Review

The Role of Clinical Pharmacogenetics and Opioid Interactions in Optimizing Treatment in Clinical Practice

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The Role of Clinical Pharmacogenetics and Opioid Interactions in Optimizing Treatment in Clinical Practice

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Abstract

Introduction: Opioids are the most commonly used analgesic drugs for acute and chronic severe pain metabolized in the liver via cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT). **Methods**: A narrative review of the literature was conducted by searching MEDLINE and PubMed databases up to October 2025, using the English language as the only restriction. Relevant studies were identified using the keywords "opioids," "pharmacogenetic," "cytochrome mutations," and "interactions." **Results**: Polymorphisms in the CYP2D6 and CYP3A4 genes can affect the pharmacokinetics, clinical effect, and safety of opioids. Furthermore, enzyme induction and inhibition using concomitant drugs or compounds (herbal or food) are variability factors in drug response that may be predictable. **Conclusion**: This review article provides an overview of the role of pharmacogenetics and opioid interactions as a rationale for multimodal approaches aimed at optimizing treatment in clinical practice, in particular opioids should be tailored to each clinical indication and patients should be stratified to receive the appropriate dose.

Keywords: opioids; pharmacogenetics; polymorphisms; drug-drug interactions

1. Introduction

Opioids are the most commonly used analgesic drugs for acute and chronic severe pain in cancer and non-cancer patients, especially in the elderly suffering from pain-related functional impairment [1,2]. Opioids use exploded in 1995 when the US Food and Drug Administration (FDA) approved oxycodone for the treatment of chronic pain in non-cancer patients. Since then, opioid prescribing in the United States has increased from 143 million prescriptions in 1991 to 219 million in 2011 [3]. Opioids induce their analgesic effect stimulating G protein-coupled receptors, particularly the μ subtype. Receptor binding alters membrane permeability to K^+ and Ca^{2+} ions and inhibits cyclic AMP (cAMP), resulting in an inhibitory action in the central and peripheral nervous system that elicits analgesia [4].

Opioids have a high rate of toxicity due to the narrow therapeutic index [2]. The most frequent adverse effects (AEs) are constipation, nausea, and vomiting. Respiratory depression is the most serious AE, although it occurs at higher doses. Hypotension, vasodilation, bradycardia, and/or QTc

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interval prolongation are the cardiac long-term AEs, while further AEs include fatigue, anxiety and depression, osteoporosis, and endocrinology disorders [5]. Genes encoding enzymes involved in opioid metabolism, as well as cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT), may harbor several polymorphisms that could affect the opioid metabolic phenotype. Therefore, pharmacogenetics may be fundamental to understanding how allelic variations can influence drug response [6].

Drug-drug interactions (DDIs) are potentially responsible for AEs and can also influence the efficacy of opioids by altering the generation of secondary active/inactive metabolites [2]. In particular, pharmacokinetic interactions deserve attention since opioids are eliminated or bioactivated through hepatic metabolism [6]. This review article provides an overview of pharmacogenetics and opioid interactions that may be useful in optimizing treatment in clinical practice.

2. Materials and Methods

This work is a narrative review aiming to summarize and critically discuss the current evidence on the impact of pharmacogenetics and drug–drug interactions on opioid pharmacokinetics and pharmacodynamics. For this purpose, a literature search was conducted in MEDLINE and PubMed databases up to October 2025, using the English language as the only restriction. The Medical Subject Heading (MeSH) and keywords: ("opioids"), AND ("pharmacogenetic") AND ("cytochrome mutations") AND ("interactions"). Additional relevant studies not captured in our initial literature search were identified by examining the reference lists of selected papers. We screened review articles, meta-analyses, and original research articles. As this is a narrative review, the study was not registered in PROSPERO, and no formal quality assessment or meta-analysis was performed, in accordance with the recommendations for non-systematic reviews.

3. Results

3. Opioid Pharmacology at a Glance

The term opioids refer to all compounds that bind to opioid receptors. Morphine and codeine are major alkaloids derived from the opium poppy, semi-synthetic drugs are synthesized from natural opioids (e.g., heroin from morphine, oxycodone from thebaine), while fully synthetic opioids include methadone, fentanyl, and propoxyphene. The action of opioids consists in stimulating the presynaptic and postsynaptic receptors of the endogenous opioid system that can be found in the central and peripheral nervous systems, as well as on the immune system cells. The opioids primarily used to manage chronic pain are morphine, oxycodone, hydromorphone, dextropropoxyphene, fentanyl, pethidine, and codeine. Methadone and buprenorphine are mainly used for addiction management [7].

