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The Correlation between Pharmacological Parameters of Oxycodone and Opioid Epidemic

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Abstract

Despite its high risk of abuse and diversion, Oxycodone remains a common choice in the management of moderate-to-severe pain. Increased consumption, largely secondary to increased prescription over the last 2 decades, has led to renewed interests in its pharmacology, and opioids in general. The behavioral impacts of oxycodone (and other opioids) are associated with several factors such as its chemical properties, pharmacodynamic properties, and pharmacokinetic parameters. The solubility and rate of absorption are essential factors that participate in the rapid concentration of oxycodone in the brain. Alterations in oxycodone metabolism have been associated with dose - dependent kinetics, first-pass metabolism, and variations in genetic characters (poor or extensive metabolizers). Receptor types, receptor affinity, and genetic variations in the receptors play a crucial role in developing drug addictions. Other factors such as gender, age, pregnancy, and lactation could play a pivotal role in changing the Pharmacokinetic and -dynamic properties which are essential in abuse liability and withdrawal syndrome. This review highlights the current views on the pharmacological parameters including the pharmaceutical chemistry, pharmacokinetics, pharmacodynamics, drug-drug interactions and toxicity of oxycodone forms on a healthy population and their role in the opioid epidemic.

Keywords: Dependence & Abuse; Oxycodone; Pharmacodynamics; Pharmacokinetics Drug-Interactions; Structure-Activity Relationship; Toxicity

Introduction

Opioid epidemic (opioid crisis) is one of the most serious drug epidemics in the US and is defined as the massive overuse of opioid drugs, whether from medical prescriptions or illegal sources that result in an increasing number of deaths and hospitalizations. On October 16, 2017, the US Government declared the opioid epidemic a public health emergency [1]. Despite over 130 individuals dying daily after overdosing on opioids in the United States, oxycodone is still one of the most effective prescribed opioids for pain relief and has been implicated as one of the main causes of the current opioid crisis [2]. Data collected from the Center for Disease Control and Prevention (CDC) shows that the total cost of misuse opioid prescription is roughly $78.5 billion a year [3]. More interestingly, the total cost of curing misuse painkillers such as oxycodone prescription among US military is roughly $ 1 billion per year [4].

Pain management is the cautious use of medications to reduce pain. Pain, which is subjective, relies upon various factors which could be biological, psychological, and social, among others. Globally, many people suffer from different kinds of pain which could be classified as acute or chronic. In the United States, more than 116 million people live with chronic pain, and the financial burden is between $560-635 billion per year [5]. Medical experts tend to prescribe opioids, which are pharmacological agents that have high effective analgesic properties, known to lessen various kinds of pain [6]. It is difficult to find a safe painkiller, one without side effects.

Opioids are frequently prescribed to alleviate pain. Because of their addictive properties, opioid drugs are currently second to marijuana, and ahead of cocaine when it comes to dependence [7]. Prescribed opioids such as oxycodone, hydrocodone, codeine & morphine are widely used in pain relief. The U.S government records show more than 289 million prescriptions for opioids (about 6.8%) from the total number of prescriptions dispensed in the U.S in 2012 [8]. Among this, hydrocodone- and oxycodone-containing products are the most prescribed opioids, accounting for about 84.9% of all prescriptions [9]. The data also indicates an annual increase in opioid prescriptions among medical experts since 2007 in the U. S [8]. Research suggests that long-term opioid treatment for chronic pain has potential risks that appear to be dose-dependent [10]. Improper use of prescribed opioid and opioid overdose has become an epidemic issue [6]. There are more than 30,000 cases of death per year in the United States due to opioid overdose [11].

Oxycodone is a semisynthetic opioid narcotic analgesic agent that is predominantly used to relieve moderate-severe pain [5]. It was first formulated in 1916 from Thebaine, a natural opioid alkaloid, and released by firm E. Merck (Darmstadt) as a compound drug called Scophedal (SEE) with scopolamine, ephedrine to be in clinical use in 1928 [12]. However, this compound was discontinued in 1987. In 1995, the FDA proved the current version of oxycodone [6]. It was the first opioid prescribed in the US to manage pain without addictive effects. This led to an increased interest in Oxycodone prescriptions, unaware of the overdose potentials [6]. Subsequent studies have shown a strong link between severe adverse effect and oxycodone dose, with a potential risk of addiction and then overdose, which could ultimately result in death [13].

Structure-Activity-Relationship of Oxycodone (Figure 1)

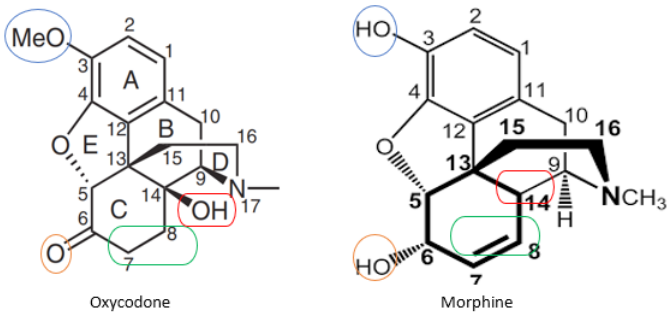

Figure 1: Structure of Oxycodone and Morphine.

Oxycodone (4,5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride) is a white, odorless crystalline powder with a molecular weight of 351.83 g/mol. It is hygroscopic, dissolves in water (1g in 6 to 7ml) and slightly soluble in alcohol (octanol-water partition coefficient 0.7) [14]. It is a low-molecular-weight opioid that is more lipophilic than morphine. Due to the alterations in structure between oxycodone and morphine, oxycodone initially undergoes less biotransformation compared to morphine and thus has higher bioavailability [15]. In addition, owing to the molecular differences between oxycodone and morphine, oxycodone has less immunosuppression compared to other opioids [16]. Therefore, studying the structure-activity of oxycodone will provide a better understanding of its pharmacological activity.

