Pharmacogenomics of oxycodone: a narrative literature review

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Oxycodone is a semisynthetic μ- and κ-opioid receptor with agonist with a broad scope of use including postoperative analgesia as well as control of neuropathic and cancer pain. Advantages over other opioids include prolonged duration of action, greater potency than morphine and lack of histamine release or ceiling effect. Individual responses to oxycodone can vary due to genetic differences. This review article aims to summarize the oxycodone literature and provide context on its pharmacogenomics and pharmacokinetics. The evidence for clinical effect of genetic polymorphisms on oxycodone is conflicting. There is stronger evidence linking polymorphic genetic enzymes CYP2D6 and CYP3A with therapeutic outcomes. Further, research is needed to discern all of oxycodone's metabolites and their contribution to the overall analgesic effect.

Oxycodone is a semisynthetic opioid analgesic that was first derived from the opium alkaloid thebaine in 1916 and introduced into clinical practice in Germany in 1917 [1–3]. In the USA, the oxycodone market share grew from 10% in 1996 to 53% in 2000, making it a leading opioid [4]. Oxycodone is a selective μ-opioid receptor agonist and at higher doses it binds to κ-opioid receptors in the central, peripheral and autonomic nervous systems [3]. Oxycodone is a selective μ-opioid receptor agonist (with potential κ-opioid receptor agonism). It is widely used in clinical practice for control of postoperative pain, neuropathic pain and cancer pain [5]. Routes of administration include intravenous (IV), intramuscular (IM), intranasal (IN), subcutaneous (SC), rectal, epidural and oral using immediate-release solutions and immediate controlled-release tablets [3].

Oxycodone is used for pain of moderate-to-severe intensity; its potency is greater than that of morphine when used for postoperative pain relief [6]. In postoperative pain management, oxycodone has shown analgesic and oral administration advantages over other strong opioids [7,8]. The duration of action is longer and it does not cause histamine release when compared with morphine which makes it more suitable for individuals with underlying disease states that exacerbate with increase histamine release [9].

In patient controlled intravenous analgesia (PCIA) following abdominal surgery, demand-only oxycodone provided comparable overall pain relief, lower pain on movement, less analgesic dose requirement and fewer adverse effects compared with continuous sufentanil infusion [10] and fentanyl [11].

Individual genetic variations can alter drug effects; hence an understanding of genetic factors is necessary. An individuals' genetic data can be used to design a targeted approach and personalized therapy [12]. This can apply to dosing guidelines, annotated drug label, potential adverse effects and the risk for hypersensitivity reactions. SNPs are responsible for these genetic variants and variants influencing oxycodone pharmacodynamics and pharmacokinetic

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Table 1. Pharmacokinetic parameters of various formulations of oxycodone.			
Formulations	Bioavailability	Time to peak concentration	Half-life
IV	100%	–	2–3 h
IM	100%	~1 h	~4.9 h
Oral	50–90%	1–1.5 h	3–5 h
Oral (extended release)	60–87%	~2.6 h	~8 h
Rectal	~62%	~2.8 h	~3.7 h

have been described. This review article will provide an overview of the literature related to the pharmacogenetics of oxycodone.

Materials & methods

Pubmed and Google Scholar search was done for related articles. MeSH terms such as oxycodone, pharmacogenetics, pharmacodynamics, pharmacokinetics, gene variants, single nucleotide polymorphism, genetic polymorphism was used to build a search. Studies that genotyped patients on oxycodone with data such as potency, adverse effects, antinociceptive effect, drug consumption and dose were selected. Citations were added to the citation manager EndNote X9. Pharmacogenetics of oxycodone affecting its pharmacokinetics and pharmacodynamics are reviewed below.

Pharmacokinetics of oxycodone

Oxycodone is available for IM, IV, SC, IN, rectal or oral (capsule or solution) administration. It has also been used epidurally in a few studies. The pharmacokinetics variability with different formulations of oxycodone has been summarized in Table 1. The bioavailability of the orally administered drug is about 50–90% [13,14] and the time to peak concentration is about 1–1.5 h. Fatty food appears to increase the bioavailability of the drug, while prolonging the time to peak concentration [15]. The bioavailability of oxycodone given rectally is similar to that of the orally administered drug (~60%) [16]. Oxycodone has a volume of distribution of 2–3.5 l/kg and a total plasma clearance of 45–48 l/h. The half-life of the drug is about 3–5 h [13,15,17–19]. Although IV oxycodone has a shorter half-life (~3 h), the duration of action is similar between these formulations [17]. The short half-life requires the drug to be given every 4–6 h. However, the controlled release oral formulation of the drug has an extended half-life of about 8 h, facilitating 12-h dosing [20].

Oxycodone is primarily bound to albumin (44–46%) and is not bound to α1-acid glycoprotein. It has a liposolubility close to that of morphine, with partition coefficients of 0.7 and 0.5, respectively [21]. The volume of distribution of oxycodone ranges from 211 to 249 l [17]. Oxycodone is extensively metabolized in the liver primarily by the CYP enzymes and in a small amount by the uridine diphosphate glucuronosyltransferases (UGT). Human intestinal microsomes have a much lower N-demethylation activity than liver microsomes, suggesting that there is minimal first pass metabolism of the drug in the gut [22]. The primary enzymes involved in metabolism are CYP2D6, CYP3A4/5, UGT1A3, UGT1A6 and UGT2B7, as demonstrated by Romand *et al.* with an *in vitro* study [23]. About 45% of the drug undergoes N-demethylation to noroxycodone noroxymorphone and α- and β-noroxycodol, about 11% of the drug undergoes O-demethylation to oxymorphone and α- and β-oxymorphol and about 8% of the drug undergoes 6-keto-reduction to α- and β-oxycodol. Noroxymorphone is a metabolite produced from O-methylation or N-methylation of noroxycodone or oxymorphone, respectively.

