Chapter 4
Opioid Drug Interactions

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Introduction

Pain experienced by patients in the intensive care unit (ICU) can manifest as acute, chronic, or acute-on-chronic. The majority of ICU patients suffer from moderate to severe pain that typically requires pharmacological interventions with a multimodal approach that will often include opioid analgesics [1]. While effective in treating pain, opioids are associated with potential drug interactions resulting in toxicity, intolerance, or therapeutic failure. An understanding of the complex interplay between drug interactions and the pharmacogenetics of opioids may provide insight into the individual variability in therapeutic response.

A drug interaction occurs when one drug modifies the action of another drug through prior or concurrent administration. Drug interactions can largely be classified as pharmacokinetic or pharmacodynamic [2]. Pharmacokinetic drug interactions result in changes to a drug's absorption, distribution, metabolism, or elimination resulting in augmented or diminished systemic concentrations. Conversely, pharmacodynamic reactions refer to the relationship between the concentration of the drug at the intended site and resulting drug effect. Pharmacodynamic drug interactions are classified as additive, synergistic, or antagonistic effects of two drugs on the same clinical endpoint. Pharmacogenomics refers to how genes affect an individual's response to drugs, potentially leading to pharmacokinetic and pharmacodynamic variability. These genetic polymorphisms may be responsible for the heterogeneity of opioid responses and potential for drug interactions.

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Potential drug interactions may occur in over half of ICU patients, a rate twice as high as patients on general wards; though, not all of these drug interactions are clinically significant [3, 4]. Approximately 5% of patients in the ICU experience an adverse drug event from a drug interaction which have been associated with prolonged ICU length of stay [3, 5]. Critically ill patients are more likely to suffer from an increased number of potential drug interactions given the intensity of their drug regimens and number of medication exposures [4]. The precise frequency and severity of opioid drug interactions in ICU patients have not been described. Therefore, an understanding of potential clinically important opioid drug interactions is a crucial component in the management of the critically ill patient.

Common Mechanisms of Opioid Drug Interactions

Since opioids are extensively metabolized by the liver, resultant drug interactions may occur via phase I and II hepatic enzymatic pathways. Phase I opioid metabolism converts the parent drug to a more water-soluble or reactive product through oxidation by cytochrome P450 (CYP450), hydrolysis, or reduction [6]. Opioid metabolism is largely driven through CYP450 enzymatic pathways, specifically the CYP3A4/5, CYP2D6, and CYP2B6 isoenzymes (Table 4.1). Drugs metabolized by CYP450 can be classified as substrates, inhibitors, or inducers. Several different drug interaction scenarios may arise with the addition or deletion of inducers and inhibitors (Fig. 4.1). For example, when a CYP450 inhibitor is combined with an opioid that is metabolized through the same isoenzyme, greater opioid concentrations will result with consequent enhanced clinical effects and a potential for toxicity. However, in cases when an opioid is a prodrug (inactive drugs metabolized to an active metabolite), the opposite scenario will occur. Phase II opioid metabolism promotes elimination through drug conjugation (e.g. glucuronidation). The most common enzymes that metabolize opioids are uridine diphosphoglucuronosyltransferases (UGTs). Conjugation of buprenorphine, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone by UGTs results in either active or inactive metabolites [7].

Energy-dependent transporters such as permeability-glycoprotein (P-gp) and organic anion-transporting polypeptides (OATPs) are located in the gut, kidneys, and blood-brain barrier [6]. These transporters act as a biological barrier by expelling drug molecules out of cells resulting in significant changes in drug absorption and disposition. Drug interactions occur as a result of inhibition and induction of P-gp. Of note, many drug interactions involve both the P-gp and CYP450 system since they share many substrates that are physiologically linked; therefore, it is often challenging to determine the specific mechanism of interaction. Several opioids such as fentanyl, methadone, meperidine, morphine, and oxycodone are substrates of P-gp. Like the CYP450 system, P-gp inhibition can increase drug exposure and the potential risk for adverse events. There are several other medications used in the critical care setting that are also P-gp inhibitors and inducers (Table 4.2).

