agonist and has superior NA reuptake inhibition. Hence, tapentadol demonstrates a lower risk of serotonin syndrome and better gastrointestinal safety profile, and is a safer option in patients with hypertension than tramadol [52].

The most commonly reported opioid-induced side effects include nausea and vomiting, sedation, dizziness, paradoxical hyperalgesia, myosis, suppression of cough reflex, pruritus and modulation of the immune system. Respiratory depression caused by reduced ventilation of CO₂ and modulation of the respiratory rhythm is a potential cause of death after an overdose. Continuous use may cause the development of tolerance and physical dependence, as well as aberrant behaviors which could lead to drug abuse and addiction [58].

Because adverse effects may profoundly influence patients quality of life and adherence to the therapy, several strategies for preventing and managing negative adverse effects are suggested; such as: dose reduction (some adverse effects are dose-dependent); opioid rotation (substituting one drug with alternate at an equieffective dose); alternating the route of administration (e.g., changing from oral administration to subcutaneous, intravenous, sublingual or transdermal); symptomatic management of side effects (for example, laxatives for constipation, anti-emetics for nausea, antihistamines for pruritus) [59].

Intentional opioids abuse, increased opioids prescribing, diversion and misuse are major public health concerns worldwide. In the USA, the fatalities from prescription opioid overdose have increased four-times between 1999 and 2015. Moreover, around 1000 nonfatal opioid overdose accidents per day alarm healthcare providers about the seriousness of the opioid crisis situation [6]. To prevent these events, the pharmaceutical industry is focused on developing abuse-deterrent formulations, for example oral formulations with polymer matrix (oxycodone) or polyethylene oxide matrix (oxymorphone, tapentadol), which are protected from crushing, extracting or dissolving the active substance in water. Furthermore, combining opioid agonist (oxycodone and buprenorphine) with an antagonist (naloxone or naltrexone) will prevent agonist effect only after intravenous misuse, and not if it is taken per os or sublingually. Incorporation of aversive ingredients, for example, lauryl sulfate or niacin in formulations with oxycodone, will provoke adverse responses if applied in higher doses or by divergent route [60,61].

In conclusion, the use of opioid analgesics for severe pain treatment is growing constantly, despite rising concerns about their effectiveness in the treatment of chronic noncancer pain. In parallel, the world is witnessing the growing...
problem of their misuse. Therefore, healthcare providers should carefully consider the benefits and risks of opioid drugs based on their pharmacological characteristics and behavioral effects that underlie therapeutic as well as adverse effects [62].

Can genes interfere with the pain treatment?
It is estimated that genetic contribution to the development of chronic pain of musculoskeletal origin is around 50%. The studies apostrophized the significance of at least six genes or gene clusters, mostly associated with opioid, adrenergic and catecholamine (i.e., dopaminergic and serotonin) pathways, which are reproducibly connected with pain development [4]. However, the genetic background of various painful conditions is beyond the scope of this review, instead focusing on genetic polymorphisms related to the effectiveness and safety of analgesics.

Polymorphisms of the gene encoding for catechol-O-methyltransferase (COMT), an enzyme that degrades catecholamines, is most frequently linked to divergent pain processing in both, animals and humans [4]. COMT has also been identified as influencing analgesic drug efficacy, as well. The most studied functional SNP of COMT is rs4680, where A to G transition results in a Val to Met amino-acid substitution, and lower enzymatic activity. Although several clinical studies demonstrated that Val158Met (AA) carriers have an increased sensitivity to the analgesic effects of opioids compared with AG and GG genotypes [63–65], further investigations into the correlation between opioid therapeutic dose range and COMT polymorphisms are warranted before drawing specific dosing conclusion [66].

Opioids' effects may be influenced by polymorphisms in OPRM1 gene encoding for the MOR, with more than 100 allelic variants identified so far. One of the most studied is the SNP rs1799971 (118 A>G), which results in Asn to Asp substitution [11]. The frequency of the OPRM1 188A>G variant differs between ethnic population, with the highest frequency among individuals of Asian ancestry (35–50%), and lesser frequency among individuals of European (15.4%), Hispanic (14%) and African ancestry (4.7%) [67]. Persuasive evidence in favor of this functional polymorphism comes from some clinical studies with morphine, where GG genotype was related to a reduced analgesic effect and requirements for higher doses [11].