3.1. Opioid Receptors

Opioid receptors are classified into three different classes: μ (as morphine), δ (as deferens, since first identified in mouse vas deferens), and κ (as ketocyclazocine) [8]. The nociceptin opioid receptor (NOP receptor) is another receptor subtype which is phylogenetically related to the others. Besides nociceptin, the NOP receptor (formerly Opioid Receptor-like receptor-1, ORL-1) can bind orphanin FQ, a neuropeptide that activates an opioid-like G protein-coupled receptor. The NOP-N/OFQ system is important in physiological processes due to its wide distribution in the brain, spinal cord, and peripheral organs [9]. Furthermore, some opioids, such as tramadol and methadone, have additional sites of action based on nonopioid receptors [4].

Opioid receptors are G protein-coupled (GPCRs) receptors [10]. They belong to the class A (rhodopsin) receptor family characterized by an extracellular N-terminal domain, seven transmembranes (7TM) helical domains connected by three extracellular and three intracellular domains, and an intracellular C-terminal tail [11]. The main endogenous analgesic ligands are

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endorphins, enkephalins, and dynorphins [12]. Enkephalins derive from pro-enkephalin and are selective δ ligands, endorphins from pro-opiomelanocortin and bind to the μ receptor, and dynorphins from pro-dynorphins and are highly selective for the μ receptor subtype. All opioid receptors modulate pain by inhibiting voltage-gated Ca^{2+} channels and/or opening K^{+} channels; as a result, neuronal excitability is inhibited [13]. Upon activations of opioid receptors, coordinated phosphorylation of the receptor by specific GPCR kinases occurs. After the interaction of the phosphorylated receptors with β-arrestin 1 and 2, desensitization and internalization may occur [14]. Endogenous and exogenous ligands may produce different effects, including respiratory depression, euphoria, and hormone release. μ and δ agonists are the predominant analgesics, while κ agonists are almost involved in dysphoria. Oxycodone is a selective μ-opioid receptor agonist which, at higher doses, can stimulate κ-opioid receptors [15]. It appears that the antinociceptive effects of oxycodone are mediated by κ-opioid receptors, while morphine mainly interacts with μ-opioid receptor subtypes [16]. Fentanyl is a potent opioid agonist widely used for severe pain that selectively binds μ-receptors while having a very low affinity for δ and κ receptor subtypes [17].

3.2. Metabolism

Most opioids undergo metabolism in the liver by CYP450 enzymes and, to a lesser extent, by UDP-glucuronosyltransferases (UGTs). Opioid metabolism can lead to the conversion of the parent drug to inactive metabolites (e.g., fentanyl) or to the activation of the prodrug to an active metabolite responsible for analgesic properties (e.g., codeine) (Table 1). The most important isoenzymes involved in opioid metabolism are CYP2D6 and CYP3A4 [18]. Age, genetic mutations, and pathophysiological changes, including renal and hepatic impairment, may also influence opioid metabolism [19].

Table 1. Opioids' major metabolites.

	CYP3A4		**CYP2D6**		**UGT2B7**	
	Active	*Inactive*	*Active*	*Inactive*	*Active*	*Inactive*
Codeine	NORC		Morphine		C-6-G	
Morphine					M-6-G	M-3-G
Tramadol		M2	M1, M5			
Fentanyl		Norfentanyl				
Hydromorphone*						H-6-G, H-3-G
Buprenorphine	Norbuprenorphine					

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Oxycodone	Noroxycodone	Oxymorphone
Methadone	EDDP, EMDP	

*Hydromorphone is in turn an active metabolite of hydrocodone and morphine. NORC: Norcodeine; C-6-G: Codeine-6-glucuronide; M-6-G: Morphine-6-glucuronide; M-3-G: Morphine-3-glucuronide; M2: N-desmethyl-tramadol; M1: O-desmethyl-tramadol; M5: O,N-didesmethyl-tramadol; H-6-G: Hydromorphone-6-glucoronide; H-3-G: Hydromorphone-3-glucuronide; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EMDP: 2-ethyl-5-methyl-3,3-diphenylpyrroline.

Tramadol is a synthetic opioid mainly metabolized by CYP2D6 (about 80%) in O-desmethyl-tramadol (M1), the active metabolite with a high affinity for opioid receptors [20]. Other metabolites are derived from CYP3A4, including N-desmethyltramadol (M2), a precursor of another active metabolite, O,N-didesmethyl-tramadol (M5). Active metabolites prolong the half-life and duration of tramadol action [21].