Like morphine, it belongs to the class of opioid analgesics. Its skeleton constitutes 5 rings; Aromatic ring (Ring A), Cyclohexane ring (Ring B), Ketone ring (Ring C), Piperidine ring (Ring D) and a Tetrahydrofuran ring (Ring E). Oxycodone differs from morphine at C3, C6, C7-C8, and C14 positions. The substitution of a methoxy group at the C3 position (etherification) decreases μ receptor affinity and increases the antitussive property [17] and it prevents extensive first-pass metabolism in conjugation with glucuronic acid and therefore has a higher bioavailability [15]. In addition, the substitution of a ketone group at C6 and removal of unsaturated bonds between C7 and C8 increase the potency of oxycodone 8-10 times more than morphine. Substitution of a hydroxyl group at the C14-α position increases μ agonist property. 3° amine in the piperidine ring is necessary for activity. The substitution of the N-methyl group increases agonist activity. However, increasing the number of carbons bound to nitrogen can increase antagonist activity [17]. Substitution of a methoxy group at C3, a ketone group at C6 and present ether group increase the lipophilicity of oxycodone.

Pharmacokinetic Properties

The correlation between the pharmacokinetic profile of oxycodone and its abuse liability was explained in the 1970s. The variety of pharmacokinetic parameters, including lipid solubility, the time to peak plasma concentration, the blood-brain barrier transport (a merging of passive diffusion and active transport in and out of the brain), and bioactive bio-transformations, have been linked to the essential abuse liability of oxycodone. Unlike morphine, oxycodone is actively transported across the blood-brain barrier which could reach 3× higher levels in the brain than blood and has a more rapid onset of effect and several active metabolites that play an important role in its greater abuse profile [18].

Absorption

The rate of oxycodone absorption and its bioavailability depends upon many aspects such as lipid solubility, molecular size, dosage form, and first-pass effects. It has been reported that high lipid solubility of opioids plays a pivotal role in the absorption and onset of action of opioid which has been linked with greater abuse potential [19,20]. When Oxycodone is administered orally, it is easily absorbed. The vast majority of absorption takes place

in the Gastrointestinal (GIT) system, with the active drug passing through the membranes of the small intestines [21]. There are some pharmacological actions of Oxycodone that might take place in the GI tract before absorption, which could cause constipation [22,23]. Bioavailability of oxycodone ranges from 60% to 80% [24]. Its oral bioavailability is higher than other opioids because of the lower first-pass effect [25].

Dosage form has an essential impact on the absorption half-life of oxycodone in healthy people.

After oral administration of oxycodone 0.15mg/kg Immediate-Release (IR) capsule, the median T_{max} was 1.5h (range 1–5), the mean C_{max} was 26ng/ml [26]. Extended Release (ER) capsule ((36mg) the median T_{max} was 4.5 range (1.5 – 9.0), the mean C_{max} was 55.3 (13.6) [27].

Following administration of oxycodone IR tablets 5 mg, the AUC was 99 (36) ng/mL/h, C_{max} was 15.6 (4.4), and T_{max} was 1.4 (0.7) Whereas, CR tablets 10 mg the AUC was 103.6 (40) ng/mL/h, C_{max} was 15.1 (4.7), and T_{max} was 3.2 (2.2) (50). T1/2 was shorter with IR tablets (3 h) than CR tablets (4–5h) [28].

After administration of oxycodone Intramuscularly (IM) (0.14mg/kg), the mean maximum plasma concentration (C_{max}) was 34ng/mL (Standard Deviation [SD] 10), median time to C_{max} (T_{max}) was 1.0h (range 0.5–1.5), [29]. While after administration of oxycodone intravenously 0.05mg/kg[3], C_{max} was about 13ng/mL (9-17) and median time to C_{max} (T_{max}) 0.42h (0.33-4) and area under the curve AUC was 70ng/Ml/h (52-88) [30]. In addition, after oral liquid administration of oxycodone (0.28mg/kg), the median T_{max} was 1h (range 0.5–1), the mean C_{max} was 38ng/mL (SD 14),) [29]. Following rectal administration of oxycodone hydrochloride extended-release tablets in healthy population, the area under the plasma concentration-time curve (AUC) and peak plasma concentration were increased by 39 and 9%, respectively, compared with oral administration [31].

Absorption of the CR preparation (OxyContin) is not meaningfully impacted via diet, except the 160mg OxyContin tablet which shows a peak plasma concentration which was 25% higher with a high-fat meal. This form is no longer commercially accessible. In addition, IR tablets with a high-fat meal show an increase in the extent of absorption with the mean value for AUC0-∞ increasing to 120% (CI = 109-132%). Furthermore, the mean value for C_{max} declines to 82% (CI = 47-91%) of the value observed under fasting conditions [32].

Distribution

While oxycodone is hygroscopic, freely soluble in water and slightly soluble in ethanol (log P = 0.7), it can pass through several biological membranes [33]. The Volume of Distribution (Vss) for oxycodone was 2.6 L/kg in an adult following IV (30). It can cross the Blood-Brain Barrier (BBB) via active transport and therefore it can rapidly concentrate in the brain and cause a fast onset of action [18].

Many studies have been conducted to assess the distribution of oxycodone through BBB. An animal study showed the unbound concentration of oxycodone in the brain was 2.5 and 6 times higher than in the blood, respectively, suggesting an active transport of oxycodone across the BBB. Interestingly, the oxycodone brain: plasma ratio seems to be dose-dependent [34,35]. In this study, oxycodone infusion was given for 6 days, and its concentration in the brain and plasma were measured. The brain: plasma ratios were 3.1 in the low-dose group (20 mg/kg/day), 1.5 in the medium-dose group (45 mg/kg/day) and 1.0 in the high-dose group (120 mg/kg/day) [36]. It has been suggested that a proton-coupled antiporter for organic cations in the endothelial cells could be the active influx transporter for oxycodone at the BBB [37,38]. Plasma protein binding is roughly 38–45%, mainly albumin, which is widely distributed in many body tissues such as the central nervous system and some peripheral tissues such as skeletal muscle, liver, intestinal tract, lungs, spleen [39-41]. Oxycodone can spontaneously cross the placenta and is excreted in human breast milk [42-44].

