

Pharmacogenomics of buprenorphine - a narrative review

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ABSTRACT

Buprenorphine, a semi-synthetic opioid, is used to treat Opioid Use Disorder (OUD) and as an analgesic. Buprenorphine's benefits over other opioids include longer duration of action, lower abuse potential, and a ceiling effect to serious adverse effects such as respiratory depression. This is a literature review of gene variants affecting the pharmacokinetics and pharmacodynamics of buprenorphine from databases, such as PubMed. Genetic polymorphisms related to metabolism and receptor binding of buprenorphine can alter the pharmacokinetics and response to buprenorphine. Specifically, genetic variants in *CYP3A4*, *UGT2B7*, *OPRM1*, *PDYN*, and *SLC6A3* may affect metabolism and clinical response to buprenorphine. There is strong evidence linking polymorphism in Cytochrome P450 3A4 (*CYP3A4*) and UDP-Glucuronosyltransferase-2B7 (*UGT2B7*), enzymes involved in buprenorphine metabolism, with dosing requirements, treatment of OUD, and pain relief. Response to buprenorphine, an effective treatment for opioid use disorder and pain management, differs significantly based on several human genetic variations. However, there is currently insufficient evidence for the clinical significance of individualized treatment of buprenorphine based on genetic variants. Therefore, it is crucial that future research should prioritize evaluating the feasibility and clinical significance of individualized risk predictions and personalized dosing of buprenorphine.

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1. Introduction

Buprenorphine is a semi-synthetic, high-affinity partial opioid receptor agonist [1–3]. Buprenorphine was developed in the 1970s for use as an analgesic, but further research revealed its potential for the treatment of Opioid Use Disorder (OUD) [2]. It has also been shown to aid in the reduction of respiratory depression caused by fentanyl exposure [3–5]. Buprenorphine originates from thebaine, an alkaloid compound from the poppy flower, and its unique structure, consisting of multiple chiral centers, a morphine-like skeleton, and a unique cyclopropylmethyl group, contributes to the effects it produces at a molecular level [5,6]. Recent studies affirm its effectiveness as a long-term treatment for OUD; in fact, a recent Cochrane meta-analysis of 31 clinical trials found that high-dose buprenorphine (>16 mg/day) reduced opioid use significantly compared to placebo. Buprenorphine is also one of the only three treatments for OUD recommended by the World Health Organization (WHO) and approved by the United States Food and Drug Administration (FDA) [1].

Buprenorphine is an effective treatment for OUD as it reduces the risk of overdose by blocking craving and withdrawal symptoms, especially in the long term, due to its partial agonism at the mu-opioid receptor, its high mu-opioid

receptor affinity, and activity as a kappa receptor antagonist [1,7]. This increased affinity allows buprenorphine to outcompete other substrates for the same receptors and remain occupied for more extended periods, resulting in lower doses producing typical opioid effects and higher doses prolonging opioid agonist effects [7]. Buprenorphine is a kappa-opioid receptor antagonist with high affinity and a weak antagonist at the delta-opioid receptor, reducing the risk of opioid withdrawal and psychomimetic or dysphoric effects [6,8].

The drug possesses a favorable therapeutic index, a slower onset of tolerance than full mu-opioid receptor agonists, an extended half-life, and reduced risk of respiratory depression – a unique effect profile not commonly found in other opiates [1,9]. A serum concentration of 1–4 ng/ml buprenorphine is needed to control opioid withdrawal symptoms, and maximal efficacy for opioid abstinence is typically reached at concentrations of 2–3 ng/ml [10]. In comparison to other opioids, such as morphine, buprenorphine is exceptionally long acting with a receptor fixation half-life of 40 minutes, which can be attributed to the drug's longer half-life in the brain than its receptor. Thus, buprenorphine can be administered fewer times throughout the day, making it a favorable treatment of OUD in a clinical setting [1,3].