Morphine and codeine are natural compounds derived from poppy seeds, codeine being a methylated derivative of morphine. Codeine is converted to morphine by CYP2D6, norcodeine (NORC) by CYP3A4, and the active metabolite, codeine-6 glucuronide (C-6-G), by UGT2B7 [22]. UGT2B7 is also responsible for transforming morphine into active (morphine-6-glucuronide, M-6-G) and inactive (morphine-3-glucuronide, M-3-G) metabolites.

Oxycodone is the most commonly used opioid analgesic for moderate and severe pain and is pharmacodynamically comparable to morphine. Its major metabolite, noroxycodone, is produced by CYP34A and has only a weak affinity for μ-opioid receptors. CYP2D6 is also involved in oxycodone metabolism [23].

Buprenorphine is extensively metabolized by CYP3A4 to norbuprenorphine, an active metabolite expressing only one-fiftieth of the analgesic potency of buprenorphine [24].

Unlike other opioids, methadone and fentanyl do not produce active metabolites. Fentanyl is mainly converted to the non-toxic and inactive metabolite, norfentanyl, by CYP3A4 [18]. The CYP3A4-derived metabolites of methadone are 2-ethylidene-1,5-dimethyl-3,3-diphenyl-pyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-pyrroline (EMDP) [19].

The morphine analog, hydromorphone, is glucuronidated in the liver by UGT1A3 and UGT2B7 to hydromorphone-6-glucuronide (H-3-G) and hydromorphone-3-glucuronide (H-6-G), without significant involvement of the CYP450 system [4]. Hydromorphone is converted to hydrocodone by CYP2D6 [25] and has also been recognized as a minor metabolite of morphine. Although the metabolic pathway has not yet been described, one hypothesis is that morphine may be converted by morphine dehydrogenase to the intermediate metabolite, morphinone, then transformed into hydromorphone by morphinone reductase (Table 1) [26].

3.3. Efflux Transporters

P-glycoprotein (P-gp) is a member of the super-family of adenosine triphosphate–binding cassette (ABC) transporters capable of binding many different substrates, including opioids [27]. Opioids can influence P-gp activity. P-gp inducers include morphine and oxycodone while buprenorphine and methadone are inhibitors of ABC transporters at the blood-brain barrier (BBB) level [28].

For example, P-gp pump fentanyl out of the central nervous system (CNS) across the blood-brain barrier, and changes in P-gp expression may be responsible for interindividual variability in fentanyl response [29]. Genetic polymorphisms in the *mdr1* gene encoding P-gp were indeed correlated with lower transporter function, resulting in an increased risk of adverse CNS effects of fentanyl [30], such as sedation and respiratory depression [31,32]. P-gp may also be involved in the development of central opioid tolerance. By inhibiting cerebral and intestinal P-gp using an inhibitor

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such as quinidine, studies have shown that healthy human volunteer subjects given oral morphine experienced a clinically relevant increase in plasma concentrations [33]. Methadone is also a substrate of P-gp. *In vivo* studies in rats, P-gp inhibitors caused higher brain concentrations and a more pronounced analgesic effect of methadone [34]. Variants 1236T, 2677T and 3435T of the *mdr1* gene lowered P-gp activity *in vitro*. In addition, individuals carrying the homozygous polymorphic haplotype (i.e., TT-TT-TT at loci rs1045642, rs2032582, and rs1128503) showed an approximately 5-fold probability of requiring a higher dose of methadone. In contrast, individuals heterozygous for these three SNPs were about 3-fold more likely to have a beneficial analgesic effect at a lower methadone dose [35].