Metabolism

Most of the Oxycodone's metabolism occurs in the liver, however, there are numerous sites in the body where metabolism can also occur. Oxycodone undergoes 2 rounds of metabolism; phase 1 metabolism mainly takes place in the liver controlled by Cytochromes P450 (CYPs), and phase 2 metabolism in which active metabolites are conjugated to hydrophilic substances through glucuronidation [45]. Thus, any functional changes in Cytochrome enzymes can lead to unwanted actions involving changes in efficacy, safety, and toxicity through phase 1 metabolism [46]. Roughly 45% of the total dose undergoes N-demethylation to form noroxycodone by CYP3A4. CYP2D6 mediates O- demethylation of oxycodone to oxymorphone at methyl group in the 17-position which is about 19% of the total dose. Oxymorphone essentially forms in liver microsomes, and its quantity relies on enzyme activity [47]. Both metabolites undergo demethylated metabolite to noroxymorphone by the action of CYP2D6 and CYP3A4 correspondingly [48]. The active metabolite (oxymorphine) has extra affinity and potency when it binds with the μ-opioid receptor which is 40 times in affinity and 14 times in potency compared to the original form [49].

Oxycodone mainly undergoes enzymatic metabolism for oxidation monitoring by CYP2D6 and CYP3A4. There are more than a million genetic polymorphisms that may be functional or nonfunctional in these enzymes. When this happens, the activity would be changed, and the pharmacodynamics outcome will be diverse. Also, genetic polymorphisms might be different from one population to another due to ethnic changes [50].

CYP2D6 genotype plays a major role in the pharmacokinetics of oxycodone and its products during metabolism. Consequently, the duration of metabolism will be changed especially in children who have genotype in CYP2D6 enzyme because it is hard to recognize if there is a metabolism phenotype and has a dominant role in metabolism duration [50]. Metabolism phenotype could be classified into poor metabolizers, intermediate metabolizers, extensive metabolizers or ultra-rapid metabolizers. An individual with CYP2D6 polymorphisms and Phenotypes requires genetic testing to determine CYP2D6 variants, which would lead to adjustments in the therapeutic dose of oxycodone [51]. As a result, the dose of oxycodone has to be readjusted based on metabolism because oxycodone and its metabolites have variations in their action from no-action to experiencing a high risk of side effects, particularly if it is consumed with another opioid [50] (Figure 2).

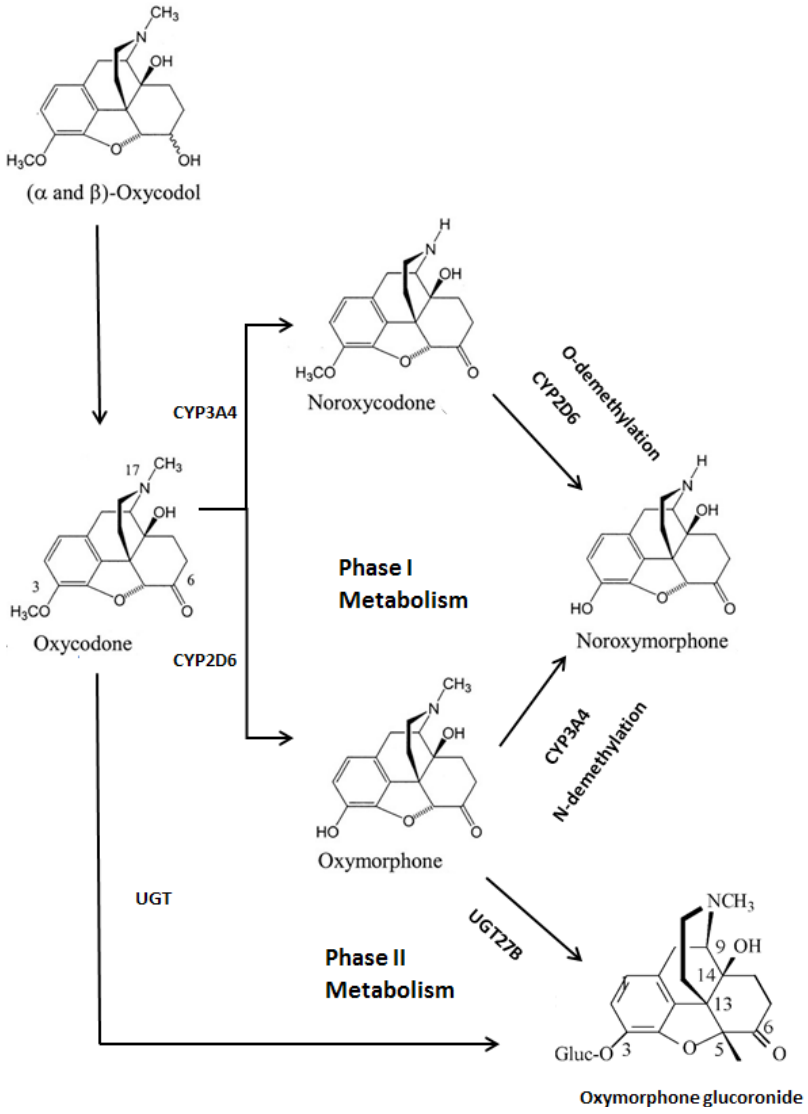

Figure 2: Phase I and Phase II metabolism of Oxycodone.

Excretion

Oxycodone and its metabolites are excreted primarily by the kidney [52]. The total plasma clearance and elimination half-life were different after administration of oxycodone in different forms. After administration of oxycodone IM (0.14mg/kg), the total plasma clearance CL was 0.78L/min (SD 0.2) and elimination half-life ($t_{½}$) *was* 4.9h (SD 0.8) (29), whereas after IV (0.05 mg/kg[3]**)**, the CL was (0.83L/min) (range 0.6–1) and ($t_{½}$) was 2.6h (range 2-3.1) [53]. The elimination half-life after administration of oxycodone 0.15mg/

kg Immediate-Release (IR) capsule, showed the $t_{½}$ was (3.8h) [26]. Whereas, $t_{1/2}$ of (ER) capsule 36 mg was about 5.6 hours under fed conditions and CL was 1.4 L/min in adults [27]. While $t_{½}$ after administration oxycodone 0.28 mg/kg oral liquid was 5.1 h (SD 1.7) (29).