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Article highlights

- Buprenorphine is a partial agonist with a high affinity at the mu-opioid receptor and an antagonist with a high affinity at the kappa receptor.
- *OPRM1* gene variant, A118G, has a variable response and efficacy for buprenorphine patients. Due to the impairment of N40D MOP receptors, buprenorphine signaling and efficacy vary.
- Variants in *OPRM1*, *UGT2B7*, *CYP3A4*, and *CYP3A5* have also shown promise in relation to buprenorphine pharmacokinetics and pharmacodynamics.
- The major enzymes involved in the metabolism of buprenorphine and the variability in buprenorphine pharmacokinetics are *CYP3A4*, *CYP3A5*, and *UGT2B7*:
- Varied phenotypes of *CYP3A4* genetic variants can affect the metabolism rate. These phenotypes are categorized as poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultra-rapid metabolizers, correlating with the succeeding metabolic rate.
- The effect of *UGT2B7* and *CYP3A5* genetic variants on the metabolism of buprenorphine needs to be studied further.
- *CYP2C8*, *CYP2C9*, and *UGT1A1* contribute to the metabolism of buprenorphine to a lesser extent; limited genotype information is available.
- Currently, there is insufficient evidence to support the use of genetic variations in making clinical decisions about buprenorphine use and personalized dosing. Further research is needed to identify novel genetic variants and improve the understanding of buprenorphine's metabolism and effects for individualized treatment.

During medically supervised opioid withdrawal, buprenorphine is administered when patients experience mild withdrawal symptoms, which are relieved once it has been initiated. To achieve this relief, daily dosages via sublingual administration can range from 8–12 mg in the first 1 to 2 days and are then lowered by 2–4 mg each subsequent day until the drug is discontinued. Buprenorphine for OUD treatment can be administered through various oral formulations, such as sublingual tablets and films alone or combined with naloxone, an opioid antagonist, to reduce the risk of inappropriate use. Buprenorphine can also be given as an implant or extended-release subcutaneous injections [5,11]. These properties of buprenorphine result in it being widely considered a safe, effective option for the treatment of OUD [1].

Although buprenorphine is widely used to treat OUD, its effects can significantly vary based on the individual patient [12]. Therefore, identifying and understanding genetic and non-genetic factors that influence the effectiveness of buprenorphine can allow for personalized treatment to improve clinical outcomes. The purpose of this review article is to provide a summary of the literature regarding the pharmacogenomics of buprenorphine.

2. Review of pharmacogenomics of buprenorphine

PubMed and Google Scholar were used to search for articles. MeSH terms such as buprenorphine, pharmacogenomics, pharmacodynamics, pharmacokinetics, gene variants, SNP, genetic polymorphism, and other relevant key terms were used to build a search. Studies that genotyped patients on buprenorphine with data such as drug concentration, efficacy, adverse effects, antinociceptive effect, drug consumption, and dose were selected. Citations were added to the citation manager Mendeley. The pharmacogenetics of buprenorphine and how it affects its pharmacokinetics and pharmacodynamics are reviewed below.

2.1. Pharmacodynamics

The pharmacodynamic properties of buprenorphine are a direct result of its distinct structure, receptor binding, and receptor signaling [5]. The primary metabolite norbuprenorphine has been known to interact with four types of receptors: mu-opioid, kappa-opioid, delta-opioid, and opioid-receptor-like 1 (*ORL1*) [5,6]. However, the effect it produces upon interaction with each of these receptors differs significantly.

Buprenorphine is a partial agonist that partially activates the mu-opioid receptor, producing effects such as euphoria, analgesia, and respiratory depression [2]. Its partial agonism at the mu-opioid receptor allows the drug to be a strong analgesic [2,6]. In conjunction with naloxone, a competitive opioid