Table 4.1 Common metabolic pathways of opioid analgesics

	Phase I pathway			Phase II pathway
Opioid	CYP2B6	CYP2D6	CYP3A4/5	UGT
Buprenorphine	–	–	Norbuprenorphine[a]	Buprenorphine-3-glucuronide[a] Norbuprenorphine-3-glucuronide[a]
Codeine[b]	–	Morphine[a]	Norcodeine	Morphine 6-glucuronide[a] Morphine 3-glucuronide
Fentanyl	–	–	Norfentanyl	–
Hydrocodone[b]	–	Hydromorphone[a]	Norhydrocodone	Hydromorphone 3-glucuronide
Hydromorphone	–	–	–	Hydromorphone 3-glucuronide
Methadone	Inactive metabolites	Inactive metabolites	Inactive metabolites	–
Meperidine	–	–	–	–
Morphine	–	–	–	Morphine 6-glucuronide[a] Morphine 3-glucuronide
Oxycodone	–	Oxymorphone[a]	Noroxycodone[a]	Inactive metabolites
Oxymorphone	–	–	–	Inactive metabolites
Remifentanil	–	–	–	–
Sufentanil	–	–	Inactive metabolites	–
Tramadol[b]	–	O-desmethyl tramadol (M1)	N-desmethyl tramadol (M2)	–

CYP cytochrome P450, *UGT* uridine diphospho-glucuronosyltransferase
[a]Active metabolite
[b]Prodrug activated by cytochrome P450 enzyme

Inhibition of CYP450 or P-gp occurs faster than drug induction, occurring over several days after introducing the inhibitor. Drug interactions mediated by enzyme induction are delayed since it takes time for the production of new enzymes. A similar delay is observed for the dissipation of the interaction when the offending drug is removed as the enzyme system gradually declines to baseline function. The area under the concentration versus time curve (AUC) can be used in the context of opioid drug interactions to represent the variation of a plasma drug concentration over time.

Pharmacodynamic drug interactions can produce desired effects or unwanted adverse effects. In general, pharmacodynamic interactions occur via various mechanisms by acting on the receptor or by interfering with the feedback mechanism of a process targeted by the other medication. Opioids result in several clinical effects other than analgesia, many of which are undesirable. Across the drug class, these

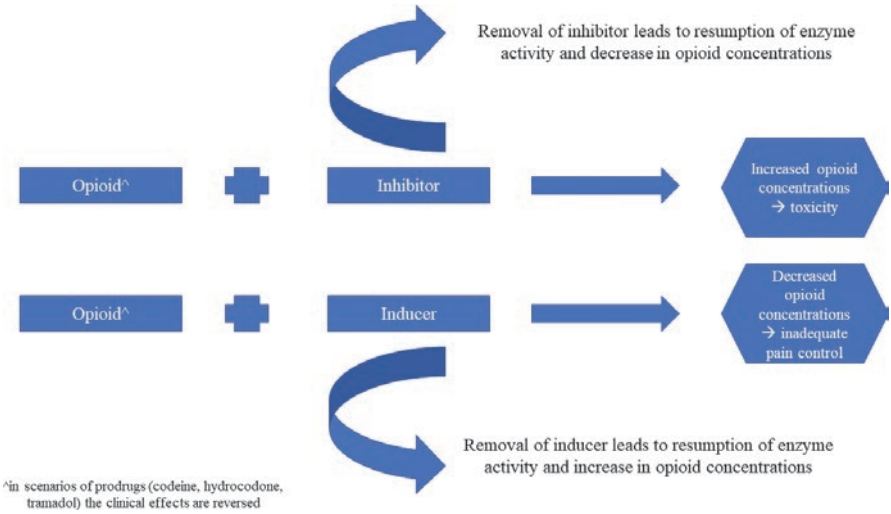

Fig. 4.1 Expected effects of opioid interactions with the addition of an inhibitor or inducer

Table 4.2 Common permeability-glycoprotein (P-gp) inhibitors and inducers

Inhibitors	Inducers
Amiodarone	Phenobarbital
Clarithromycin	Phenytoin
Cyclosporine	Rifampin
Diltiazem	
Erythromycin	
Itraconazole	
Ketoconazole	
Ritonavir	
Verapamil	

include central nervous system depression, respiratory depression, and constipation. Specific opioids harbor additional unique adverse effects related to central nervous system or cardiovascular toxicity.