As oxycodone is metabolized in the liver and excreted via kidney, excretion, and clearance of oxycodone are affected by renal and hepatic dysfunction. A recent study illustrates that elimination ($t_{½}$) of oxycodone is slightly prolonged in patients with renal insufficiency compared to healthy people ($t_{½}$ median 3.9 vs. 2.3h). This was mainly due to decreased total plasma clearance (0.8 vs. 1.1L/min), and an increased volume of distribution (4.0 vs. 2.4 L/kg). Besides, the inter-individual variation is widespread in renal dysfunction patients ($t_{½}$ 1.8–25.7 vs. 1.3–4.0h) [54]. Furthermore, other data show that hepatic impairment also meaningfully impacts the PK of oxycodone. After administration of a CR oxycodone, 20 mg tablet to patients with hepatic impairment, the elimination half-life ($t_{½}$) was longer (7.7 vs. 5.4h), AUC was higher (387 vs. 199ng·h/mL) and C_{max} was higher (25 vs. 17ng/mL), compared with healthy controls [55] (Table 1).

	AUC (ng/mL/h)	t½ (h)	C_{max} (ng/mL)	T_{max} (h)	CL (L/min)
Intravenously, 0.05 mg/kg[3]	70ng/Ml/h (52-88)	2.6 h (range 2–3.1).	13 ng/mL (9-17)	0.42 h (0.33-4)	0.83 (0.6–1.0)
Intramuscularly, 0.14 mg/kg	208 (49)	4.9 h (SD 0.8),	34 ng/mL	1.0 h (range 0.5–1.5)	0.78 L/min (SD 0.2)
Orally, liquid, 0.28 mg/kg	245 (84)	5.1 h (SD 1.7)	38 ng/mL (SD 14)	1 h (range 0.5–1)	
Orally, IR Capsule 0.15 mg/kg,		(3.8 h)	26 ng/ml	1.5 h (range 1–5)	
Orally, ER Capsule 36 mg	540 (143)	5.6 hours	55.3 (13.6)	4.5 (range1.5 – 9.0)	1.4 L/min
Orally, IR tablet, 5 mg	99 (36)		15.6 (4.4)	1.4 (0.7)	
Orally, CR tablet, 10 mg	104 (40)		15.1 (4.7)	3.2 (2.2)	

Table 1: Pharmacokinetic parameters of oxycodone forms in healthy subjects.

Sex Differences, Age, Pregnancy, and Lactation in The PK of Oxycodone

Pharmacokinetic parameters of oxycodone are diverse when it comes to age, gender, and pregnancy status of patients. Age is an important factor affecting the pharmacokinetics of oxycodone. The plasma concentrations, AUC and half-life of oxycodone are higher in adults compared to younger patients after administration of different oxycodone forms, whereas, the clearance has been found lower in adults and prolonging half-life [51,56,57].

The clearance of Oxycodone increases with age in the first 6 months after birth. In vitro study of oxycodone metabolism in human hepatocytes from different age groups showed that fewer metabolites of oxycodone are formed in infants than in older subjects, indicating that metabolism of oxycodone is not fully matured in neonates [58]. Another PK study in children shows that CL and $t_{1/2}$ exhibited excessive interindividual variation in infants aged ≤ 2 months, whereas, in infants with age < 6 months, both CL and $t_{½}$ were associated with age [59]. Moreover, a Population pharmacokinetic analysis study has been performed to assess the impact of gender in PK of oxycodone with no gender effect observed on the pharmacokinetics of oxycodone.

Several physiological and anatomical alternations can be found in a female body that could take place during Pregnancy and labor which could affect body composition and gastrointestinal, circulatory, renal and hepatic functions. These changes can strongly affect PK accordingly [60,61]. One of the most devastating ramifications of the opioid epidemic is the increased incidence of newborns undergoing withdrawal syndrome due to opioid use and misuse during pregnancy [3]. A study of PK of oxycodone in women in labor and neonates after administration of oxycodone I.V. for pain relief in the first stage of labor, found that non-

pregnant women had lower clearance, a high volume of distribution and a longer elimination half-life as opposed to pregnant women [62]. It found that maternal Oxycodone concentrations were comparable to those of neonates. Maternal plasma concentrations of oxycodone can be used to predict fetal exposure. In this study, neonates showed slight exposure to oxycodone metabolites which suggest that metabolites can cross the placenta less efficiently than oxycodone [62].

Pharmacodynamic Properties and Genetic Variation

Several pharmacodynamic activities have been identified as prospective mediators of opioid tolerance. These variations include receptor subtypes, receptor affinity, genetic predisposition, cross-tolerance, and receptor attaching in the peripheral nervous versus the central nervous system [63].

Oxycodone is an agonist for the μ-opioid receptors and can bind to other opioid receptors at a higher dose. These receptors exist in several tissues including the Central Nervous System (CNS) such as the respiratory center in the brain stem, the cough center in the medulla, muscles of the pupils, gastrointestinal tract, the Cardiovascular System (CVS), and the endocrine system, [64].

Once oxycodone enters the brain, it works as an agonist at mu, kappa, and delta-opioid receptors that are in the central nervous system and also, the peripheral nervous system. It binds to coupled G- protein receptors and acts as modulators, which stimulates the exchange of GTP to GDP on the G-alpha subunit [65]. A study was conducted to assess the ability of oxycodone and its metabolites to cause stimulation of the G-proteins coupled to the μ-opioid receptor. In vitro, oxycodone is a partial agonist, with oxymorphone displaying 30- to 40-fold greater strength than the parent drug [66,67].

Oxycodone inhibits adenylate cyclase which results in reduced intracellular CAMP. Oxycodone closes calcium channels (by an agonist of kappa-receptor) and prevents entrance of calcium ions inside the neuron and open potassium channels (by mu and delta receptor agonist) and increase potassium influx to extracellular space which causes inhibition on neurotransmitter release from the presynaptic terminal of the neurons such as substance P, GABA, dopamine, acetylcholine, and noradrenaline. This leads to membrane hyperpolarization of the nerve cell. These neurotransmitters are very important in the transmission of pain, thus, activation of opioid receptors leads to decreased release of these substances, eliciting a strong painkiller effect [65].

Studies have shown that Polymorphisms in numerous genes, including genes encoding opioid receptors and ligands, are associated with drug addiction [68].