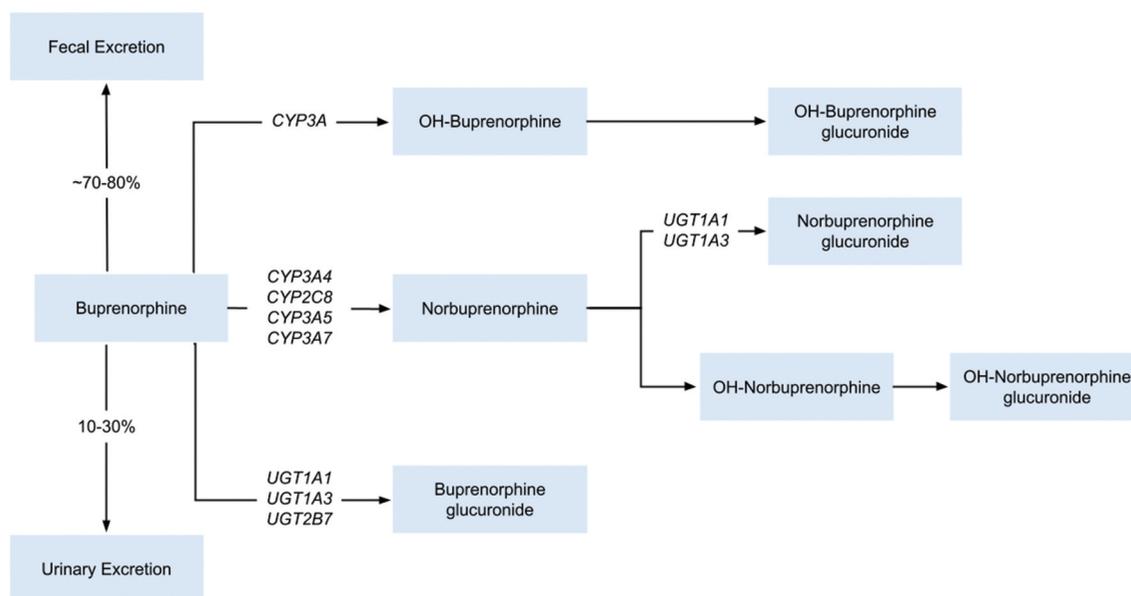


Figure 1. Buprenorphine Metabolism.

receptor antagonist, buprenorphine is commonly used to treat OUD in the United States because its higher affinity and strong binding capacity at the mu-opioid receptor results in a protective effect against overdose with full opioid agonists, including heroin and fentanyl, which in recent years have caused the opioid crisis and thousands of deaths in the United States [13].

Buprenorphine also interacts with the kappa-opioid receptor as an antagonist, and the delta-opioid receptor as a weak antagonist [13,14]. The presence of inverse agonist activity at the kappa-opioid receptor has been hypothesized to explain the anti-hyperalgesic activity as well as the reduced sedation and dysphoria associated with buprenorphine due to the upregulation of dynorphin. Buprenorphine's ability to reduce depression and suicidal ideation likely results from kappa-opioid receptor antagonism, which has been found to contribute to antidepressant activity [14]. On the other hand, buprenorphine's property as a delta-opioid receptor antagonist reduces the risk of severe adverse effects that often occur with other opiates, such as constipation, respiratory depression, anxiety, and addiction [5].

An additional receptor that buprenorphine has been shown to interact with is *ORL1*. Unlike the mu-, kappa-, and delta-opioid receptors, the *ORL1* receptor represents the first of a non-opioid class of opioid receptors categorized as opioid receptor-like [15]. Buprenorphine activation of the *ORL1*-receptor leads to a loss of its antinociceptive effects by compromising its mu opioid receptor-mediated actions [16]. Furthermore, Lee et al. found that, when used in conjunction with each other for treatment of OUD, methadone, and buprenorphine exert adenylate cyclase activity changes that are initially different yet eventually convergent within cells that express both the mu-opioid receptor and ORL1-receptor [15].

2.2. Genetic factors affecting pharmacodynamics

Previous studies on the genetic variants affecting the pharmacodynamics of buprenorphine have focused on dose requirements or response in patients for the treatment of OUDs. In this section, different study outcomes regarding the genetic polymorphisms affecting the pharmacodynamics of buprenorphine will be discussed.

2.2.1. Opioid receptor mu 1 Gene (*OPRM1*)

The *OPRM1* gene that encodes the mu-opioid receptor has been proven to possess genetic variations that contribute to variable response and efficacy in buprenorphine-treated patients [17]. Among gene variants identified, the N40D (A118G) variant is the most common, with a frequency of 10% to 50% in the population [18]. This variant arises from an SNP at nucleotide 118, resulting in an asparagine to aspartic acid amino acid exchange in the N-glycosylation site of the mu-opioid receptor [19]. A drug interaction study conducted by Knapman et al. revealed that N40D mu-opioid receptors are impaired when buprenorphine signaling occurs to effectors, resulting in a reduction of both the efficacy of buprenorphine by over 50% for AC inhibition and ERK1/2 phosphorylation and its potency by threefold for potassium channel efflux [18]. Furthermore, the A6V variant of the mu-opioid receptor, an

SNP in the receptor's N-terminal domain, decreases signaling to AC inhibition and ERK1/2 phosphorylation for many clinically significant opioids, including buprenorphine [20].