Oxycodone, oxymorphone and noroxymorphone also undergo conjugation with the help of UGT [23]. The minimally formed conjugated products are readily eliminated in the urine and therefore found in very low concentrations in the body. CYP3A4/5 and CYP2D6 are the primary enzymes involved in N-demethylation and O-demethylation of oxycodone, respectively [22,24]. Oxymorphone is ten-times more potent than the parent drug, but is formed in clinically negligible quantities and has a relatively lesser penetration across the blood–brain barrier [24]. Noroxymorphone, although less potent than oxymorphone, is present in a higher concentration than oxymorphone and it also minimally crosses the blood–brain barrier. Consequently, both of these potent metabolites have been shown to cause no significant clinical effect in a pharmacokinetic–pharmacodynamic modelling study [24].

The metabolic pathways of oxycodone are described in Figure 1 [19,24–28]. Metabolites of oxycodone have a longer half-life (about 5.8, 8.8 and 9 h for noroxycodone, oxymorphone and noroxymorphone, respectively) [24]. Consequently, with chronic therapy, the levels of the primary metabolite noroxycodone can exceed the concentrations of
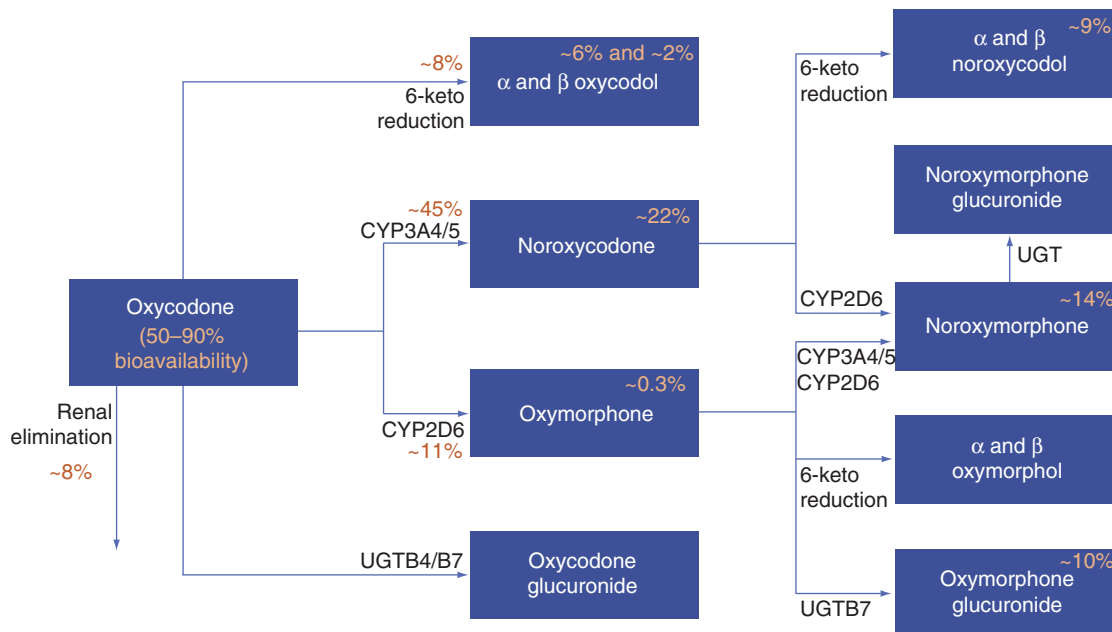
Figure 1. Oxycodone primarily gets metabolized to noroxycodone and oxymorphone and later to noroxymorphone. The drug and it metabolites can also undergo glucuronidation before elimination. Oxycodol, noroxycodol and oxymorphol are reductive metabolites of oxycodone, noroxycodone and oxymorphone respectively, with each of them having two stereoisomers (α and β). % mentioned next to an arrow represents the percentage of drug eliminated in that specific pathway and % mentioned in the boxes represent the percentage of eliminated metabolite compared with the parent drug. Pathways with no % mentioned have very minimal contribution to the drug's elimination.
CYP: Cytochrome P450; UGT: Uridine 5′-diphospho-glucuronosyltransferase or UDP-glucuronosyltransferase.

the parent drug [29]. About 10–19% of the drug is excreted unchanged by the kidneys [13,15,24]. The conjugated products of the drug and the metabolites (oxymorphone and noroxymorphone) are also renally excreted.

Given the high amount of hepatic metabolism, hepatic dysfunction increases the maximum concentration (C_{max}) and area under curve (AUC) of oxycodone. In a study of controlled-release oxycodone pharmacokinetics with 24 subjects, hepatically-impaired patients had a 40% increase in C_{max}, a 90% increase in AUC and a longer half-life (7.7 vs 5.4 h) compared with healthy patients [30]. In a Phase I study of 18 patients with hepatic dysfunction, C_{max} and AUC showed a steady increase with decreasing hepatic function. The AUCs were 105.7, 134.7 and 218 for normal, mild and moderately impaired hepatic function, respectively [31]. Tallgren *et al.* studied the pharmacokinetics of oxycodone in six end-stage cirrhosis patients before and after liver transplantation. The elimination half-life reduced from 13.9 to 3.4 h soon after transplant, which highlights the danger of using it in severely impaired hepatic patients [32].

Although only 10–14% is eliminated renally, patients with severely impaired renal function have increased half-life, increasing the exposure of the drug. Elimination of its metabolites, including the more potent metabolite oxymorphone, is severely impaired. The volume of distribution is increased in uremic patients due to the increase in fat-tissue index caused by the decrease in lean tissue mass index [33,34]. Malhotra *et al.* showed that the mean AUCs were 210.7, 271.6, 299.5 and 493.5 in individuals with normal, mild, moderate and severely impaired renal function [31]. A dose reduction by 50% is advised if a patient's glomerular filtration rate is less than 50 ml/min [15,35]. The physicochemical properties of oxycodone suggest it to be dialyzable, although there is no available data to confirm this [34].