The positive subjective impacts and the rewarding of oxycodone (and other opioids) have been connected to its stimulation of the μ-opioid receptor, which activates the reward center of the brain to release dopamine, whereas, the κ-opioid receptor is thought to mediate dysphoria. It has been anticipated that genetic factors contribute around 80% of the susceptibility to Opioid Use Disorder (OUD). Variation in the genes that encode these opioid receptors has been associated with maladaptive opioid use [69].

Variations in the OPRM1 gene have been considered as risk factors for opioid addiction [70]. It has been reported that the most widespread SNPs in the OPRM1 gene occurred at A118G. A118G variant is markedly linked to opioid dependence ethnic variation and addiction as it could change the functional properties of the human mu-opioid receptor [71]. Whereas, variation in the genes that encode the δ- and κ-opioid receptors (OPRD1, OPRK1) have been correlated with the effectiveness of OUD pharmacotherapy and the severity of opioid withdrawal. It has been reported that genetic variation in dopamine receptor polymorphisms has been linked to cue-elicited opioid craving [69].

Drug-Drug Interaction (DDIs)

Over the past few decades, researchers studied oxycodone's interaction because it is a highly prescribed painkiller agent. The interactions with oxycodone could take place whether pharmacokinetically or pharmacodynamically and in some cases, both [72]. It has been shown that oral oxycodone has high drastic potential interaction compared with other forms as some first-pass metabolism in the intestine [73]. The interaction could take place by different methods such as CYP2D6 or/and CYP3A4 substrates, anticholinergic-like effects, CNS depression, delays gastric emptying, hypotensive impacts, reduces seizure threshold, opioid agonist, and serotonergic effects. As Oxycodone works in several parts of the body especially the brain's part that controls breathing, a CYP2D6 or/and CYP3A4 substrates or competitive receptors drugs could strengthen the negative impact and might cause a serious problem. Therefore, attention to these new interactions will assist patients to maximize oxycodone efficacy and minimize adverse outcomes. There are a lot of medications that can interact with oxycodone [74,75].

Pharmacokinetic DDIs:

Pharmacokinetic DDIs take place either via inhibition or induction of oxycodone metabolism through CYP450 enzymes or inhibition of the metabolism of the other agents exerted via oxycodone or by reducing the renal elimination of oxycodone [76].

Interacting drug class	Mechanism	Potential effect
Telithromycin	a strong CYP3A4 inhibitor	It increases oxycodone effects which could lead to fatal respiratory depression.
Amiodarone, Aprepitant	a moderate CYP450 3A4 inhibitor	Increase oxycodone concentration and; therefore, increase the risk of CNS. respiratory depression, and psychomotor impairment
Apalutamide	a strong CYP450 3A4 inducers	Co-administration with oxycodone may decrease the plasma concentration of oxycodone levels and reduce the effectives of oxycodone
Atazanavir, Ceritinib, Fluconazole	a strong CYP450 3A4 inhibitor	Increase oxycodone concentration and; therefore, increase the risk of CNS. respiratory depression, and psychomotor impairment
Chloramphenicol, Clarithromycin, Conivaptan, Darunavir, Delavirdine, Erythromycin, Ketoconazole	a strong CYP450 3A4 inhibitor	Coadministration with these drugs could raise plasma concentration of oxycodone leading to drowsiness, dizziness, lightheadedness, difficulty concentrating, and impairment in thinking and judgment. In severe cases, low blood pressure, respiratory distress, fainting, coma, death may occur
Ciprofloxacin	a moderate CYP450 3A4 inhibitor	Ciprofloxacin raises the plasma concentration of oxycodone leading to drowsiness, dizziness, lightheadedness, difficulty concentrating, and impairment in thinking and judgment. In severe cases, low blood pressure, respiratory distress, fainting, coma, and might cause death
Cobicistat	a strong CYP450 3A4 inhibitor	Cobicistat increases the plasma concentrations of oxycodone and; therefore increase the risk of respiratory depression, CNS, and psychomotor impairment
Crizotinib	a moderate CYP3A4 inhibitor	Crizotinib increase the plasma concentrations of oxycodone increases the plasma concentrations of oxycodone and; therefore increases the risk of respiratory depression, CNS, and psychomotor impairment.
Cyclosporine	a moderate CYP3A4 and P-gp inhibitor	It increases the plasma concentrations of oxycodone and increases the risk of CNS and respiratory depression, psychomotor impairment
Dabrafenib	a moderate CYP450 3A4 inducer	Dabrafenib decreases plasma concentration and the efficacy of oxycodone.
Enzalutamide	a strong CYP450 3A4 inducer	it reduces plasma concentration and effectiveness of oxycodone and leading to watery eyes, runny nose, sneezing, yawning, excessive sweating, goosebumps, fever, chills, flushing, restlessness, irritability, anxiety, depression, pupil dilation, tremor, rapid heartbeat, body aches, abdominal cramping, loss of appetite, nausea, vomiting, diarrhea, and weight loss
Erdafitinib	inhibitor as well as an inducer of CYP450 3A4	Erdafitinib changes the plasma concentrations of oxycodone resulting in increased toxicity and or decreased efficacy of oxycodone
Goldenseal	strong oCYP3A4 and CYP2D6 inhibitor	Goldenseal raises oxycodone concentration and; therefore increase the risk of CNS, respiratory depression, and psychomotor impairment
Grapefruit	a strong CYP3A, CYP2D6, and P-gp inhibitors	Grapefruit increases the plasma concentrations of oxycodone and; therefore increases the risk of CNS, respiratory depression, and psychomotor impairment.