Opioid Drug Interactions Commonly Encountered in the Critically Ill Patient

CYP450 Enzyme Modulation

Since many opioids are metabolized by the CYP450 system, they are susceptible to interactions with other drugs that inhibit or induce these enzymes. Many prescribed opioids in ICU patients, such as fentanyl, oxycodone, hydrocodone, tramadol,

methadone, sufentanil, and buprenorphine, are metabolized predominantly by CYP3A4. A study of healthy volunteers found that inhibition of CYP3A4 with ketoconazole increased oxycodone's half-life from 4.1 to 5.5 hours and the AUC by 84% [8]. Conversely, the addition of a strong CYP2D6 inhibitor, quinidine, significantly increased oxycodone AUC by 42%, and the combination of the two inhibitors increased AUC by 209% as well as the peak concentration (Cmax) by 58% [8]. Induction of these enzymes may increase drug clearance and reduce analgesic effects for patients receiving opioids metabolized by the same pathway. Other opioids however, such as remifentanil and hydromorphone that are not metabolized through any CYP450 pathway, would not be subject to any CYP450 enzyme-mediated drug interactions.

Fentanyl is one of the most common opioids used in the ICU setting and is a major substrate of CYP3A4. However, because of its high hepatic extraction ratio, indicating that its clearance is primarily dependent on hepatic blood flow, enzyme interactions may be less apparent compared to that of other opioids. For example, a pharmacokinetic study in healthy volunteers found no difference in fentanyl concentrations with concomitant administration of itraconazole, a strong CYP3A4 inhibitor [9]. In contrast, voriconazole, an azole antifungal extensively metabolized by CYP450 isoenzymes, decreased fentanyl clearance by 23% and increased AUC by 39% [10]. Regarding enzyme induction, a study conducted in patients receiving chronic antiepileptic drugs reported substantial fentanyl dose escalations required to manage pain during craniotomy as the number of baseline antiepileptics increased [11]. Expected CYP-mediated drug interactions with fentanyl are displayed in Table 4.3.

CYP2D6 plays a role as a major pathway for codeine and a minor pathway for oxycodone, hydrocodone, tramadol, and methadone. Tramadol is additionally metabolized by CYP2B6 and methadone is metabolized by a number of additional enzymes including CYP2B6, CYP2C9, and CYP2C19. Notably, the true metabolic pathway for methadone has been scrutinized in recent years, with some investigations concluding that CYP3A4 is not a significant pathway for its clearance [12]. Certain opioids are prodrugs or are active drugs metabolized to active metabolites. In these examples, the effect of enzyme inhibition or interaction is more complex. For example, codeine is a prodrug that is predominantly metabolized to its active form morphine by CYP2D6, and a second pathway (CYP3A4) metabolizes codeine to norcodeine, an opioid with little activity. Inhibition of CYP2D6 will reduce the concentrations of morphine and therefore reduce the overall analgesic effect, while

Table 4.3 Effects of enzyme inhibition and induction on fentanyl

Enzyme effect of concomitant drug	Effects on substrate	Expected clinical effects
CYP3A4 inhibitor	↓ fentanyl metabolism ↑ fentanyl concentrations	↑ opioid effect
CYP3A4 inducer	↑ fentanyl metabolism ↓ fentanyl concentrations	↓ opioid effect

CYP cytochrome P450

Table 4.4 Effects of enzyme inhibition and induction on the effects of tramadol

Enzyme effect of concomitant drug	Effects on substrate and its metabolites	Expected clinical effects
CYP3A4 inhibitor	↑ tramadol ↑ M1 (active) ↓↓ M2 (inactive)	↑ serotoninergic effect ↑ opioid effect
CYP3A4 inducer	↓↓ tramadol ↓↓ M1 (active) ↑↑ M2 (inactive)	↓ serotonergic effect ↓↓ opioid effect
CYP2D6 inhibitor	↑ tramadol ↓↓ M1	↔/↑ serotonergic effect ↓↓ opioid effect
CYP2D6 inducer	N/A[a]	