The CYP3A4 enzyme is a major contributor to the metabolism of oxycodone – about sevenfold higher than the CYP2D6-related metabolism [24]. CYP3A4 could be a target for drug interactions, as inhibition or induction of the enzyme could change the levels of the drug. In a drug interaction study conducted by Samer *et al.*, administering oxycodone with ketoconazole (a strong CYP3A4 inhibitor) led to a tripling of oxymorphone concentration and reduction of noroxycodone and noroxymorphone AUCs by 80% [36]. Similar results were obtained in other studies where telithromycin and itraconazole increased the AUC of oxycodone by 80 and 144%, respectively, by inhibiting

CYP3A4 [37,38]. In a placebo-controlled randomized crossover drug interaction study with rifampicin, the AUC of oxycodone was reduced by two- and sevenfold when administered IV and orally, respectively. As expected, the AUC of noroxycodone increased [39].

Quinidine, an inhibitor of CYP2D6, was investigated with oxycodone in a drug interaction study by Samer *et al.* Results showed a 40% decrease in C_{max} and AUC of oxymorphone and 80% decrease in the C_{max} and AUC of noroxymorphone, along with an increase in the AUC in oxycodone and noroxycodone. Although the available evidence is conflicting, use of an alternative drug in CYP2D6 poor or ultra-rapid metabolizers is recommended [36].

Women metabolize oxycodone faster than men, with higher levels of metabolites compared with men [25]. This could be due to the increased CYP3A4 expression and activity generally seen in women [40]. However, in one of the older studies, women consistently showed a higher level of oxycodone AUC compared with men across age groups [30]. This study failed to adjust for body weight, which might be responsible for the observed difference.

Race does not have any effect on the pharmacokinetics of oxycodone [15]; however, oxycodone pharmacokinetics seem to differ with the extreme ages. Kokki *et al.* found that the elimination half-lives across extremely preterm neonates, preterm neonates, older neonates and infants aged 6–24 months were 8.8, 7.4, 4.1 and 2 h, respectively [41]. Similar results were shown in a population pharmacokinetic study, where the clearance increased with age and the volume of distribution reduced with age in children less than 1 year of age [42]. Children more than 6 months of age reach adult metabolic activity fairly quickly [43]. One *in vitro* study using cryopreserved hepatocytes from different age groups showed that change in CYP3A activity across various age groups is the major determinant of their metabolic clearance [44].

The AUC indicative of exposure of oxycodone is greatly increased in the elderly. Patients above 70 years of age were found to have 50–80% higher exposure to oxycodone [45]. In a population pharmacokinetic study by Saari *et al.* with 77 individuals ranging from 19–89 years of age, lean body mass and age were found to be significant covariates on the clearance of the drug. Age was associated with a proportional decrease in clearance [46].

Genetic factors affecting the pharmacokinetics of oxycodone

All known genetic factors affecting the pharmacokinetics of oxycodone are related to the metabolism of the drug involving genetic polymorphism in the related enzymes. While the genetic variants of *CYP3A* and *CYP2D6* are well characterized, the genetic variations of *UGTB7* are not. The pharmacological effects of the various genes and their variants are summarized in Table 2.

CYP3A

CYP3A is the major metabolizing enzyme for more than 50% of the drugs administered in clinical care. Generally, variants in *CYP3A4* occur in less than 5% of the population as a heterozygous allele. Also, there is no evidence of a null allele (nonfunctional allele) known with *CYP3A4* as seen with the other *CYP* genes. *CYP3A4* has many genetic variants, yet few of them (*1b, *2, *3* and *22*) result in clinically relevant phenotypes [59]. *CYP3A5*3*, a nonfunctional variant, is the most common variant of *CYP3A5* – seen in 85% of Caucasians and 65% of Asians. It is commonly linked with *CYP3A4*1b*. *CYP3A7* is the major *CYP3A* isoform in the fetal liver. Although genetic variation will be important in the metabolism of oxycodone, it has not been well studied under *in vivo* or *in vitro* conditions.

There is very sparse information available on the effect of *CYP3A* genetic variation on the metabolism of oxycodone. In a study by Naito *et al.*, *CYP3A5*3* decreased the 12 h trough concentration of noroxycodone and was associated with increased incidence of dose escalation in a multivariate analysis [56]. This could have been due to decreased synthesis of the active metabolite noroxymorphone from noroxycodone.

CYP2D6

Genetic variations seen with *CYP2D6* include gene duplications, tandem arrangements, gene deletion and extensive regular allelic variants. This complex variation in the genotype gives rise to the poor metabolizers (PM; homozygous for reduced-function variant allele), intermediate metabolizers (IM; heterozygous for nonfunctional allele with a normal function allele) and extensive or normal metabolizers (EM/NM; homozygous wild-type alleles) phenotypes. The most commonly studied variants are *CYP2D6*2, *3, *4, *5, *10, *17* and *41*. The *1* and *2* alleles have normal activity while the *10, *17* and *41* alleles have reduced activity and *3, *4* and *5* alleles have null activity [60] Duplications of the normal activity alleles result in the UM phenotype. The incidence of each of these variants