Idelalisib, Itraconazole, Nelfinavir, Netupitant, Ritonavir, Saquinavir, Tipranavir, Voriconazole	strong inhibitor of CYP3A4	Coadministration of oxycodone with these drugs could increase the plasma concentrations of oxycodone and; therefore increase the risk of CNS, respiratory depression, and psychomotor impairment.
Indinavir, Mifepristone	a strong CYP3A4 inhibitor	These drugs increase the efficacy of oxycodone, leading to fatal respiratory depression.
Isavuconazonium	a moderate CYP3A4 inhibitor	May increased or prolonged oxycodone efficacy including fatal respiratory depression
Lopinavir/ Ritonavir	A strong CYP3A, CYP2D6, and P-gp inhibitors	It increases the efficacy of oxycodone, leading to fatal respiratory depression.
Lorlatinib	a moderate CYP450 3A4 inducer	Lorlatinib reduces the efficacy and plasma concentration of oxycodone. Therefore, withdrawal symptoms may occur such as watery eyes, runny nose, sneezing, yawning, excessive sweating, fever, chills, flushing, restlessness, irritability, anxiety, depression, pupil dilation, tremor, rapid heartbeat, and kicking, abdominal cramping, loss of appetite, nausea, vomiting, diarrhea, and weight loss.
Lumacaftor/ Ivacaftor	a strong CYP3A4 inducer	decrease oxycodone concentrations which lead to reducing in efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence
Modafinil	a weak CYP450 3A4 and P-gp inducers	Modafinil reduces the efficacy and plasma concentration of oxycodone. Therefore, withdrawal symptoms may occur such as watery eyes, runny nose, sneezing, yawning, excessive sweating, fever, chills, flushing, restlessness, irritability, anxiety, depression, pupil dilation, tremor, rapid heartbeat, and kicking, abdominal cramping, loss of appetite, nausea, vomiting, diarrhea, and weight loss.
Nilotinib	a moderate CYP3A4 inhibitor	May increase the plasma concentrations of oxycodone and the risk of CNS and respiratory. depression, psychomotor impairment
Posaconazole	a strong CYP3A4 inhibitor	May increased or prolonged oxycodone efficacy including fatal respiratory depression
Ribociclib	a moderate CYP3A4 Inhibitor	Ribociclib effects on oxycodone metabolism. It increases the serum concentration of oxycodone and its active metabolite Oxymorphone which could lead to enhance the toxic effect
Rifabutin, Rifapentine	moderate CYP3A4 inducer	They reduce plasma oxycodone concentrations and efficacy of oxycodone
Rifampin	a strong CYP3A4 inducer	It decreases plasma oxycodone concentrations and efficacy of oxycodone

Table 2: Pharmacokinetic DDIs.

Pharmacodynamic DDIs

Pharmacodynamic DDIs could happen by enhancing the analgesic efficacy and toxicity through oxycodone and nonopioid mechanisms. Also, they take place either by reversal or inhibition of the impact of oxycodone via blocking the opioid receptors, or by alteration of dopaminergic, cholinergic, adrenergic, and serotoninergic activity in the central nervous system [76].

Interacting drug class	Mechanism	Potential effect
Alcohol	additive effects	Alcohol increases the impact of oxycodone, leading to Drowsiness, dizziness. Also, they could increase the risk for overdose; slowed or difficulty breathing; reduced motor control; unusual behavior; memory problems
Atropine And Scopolamine,	additive effects	They increase the risk of urinary retention, severe constipation, which may lead to paralytic ileus
Cannabinoids	synergistic antinociceptive impact	It may cause profound sedation, respiratory depression, coma, and death
Buprenorphine, Butorphanol, Nalbuphine, And Pentazocine	antagonistic effects; additive effects	Coadministration of these drugs with oxycodone decrease the impact of. Oxycodone, and may increase the danger of risk of intense respiratory and CNS depression, hypotension psychomotor impairment, hypotension, intense constipation, and paralytic ileus.
Chlordiazepoxide, Oxazepam, Temazepam, Lorazepam.	Additive effects	Increase the risk of intense hypotension, vasodilation and severe respiratory depression, psychomotor impairment.
Citalopram, Buspirone, Almotriptan, Escitalopram, 5-HTP	Additive effects	Coadministration of These drugs with oxycodone could affect the serotonergic neurotransmitter system which leads to serotonin syndrome. Increase the risk of intense respiratory depression, psychomotor impairment.
Clomipramine, Desipramine, Cyclobenzaprine, Eletriptan, Mirtazapine, Amitriptyline, Amoxapine	additive effects	Coadministration of These drugs with oxycodone raises the risk of hypotension and intense respiratory depression, psychomotor impairment, serotonin syndrome, intense constipation, and paralytic ileus.
Imipramine, Methadone, Nortriptyline, Oxycodone, Oxymorphone, Morphine, Hydrocodone, Cocaine, And Hydrocodone, Meperidine	Additive effects	Coadministration of These drugs with oxycodone could cause hypotension and intense respiratory depression, psychomotor impairment, intense constipation, and paralytic ileus
Isocarboxazid, Levomilnacipran, Levorphanol, Milnacipran, Naratriptan, Rizatriptan, Sertraline, Tramadol, Trazodone, Trimipramine	additive effects	Increase the risk of intense hypotension, respiratory and CNS. depression, psychomotor impairment, and effect serotonergic neurotransmitter system which lead to serotonin syndrome
Kava	Additive effects	Kava increases the risk of severe respiratory and depression, and psychomotor impairment.
Linezolid	synergistic effects, linezolid reversibly inhibits monoamine oxidase	Linezolid Increases the risk of serotonin syndrome
Lofexidine	Additive effects	Lofexidine could lead to intense hypotension, respiratory depression, psychomotor impairment

Methylene Blue	synergistic effects, methylene blue reversibly inhibits monoamine oxidase	Methylene Blue could cause hypotension, respiratory depression, psychomotor impairment, and effect serotonergic neurotransmitter system which lead to serotonin syndrome, and orthostasis
Midazolam	additive effects; antagonistic effects, oxycodone may decrease seizure threshold	Midazolam could cause hypotension, respiratory depression, psychomotor impairment; may change seizure control
Revefenacin Inhaled	Additive effects	Increase. risk of intense constipation/paralytic ileus, and other anticholinergic adverse impacts
Selegiline Transdermal	Additive effects	Coadministration with oxycodone may cause psychomotor impairment, hypotension and intense respiratory depression, serotonin syndrome, and orthostasis.
Tapentadol	Additive effects	Coadministration with oxycodone could lead to intense hypotension, psychomotor impairment intense respiratory depression, constipation, paralytic ileus.
Venlafaxine, Vilazodone, Zolmitriptan1, Sumatriptan	Additive effects	Coadministration with oxycodone may cause psychomotor impairment, hypotension and intense respiratory depression, and serotonin syndrome.