CYP cytochrome P450, *M1* O-desmethyl tramadol, *M2* N-desmethyl tramadol
↑ and ↓ indicate a small increase/decrease; ↑↑ and ↓↓ indicate a large increase/decrease; ↔ indicates no change
[a]CYP2D6 generally considered not inducible

inhibition or induction of CYP3A4 will not have a significant impact on the drug's effect.

Another complex example is tramadol, which has weak opioid activity but inhibits reuptake of serotonin and norepinephrine. It is metabolized via CYP2D6 to a metabolite M1 (O-desmethyl tramadol) which has more potent opioid activity. CYP3A4 and, to a lesser extent, CYP2B6 also metabolize tramadol to inactive metabolites including M2 (N-desmethyltramadol). Although the opioid effects are mediated through CYP2D6, modulation of CYP3A4 can produce more or less parent drug available for conversion to M1. Concomitant administration of medications that induce or inhibit CYP3A4/2D6 thus increase the risk of substantial drug interactions with tramadol (Table 4.4).

Methadone has inconsistent and sometimes unpredictable interactions with different enzyme modulators. For example, administration with the CYP3A4/CYP2B6 inducer efavirenz decreases methadone Cmax and AUC by approximately 50%, necessitating a 22% increase in dose [13]. Similarly, other enzyme inducers like rifampin and antiepileptics will decrease methadone concentrations via CYP2B6 induction and may precipitate opioid withdrawal. However, antiretroviral regimens containing ritonavir, which predominantly acts as a CYP450 inhibitor of various enzymes, may have little effect or may actually decrease methadone concentrations (Table 4.5). The mechanism for this is unclear; despite the strong CYP3A4 inhibition from ritonavir there may be reduced methadone concentrations due to CYP2B6 induction or an atypical mechanism [12]. Case reports have described opioid toxicity and respiratory depression when ciprofloxacin was initiated in patients receiving chronic methadone, yet, considering that ciprofloxacin is a weak CYP3A4 and moderate CYP1A2 inhibitor, a significant interaction between the two would not generally be expected [14].

Several classes of drugs result in clinically important drug interactions with opioids. Various antimicrobials, antiepileptic drugs, cardiovascular drugs, and

Table 4.5 Expected drug interactions between antiretrovirals and opioids

Antiretroviral class[a]	Antiretroviral	Enzyme effects	Interactions with opioids
Protease Inhibitors	Atazanavir	3A4 inhibitor (strong)	All (except tipranavir) will ↑ opioid effects of oxycodone, fentanyl, hydrocodone, buprenorphine, and sufentanil
	Darunavir	3A4 inhibitor (strong), 2D6 inhibitor (moderate)	
	Fosamprenavir	3A4 inhibitor (moderate)	
	Indinavir	3A4 inhibitor (strong)	
	Nelfinavir	3A4 inhibitor (strong)	Darunavir and tipranavir may ↓ opioid effect of codeine and tramadol
	Ritonavir	3A4 inhibitor (strong), 2B6 inducer (moderate)	
	Saquinavir	3A4 inhibitor (strong)	
	Tipranavir	2D6 inhibitor (strong)	
Non-nucleoside Reverse Transcriptase Inhibitors	Delavirdine	3A4 inhibitor (weak)	Efavirenz and nevirapine will ↓ opioid effect of methadone
	Doravirine	None	Etravirine will ↓ opioid effects of oxycodone, fentanyl, hydrocodone, buprenorphine, and sufentanil
	Efavirenz	2B6 inducer (moderate), 3A4 inducer (moderate)	
	Etravirine	3A4 inducer (moderate)	
	Nevirapine	2B6 inducer (moderate)	
	Rilpivirine	None	
Others	Cobicistat	3A4 inhibitor (strong)	Cobicistat will ↑ opioid effects of oxycodone, fentanyl, hydrocodone, buprenorphine, and sufentanil
	Enfuvirtide	None	
	Maraviroc	None	