In contrast to the limited evidence surrounding genes involved in pharmacodynamics of analgesics having an impact on their pharmacological profile, the highly polymorphic genes encoding for enzymes responsible for analgesic metabolism can significantly change drugs effects and their fate in the organism. For example, the hepatic enzyme CYP2C9 is involved in the biotransformation of several analgesics, including celecoxib, flurbiprofen, meloxicam, piroxicam, diclofenac and neurologic agents like phenytoin and fosphenytoin. Up to now, 67 allelic variants of the CYP2C9 gene have been identified altogether [68]. It is estimated that CYP2C9*2 and CYP2C9*3 are present in European population with the prevalence of 14 to 8%, respectively. These variants can decrease NSAID metabolism, resulting in elevated NSAID concentrations, as well as increased risk for adverse events and overdose. It has been shown that the risk for upper gastrointestinal bleeding associated with NSAIDs is higher in people carrying the CYP2C9*3 variant [69]. Presence of the *2 and *3 alleles is also associated with elevated concentrations of phenytoin and fosphenytoin, resulting in an increased risk of toxicity. The Clinical Pharmacogenomics Implementation Consortium has authored guidelines on phenytoin/fosphenytoin dosing and CYP2C9 phenotype, recommending physicians consider reducing phenytoin/fosphenytoin dose by 25% in CYP2C9 intermediate metabolizers (i.e., *1/*2 or *1/*3), and reducing the dose by 50% in CYP2C9 poor metabolizers (i.e., *2/*2, *2/*3, *3/*3), and recommend therapeutic drug monitoring to avoid toxicities [70].

Furthermore, CYP2D6 is responsible for the metabolism of many opioid analgesics, including codeine, oxycodone and tramadol. Its function is directly related to the number of wild-type or abnormal alleles inherited, so patients can be categorized as poor, intermediate, extensive or ultrarapid metabolizers [7]. The analgesic effects of codeine and tramadol are attributed to their O-demethylation via CYP2D6 to a more potent MOR agonists morphine and O-desmethyltramadol, respectively. Thus, poor metabolizers cannot experience a full analgesic effect after standard dosing of these drugs opioid prodrugs. On the contrary, ultrarapid metabolizers have a higher risk of adverse effects and overdose, due to an increased concentration of those active metabolites. It is estimated that codeine therapy poses a risk of either lack of effect or adverse drug reactions for around one out of seven Caucasians due to extremely low or high morphine formation [71]. Because of the risks associated with CYP2D6 ultrarapid metabolism, breastfeeding is not recommended during treatment with codeine or tramadol. Additionally, the US FDA has issued a black box warning for children who are CYP2D6 ultrarapid metabolizers and prescribed codeine following a tonsillectomy or adenoidectomy, due to previous reports of respiratory depression and death in children taking codeine who were identified as CYP2D6 ultrarapid metabolizers [72].
### Table 3. Polymorphisms of genes related to analgesic drug action.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Protein</th>
<th>Gene</th>
<th>Genotype</th>
<th>PK/PD effects</th>
<th>Effect on clinical outcomes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>COMT</td>
<td>COMT</td>
<td>rs4680; 158 A→G</td>
<td>Lower enzymatic activity</td>
<td>Reduced drug dosage</td>
<td>[11,65,66]</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>MOR</td>
<td>OPRM1</td>
<td>rs1799797; 118 A→G</td>
<td>Loss of a N-glycosylation site in the extracellular region of the receptor</td>
<td>Reduced analgesic effect and requirements for higher doses</td>
<td>[11,67]</td>
</tr>
<tr>
<td>Celecoxib, flurbiprofen, meloxicam, piroxicam, diclofenac, phenytoin and fosphenytoin</td>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>rs1799853; CYP2C9*2</td>
<td>Reduced enzymatic activity</td>
<td>Elevated NSAID concentrations, increased risk for adverse events (higher risk for upper gastrointestinal bleeding) and overdose</td>
<td>[11,69,70]</td>
</tr>
<tr>
<td>Codeine, oxycodone, tramadol</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP2D6*1/*1xN</td>
<td>Ultrarapid metabolizers</td>
<td>Higher risk of adverse effects and overdose</td>
<td>[11,71,72]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs3892097; CYP2D6*4</td>
<td>Poor metabolizers</td>
<td>Poor metabolizers cannot experience a full analgesic effect after standard dosing of opioid prodrugs</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>CYP2B6</td>
<td>CYP2B6</td>
<td>rs3745274: c.516G&gt;T</td>
<td>Reduced enzymatic activity</td>
<td>Dosage adjustment</td>
<td>[73–75]</td>
</tr>
</tbody>
</table>