Gene	Variant	Effect	Study (year)	Ref.
OPRM1				
	rs1799971 (118A>G)	i. Reduced antinociceptive effect exposed to experimental pain ii. Reduced ability to keep focus	Zwisler et al. (2010)	[47]
		No difference in any of the pain measurements or adverse drug reactions in the first 24 h after surgery	Zwisler et al. (2012)	[48]
		Reduced analgesic response to experimental visceral pressure	Olesen et al. (2015)	[49]
		Gene dosage effect with the GG genotype requiring the highest dose	Cajanus et al. (2014)	[50]
		Higher dose in GG compared with the AA and the AG genotypes in patients with cancer pain	Lin et al. (2018)	[51]
	rs589046 (C>T)	Improved analgesic response to experimental skin heat and visceral pressure	Olesen et al. (2015)	[49]
	rs563649 (C>T)	Improved analgesic response to experimental skin heat	Olesen et al. (2015)	[49]
	rs9479757 (G>A)	Improved pain tolerance threshold to experimental visceral pressure	Olesen et al. (2015)	[49]
	rs533586 (C>A/T)	Poor analgesic response to experimental visceral pressure	Olesen et al. (2015)	[49]
OPRD1				
	rs419335 (A>G)	Poor analgesic response to experimental visceral heat	Olesen et al. (2015)	[49]
	rs2234918 (C>G/T)	Improved analgesic response to experimental muscle pressure	Olesen et al. (2015)	[49]
ABCB1				
	C3435T	Less pronounced adverse drug reactions: nausea/vomiting, tiredness/drowsiness, itching and for the total sum of adverse drug reactions	Zwisler et al. (2010)	[47]
		No difference in any of the pain measurements or adverse drug reactions in the first 24 h after surgery	Zwisler et al. (2012)	[48]
	G2677T/A	i. Variant T allele had improved antinociceptive effect of oxycodone ii. Lesser adverse drug reactions like nausea/vomiting, dizziness, itching and increased adverse drug reactions like urine retention, headaches iii. 3435CC-2677GG was associated with reduced antinociceptive effect of oxycodone	Zwisler et al. (2010)	[47]
		No difference in any of the pain measurements or adverse drug reactions in the first 24 h after surgery	Zwisler et al. (2012)	[48]
		Increased risk of sedation in breastfeeding mothers. No association with oxycodone-induced depression in neonates.	Lam et al. (2012)	[52]
COMT				
	Multiple SNPs	22 SNPs within or nearby the COMT gene showed i. 3 SNPs, rs4646312, rs2239393 and rs4818 associated with pain intensity during motion ii. rs887200 (recessive model) and rs1544325 (dominant model) associated with cold pain iii. No association with total oxycodone consumption after multiple testing correction.	Kambur et al. (2013)	[53]
CYP2D6				
	PM and EM	i. PM had an increase in pain tolerance thresholds ii. Plasma oxymorphone/oxycodone ratio was lower in PM compared with EM	Zwisler et al. (2009)	[100]
	IM/PM, EM and UM	AUC of oxymorphone were increased while that of noroxycodone were reduced in UM compared with others	Samer et al. (2010)	[36]
	IM/PM, EM and UM	i. CYP2D6 ultra-rapid metabolizers experienced increased pain tolerance thresholds ii. Inverse relation between activity and sedation iii. Psychomotor testing by mean of the digit symbol substitution test should gene dose effect	Samer et al. (2010)	[54]
	PM, EM and UM	i. Significant increase in serum concentrations of oxymorphone and noroxymorphone from PM to EM and from PM to UM ii. No difference between the groups with regard to pain, tiredness and nausea	Andreassen et al. (2012)	[55]
	*4/*4	Trend toward decreased clearance but the effect could not be observed in population pharmacokinetic analysis	Saari et al. (2012)	[46]

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

All effects are in relation to the variant allele as notated in the variant column unless otherwise specified.
AUC: Area under curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultra-rapid metabolizer.

Table 2. Genetic variants affecting the pharmacodynamics and the pharmacokinetics of oxycodone (cont.).

Gene	Variant	Effect	Study (year)	Ref.
	PM, IM and UM	Oxymorphone trough concentrations were higher in EM than in IM but did not affect dose escalation	Naito *et al.* (2013)	[56]
	PM, IM, EM and UM	C_{max} and AUC of oxymorphone and oxymorphone/oxycodone ratio, was increased with EM compared with PM and IM	Balyan *et al.* (2017)	[57]
	PM, IM, EM and UM	i. *6 and *9 alleles were associated with therapeutic failure in chronic low back pain ii. UM (CYP2D6*2N) associated with an increased risk of side effects	Dagostino *et al.* (2018)	[58]
CYP3A5				
	*3	i. Daily dose escalation rate was increased ii. Noroxycodone trough concentrations were increased with *1	Naito *et al.* (2013)	[56]

All effects are in relation to the variant allele as notated in the variant column unless otherwise specified.
AUC: Area under curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultra-rapid metabolizer.

differs greatly between ethnic groups. All of these factors contribute to the high variation in enzymatic activity of CYP2D6 seen between individuals.

Balyan *et al.* studied the effect of *CYP2D6* genetic polymorphism on oxycodone pharmacokinetics in 30 children. Though there were no changes in pharmacokinetic outcomes of oxycodone, oxymorphone C_{max}, AUC and oxymorphone/oxycodone ratio, were increased in children with EM genotype and phenotype compared with PM and IM phenotypes [57]. Similar results were observed in a much smaller study proving the significance of CYP2D6 in the formation of oxymorphone. Further, this study showed that the UM patients have reduced noroxycodone concentrations [36]. In a population pharmacokinetic modelling study, although univariate analysis showed lower clearance in individuals with *CYP2D6*4/*4*, it did not improve the final fit of the model and, therefore, was omitted [46]. A large genotyping study of 450 cancer patients revealed that patients with PM phenotypes had lower concentrations of oxymorphone and noroxymorphone, while the levels of oxycodone and noroxycodone were unaffected between PM, EM and UM phenotypes. The daily intake of doses did not differ between the groups [55]. Similar results with decreased oxymorphone and unaffected oxycodone levels were also seen in other studies [56,61]. None of these studies found a difference in responder rates despite the high degree of genetic variation. Liukas *et al.* found no significant correlation between the oxycodone concentrations and genotype, although there was a trend toward higher plasma oxycodone and noroxycodone concentrations and lower oxymorphone and noroxymorphone concentrations in PM and IM compared with the EM and UM phenotypes, signifying the possibility of such an effect [45].

Pharmacodynamics of oxycodone

Oxycodone is an opioid receptor agonist with a weak affinity for the µ-opioid receptor and minimal or no affinity for the delta-opioid receptor and a subtype of the κ-opioid receptor [62,63]. The exact mechanism of action of oxycodone is not fully known. Oxycodone and its active metabolites can selectively bind to the µ-opioid receptor, at higher doses the κ- and δ-opioid receptors in the CNS and periphery and induce a G-protein-coupled receptor signaling pathway. Oxycodone has a lower binding affinity for the µ-opioid receptor than methadone and morphine, although its active metabolite (oxymorphone) has greater affinity that the parent drug [3,64].