4. Adverse Drug Reactions

The use of opioids is often associated with the development of AEs that can limit the effectiveness of the treatment. Constipation is one of the most common gastrointestinal AEs of opioids that varies among patients with a range of 40-95%. Indeed, it is pivotal that patients do prophylactic treatments for maintaining an acceptable bowel peristalsis. Usually, clinicians recommend to drink lot of water and to increase the intake of fibers and physical activity. If these measures are ineffective, stool softeners (such as sorbitol), senna, or laxatives are required. The morphine seems to be the most potent opioids for inducing constipation. Despite, evidences on constipation and the route of administration are limited, transdermal fentanyl could be a valid alternative in patients suffering from severe constipation. Nausea and vomiting are the other two most common gastrointestinal AEs. Nausea, that occurs in about 25% of patients, is often transient and pharmacological treatment such as antipsychotics, metoclopramide or serotonin antagonists are used especially in cases of vomiting. The most serious AE, fortunately uncommon, is respiratory depression because of the potentially fatal outcome, usually related to an overdose of opioids. The pharmacological treatment for respiratory depression is naloxone [36,37]. In some cases, the long-term use of opioids is associated with AEs such as tolerance and hyperalgesia. The increase in daily doses may overcome the tolerance effect of prolonged administration issue, but it may augment the risk of dependence and addiction [38]. Research efforts have focused on the development of new categories of opioids (e.g., tapentadol) to reduce the risk of addiction while maintaining the analgesic efficacy [39,40]. Moreover, the progressive increase of opioids dosage can cause hyperalgesia (opioid-induced hyperalgesia, OHI), a nociceptive sensitization, which often requires dose tapering or treatment discontinuation [38]. Therefore, the clinical management of opioids may be difficult based on the on identify patients who potentially could develop opioid use disorders [41].

5. Pharmacogenetics

5.1. CYP2D6

CYP2D6 has involved in the metabolism of most opioids, and the CYP2D6 gene is highly polymorphic, with more than 100 SNPs associated with significant variability with ethnicity and race [42]. Moreover, more than one CYP2D6 gene copy can be present on the same chromosome, resulting in an ultra-rapid metabolizer phenotype as depicted below [43,44]. The CYP2D6*1, *2, and *35 polymorphisms do not have any effect on enzyme activity, while others may result in alleles being missing (CYP2D6*3, *4, and *6) or deficient (CYP2D6*9, *10, *17, *29, and *41) in CYP2D6 activity. The CYP2D6*5 polymorphism causes gene deletion, resulting in an allele without function. There are four different phenotypes identified based on the allelic combination: poor (PM), intermediate (IM), extensive (EM), and ultra-rapid (UM) metabolizers [45,46]. CYP2D6 PMs are prevalent in European and Jewish subjects instead, IMs in African and African-American populations, and EMs in East Asians and South-Central Asians. CYP2D6 UMs are more frequent in Jewish and Middle Eastern subjects than in other ethnic groups [45]. Reduced or absent CYP2D6 activity may result in little or no conversion of opioid prodrugs to their active metabolites, which may require dose adjustment to

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maintain therapeutic effect. Conversely, UMs produce more active metabolites with a higher risk of developing adverse events (Table 2) [47,48].

Table 2. Polymorphisms in genes coding for enzymes responsible for opioids metabolism.

Gene	Polymorphism	Drug
CYP2D6	*1, *2, *35	Tramadol
	*3, *4, *6	Morphine, codeine
	*9, *10, *17, *29, *41	Hydromorphone
CYP3A4	*1b, *2, *3, *22	Morphine, codeine, oxycodone, buprenorphine, fentanyl
CYP3A5	*1b, *2, *3, *22	Methadone, fentanyl, alfentanil
CYP2B6	*6	Methadone
ABCB1	1236C>T, 3435C>T and 2677G>T/A	Morphine, fentanyl
UGT2BT	802T>C and 900G>A	Morphine

5.2. CYP3A4/5

Most of the genetic polymorphisms found in the CYP3A4 gene result in a reduced enzyme activity, with CYP3A4*1b, *2, *3, and *22 being the most relevant in terms of phenotypic change [49]. For example, several lines of evidence demonstrated that heterozygous patients carrying the CYP3A4*22 allele had a 47% reduction in fentanyl clearance [50]. CYP3A5 metabolizes many of the same drugs as CYP3A4. High interethnic variability in CYP3A5 expression has been observed due in part to 4 different possible alleles for this gene *1, *3, *6 and *7 [51,52]. The *3, *6 and *7 alleles are responsible for the synthesis of a nonfunctional truncated protein while the *1 allele is associated with normal enzyme activity [53,54]. In 70% of Caucasians, the *3 variant is expressed resulting in null enzyme activity [55]. In Takashina et. *al*'s study of cancer patients who were shifted to transdermal administration of fentanyl, the CYP3A5*3 variant appears to be associated with increased plasma concentration of fentanyl and a higher incidence of CNS AEs than the *1 variant (Table 2) [32].

5.3. CYP2B6

CYP2B6 exhibits various polymorphisms and is mainly involved in methadone metabolism. The 516G>T and 785A>G polymorphisms in the CYP2B6*6 allele have been associated with reduced enzyme activity, and individuals homozygous for these variants may require lower doses than heterozygous or non-carriers subjects [56,57]. Studies on the impact of CYP2B6 genotype on pharmacokinetics have provided conflicting results (Table 2) [58,59].