Table 3: Pharmacodynamic DDIs.

Pharmacokinetic and Dynamic DDIs

Pharmacokinetic and Pharmacodynamic DDIs take place when oxycodone interacts with other agents at the level of metabolism, absorption or excretion, and receptor sites where they could have potentiating or additive impacts [76].

Interacting drug class	Mechanism	Potential effect
Verapamil	a moderate CYP3A4 inhibitor, additive effects	Co-administration of these drugs could lead to an increase in oxycodone levels and increase the risk of hypotension and respiratory depression, and psychomotor impairment.
Stiripentol	CYP3A4 inhibitor, additive effects; antagonistic impacts, oxycodone may reduce the seizure threshold.	Stiripentol increases the serum concentration of oxycodone, resulting in respiratory depression, psychomotor impairment profound sedation, coma, and death or reduce the efficacy; may change seizure control
St. John's Wort	CYP3A4 inducer, additive effects,	St. John's Wort reduces oxycodone levels resulting in an increase in the risk of serotonin syndrome, and a decrease in the efficacy of oxycodone.
Primidone	additive effects; antagonistic effects. CYP3A4 Inducer, oxycodone may reduce the seizure threshold	Co-administration with oxycodone could reduce oxycodone levels, leading to reduce the efficacy, and Increase the risk of profound respiratory depression, psychomotor impairment, and may change seizure control.

Phenobarbital	CYP3A4 Inducer, additive effects; antagonistic impacts,	Phenobarbital reduces oxycodone levels, leading to reduce the efficacy, Increase the risk of profound respiratory depression, psychomotor impairment, and may change seizure control.
Paroxetine	CYP2D6 inhibitors, additive impacts.	Paroxetine reduces the efficacy and levels of active metabolite oxymorphone and Increase the risk of psychomotor impairment, profound respiratory depression, and affect serotonergic neurotransmitter system resulting in serotonin syndrome
Nefazodone	CYP3A4 inhibitors, additive effects)	Nefazodone raises oxycodone levels, leading to respiratory depression, hypotension, and psychomotor impairment, Serotonin syndrome, severe constipation/paralytic ileus.
Mitotane	a strong CYP3A4 inducer, additive effects	Co-administration of these drugs could lead to an increase in oxycodone levels and increase the risk of hypotension and respiratory depression, and psychomotor impairment
Fosphenytoin	a strong CYP3A4 inducer, additive impacts; antagonistic impacts.	Co-administration with oxycodone could increase the serum concentration of oxycodone, causing respiratory depression, psychomotor impairment profound sedation, coma, and death.
Fluvoxamine	CYP3A4 and CYP2D6 inhibitors, additive impacts.	Fluvoxamine increases the risk of profound respiratory and CNS. depression, psychomotor impairment, and effect serotonergic neurotransmitter system which leads to serotonin syndrome.
Fluoxetine	CYP3A4 inhibitors, additive impacts	Fluoxetine reduces the efficacy and levels of active metabolite oxymorphone. Also, it could cause profound respiratory depression, psychomotor impairment, and effect serotonergic neurotransmitter system resulting in serotonin syndrome
Flibanserin	CYP3A4 inhibitor, additive impacts	Flibanserin increases the risk of hypotension and respiratory depression, and psychomotor impairment.
Efavirenz	a moderate CYP3A4 inducer additive effects)	Efavirenz reduces efficacy. It increases the risk of profound respiratory depression, psychomotor impairment.
Diltiazem	a moderate CYP3A4 inhibitor and additive effects.	Diltiazem raises oxycodone levels, leading to an increase in the risk of hypotension and respiratory depression, and psychomotor impairment.
Clobazam	CYP3A4 inducer, additive effects; antagonistic effects.	It reduces the efficacy Increase the risk of profound CNS and respiratory depression, psychomotor impairment and may change seizure control
Alprazolam	CYP3A4 inhibitor, additive effects	Co-administration of these drugs could lead to central nervous system depression can lead to serious side effects such as respiratory distress, coma, and even death.

Table 4: Pharmacokinetic and Dynamic DDIs.

Oxycodone Toxicity

Despite its toxic profile and abuse potential, Oxycodone remains a common choice in the management of chronic non-cancer pain [76]. There are subtle differences in the analgesic potential of Oxycodone and Morphine and no significant evidence exists in demonstrating their adverse effects [77]. In a study to assess the efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain, oxycodone showed a similar adverse event profile to other opioids [78]. Adverse effects of oxycodone are related to its effect on receptors and direct effects on the central nervous system, the brain & spinal cord, is the primary site of its analgesic action [79]. Oxycodone acts on Mu and kappa receptors in the Central Nervous System (CNS), which produces direct effects on the Cardiovascular (CVS) and Gastrointestinal (GIT) systems (Al-Hasani & Bruchas, 2011). Commonly reported

adverse effects following the use of oxycodone in adults to include constipation, nausea, vomiting, dizziness, pruritus, somnolence, dry mouth, headache, sweating while those in children include nausea & vomiting, pyrexia, constipation, headache [80].

In the CNS, Oxycodone mediates its major therapeutic action, analgesia, by mu and kappa receptors. It has a direct action on the respiratory center in the brain stem depressing respiratory drive (causing carbon dioxide retention) and cough reflex [64,81]. Oxycodone increases GIT smooth muscle tone in the stomach and duodenum reducing motility. This increases gastric emptying time causing constipation [64,82]. In the CVS, Oxycodone may cause degranulation of mast cells, causing histamine release, associated with orthostatic hypotension- (dizziness, lightheadedness), pruritus, flushing, red eyes and sweating [64,83].