The active metabolite contributes largely to the pharmacodynamic characteristics of oxycodone [3,65]. Oxymorphone formed from 3-O-demethylation of oxycodone has two- to five-times the µ-opioid receptor affinity and analgesic potency than morphine [66] while it is 14-fold more potent with 40-times higher µ-opioid receptor affinity than its parent drug oxycodone [67]. A larger primary active metabolite, noroxycodone, produced from N-demethylation of oxycodone has four-times lower µ-opioid receptor-binding affinity [66] and a poor antinociceptive potency in rats. However, noroxymorphine, a further metabolite of noroxycodone, is a more potent shifter of D-ala2,N-MePhe4,Gly-ol (DAMGO)-enkephalin from the µ-opioid receptor in rat brain when compared with oxycodone [64,66,68]. The opioid receptor-binding attributes are yet to be characterized for other metabolites obtained via reduction of oxycodone to α- and β-oxycodol, noroxycodone to α- and β-noroxycodol and oxymorphone to α- and β-oxymorphol [22,66]. However, α- and β-oxymorphol have been shown to be two- to threefold more potent than oxycodone, despite having low plasma concentration after administration of oxycodone [66]. Klimas *et al.* [69] described the contribution of oxycodone and its metabolites to the general analgesic effect. Their results showed

that, even though oxymorphone and noroxymorphone have much higher μ-receptor affinity than oxycodone, oxycodone is accountable for 83 and 95% of analgesic effect during oral and IV administration, respectively.

When oxycodone is compared with morphine, several studies [3,64,66,70,71] have shown its lower affinity for the μ-opioid receptor. Likewise, the potency of oxycodone in the μ-opioid receptor activation of intracellular G proteins is lower than that of morphine [66]. However, Silvasti *et al.* [72] showed both drugs to be equipotent in a study of 50 patients that compared the analgesic efficacy of oxycodone and morphine in postoperative PCIA. Equal analgesia was also demonstrated following PCIA titration in the management of cancer pain [73].

Oxycodone & breastfeeding

Pain can hinder a woman's ability to care for herself and her newborn; however, opioid use has been linked to birth defects [74,75]. Opioid pain medication intervention is one of the reasons for late breastfeeding initiation after birth [76]. Niklasson *et al.* [77] evaluated the efficacy and safety of oral oxycodone for postoperative analgesia in 80 women following cesarean section, showing reduced pain intensity, provoked pain and total opioid consumption with oxycodone compared with IV morphine/codeine. They also reported no serious adverse events in mothers and newborns. Conversely, Lam *et al.* [52] showed a 20% incidence of CNS depression in neonates breastfed by mothers receiving oxycodone compared with 16.7% on codeine and 0.5% on acetaminophen. A case reported by Timm also described oxycodone intoxication of a breastfed neonate [78].

Oxycodone use disorder insights from animal studies

Oxycodone is a leading contributor to the global opioid abuse crisis. Opioid reward is generally believed to be mediated by activation of μ-opioid receptors located on GABAergic interneurons or afferents in the ventral tegmental area [79] and central dopaminergic system [80]. A highly selective dopamine (DA) D3 receptor antagonist, VK4-40 was examined on the rewarding and analgesic effects of oxycodone in rodents; VK4-40 produced a dose-dependent reduction in oxycodone self-administration and blocked the oxycodone brain stimulation reward pathway [80]. In addition, VK4-40 showed antinociceptive properties as efficacious as oxycodone, possibly by augmenting opioid analgesia via DA-dependent mechanisms [80]. The observation that dopamine antagonists inhibit oxycodone self-administration is supported by other studies including heroin self-administration in wildtype, but not in D3R-knockout mice [81] and oxycodone self-administration in rats [82].

OrxR1 and OrxR2 have been associated with regulation of motivation, arousal and stress. After rats were taught to self-administer oxycodone, blockade of OrxR1 was shown to be associated with decreased oxycodone self-administrations and oxycodone-seeking behavior whereas blockade of OrxR2 had no such effects [83,84] The investigators then examined if immunochemotherapy directed against oxycodone would alter antinociception action or intravenous self-administration rate. In those rats trained to self-administer oxycodone, administration of an immunoconjugate vaccine (Oxy-TT) reduced oxycodone concentrations in brain by 50% and vaccination decreased the rat's oxycodone intake and provided protection against the reinforcing effects of oxycodone. The exact neuronal pathways that lead to opioid addiction and abuse need further investigating. However, promising new research and drugs are providing light on potential areas that can be targeted to help decrease opioid use, treat those already addicted and help combat relapse.

Genetic factors affecting the pharmacodynamics of oxycodone

Genetic variations influence the response to opioids including oxycodone. Most of the studies related to genetic variability influencing the pharmacodynamics of oxycodone have focused on the antinociceptive, pupil, sedation and adverse effects of oxycodone. The best-characterized genetic variants involve the opioid receptors and P-glycoprotein transporter. This section will compare different study outcomes in relation to the pharmacogenomics of oxycodone.

Oxycodone & clinical outcomes
Opioid receptors

Opioid receptor polymorphisms mediate various analgesic and adverse effects by impacting the expression and function of binding sites. Approximately 100 variants of the μ-opioid receptor gene (*OPRM1*) have been identified [85]. A small number of *OPRM1* mutations based on allelic frequency affect opioid therapy [86]. *OPRM1* polymorphism is an important factor influencing opioid pharmacodynamics.

The *A118G* SNP of *OPRM1* was found to have a variant allele frequency of 10–15% in the Caucasian population [86]. The SNP *118A>G* (*rs1799971*) on chromosome 6 in *OPRM1* leads to substitution of aspartate for asparagine, changing the N-glycosylation of the receptor protein [87]. This change can affect the response to opioid analgesia. Olesen *et al.* [49] evaluated 19 opioid receptor genetic polymorphisms and found that variability in oxycodone response to skin heat was associated with *OPRM1* SNPs *rs589046* and *rs563649* (p < 0.0001). The *OPRM1* SNPs *rs589046* (p = 0.015), *rs1799971* (p = 0.045), *rs9479757* (p = 0.009) and *rs533586* (p = 0.046) were associated with variability in oxycodone response to visceral pressure. Delta opioid receptor (*OPRD1*) SNP rs419335 reached oxycodone visceral heat threshold (p = 0.015) while *OPRD1* SNP *rs2234918* (p = 0.041) was associated with muscle pressure. However, no association was found between κ-opioid receptor (*OPRK1*) SNPs and oxycodone response for any of the pain modalities.