2.2.2. Prodynorphin (*PDYN*)

The *PDYN* gene is suspected to affect patient responses to buprenorphine/naloxone treatment for cocaine dependence. As evaluated by Nielsen et al., among those with the rs1022563 A-allele or rs1997794 A-allele carrier group, patients receiving the buprenorphine/naloxone treatment tested positive for cocaine fewer times than those taking the placebo. On the other hand, no difference was found in the rs1022563 GG or rs1997794 GG groups, indicating that *PDYN* variants can be used in identifying patients that may have greater potential for the buprenorphine/naloxone treatments [21].

2.2.3. Solute carrier family 6 member 3 (*SLC6A3*)

The *SLC6A3* gene codes for the human dopamine transporter (*DAT1*). This transporter contributes to the pathophysiology of the central and peripheral nervous system and, consequently, the effectiveness of buprenorphine [22]. Gerra et al. found that individuals unresponsive to buprenorphine often possess a higher frequency of allele 10, while those that are responsive possess a higher frequency of allele 6, 7, and 11. Polymorphisms in the genes that code for *DAT1* are thought to impact the effectiveness of buprenorphine due to associations of transporter concentration with overall sensitivity to kappa receptor stimuli, thereby influencing a dopamine-mediated component in buprenorphine function [23].

2.3. Pharmacokinetics of buprenorphine

2.3.1. Absorption

Buprenorphine is a lipophilic drug with pKa of 8.5 and 10.0 for the ammonium and phenol groups, respectively. Buprenorphine can be administered through intramuscular or slow intravenous injection at an analgesic dose range of 0.3–0.6 mg every 6–8 hours, sublingually, transdermally as skin patches, and by buccal and oral mucosal route (Table 1) [13,31]. The mean time to reach maximum plasma concentrations after sublingual administration ranges from 40 minutes to 3.5 hours (t_{max}) for single-dose administrations [3]. Buprenorphine has a low oral bioavailability due to the extensive first-pass of its dual-phase metabolic process. However, when given sublingually, bioavailability ranges from 30–50% [26,27]. When buprenorphine is administered orally or sublingually, there is a variable susceptibility to drug interactions due to significant inter-individual differences in the metabolism of buprenorphine through N-dealkylation to norbuprenorphine by cytochrome P450 family members (CYP3A4 and CYP3A5) in the gut and liver [3,31].

2.3.2. Distribution

Buprenorphine has a volume of distribution of 188–355 L, indicating extensive distribution within the body [3]. Buprenorphine is highly (96%) bound to plasma proteins such as albumin and α - and β -globulin. Buprenorphine has a rapid onset after intravenous administration, reaching a peak plasma concentration between 5 and 15 minutes [26]. Buprenorphine can cross the blood-brain barrier, as well as

Table 1. Pharmacokinetic parameters of various formulations of buprenorphine.

Formulation	Bioavailability	Time to peak concentration (hours)	Half-life (hours)
Intravenous	100% [24]	0.083–0.25 [26]	21.8–28.0 [29]
Buccal	46–51% [25]	2.5–3.0 [25]	27.6 [30]
Sublingual	30–50% [26,27]	0.66–3.5 [3]	25.0–70.0 [6]
Transdermal	15% [28]	17.0 [28]	26.0 [28]

norbuprenorphine, one of its metabolites, depending on the dose and expression of efflux transporters. After regular maintenance doses, only buprenorphine was found in the brain postmortem. However, following a buprenorphine overdose, both buprenorphine and norbuprenorphine were found in the brain postmortem. Brown et al. observed that norbuprenorphine is found in low concentrations in the brain, indicating that norbuprenorphine does not impact buprenorphine's clinical effects [32]. Following an overdose, the presence of buprenorphine and norbuprenorphine in the brain postmortem is speculated to be effluxed by a transport system, such as P-glycoproteins [3,32]. Thus, it is likely that at the time of death that norbuprenorphine is redistributed to the brain due to the loss of P-glycoproteins.