5.4. UGT2B7

Another enzyme involved in opioid metabolism is UGT2B7. This enzymatic isoform can convert morphine into morphine-3-glucuronide (M-3-G) and M-6-G, the latter being the active metabolite responsible for the analgesic activity. The most studied polymorphisms are UGT2B7 802 T>C and 900G>A. Patients with the UGT2B7 802CC genotype appear to have an increased metabolism of morphine and a higher M-6-G/M-3-G ratio than those with the CT or TT genotypes, thus requiring a

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lower morphine dose. Furthermore, one study found that individuals carrying UGT2B7 802T had extensive analgesia compared with UGT2B7 802C homozygotes, most likely due to reduced glucuronidation activity; in contrast, other studies have found no correlation between the 802T variant and treatment response [60,61].

Moreover, while several lines of evidence suggest that the UGT2B7-900G>A variant is associated with higher enzymatic activity than wild-type UGT2B7-900G, other studies have shown no impact of this polymorphism on morphine pharmacokinetics [60–62].

Despite these findings, no statistically significant differences in the plasma concentration of morphine and its metabolites were observed between the different genotypes; however, multivariate stepwise linear regression models could identify a significant association between the CC genotype and morphine dose (Table 2) [63,64].

5.5. P-gp

Opioid pharmacokinetics can also be influenced by the activity of membrane transporters, such as P-gp (or ABCB1), which actively transports drugs out of CNS. Among the 50 SNPs identified, those of greatest interest are c.1236C>T, c.2677G>T/A, and c.3435C>T, located in exons 12, 21 and 26, respectively. These polymorphisms are more frequent in Caucasian and Asian populations than in Africans [60–65]. A study in healthy individuals carrying the c.3435TT genotype a reduced expression of the transporter at the duodenal level [66], which could potentially also influence P-gp expression at the blood-brain barrier. This correlates with the elevated concentration of morphine at the cerebrospinal fluid level observed after intravenous infusion in c.3435TT subjects. Consequently, patients harbouring this genetic variant have a higher risk of opioid-related AEs requiring dose reduction [67]. Rhodin *et al.* conducted a study in patients with chronic back pain treated with remifentanil and found an increased frequency of AEs such as sweating, sedation, tension, and stress in homozygous c.3435T/T carriers compared with heterozygotes c.3435C/T and homozygotes c.3435C/C [68]. Moreover, a study investigated the correlation between c.3435C/T SNP in the *mdr1* gene and opioid consumption for controlling post-operative pain in 152 patients undergoing a nephrectomy. The involvement of *mdr1* polymorphisms in opioid consumption provides evidence of their role in guiding acute pain therapy in post-operative patients [69]. Regarding the c.1236C>T polymorphism, Fujita et al. observed a higher frequency of fatigue after morphine intake in CC individuals compared with TT ones, and that finding was also confirmed by higher morphine clearance in c.1236TT individuals [70]. Another study demonstrated that the c.2677G>T/A and the c.1236C>T SNPs in the *mdr1* gene were associated with a lower incidence of CNS Aes, such as drowsiness, confusion, and hallucinations, after morphine administration (Table 2) [71].

5.6. OPRs

The *oprm1* gene encodes for the μ-opioid receptor. The c.118A>G polymorphism causes an exchange of amino acids in the extracellular domain of the receptor, with a reduced opioid binding affinity. The 118G allele is more frequent in Asian populations (40%-50%), moderate in European populations (15%-30%), and infrequent in African populations [56]. Clinical studies in postoperative pain treated with morphine or fentanyl showed that individuals carrying the polymorphic G allele required higher doses than wild-type AA homozygotes [72]. Another study showed that OPRM1 c.118A/A homozygotes had higher pain relief after opioid treatment than G/G homozygotes, whereas no difference was observed between A/G heterozygotes and G/G homozygotes. These findings suggest that individuals carrying at least one G allele may respond less to morphine than A/A homozygotes [60,73]. The 118G allele also appears to be associated with several phenotypes, including opioid dependence, while other drugs of abuse, i.e., alcoholism, may blunt the hypothalamus pituitary adrenal (HPA) axis response to stress, reducing the efficacy of opioids in clinics. Furthermore, some studies found a positive effect of the 118G allele on the response to treatment with naltrexone, an opioid antagonist [56,74,75]. KOR is an opioid receptor encoded by the *oprk1* gene. KOR plays a role in pain perception and mediates the hypo-locomotor, analgesic, and

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adverse reactions of synthetic opioids. Variations in this gene have also been associated with alcohol dependence and opioid addiction. Genetic variability of OPRK1 has been shown to modulate methadone efficacy, and polymorphisms rs3802279 CC, rs3802281 TT, and rs963549 CC appear to be associated with lower methadone maintenance dose per day. The haplotypes rs10958350-rs7016778-rs12675595 are instead associated with withdrawal symptoms [76,77].