Zwisler *et al.* [47] studied the association between the variant allele of the *OPRM1* SNP *A118G* and altered antinociceptive effect and adverse drug reactions of oxycodone. In 33 healthy subjects exposed to experimental pain (including electrical stimulation and cold pressor test), the authors found that the variant G allele was associated with reduced antinociceptive effect when measured by pain tolerance threshold to single electrical nerve stimulation (8% increase vs 25% for the wild-type carriers, p = 0.007).

In contrast, Zwisler *et al.* [48] later showed no association between *OPRM1* SNP *A118G* and the analgesic effect of IV oxycodone for clinical postoperative pain in 268 patients. Similarly, Skarke *et al.* [88] showed no effect of *A118G* genotype on the response to transcutaneous electrical stimulation for morphine and morphine-6-glucuronide (M6G). Carriers of the G allele had less nausea and vomiting after receiving M6G but not morphine.

The association between *OPRM1* SNPs and postoperative analgesic requirement in surgical patients remains controversial. Hayashida *et al.* [89] studied 138 Japanese patients following major open abdominal surgery and found that the 118G homozygous (*GG*) patients required 24-h postoperative analgesics more than 118A homozygous (AA) and heterozygous (AG) patients. This relationship was verified between *OPRM1 118A/G* gene polymorphism and oxycodone analgesic dose in patients with cancer pain when investigated by Lin *et al.* [51]. The authors genotyped 203 patients with moderate-to-severe cancer pain and showed that the dosage of oxycodone in *GG* genotype was significantly higher than that in *AA* genotype and *AG* genotype (15.44 ± 10.19 for *GG* vs 10.25 ± 4.53 for *AA* and 10.49 ± 5.26 for *AG* on day 3; 89.15 ± 27.69 for *GG* vs 43.59 ± 12.19 for *AA* and 48.27 ± 18.79 for *AG* on day 30 after treatment; p < 0.05). In another similar study with a group of 1000 women received oxycodone after breast cancer surgery [50], a similar conclusion was obtained when they demonstrated that the *118A>G* variant was associated with the amount of oxycodone requested for adequate analgesia. The highest oxycodone consumption was shown in patients with *GG* genotype (0.16 mg/kg), moderate for *AG* genotype (0.13 mg/kg) and lowest for *AA* genotype (0.12 mg/kg). Conversely, Naito *et al.* [90], studied 62 cancer patients and reported that *OPRM1 A118G* SNP had no effect on dose escalation for patients receiving oxycodone. Likewise, Kim *et al.* [91] did not find any association between postoperative fentanyl consumption and genetic polymorphisms of *OPRM1* in 196 Korean gynecologic patients.

ATP-binding cassette subfamily B member 1 (ABCB1)

Zwisler *et al.* [47] studied the association between the variant allele of the SNPs *C3435T* and *G2677T/A* in the *ABCB1* gene and altered antinociceptive effect and adverse drug reactions of oxycodone. In 33 healthy subjects exposed to experimental pain (electrical stimulation and cold pressor test), they showed that carriers of the variant *T* allele in the SNP *C3435T* had less adverse drug reactions on oxycodone when compared with carriers of the wild-type genotype. Likewise, for SNP *G2677T/A*, carriers of the variant *T* allele had a better antinociceptive effect of oxycodone than the wild-type genotype in the cold pressor test (25% reduction vs 15%, p = 0.015) and less adverse drug reactions. The combined wild-type genotype *3435CC-2677GG* had less antinociceptive effect in the cold pressor test (13% reduction vs 23%, p = 0.019) and more severe adverse drug reactions than carriers of the variant alleles. However, Zwisler *et al.* [48] did not find any association between SNPs *C3435T* and *G2677T/A* in *ABCB1* and the analgesic effect of IV oxycodone in clinical postoperative pain in 268 patients. This finding was attributed to the fact that patients were in an uncontrolled environment and were also co-medicated with inhibitors and substrates of P-glycoprotein. In cancer patients receiving oxycodone, no significant difference was found between oxycodone consumption and *ABCB1* SNPs [90].

Catechol-O-methyltransferase

The effect of SNPs in catechol-O-methyltransferase (*COMT*) was studied by Kambur *et al.* [53]. Although there were multiple SNPs identified to be related with pain during motion and cold pain, there was no association between the SNPs and postoperative oxycodone consumption.

Genetics related to nursing mothers & neonates

Opioids are prescribed to >80% of women following Caesarean section and up to 30% of women following vaginal delivery and millions of women breastfeed while receiving opioids each year [92]. The US FDA's 2017 updated warning recommends against using codeine and tramadol in breastfeeding women due to excess sleepiness and serious breathing problems including death in breastfed infants [93]. Codeine and tramadol are metabolized in the liver to active/more potent metabolites by an enzyme called cytochrome P450 isoenzyme 2D6 (CYP2D6). CYP2D6 ultra-rapid metabolizers convert codeine to morphine and tramadol to an active metabolite, M1, faster and to a greater extent than in other people. In such mothers, unsafe levels of morphine and M1 are found in blood and breast milk [93] and most are unaware of their CYP2D6 metabolic status as an ultra-rapid metabolizer and the associated risks [93].

Lam *et al.* [94] investigated the effect of maternal *CYP2D6*, *CYP345*, *ABCB1* and *OPRM1* polymorphisms in relation to both neonatal and maternal CNS depression after oxycodone use during lactation. No association was found between the maternal genetic variants and oxycodone induced depression in neonates. However, the authors did note that mothers of symptomatic infants used oxycodone longer than asymptomatic infants and carriers of at least one copy of the *ABCB1* 2677 T variant experienced an increased risk of sedation.