COMT: Catechol-O-methyltransferase; MOR: Mu (µ) opioid receptor; NSAID: Nonsteroidal anti-inflammatory drug; PD: Pharmacodynamics; PK: Pharmacokinetics; xN: The number of gene copy.

Other analgesic agents, like propofol, are also metabolized via the CYP450 pathway. Propofol is metabolized by CYP2B6, with only a few clinical studies identifying the CYP2B6 c.516G>T polymorphism impacting the metabolic profile of propofol. Further studies with larger patient populations are necessary to further characterize the impact of CYP2B6 polymorphisms on the pharmacokinetics of both ketamine and propofol [73–75] (Table 3).

Variations in genes coding for UGT superfamily may potentially play a significant role in the clearance of most analgesic drugs since glucuronidation is an important final step in drugs biotransformation. Because the major pathway for the metabolism of morphine is glucuronidation, genetic polymorphism in UGT2B7 was investigated in several studies. Although the results are mostly inconclusive, in one study it was shown that in patients with sickle cell anemia, the presence of UGT2B7–840G allele significantly decreased morphine biotransformation into the final metabolites, morphine-3- and morphine-6 glucuronide [76]. Among nonopioid analgesics, there is evidence that polymorphism in the UGT1A gene (rs8330) is connected to the increased paracetamol glucuronidation in the liver. This can be an important determinant of an individual’s risk for paracetamol-induced liver injury [77].

The efficacy and safety of opioids may additionally be compromised by polymorphisms of genes encoding for different transporters that regulate drugs absorption, distribution and elimination. Among those, the most investigated is P-gp, which belongs to the ATP-binding cassette (ABC) superfamily of efflux transporters. ABCB1 gene encodes for P-gp, and is highly polymorphic, with 38 SNPs identified in the coding region. The best characterized is the functional SNP rs1045642 (3435C>T), which does not change the amino acid sequence, results in reduced P-gp function. The frequency of this type of polymorphism is 50–60% among Caucasians, 40–50% among Asians and 10–30% among Africans [42]. Due to the distribution of P-gp in the blood–brain barrier, this polymorphism might affect the penetration of the drugs, like morphine, methadone and fentanyl, into the brain and consequently their efficacy. For these drugs, dose adjustments might be needed in patients with ABCB1 polymorphism; however, there are no clear guidelines regarding this issue [7].

In summary, allelic variants in genes coding for target proteins, transporters and enzymes, which govern analgesic drugs action and their fate in the organism might explain interindividual variability in pain perception, severity and in drug-induced pain relief and toxicities. Therefore, the relevance of pharmacogenetics in optimizing pain therapy is more than obvious but clear guidelines for its implementation in the clinical settings are required. For now, the Clinical Pharmacogenetics Implementation Consortium has established guidelines on individualizing treatment with tramadol and codeine based on the rate of CYP2D6 metabolism [11].