5.7. COMT

The *comt* gene encodes for the enzyme catechol -O- methyltransferase (COMT) that regulates μ-receptor (MOR) density in the brain by affecting pain perception [78–80]. In subjects with genotype c.472G>A, a lower concentration of met-enkephalin and higher expression of MOR was found [80]. In agreement with those findings, those individuals seemed requiring a lower dose of opioids for neoplastic and postoperative pain control [81–86]. Several SNPs in the *comt* gene, including c.1-98A>G (rs62699), 186C>T (rs4633), c.408C>G (rs4818), and c.472G>A (rs4680), are associated with a different response to opioids. In the study by Lotta *et al*. three genotypes associated with the c.472G>A variant corresponded to different levels of COMT enzyme activity. Individuals with homozygous AA genotype have higher pain sensitivity due to lower enzyme activity, in contrast, GA heterozygotes have intermediate activity and GG homozygotes have high enzyme activity and thus lower pain sensitivity [87]. This was also confirmed by Henker and coworkers in a study of opioid treatment of postoperative pain, in which GG homozygous and AG heterozygous patients showed lower pain scores than AA homozygous patients [88]. In contrast, another study related to morphine intake for the management of neoplastic pain found the use of a higher dose of opioid in individuals with the GG genotype compared with those with the AG and AA genotypes. This could be due to suppression of enkephalin production secondary to altered COMT enzyme activity resulting in upregulation of opioid receptors in homozygous AA patients in contrast to what was observed in G/G patients [89].

5.8. OCT

OCT1 is an influx transporter coded by the *slc22a1* gene especially expressed in the liver that recognizes morphine and tramadol as substrates. The *slc22a1* gene is highly polymorphic; the variants OCT1*2, *3, *4, *5, and *6, are associated with loss of OCT1 activity resulting in reduced hepatic uptake, increased plasma concentration of morphine and tramadol, and thus altered treatment efficacy. Children homozygous for variants associated with loss of function of OCT1 have significantly lower opioid clearance [60,90–92].

5.9. ARRB2-Dcc

A recent prospective, multicenter, open-label study investigating the correlation between polymorphisms in the *β2-arrestin* gene (ARRB2) and clinical response to methadone for pain relief in advanced cancer was carried out [93]. The results suggested that polymorphisms in ARRB2 influenced the response to methadone and pain severity. Furthermore, a translational study using mice focusing on the role of the *mpdz* gene showed that genotypic variants of this gene are associated with altered opioid tolerance and opioid-induced hyperalgesia [94]. Finally, heterozygous variants of the Netrin 1 Receptor Dcc gene are associated with a decreased tendency in developing opioid-induced hyperalgesia after chronic administration of morphine [95]. These studies highlighted the pivotal role of pharmacogenetics in opioids for determining the accurate dose to treat pain, especially in the era of personalized medicine [96]. For the above reasons more randomized controlled trials are critically needed to elucidate the potential role of these biomarkers to translate and enhance their use in clinical practice.

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6. Opioids Interactions

6.1. Drug Interactions

Co-administration of drugs that induce or inhibit enzymes involved in opioid metabolism can generate interactions with clinical consequences. Induction of CYP450 isoenzymes that metabolize opioid prodrugs can lead to inadequate analgesia, as for oxycodone [97,98]. Conversely, inhibition of CYP3A4 and CYP2D6 can enhance the risk of opioid-induced toxicity when the enzymes catalyze the conversion of the active parent drug to inactive metabolites, as observed with methadone [99] and fentanyl [97].