2.3.3. Metabolism & elimination

Buprenorphine has a half-life of around 20 to 70 hours via routes of administration that prolong its half-life, such as sublingual and transdermal. Buprenorphine is primarily eliminated by hepatic metabolism via phase 1 and phase 2 pathways. The main metabolic pathway is the hepatic N-dealkylation of buprenorphine to norbuprenorphine in the liver through *CYP3A4* (65%) [3,31,33–35]. The drug is also metabolized by other *CYP* enzymes, such as *CYP2C8* and *CYP2C9* (30%), and UDP-glucuronosyltransferase (*UGT*) isoforms, which metabolize buprenorphine and the norbuprenorphine formed from the phase 1 pathway [17,31,35] (Figure 1). Buprenorphine can also undergo direct glucuronidation via phase 2 metabolism without prior *CYP*-mediated transformation. Rouguieg et al. reported that glucuronide conjugation into biologically active 3-glucuronides occurs for buprenorphine by *UGT2B7* and *UGT1A1* and norbuprenorphine by *UGT1A3* and *UGT1A1* [31,36,37].

Cone et al. assessed the presence of buprenorphine and its metabolites, norbuprenorphine, and demethoxybuprenorphine (DMB), in the urine and feces using gas chromatography with an electron-capture detector [38]. Following an oral administration of a 40 mg dose of buprenorphine, which is a high dose as buprenorphine is usually administered sublingually between 8 and 12 mg, DMB was not present in the urine or feces. In urine, 10–30% of the dose was primarily excreted as polar conjugated forms of buprenorphine and norbuprenorphine [3,33,38]. In feces, there were high concentrations of free and conjugated norbuprenorphine, indicating that the majority of the oral buprenorphine dose is unabsorbed and ~70–80% is fecally excreted. Additionally, conjugated buprenorphine is secreted in the bile [3,6]. It is suggested that glucuronated forms of buprenorphine and norbuprenorphine enter the bile and are excreted in the small intestine, hydrolyzed in the intestinal flora, and undergo partial enterohepatic recirculation, or excreted in feces [3,31,38,39].

2.4. Genetic factors affecting pharmacokinetics

The pharmacokinetics of buprenorphine are affected by genetic polymorphisms related to the metabolizing enzymes *CYP3A4* and *UGT2B7*. There are limited clinical studies demonstrating an association of the genetic polymorphisms in these enzymes with drug exposure and pharmacological effects (Table 2).

2.4.1. Genetics affecting bioavailability

Buprenorphine is a highly lipophilic drug that is absorbed primarily through gastrointestinal and/or mucosal membranes. Since buprenorphine is metabolized by *CYP3A4* and *CYP3A5* enzymes expressed in the gut, a genetic polymorphism in *CYP3A4* and *CYP3A5* is expected to impact oral bioavailability [17,45]. When administered via the sublingual route, gastrointestinal cytochromes are bypassed, and liver rather than gastrointestinal *CYP3A4* impacts buprenorphine metabolism [35]. Norbuprenorphine, a major metabolite of buprenorphine administered sublingually, is effluxed by P-glycoprotein. This may influence its tissue distribution, particularly across the blood-brain barrier [32,46]. While genetic polymorphisms in hepatic *CYP3A4*, *CYP3A5*, or P-glycoprotein may theoretically impact metabolism or distribution, current evidence does not support a significant effect on the clinical bioavailability of buprenorphine [17,45].

2.4.2. Genetics affecting distribution

Since buprenorphine is not a P-gp substrate as evaluated in human MDCKII-MDR1, human Caco-2 cells, and P-gp-deficient mice, P-gp does not influence the distribution of buprenorphine-3-glucuronide or norbuprenorphine-3-glucuronide in the brain [32].

2.4.3. Genetics affecting metabolism

Buprenorphine metabolism is primarily (95%) mediated by *CYP* enzymes, such as *CYP3A4* and *CYP3A5*, and *UGTs*, such as *UGT1A1*, *UGT1A3*, and *UGT2B7*; therefore, genetic polymorphism in enzymes involved in the metabolism of buprenorphine is expected to have an impact on its pharmacokinetics [3,17,47]. The *UGT2B7* gene possesses two polymorphisms, rs7439366, and rs7662029, which have the potential to affect the efficacy of buprenorphine treatment within the human body. As evaluated by Kaya-Akyüzlü et al., OUD patients with rs7439366 CC or rs7662029 GG genotypes had lower dose-normalized and dose/kg-normalized buprenorphine levels. Thus, it was concluded that genetic polymorphisms in the *UGT2B7* gene play a crucial role in the metabolism of buprenorphine [43]. However, limited direct data exists in the literature.

Table 2. Genetic variants affecting the pharmacodynamics and the pharmacokinetics of buprenorphine.