Both oxycodone and hydrocodone are also metabolized by CYP2D6 and have the same risk for life-threatening respiratory depression in an infant breastfeeding from an ultra-rapid metabolizer mother. It took >20 years to recognize the life-threatening complications and deaths associated with codeine from CYP2D6 genetic variations in children undergoing tonsillectomy and nursing mothers. If we are not proactive in identifying those at risk and modifying their management, oxycodone (and hydrocodone) that are more potent and addictive than codeine (morphine) would unfortunately pose greater risks to these vulnerable patient populations.

Genetics related to oxycodone abuse

There has been an increase in abuse of prescription opioids including oxycodone, which contributes significantly to opioid overdose deaths. Wightman *et al.* [95] compared the likeability and/or abuse potential of hydrocodone, oxycodone and morphine and reported that oxycodone demonstrated high abuse liability based on its high likability scores and a relative lack of negative subjective effects. Jones *et al.* [96] analyzed variations in the genes that encode for μ-, k- and δ-opioid receptors and the dopamine metabolizing enzyme, COMT. Genetic variants in the μ- (*rs6848893*) and δ-opioid receptor (*rs581111*) influenced the responses to oxycodone administration [96]. Furthermore, self-reported 'stimulated' effects of oxycodone varied significantly as a function of *COMT* rs4680 genotype [96].

OPRM1 gene encodes the primary receptor target for most opioids. The largest and recent genome-wide association study in adults identified OPRM1 *rs1799971* as associated with opioid use disorder, genome-wide significance; $p = 1.51 \times 10^{-8}$ [97], *DRD2* gene encodes central dopamine receptor 2. DRD2 genetic variants, *rs1076560* and *rs1800497* (*TaqA1* of *ANKK1*), have been associated with OD, opioid addiction [98,99].

Cytochrome P450 (CYP) 2D6, CYP3A genetic polymorphism & oxycodone pharmacodynamics

Oxycodone pharmacodynamics are largely dependent on metabolic activity of the polymorphic enzymes CYP2D6 and CYP3A. This was demonstrated by Dagostino *et al.* [58] when they *CYP2D6*-genotyped 224 patients with chronic low back pain (CLBP). Carriers of *CYP2D6*6* and *9*, with reduced and absent enzymatic activity, respectively, were associated with therapeutic failure. CYP2D6 ultra-rapid metabolizers (UM) (*CYP2D6*2N* patients) had increased risk of side effects and rare alleles like *CYP2D6*1/*11*, **4/*6* and **41/*2N* demonstrated strong associations of efficacy and side effects with chronic opioid treatment.

Samer *et al.* [54] also corroborated these effects in a study of ten healthy volunteers genotyped for *CYP2D6* in which experimental pain (cold pressor test, electrical stimulation, or thermode), pupil size, psychomotor effects and toxicity were assessed after oral oxycodone. The *CYP2D6* UM demonstrated an increased pharmacodynamic effect with 1.5- to sixfold increase of analgesic effect as compared with extensive metabolizers (EM) (subjective pain threshold) after electrical stimulation, tolerance to cold pressor test, thermal pain threshold). Conversely, poor

metabolizers (PM) had a two- to 20-fold reduction of analgesic effects but cold pressor test and pupil size were unchanged relative to EM. In a different experimental pain study of 33 healthy volunteers, Zwisler *et al.* [100] found less reduction in pain area under curve on oxycodone for PM compared with EM (14 vs 26%, p = 0.012) following cold pressure. In the same study [54], the pharmacodynamic effect of drug–drug interaction after CYP2D6 blockade with quinidine showed reduced subjective pain threshold for oxycodone by 30%, while blockade of CYP3A4 with ketoconazole increased the analgesic efficacy and toxicity of oxycodone in *CYP2D6* UM. Similarly, Hagelberg *et al.* [101] also demonstrated increased pharmacodynamic effects of oxycodone when administered with voriconazole to 12 healthy subjects. However, Zwisler *et al.* [61] found no difference in postoperative analgesic effect of oxycodone between the PM and EM of *CYP2D6* in 270 patients.

CYP2D6 & Opioids Clinical Pharmacogenetics Implementation guidelines & translational implications

The Clinical Pharmacogenetics Implementation guidelines recommend against or caution using opioids that are metabolized by CYP2D6 (codeine, tramadol, hydrocodone and oxycodone) in ultra-rapid and poor metabolizers [102,103]. Unfortunately, stronger opioids such as oxycodone and hydrocodone are now increasingly prescribed as alternatives to codeine and tramadol in children and nursing mothers [92,104]. The CYP2D6 metabolites of oxycodone (oxymorphone) and hydrocodone (hydromorphone) are five- to 14-fold stronger than codeine's and tramadol's CYP2D6 metabolites. This shift in clinical practice to stronger opioids such as oxycodone places new mothers and their breastfed infants at greater, currently unknown, risk of adverse effects (life-threatening respiratory depression, persistent opioid use, addiction and accidental ingestion by young children) [105]. The practice of prescribing oxycodone as an alternative to codeine without considering *CYP2D6* genotype is reported to be dangerous for breastfed newborns [52,78] and nursing mothers [94] as oxycodone caused significant CNS depression [52,94], infantile life-threatening respiratory depression [78] and death [106].

Conclusion

Oxycodone has several favorable pharmacodynamic and pharmacokinetic properties which account for its use in treating postoperative and cancer pain. However, its metabolism and effects are influenced by several genetic polymorphisms that can cause considerable variability in its efficacy and safety. There is growing evidence linking polymorphic genetic enzymes CYP2D6 and CYP3A with clinical outcomes. Further research is needed to study the effects of these genetic polymorphisms, the contribution of oxycodone's metabolites to the overall clinical effects and impact on inter-individual variations in clinical effects. Understanding of the effect of genes related to opioid use disorder is warranted to aid in safe use of this commonly prescribed opioid.

Future perspective

Due to altered CYP2D6 metabolism, severe adverse effects such as life-threatening respiratory depression from codeine [107–110] and tramadol [111,112] were reported, resulting in the FDA's strongest black box warning contraindicating the use of codeine for the treatment of pain following tonsillectomy and adenoidectomy in children [113] and in nursing mothers. CYP2D6 genetic factors are also known to affect the metabolism of oxycodone and increase the risk in vulnerable populations. With the FDA warnings on codeine and tramadol in vulnerable patients, despite higher abuse potential than codeine and tramadol and metabolism by CYP2D6 pathway, oxycodone is used currently as a preferred opioid analgesic. Therefore, large and robust studies exploring pharmacokinetics, clinical outcomes and pharmacogenetics are needed to improve understandings of inter-individual variabilities in metabolism and clinical responses and to minimize risks of immediate and long-term adverse outcomes risks associated with oxycodone.