**Pharmacogenomics in pain management**

Successful pain management requires the delivery of analgesia with minimal risk of adverse drug reactions. Clinicians treating pain have noted that responses to pain medications can vary to a great degree (~40-fold). Almost 50% of all patients experience inadequate pain relief and serious adverse drug reactions with many of the most commonly used perioperative analgesics [78].
At this point the following drugs for the pain treatment contain pharmacogenomics information in FDA label, Clinical Pharmacogenetics Implementation Consortium or Dutch Pharmacogenetics Working Group clinical guidelines: opioids (codeine, oxycodone, tramadol) and nonopioid, anti-inflammatory and neuropathic pain drugs (celecoxib, amitriptyline, desipramine, clomipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, venlafaxine). In collaboration with OneOme, St Catherine's Hospital just launched innovative pharmacogenomics tests (RightMed©) ‘covering’ following genes: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, OPRM1 and COMT in order to have as successful pain management as possible with minimal risk of adverse drug reactions.

**Possible influence of epigenetics on the pain treatment**

Development of sensitization of the nociceptive system (after tissue and/or peripheral nerve injury or prolonged inflammation) and pain chronification (the transition of acute to chronic pain) are under strong influence of environmental factors, such as diet, exercise, stress, toxins, medications, drug abuse and many others which alter the genes involved in pain perception and predispose individual vulnerability toward painful signals [79–81]. For example, among female smokers’ chronic pain condition has been reported more frequently than in female nonsmokers, although the evidence for a direct causal relationship between smoking and pain is relatively weak [11,80].

Epigenetic changes such as histone acetylation regulated by histone acetyltransferases and histone deacetylases, DNA methylation regulated by DNA methyltransferases and miRNAs dysregulation are contributing factors for onset and progression of different pain types, as was repeatedly demonstrated in different animal pain models [79,82].

In the experimental model of postsurgical pain in mice it was demonstrated that epigenetic changes in genes coding for brain-derived neurotrophic factor and dynorphine contribute to postoperative hypersensitization and reduce opioid response after prolonged treatment [83]. This result, when combined with other studies suggest that epigenetic modifications probably contribute to the opioid analgesics effects on pain and on their adverse effects, such as paradoxical hyperalgesia and addiction [82,84]. Recently, Li et al. showed that DNA demethylation of chemokine receptor CXCR4 gene promoter region significantly contributes to inflammatory hyperalgesia in rats [84].

Although mostly preclinical, findings from different pain models provide a theoretical basis for the treatment of chronic pain from an epigenetic point of view. Hypothetically, pain therapy might benefit from drugs that are able to modulate epigenetic contribution to pain pathophysiology (such as histone deacetylases and DNA methyltransferase inhibitors). Despite several drugs in the preclinical and clinical phases of the investigation, it will take some time before we can improve the pain treatment with epigenetic modulators [82].

Even though it was demonstrated in human gastric mucosa and colon carcinoma cells that a long-term administration of different NSAIDs affects epigenetic modulation of several growth genes, similar effects were not demonstrated for pain-related genes so far [85]. On the contrary, opioids are associated with different types of epigenetic regulation, such as miRNA upregulation and downregulation [86], increased methylation of OPRM1 gene [87].

In conclusion, research on epigenetic mechanisms related to the pain and analgesic drug actions is becoming an interesting field for researchers and clinicians, but for now, we can only speculate about the contribution of epigenetics to the pain treatment.

**Conclusion & future perspectives**

Despite an enormous effort put to the pain investigation during past several decades, chronic pain still represents a huge challenge for both researchers and clinicians. Findings from the laboratories contribute to the clarification of complex pain pathophysiology; however, the pain treatment in clinical practice is still grounded on two classes of analgesic drugs. Basic knowledge about their pharmacology and side effects profile is warranted for effective and safe pain treatment. Considering challenges in individual pain treatment, pharmacogenomic studies might be of crucial importance in clarifying interindividual differences in analgesic effect and tolerability of the drugs. However, with the exception of codeine and tramadol, guidelines supporting pharmacogenetic testing that assist in selecting the optimal dose for the individual patient are currently lacking. A multidisciplinary team approach may be the best way toward enabling timely, evidence-based, cost-effective and most importantly, successful pain management interventions [88,89].
## Executive summary

### Nonsteroidal anti-inflammatory drugs as a first-line therapy to combat the pain
- Nonsteroidal anti-inflammatory drugs are considered first-line therapy for managing a pain of low to medium intensity of different localization and etiology.
- Factors to keep in mind include: COX1/COX2 selectivity, type of pharmaceutical formulation, patient history of severe renal or liver impairment, potential gastro- and cardiotoxicity.