Antidepressant drugs, including fluoxetine, paroxetine [100], and bupropion [101], have been found to increase plasma concentrations of tramadol through the inhibition of CYP2D6. This effect may decrease the analgesic efficacy of tramadol due to a reduced formation of the active metabolite O-desmethyl-tramadol (M1) [102] while enhancing the risk of serotonergic syndrome [103]. This is possible because the active metabolite O-desmethyl-tramadol (M1) is responsible for the complementary mechanisms that increase the analgesic effect of tramadol, while the levorotatory (-) enantiomer inhibits norepinephrine reuptake, affecting the adrenergic system, the dextrorotatory (+) enantiomer binds to opioid receptors and inhibits cellular reuptake of serotonin, increasing the risk of serotonergic syndrome [104]. In addition, the CYP2D6-mediated transformation of codeine to morphine may also be impaired by the concomitant use of selective serotonin reuptake inhibitors (SSRIs) resulting in a loss of analgesic efficacy [105,106], despite atypical opioids (e.g., tramadol and tapentadol) acts also through the inhibition of serotoninergic and noradrenergic descendent pathways that control nociception at the spinal level. The identical mechanism may explain the reduced analgesic efficacy observed in patients giving tramadol [97] or codeine [99] with the H2-receptor antagonist cimetidine. The antiarrhythmic drugs quinidine and amiodarone can also interact with opioids. Quinidine [107] and the active metabolite of amiodarone, N-derivative of monodesethyl-amiodarone [108], have been found to reduce the CYP2D6-mediated activation of codeine and tramadol, respectively [100]. Ondansetron, an antiemetic used to control tramadol-induced nausea and vomiting, may reduce the formation of the active metabolite of tramadol (M1) by a metabolic competition on CYP2D6 [103]. Therefore, it is important to evaluate whether patients could receive an adequate analgesic response and adjust the tramadol dose, accordingly. In addition, concurrent treatment should be stopped if serotonin syndrome occurs. Antiretroviral ritonavir is another potent CYP2D6 inhibitor that impairs the efficacy of codeine [101].

Unlike opioid prodrugs, oxycodone-induced analgesia is primarily due to the parent drug. Consequently, induction of CYP3A-mediated metabolism m[109,110ay lead to treatment failure, while enhanced opioid effects are expected when combining oxycodone with potent CYP3A inhibitors [97]. For example, the induction of CYP2D6 and CYP3A4 by rifampicin decreases the plasma concentrations of oxycodone after oral or intravenous administration [109,110]. Conversely, inhibition of hepatic and/or intestinal CYP3A activity by azole derivatives leads to increased exposure to oral oxycodone in healthy subjects enhancing its analgesic effects and increasing the risk of serious adverse reactions [85,86]. Methadone and fentanyl are potent analgesic opioids mainly metabolized by CYP3A4 [97,99]. Enzyme inhibition by antiretroviral and antimicrobial drugs or antibiotics leads to increased blood levels of fentanyl with a risk of respiratory depression (Table 3) [97]. Similar clinical consequences have been observed in patients taking methadone in combination with ritonavir, ketoconazole or itraconazole, ciprofloxacin, clarithromycin, and the Ca2+ antagonist, diltiazem [99].

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Table 3. Opioid-drug interactions.

Drug	**CYP3A4**		**CYP2D6**		**Clinical consequences**
	Inducer	*Inhibitor*	*Inducer*	*Inhibitor*	
Tramadol				Antidepressants (fluoxetine, paroxetine, bupropion)	Increased plasma concentration of tramadol and reduced analgesia
Codeine				Antidepressants (fluoxetine, paroxetine, bupropion), Antihistamines (cimetidine) Antiarrhythmic drugs (amiodarone, quinidine) Antiemetics (ondansetron) Antiretrovirals (ritonavir)	Increased plasma concentration of tramadol and reduced analgesia
Morphine				Antiarrhythmic drugs (quinidine, amiodarone)	Increased plasma level of morphine reduced analgesia
Oxycodone	Antibiotic (rifampicin)		Antibiotic (rifampicin)		Reduced plasma concentration of oxycodone and reduced analgesia
		Antimicrobial (voriconazole, itraconazole, ketoconazole)			Increased plasma concentration of oxycodone

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			and risk of serious adverse drug reaction
Fentanyl		Antiretrovirals (ritonavir, nelfinavir) Antimicrobials (voriconazolo, ketoconazole, itraconazole) Antibiotics (ciprofloxacin, troleandomycin , clarithromycin)	Increased plasma levels of fentanyl and risk of respiratory depression
Methadone	Antibiotics (rifampicin), anticonvulsants (carbamazepine) , antiepileptics (phenytoin), barbiturates (pentobarbital)		Decreased of plasma level of methadone and increased risk of opioid withdrawal
		Antiretroviral drugs (ritonavir, nelfinavir), antimicrobial (voriconazolo, ketoconazole, itraconazole), antibiotics (ciprofloxacin, troleandomycin clarithromycin) , Ca2+ antagonist (diltiazem)	Increased plasma level of methadone and risk of sedation, confusion, and respiratory depression and/or QT prolongation or torsade de pointes