Oxycodone Controlled Release (CR) was reported in a clinical trial to cause constipation, nausea, and/or somnolence, in approximately 23% of patients and between 12% and 13% experienced dizziness, pruritus, and/or vomiting. 82% of patients with chronic osteoarthritis or low back pain, taking oxycodone extended-release enrolled in a phase 3 trial, experienced at least one side effect [84]. Patients currently taking oxycodone for nonmalignant pain were recruited for a nationwide online survey to assess side effect frequency, degree of bother, and impact on health-related quality of life (HRQoL). About 4/5th of the respondents were bothered by side effects, with less than 2/5th quite a bit or extremely bothered. Over half were bothered by drowsiness (56.2 percent) and constipation (53.1 percent), over two-fifths by lightheadedness (43.6 percent) and dizziness (42.1 percent), approximately one-third by headache (33.1 percent) and nausea (31.3 percent), 27.6 percent itching, and 14.8 percent vomiting [85]. A controversial association exists between oxycodone (and other opioids) and cancer progression and recurrence [86,87]. However, more clinical studies are needed to validate this association [88]. Recent studies suggest a tumor-enhancing ability of oxycodone, being a strong mu receptor agonist (Nelson et al., 2019). These studies indicate a possible future clinical application of opioid antagonists, which may enable clinicians to use opioids more effectively [89].

Oxycodone Overdose

Oxycodone overdose results primarily from tolerance or accidental ingestion [76]. This may manifest by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, pupillary constriction (pupils may be dilated in the setting of hypoxia), and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur [64]. A retrospective population-based study conducted among North Carolina residents in 2010, revealed that immediate-release oxycodone accounted for the greatest death from opioid-related deaths, with the most common strength being 10m [90]. Differing considerations, however, exists between doses that produce toxic effects among individuals. Genetic variations affecting enzymatic induction and metabolism of oxycodone, presence of systemic health conditions are some factors identified in determining the toxic level of oxycodone. The median ingested dose in a retrospective clinical database study of 137 overdose cases of oxycodone was 70 mg for the Immediate Release (IR), and up to 240 mg for Sustained Release (SR) oxycodone [91]. In a study examining 70 cases of fatal oxycodone toxicity, mean oxycodone blood concentration causing toxicity was put at 0.40mg/L [92]. Toxicity increases when co-administered with drugs with possible interactions (See Drug-drug interactions above) and pre-existing systemic conditions [93] (Darke, et al., 2011).

Dependence & Abuse

Dependence and abuse result from brain abnormalities caused by chronic use of Oxycodone (as with other opioids). Oxycodone binds to mu-opioid receptors on opiate-sensitive neurons in the mesolimbic system in the brain, which houses the reward center and controls feelings of relaxation and pleasure [94]. Once activated, the Ventral Tegmental Area (VTA), a part of the mesocorticolimbic dopamine system, causes the release of dopamine from the Nucleus Accumbens (NAc) [95]. The released Dopamine produces a feeling of pleasure [96]. This pleasurable feeling becomes associated with the present condition and environment which is recorded in the brain as memories. This birth craving, as such pleasurable feelings, becomes repeatably desirable. Alterations in brain function following continued exposure to oxycodone lead to tolerance and subsequently dependence, as the Mu and Kappa receptors become less responsive to usual doses of oxycodone [97]. Dependence and withdrawal result due to changes in the Noradrenaline-containing Locus Coeruleus (LC). Oxycodone binds to Mu receptors in the LC, inhibiting the release of Noradrenaline (NA) causing drowsiness, hypotension, and bradypnea. These receptors gain increased activity with repeated exposure to oxycodone, such that there is an increased NA release in its absence causing withdrawal symptoms mediated primarily by the release NA such as anxiety, jitters, muscle cramps, diarrhea [98]. This creates a vicious cycle as the withdrawal symptoms/craving for pleasurable feelings, lead to the consumption of higher and higher doses of oxycodone.

Discussion

The rise of oxycodone prescription in the late 20th century was due to its potency and conception of possessing non-addictive properties. This notion was debunked by several studies that proved the addictive side of oxycodone. It was heavily prescribed in the US market which constituted up to 89% of all the opioid prescriptions. This may have caused the widespread awareness of

the properties of the drug and may have given rise to its illegal market, leading to abuse. Its lipophilic nature causes it to be absorbed efficiently in the GI tract. High concentrations have been observed in the brain when compared to plasma at lower doses, suggesting its ability to cross the blood-brain barrier. It can cross the placental barrier more efficiently compared to its other metabolites, possibly affecting neonates. Its fate in the body is dominantly regulated by CYP2D6 enzymes. Differing individual metabolisms affect the pharmacokinetics and pharmacodynamics of this drug. It binds to the opioid receptor, which upon downstream signaling causes euphoria by releasing dopamine. This craving for dopamine release increases when a dose administered no longer is as sensitive. Desensitization of the receptors causes tolerance and hence increases the drug abuse. Excessive administration of this drug in the body causes overdosing, leading to circulatory collapse, cardiac arrest and ultimately death Polymorphism in the genetic makeup has been linked to increased drug addiction as it overexpresses the opioid receptors. Correlation between gender and drug abuse has not been substantiated [99-103].

Use of this opioid has a wide range of side effects which include constipation, nausea, vomiting, dizziness, pruritus, somnolence, and dry mouth, headache, sweating while those in children include nausea & vomiting, pyrexia, constipation, headache. Exacerbating its side effects and possible implications, recent studies link the use of Oxycodone to cancer progression. However, further studies may suggest an opioid antagonist regulates the use of Oxycodone [104-110].

Conclusion

The opioid epidemic (opioid crisis) is one of the most challenging issues in the US that is caused by immense overuse of opioid drugs, Oxycodone is one of narcotic agent derivative of thebaine and widely used to alleviate severe acute or long-term pain conditions. The diversity of pharmacokinetic and pharmacodynamic parameters of oxycodone and genetic variation has been linked to opioid tolerance as well as abuse liability. Also, other factors such as gender, age, and pregnancy and lactation could play an important role in changing the Pharmacokinetic and dynamic properties which are essential in abuse liability and withdrawal syndrome. Many cases of overdose and opiate toxicity are repeatedly stated in the United States. Oxycodone works in several parts of the body especially the location within the brain that controls breathing. As a result, high doses of oxycodone can result in an overdose which could end up causing respiratory depression and death. Combining oxycodone with other drugs could increase the risk of respiratory depression and death by pharmacokinetic, pharmacodynamic, and both interactions. Therefore, considering these interactions will encourage awareness by both healthcare professionals and their patients.

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