CYP cytochrome P450

[a]Nucleoside reverse transcriptase inhibitors and integrase inhibitors do not have any clinically relevant CYP450-mediated drug interactions

psychotherapeutics can affect CYP450 metabolism. Drugs that may be encountered in the ICU setting which modulate CYP3A4 or CYP2D6, the most prevalent enzymes responsible for opioid metabolism, are listed in Table 4.6. Careful dosage adjustments and monitoring are necessary in order to avoid adverse drug interactions.

Table 4.6 Drugs that inhibit or induce CYP3A4 and CYP2D6

CYP3A4 Inhibitors		CYP3A4 Inducers		CYP2D6 Inhibitors	
Moderate	Strong	Moderate	Strong	Moderate	Strong
Antiretrovirals Amprenavir Delavirdine Fosamprenavir	*Antiretrovirals* Atazanavir Cobicistat Darunavir Lopinavir Ritonavir Saquinavir	*Antiretrovirals* Efavirenz Etravirine	*Antiepileptics* Carbamazepine Phenobarbital Phenytoin	*Antiretroviral* Darunavir	*Antiretroviral* Tipranavir
Antibacterials Erythromycin		*Antitubercular* Rifabutin Rifapentine	*Antitubercular* Rifampin	*Antidepressant* Duloxetine	*Antidepressants* Bupropion Fluoxetine Paroxetine
Antifungals Fluconazole Isavuconazole	*Antibacterials* Clarithromycin	*Others* Bosentan Modafinil Nafcillin			
Cardiovascular Amiodarone Diltiazem Verapamil	*Antifungals* Itraconazole Ketoconazole Posaconazole Voriconazole				
Others Conivaptan	*Others* Nefazodone				

CYP cytochrome P450

P-glycoprotein Interactions

Induction of P-gp may lead to overexpression of P-gp and contribute to opioid tolerance specifically with morphine and fentanyl, but not meperidine [15]. When an opioid that is a P-gp substrate is introduced with a P-gp inducer, there will be a decreased concentration in the central nervous system, leading to a loss of analgesia. Carbamazepine, recommended by recent guidelines for the treatment of neuropathic pain in critically ill patients [1], acts as an inducer of both P-pg and CYP3A4. Chronic administration of carbamazepine can lead to tolerance of specific opioids through a dual interaction at the level of P-gp (decrease penetration into the brain due to the back-transport of the drug) and CPY3A4 (increased metabolism). On the contrary, an increase in sensitivity and duration of analgesia can occur with the acute administration of a P-gp inhibitor. Loperamide, an opioid used as an anti-diarrheal agent, does not exert sedative effects as a direct result of P-gp-mediated efflux at the blood-brain barrier. Combining loperamide with a P-gp inhibitor, such as quinidine, may result in moderate respiratory depression, not otherwise observed with loperamide [16]. Plasma morphine concentrations, but not its metabolites, were increased in the setting of P-gp inhibition with itraconazole in 12 healthy volunteers [17]. The authors concluded that P-gp inhibition of morphine may increase the concentration of the parent drug without affecting the downstream metabolism of the glucuronides. It was unclear whether this increase in morphine concentration in the plasma correlated to the concentration in the brain.

There are many in vitro P-gp studies looking at the possibility that P-gp substrates, including opioids, have inhibitory properties as well [18]. The few opioids studied include fentanyl, morphine, and sufentanil, with digoxin as the standard P-gp substrate used to test the opioids and determine if P-gp is inhibited. Morphine and its metabolites did not inhibit the transport of digoxin and therefore not considered a P-gp inhibitor. The other opioids inhibited P-gp activity at high concentrations. Nonetheless, it is difficult to translate this in vitro data into clinically meaningful conclusions.