Gene	Allele/Haplotype	General Effect	Specific Effect and Clinical Relevance	Study with Reference
<i>CYP3A4</i>	<i>CYP3A4</i> 290 A > G (AA)	Pharmacokinetic	Nonwild-type genotypes had decreased pain control; homozygous wild-type genotypes (AA) had better pain control.	Blanco et al. [40]
	<i>CYP3A4</i> × 1/*1B		Ultrarapid metabolizer phenotype necessitates a higher dose to reduce the number of relapses compared to the standard dosing of patients with this SNP.	Ettienne et al. [41]
	<i>CYP3A4</i> × 1/*1B; <i>CYP3A4</i> × 1 (wildtype)		Compared to the wild-type phenotype, an accelerated rate of metabolism in the <i>CYP3A4</i> × 1 B.	Ettienne et al. [42]
<i>UGT2B7</i>	rs7439366 (CC) rs7662029 (GG)	Pharmacokinetic	Lower dose-normalized (buprenorphine/dose) or dose/kg-normalized buprenorphine (buprenorphine/dose.kg ⁻¹) levels.	Kaya-Akyüzlü et al. [43]
	<i>UGT2B7</i> × 1/*1; <i>UGT2B7</i> × 1/*2; <i>UGT2B7</i> × 1/*1 rs7439366		The presence of SBP 802 C > T (<i>UGT2B7</i> × 2/*2) has a worse analgesic response to transdermal buprenorphine postoperatively from thoracic surgery.	Sastre et al. [44]
<i>OPRM1</i> A118	A118G(N40D)	Pharmacodynamic	The efficacy of buprenorphine was reduced by over 50% for AC inhibition and ERK1/2 phosphorylation, and its potency was reduced threefold for K channel activation at MOPr-N40D.	Knapman et al. [18]
	rs1799971 (A6V)		Decreases in signaling to AC inhibition and ERK1/2 phosphorylation.	Knapman et al. [20]
<i>PDYN</i>	rs1022563 (A-allele) rs1997794 (A-allele carrier group)	Pharmacodynamic	When receiving buprenorphine/naloxone treatment for cocaine dependence, participants tested positive for cocaine fewer times than the placebo group.	Nielsen et al. [21]
	rs1022563 (G) rs1997794 (G)		No difference was found in testing positive for cocaine.	Nielsen et al. [21]
<i>SLC6A3</i>	DAT 1 Allele 10	Pharmacodynamic	Unresponsive to buprenorphine treatment for opioid dependence due to the influence on the effects of buprenorphine-induced dopamine release.	Gerra et al. [23]

2.4.4. Cytochrome P450 family 3 subfamily a member 4 (*CYP3A4*) and member 5 (*CYP3A5*)

Genetic variants of *CYP3A4* affect the metabolism rate for drugs such as buprenorphine, which can be categorized into four phenotypes: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultra-rapid metabolizers. The *CYP3A4* × 1B allele has been categorized as an ultra-rapid metabolizer in a study conducted by Ettienne et al., but has also been perceived as an extensive metabolizer in a study conducted by Westlind-Johnsson et al. Additionally, *CYP3A4* × 1/*1 has been categorized as an extensive metabolizer [41,48]. Variations of *CYP3A4* and *CYP3A5* alter analgesic response and the metabolism of buprenorphine, which can change the dosage needed for a patient to experience a similar therapeutic effect. Studies have shown that the ultrarapid metabolizer phenotype associated with the *CYP3A4* and *CYP3A5* genes often results in the use of higher doses of buprenorphine, as they metabolize the drug much quicker than the normal patient [17]. Blanco et al. found that homozygous AA carriers of the *CYP3A4* gene respond better to a buprenorphine transdermal therapeutic system treatment [40]. Moreover, Ettienne et al. observed that *CYP3A4* × 1/*1B is an ultra-rapid metabolizer genotype, requiring an increased dose of buprenorphine in comparison to the standard dosing of patients with this single-nucleotide polymorphism (SNP) to reduce the number of relapses compared to *CYP3A4* × 1, the wild-type phenotype [41,42].

2.4.5. UDP glucuronosyltransferase family 2 member B7 (*UGT2B7*)

Sastre et al. studied the potential of a cytosine or thymine substitution at nucleotide 802 of the *UGT2B7* gene to affect postoperative buprenorphine analgesia [44]. After 48

postoperative hours, patients carrying the *UGT2B7* × 2/*2 genotype reported a higher prevalence of severe pain. In a final survey, 38% of *UGT2B7* × 2/*2 patients had severe pain, and 17% of *UGT2B7* × 1/*1 patients experienced severe pain. The polymorphism was found to worsen the response of patients to postoperative transdermal buprenorphine in thoracic surgical procedures [44].