In addition to respiratory depression, concomitant use of drugs that inhibit methadone metabolism may increase the incidence of QTc interval prolongation and torsades de pointes [111,112]. Conversely, induction of CYP3A4 activity by antibiotics, anticonvulsant/antiepileptic

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drugs, and barbiturates can lead to withdrawal syndrome symptoms [113]. The UGT is the other enzyme that metabolized opioids, especially morphine, as already mentioned. Nowadays, few evidence are available about drugs that can influence (inhibit or induce) the UGT activity. Some *in vivo* studies showed an alteration of morphine's pharmacokinetic when co-administered with other drugs, like a decrease in active metabolites (M3G and M6G), but how much is the contribution of UGT on this effect remained unknown [114].

6.2. Herb-Food Interactions

CYP3A4 and CYP2D6 are the two main isoenzymes of the CYP450 family involved in opioid metabolism [18], which can be inhibited or induced by some herbs and food. The best-known interactions are those with grapefruit juice (a CYP3A4 inhibitor) and Saint John's wort (a CYP3A4 inducer). Strong/moderate CYP3A4 inhibitors also include Sevilla orange, lime, cranberry, and goldenseal, while ginseng and licorice are CYP3A4 inducers. Ginkgo and piperine/pepper extracts are the exceptions due to their dual activity on CYP3A4. The likelihood of interaction between CYP2D6 substrates and herbs or foods is lower than with CYP3A4 substrates. Goldenseal and black seed are strong inhibitors of CYP2D6, while ginseng and kudzu are mild/moderate inhibitors; on the other hand, no inducers of CYP2D6 with clinically relevant activity were identified [115]. Furthermore, it is also important to point out that the likelihood of causing a significant interaction from herbs or food can depend on the strength of the active ingredient in them and the amount taken.

7. Conclusions and Future Directions

Opioids are the most potent analgesic drug class commonly used in clinical practice for pain management. They are mainly metabolized in the liver by CYP450 and UGTs enzymes and CYP2D6 and CYP3A4 isoenzymes. In this regard, the metabolism is responsible for producing inactivate metabolites or in improving their activities. For the above reasons, the induction or the inhibition of metabolism through the use of concomitant other drug classes or compounds which modulate the activity of CYP2D6 and CYP3A4 may produce drug-drug interactions which could be responsible for inadequate analgesia or toxicities. Thus, the concurrent use of inducers or inhibitors of these isoenzymes should be deeply investigated.

The presence of polymorphisms in CYP2D6 and CYP3A4 genes strictly related to ethnicity and race may influence opioid pharmacokinetics and great efforts are needed to personalize opioid treatments [6]. This appears to be a challenging goal in clinical practice due to the limited availability of clinical data regarding the correlation between opioid pharmacogenetics and clinical outcomes. Currently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend only CYP2D6 genotyping as a tool to identify the subset of patients who could benefit from codeine, tramadol, and hydrocodone treatment optimization [48]. Therefore, further evidence on the role of pharmacogenetics in the clinical management of opioids are urgently needed to translate this information into the real-life setting. Starting from the significant impact of CYP2D6 polymorphisms on opioid pharmacology and adoption of CYP2D6-guided prescriptions in which a body of literature has proved, some promising biomarkers are under investigation. For example, promising candidate biomarkers without therapeutic recommendations are CYP2D6 for oxycodone and methadone, and OPRM1 or COMT for opioids.

In closing remarks, the role of pharmacogenetics in pain relief has emerged in the last decade as pivotal for achieving multimodal approaches and tailored therapies for patient management. In this regard, dissecting biology through genetic fingerprinting would open a new avenue for pain treatment in terms of more accurate dosing and schedule to prevent treatment-related toxicities and maximize the effect in different patients and settings. The landscape of pain management is very wide and may vary from acute to chronic severe pain including all cancer, musculoskeletal, post-surgical, trauma, and dental pain. Thus, their use will grow up soon. For the above, there has been an emerging recognition that opioids should be tailored to each clinical indication and patients should be stratified

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to receive the appropriate dose. A more deepened use and combination of PGx and DDI analysis would definitely benefit for the management of patients with mild to severe pain.

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