While P-gp inhibition and induction can certainly cause significant drug interactions, it is important to recognize that it is often not possible to predict the magnitude of undesirable outcomes. Clinicians should monitor for opioid tolerance in patients who are receiving concomitant P-gp inducers and consider switching to agents that are not P-gp substrates. Of note, it may take up to a couple of weeks to see the maximum induction effect, exposing suboptimal pain management. For patients receiving P-gp inhibitors, it is prudent to monitor for enhanced analgesia and opioid-related adverse effects.

Synergistic Pharmacodynamic Interactions

Central Nervous System and Respiratory Depression

Central nervous system and respiratory depression are life-threatening effects that can arise from opioids, especially when used in combination with other medications with similar side-effect profiles. Aside from inappropriate dosing or enzyme-related

drug interactions, synergistic effects with other sedating medications are thus a potential risk factor. This can be a significant problem in the ICU setting since multiple sedating medications are frequently used simultaneously to treat anxiety, agitation, and/or for procedural sedation.

A retrospective study of over 21 million hospitalized medical and surgical patients evaluated the risk of cardiac arrest associated with opioids and sedatives and patient-specific risk factors [19]. In addition to benzodiazepines, other sedating drugs including certain antidepressants, anticonvulsants, antiemetics, and sleep aids were included. Opioids and sedatives were both found to be significantly associated with cardiac arrest, though the risk was highest with both combined (adjusted odds ratio 3.83 for medical patients and 2.34 for surgical patients). Other risk factors common to both medical and surgical patients included Hispanic origin, mild liver disease, obesity, and chronic obstructive pulmonary disease. The Joint Commission has identified several other risk factors for oversedation and respiratory depression from opioids, including sleep apnea, older age, opioid naïve status, snoring, post-surgery, increased opioid dose requirement, longer length of time receiving general anesthesia, preexisting cardiac or other organ disease, thoracic or other surgical incisions, and smoking [20]. In 2016, the United States Food and Drug Administration (U.S. FDA) warned of the risks of the combination of opioid pain or cough medications with benzodiazepines and other sedating drugs [21]. They cited several studies, which link this combination with an increased risk of emergency department visits and fatal overdoses, and have since required opioid manufacturers to disclose these risks in boxed warnings. While these warnings are based on outpatient prescriptions, such drug combinations in inpatients should be approached cautiously, used only if alternatives are ineffective, and at the lowest effective doses.

Serotonin Syndrome

Opioids have been associated with serotonin syndrome at the neurotransmitter level in patients who are receiving serotonin reuptake inhibitors and other serotonergic medications. Serotonin syndrome is a potentially life-threatening syndrome caused by the excessive buildup of serotonin, leading to hyperactivity of the peripheral and central nervous systems. The proposed mechanisms for opioids' serotonergic effect include serotonin reuptake inhibition or an increase of serotonin release at presynaptic inhibitory serotonin neurons.

Pain and mental health disorders frequently coexist. For example, chronic pain can lead to depression, placing the patient at risk when opioids and antidepressants are prescribed together. In 2016, the FDA issued a safety announcement, warning of safety issues with opioid pain medications including the interaction with antidepressants and migraine medications increasing the risk of serotonin syndrome [22]. Although the FDA mandated label changes for all opioids to include these necessary warnings, not all opioids have been associated with serotonin syndrome. Individual case reports and animal studies have highlighted certain opioids such as tramadol, fentanyl, hydromorphone, oxycodone, meperidine, methadone, buprenorphine, and dextromethorphan, with tramadol and meperidine as the highest offenders [23–27]. Antidepressants at risk for

interactions include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and atypical antidepressants which share unique or combined mechanisms (Table 4.7). Linezolid has also been rarely implicated as a precipitant for serotonin syndrome due to its effect as a weak MAOI [27].