2.5. Special considerations in children

The clearance of buprenorphine normalized to body weight appears to be higher in pediatric patients [49]. The metabolism of buprenorphine in children, especially neonates and infants, could be affected by the lack of development of *CYP3A4* in the first few weeks after birth, reaching 30–40% of adult levels at 4 weeks and full adult levels at 3 years of age [50,51]. Similarly, the metabolism could also be attributed to lower *UGT2B7* activity levels in the first 10 days after birth, increasing in the first two weeks, and reaching adult levels at 2 years of age [51]. Re et al. observed that children do not exhibit the ceiling effect adults experience when exposed to buprenorphine, leaving children at risk of possible respiratory depression and intoxication [52]. There is limited data on the pharmacogenomic effects of buprenorphine exposure in children.

2.6. Buprenorphine and pregnancy

Buprenorphine has emerged as a treatment for pregnant women who have OUD due to its benefits for both the pregnant woman and the neonate. Improved outcomes include a lower relapse risk for pregnant women, a decrease in the severity and duration of neonatal opioid withdrawal syndrome (NOWS), and a greater birth weight in comparison to methadone maintenance treatment [53–55]. However, prenatal exposure to buprenorphine can

increase the risk of congenital, neurodevelopmental, cognitive, and motor abnormalities [56–60]. Additionally, buprenorphine can cross into breast milk and the placenta [3,61]. When buprenorphine and norbuprenorphine concentrations were measured in the milk samples of seven pregnant opioid-dependent women (median, 7 mg/day; range, 2.4–24 mg), the mean (95% confidence interval) buprenorphine concentration was 3.65 (1.61–5.71) µg/L and norbuprenorphine concentration was 1.94 (0.79–3.08) µg/L in the breast milk [62]. The infant cord plasma buprenorphine concentration range of three opioid-dependent women maintained on 8–12 mg/day of buprenorphine in their last few months of pregnancy was between 0.10 and 0.14 mg at delivery [3,63]. Bastian et al. and Caritis et al. reported that plasma concentrations of buprenorphine are lower during pregnancy than postpartum [64,65]. This is due to the increase in *CYP*- and *UGT*-mediated metabolism of buprenorphine, causing an increase in clearance of buprenorphine during pregnancy [66]. This data suggests that pregnant women may need a higher daily dose or a more frequent dosing interval of buprenorphine to have a plasma buprenorphine concentration of at least 1 ng/mL, which prevents withdrawal symptoms and provides therapeutic effects similar to those of a non-pregnant patient [64–66].

3. Conclusion

Buprenorphine has several favorable pharmacokinetic and pharmacodynamic properties, which are advantageous in its treatment of OUD and pain management. Research has linked polymorphic genetic enzymes involved in buprenorphine metabolism, such as *CYP3A4* and *UGT2B7*, with buprenorphine dosage requirements and differential clinical outcomes. However, there is a lack of established evidence regarding the effect various genetic polymorphisms have on pharmacodynamic markers, including cravings, relapse, pain, respiratory depression, and pharmacokinetics, which could contribute to variable exposure, efficacy, and dosing regimen. Furthermore, *CYP3A4* enzyme levels involved in the metabolism of buprenorphine in neonates and children are significantly lower than in adults. Additionally, pregnant women using buprenorphine therapy may require greater and/or more frequent dosing of buprenorphine. These physiological effects (e.g., age, pregnancy), combined with the many genetic variations that potentially influence the drug's effect, make the need for individualized dosage and treatment stronger than ever before.

4. Future perspective

At present, however, there is simply insufficient evidence to support the use of genetic variations in making clinical decisions about buprenorphine use and precision dosing. Additionally, candidate gene analysis as a methodology limits analysis to genes based on prior knowledge and attempts to establish relationships between genes and phenotypes without considering other genome-wide influences, making conclusions not entirely reliable. Thus, further research through well-powered clinical studies and genome-wide association studies is vital to verifying or challenging the existing findings, identifying novel genetic variants, and improving the

understanding of inter-individual variability in buprenorphine's metabolism and effects.

Author contributions

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