### Opioid agonists as the most powerful weapon to conquer the pain
- Opioids relieve moderate to severe acute and chronic pain in cancer patients and patients experiencing nonmalignant pain.
- Affinity to opioid receptors, CYP2D6 metabolizer type and abuse-deterrent formulations are some of the main points to consider when choosing an opioid drug.

### Can genes interfere with the pain treatment?
- Allelic variants in genes coding for target proteins (OPRM1), transporters (P-gp) and enzymes (CYP2D6, UGT, COMT) might explain interindividual variability in pain perception, severity and in drug-induced pain relief and toxicities.

### Pharmacogenomics in pain management
- Almost 50% of all patients experience inadequate pain relief and serious adverse drug reactions with many of the most commonly used perioperative analgesics.
- In collaboration with OneOme, St. Catherine’s Hospital just launched innovative pharmacogenomics tests (RightMed®) “covering” following genes: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, OPRM1, and COMT.

### Possible influence of epigenetics on the pain treatment
- Epigenetic modifications probably contribute to the opioid analgesics effects on pain and on their adverse effects, such as paradoxical hyperalgesia and addiction.
- Opioids are associated with different types of epigenetic regulation, such as miRNA upregulation and downregulation, increased methylation of OPRM1 gene, but no such evidence has emerged for nonsteroidal anti-inflammatory drugs and pain-related genes.

### Conclusion
- Considering challenges in individual pain treatment, pharmacogenomic studies might clarify interindividual differences in analgesic efficacy and tolerability.
- A multidisciplinary team approach may enable timely, evidence-based, cost-effective and most importantly, successful pain management interventions.

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No writing assistance was utilized in the production of this manuscript.

## Author's contributions
L Bach-Rojecky was responsible for conception of the work, literature search, drafting the text and final approval. D Vadunec was responsible for literature search, drafting the text, figures designing and final approval. K Žunić was responsible for literature search, drafting the text, manuscript editing and final approval. J Kurija was responsible for literature search, drafting the text, table designing and final approval. S Šipicki was responsible for literature search, drafting the text, table designing and final approval. R Gregg was responsible for drafting the text, critical revising of the manuscript and final approval. I Mikula was responsible for drafting the text, critical revising of the manuscript and final approval. D Primorac was responsible for conception of the work, drafting the text, critical revising of the manuscript and final approval.
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Papers of special note have been highlighted as: ● of interest; ●● of considerable interest


● Summarizes pharmacological characteristics of nonsteroidal anti-inflammatory drugs with focus on their safety and tolerability profile.


● Provides an overview of the epidemiology, phenotypic characteristics and genetic factors that are associated with musculoskeletal pain conditions.


● Focuses on the pharmacogenetics of opioids and discusses their possible influence on clinical practice.

A personalized approach to pain therapy – Review


● This meta-analysis of randomized trials of NSAIDs provides data about their vascular and gastrointestinal safety profile among different types of patients, particularly those at increased risk of vascular disease.


61. Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies.


- The authors discuss recent research to address common misconceptions regarding the abuse-related risks of opioid analgesics, and highlight strategies to minimize those risks.


- Provides recommendations about safe and effective opioid prescribing for the treatment of chronic pain.


77. Court MH, Freytsis M, Wang X et al. The UDP-glucuronosyltransferase (UGT) 1A polymorphism c.2042C>T is associated with increased human liver acetaminophen glucuronidation, increased UGT1A exon 5a/5b splice variant mRNA ratio, and decreased risk of unintentional acetaminophen-induced acute liver failure. J. Pharmacol. Exp. Ther. 345(2), 297–307 (2013).


- Critically summarizes data on epigenetics and pain, focusing on new approaches to the drug modulation of the pain epigenome.


- Highlights multiple biopsychosocial factors that contribute to interindividual differences in the experience of pain.