Table 4.7 Expected drug interactions between antidepressants and opioids

Antidepressant class	Antidepressant	Enzyme inhibition	Interactions with opioids
Selective serotonin reuptake inhibitors	Citalopram	CYP2D6 (weak)	Serotonin syndrome[a]
	Escitalopram	CYP2D6 (weak)	
	Fluoxetine	CYP2D6 (strong)	Paroxetine and fluoxetine may ↓ opioid effect of codeine and tramadol
	Fluvoxamine	CYP2D6, CYP3A4 (weak)	
	Paroxetine	CYP2D6 (strong)	
	Sertraline	CYP2D6 (weak)	↑ seizure risk with tramadol, meperidine
	Vortioxetine	None	
	Vilazodone	None	
Serotonin-norepinephrine reuptake inhibitors	Desvenlafaxine	None	Serotonin syndrome[a]
	Duloxetine	CYP2D6 (moderate)	Duloxetine may ↓ opioid effect of codeine and tramadol
	Levomilnacipran	None	
	Milnacipran	None	
	Venlafaxine	CYP2D6 (weak)	Additive QT prolongation (especially citalopram, escitalopram) with methadone
			↑ seizure risk with tramadol, meperidine
Tricyclic antidepressants	Amitriptyline Amoxepine Clomipramine Desipramine Doxepin Imipramine Nortriptyline Protriptyline Trimipramine	None	Serotonin syndrome [a]
			Additive sedation (especially amitriptyline, doxepin, trimipramine)
			Additive QT prolongation (especially amitriptyline, doxepin, imipramine) with methadone
			↑ seizure risk with tramadol, meperidine
Serotonin reuptake inhibitor/antagonist	Trazodone	None	Additive sedation
	Nefazodone	CYP3A4 (strong)	Nefazodone will ↑ opioid effects of oxycodone, fentanyl, hydrocodone, buprenorphine, and sufentanil
			Serotonin syndrome[a]
			↑ seizure risk with tramadol, meperidine

(continued)

Table 4.7 (continued)

Antidepressant class	Antidepressant	Enzyme inhibition	Interactions with opioids
Monoamine oxidase inhibitors	Phenelzine Isocarboxazid Selegiline Trancylcypromine Meclobemide	None	Serotonin syndrome[a]
			↑ seizure risk with tramadol, meperidine
Atypical antidepressants	Bupropion	CYP2D6 (strong)	Bupropion may ↓ opioid effect of codeine and tramadol
	Mirtazapine	None	↑ seizure risk with combination of bupropion with tramadol, meperidine

CYP cytochrome P450
[a]Especially meperidine and tramadol
[b]Meperidine contraindicated with monoamine oxidase inhibitors

Fentanyl is serotonergic through multiple potential mechanisms, including direct serotonin agonism and weak reuptake inhibitory properties. There are no reports of serotonin syndrome in patients on fentanyl monotherapy, despite the multiple mechanisms that increase serotonin levels. Most reports of fentanyl precipitating serotonin syndrome are in patients receiving a different serotonergic agent or on other opioids as well [24].

Tramadol is a central opioid receptor agonist and a serotonin and norepinephrine reuptake inhibitor. These characteristics make it an appealing agent for patients suffering from both pain and depression. At high doses, it may also induce the release of serotonin in addition to inhibiting reuptake, leading to reports of tramadol alone causing serotonin syndrome. There are also multiple cases of serotonin syndrome observed when tramadol is combined with antidepressants [25]. This combination has been specifically implicated as a frequent cause of fatal drug toxicity related to tramadol [28]. Additionally, certain antidepressants may alter the metabolism of tramadol and further increase its serotonergic effects. The timing of the onset of serotonin syndrome can vary from a few days to over a month after tramadol initiation in patients established on their antidepressant therapy.

Methadone is another agent frequently reported to be associated with serotonin syndrome. The mechanism of increased serotonin by methadone is through serotonin reuptake inhibition at a greater rate than other opioids. Serotonin syndrome has been reported when methadone is combined with serotonergic antidepressants and linezolid [26, 27].

Although a greater risk exists when combining opioids with other serotonergic medications, combining these agents is not an absolute contraindication. In general, the incidence of serotonin syndrome is very low and the number of cases involving opioids is even lower. The combination of drug classes can be prescribed safely with proper monitoring and patient counseling. In the event of serotonin syndrome development, clinicians should immediately remove offending agents and symptoms will likely subside quickly with a low likelihood of recurrence.