Executive summary

- Oxycodone is a semisynthetic opioid analgesic. It acts as a selective μ-opioid agonist and potential kappa receptor agonist, with little to no affinity for the delta receptor.
- The μ-opioid receptor's binding affinity is greater for methadone and morphine than for oxycodone; however, oxymorphone, the active metabolite of oxycodone, has a greater binding affinity than oxycodone.
- Oxymorphone is 14-times more potent and has a 40-fold higher μ-opioid receptor affinity than its parent drug oxycodone. Noroxycodone has four-times less μ-opioid receptor-binding affinity and poor antinociceptive potency in rats. Noroxymorphone, a further metabolite of noroxycodone, is a more potent shifter of DAMGO enkephalin from the μ-opioid receptor in rat brains.

- One study analyzed the general analgesic effects of oxycodone and its metabolites, revealing that even though oxymorphone and noroxymorphone have much higher μ-receptor affinities than oxycodone, oxycodone is accountable for 83 and 95% of the analgesic effect during oral and intravenous (IV) administration, respectively. This may be attributed to limited crossing of the blood–brain barrier for oxymorphone and noroxymorphone.

- Oxycodone has lower μ-opioid receptor affinity and G-protein activation than morphine. However, through the utilization of patient-controlled IV analgesia, equal analgesic efficacy was found for treating postoperative and cancer pain.

- Breastfeeding mothers taking oxycodone showed reduced pain and total opioid consumption as compared with breastfeeding mothers using IV morphine/codeine. No serious adverse events were found in mothers or newborns. Rates of CNS depression in newborns were 20.1% with oxycodone, 16.7% with codeine and 0.5% in acetaminophen groups.

- *OPRM1* polymorphism is an essential factor influencing the pharmacodynamics of opioids. About 100 variants of the *OPRM1* gene have been identified. SNP 118>G (*rs1799971*) variant (G-allele) showed a strong association with the amount of oxycodone for sufficient analgesia.

- Variability was also found regarding skin heat with genetic polymorphisms *OPRM1* SNPs *rs589046* and *rs563649*. Variability was found with visceral pain *rs589046*, *rs1799971*, *rs9479757* and *rs533586*. No association was found for the κ-opioid receptor (*OPRK1*) SNPs for any pain modalities.

- SNP A118G in the *OPRM1* gene was linked with reduced antinociceptive effect. C3435T (*ABCB1* gene) T allele variant had less adverse drug reactions to oxycodone compared with wild-type alleles. However, G2677T/A (*ABCB1* gene) carriers of T allele had better antinociceptive effect of oxycodone than the wild-type genotype and less adverse drug reactions. The combined 3435CC-2677GG had reduced antinociceptive and more severe adverse drug reactions than carriers of the variant alleles.

- Conversely, a different study did not find any association between SNPs A118G, C3435T and G2677T and IV analgesic effect in postoperative pain. Confounding factors included an uncontrolled environment and inhibitors of P-glycoprotein.

- One study found that, following major open abdominal surgery, patients with 118A homozygous (GG) required more 24-h postoperative analgesics than 118A homozygous (AA) and heterozygous (AG) patients. This relationship was verified in another study regarding cancer pain. This relationship was further strengthened by a study that looked at oxycodone with extensive research on adequate analgesia.

- No effect of polymorphisms in catechol-O-methyltransferase was found to be associated with postoperative oxycodone consumption. The pharmacodynamics of oxycodone is mostly dependent on polymorphic enzymes CYP2D6 and CP3A. CYP2D6 PM phenotype shows decreased efficacy, while UM shows strong efficacy and increased side effects. The blockade of CYP3A4 increased the analgesic efficacy and toxicity of oxycodone.

- The primary enzymes involved in the metabolism of oxycodone are CYP2D6, CYP3A4/5, UGT1A6, UGT1A3 and UGT2B7. Oxycodone is comprehensively highly metabolized in the liver by CYP enzymes (and in a limited amount by uridine diphosphate and UGT). Oxycodone is weakly metabolized by intestinal microsomes. A total of 45% of the drug is converted to noroxycodone, 11% to oxymorphone and 8% to α- and β-oxycodol.

- Many studies show that inducing the CYP3A4/5 pathway reduces area under curve (AUC) of oxycodone, while inhibiting the pathway increases AUC. However, inducing the CYP2D6 pathway increases the AUC.

- Women were found to have higher CYP3A4 expression and metabolize oxycodone faster than men. Clearance is lowest in preterm neonates and increases as term neonates transition to infants; however, increasing age was associated with a proportional decrease in clearance. Children older than 6 months of age reach peak metabolic activity quickly. Changes in CYP3A activity seems to be responsible for these differences. One study also found that lean body mass and age were significant covariates on clearance of oxycodone.

- Sparse information is available regarding *CYP3A* genetic variation and its outcomes on oxycodone. One study found *CYP3A5*3* decreased 12 h concentration and increased incidence of dose escalation.

- *CYP2D6* genetic variations give rise to poor metabolizers (homozygous for reduced function allele), intermediate metabolizer (heterozygous) and extensive or normal metabolizer (homozygous for wild-type allele) Most common variants include *CYP2D6 *2, 3, 4, 5, 10, 17* and *41*. *CYP2D6 *1* and *2* have normal activity; *10*, *17* and *41* have reduced activity and *3, *4* and *5* have null activity. Duplications of normal alleles result in ultra-rapid metabolizers. Incidence differs between ethnic groups.

- Oxycodone has high hepatic metabolism and care must be taken when given to patients with hepatic dysfunction. Although only 10–14% of oxycodone is renally eliminated, a dose reduction is advised when glomerular filtration rate is less than 50 ml/min.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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