QT-Interval Prolongation and Torsades de Pointes

Several opioids have been associated with QT-interval prolongation and an increased risk of torsades de pointes (TdP). These drugs have the potential to inhibit the human ether a go-go related-gene (HERG) channel which prolongs the action potential and the QT interval. QT prolongation has been observed with oxycodone, buprenorphine, and methadone [29]. Numerous reports of TdP and sudden death have been linked to methadone, which appear to occur more frequently with high methadone doses and in individuals with long QT syndrome or hypokalemia. Similar reports are rare to nonexistent with oxycodone and buprenorphine [29].

A number of risk factors are associated with TdP, and several have implications for drug interactions. These include high drug concentration, administration of more than one drug that can prolong the QT interval, and electrolyte disturbances [30]. Therefore, QT-prolonging agents such as methadone are expected to have a higher risk of TdP when combined with other QT-prolonging drugs including azole antifungals, macrolide and fluoroquinolone antibiotics, some SSRIs and TCAs, calcium channel antagonists and amiodarone, and many antipsychotics. Additionally, drugs that increase methadone concentrations (e.g. CYP2B6 inhibitors) or promote hypokalemia (e.g. loop diuretics) may also increase the risk of TdP.

Seizures

Certain opioids have been associated with a rare incidence of seizures. Tramadol, at therapeutic doses and in overdoses, can precipitate seizures, and the prescribing information warns about concomitant use of tramadol with various antidepressant classes, other opioids, neuroleptics, and other drugs that reduce the seizure threshold. Other opioids that are potentially neuroexcitatory appear to be related to opioid metabolites including normeperidine, morphine-3-glucuronide, and hydromorphrone-3-glucuronide [31]. However, none of these metabolites are generated via CYP450 metabolism; therefore, drug interactions increasing this risk are unlikely, except theoretically the combination with drugs that decrease the seizure threshold.

Interaction at the Mu-Opioid Receptor

Medications that are opioid antagonists or partial agonists are expected to interact with pure opioid agonists. In certain scenarios, this is expected and desired, for example, administering naloxone (a pure opioid antagonist) to treat opioid toxicity or overdose or naltrexone (another pure opioid antagonist) for chronic opioid or alcohol dependence. However, partial agonists, including buprenorphine, nalbuphine, and butorphanol, may also reduce opioid effects and produce withdrawal symptoms when administered to patients on chronic opioid therapy [32]. The partial agonist can displace the opioid from the mu receptor but produce less agonism at the receptor.

Conversely, patients who are maintained chronically on a partial agonist, particularly important for buprenorphine used for opioid maintenance therapy, may experience reduced effects of pure opioid agonists and require increasing agonist doses for effect. This interaction may be particularly relevant for a patient on chronic buprenorphine who needs treatment for acute pain. There is no high-quality evidence to guide the appropriate management of patients maintained on buprenorphine who have acute pain, so recommendations differ regarding discontinuing or maintaining buprenorphine during acute illness. Naltrexone, on the other hand, should be held prior to a planned surgery (72 hours for oral naltrexone and 30 days for intramuscular) and can be resumed when opioid agonists are no longer required.

Project SHOUT (Support for Hospital Opioid Use Treatment) has recently provided guidelines on the treatment of acute pain in patients maintained on drugs for opioid use disorder [33]. Patients on buprenorphine who experience acute pain due to surgery, for example, can receive the same total daily dose split into three times daily dosing to maximize the analgesic effects of buprenorphine. Additional analgesia can be achieved with multimodal therapy depending on the type of pain or concomitant disease states. If opioids are required for severe pain, higher doses than usual may be required. In general, it is not recommended to discontinue buprenorphine, as higher opioid doses may be required, and patients may be at an increased risk for relapse of their opioid use disorder. It is important to confirm that the patient is currently taking buprenorphine if deciding to continuing therapy, and it is good practice to include the patient's outpatient provider in these decisions.

Pharmacogenomic-Related Interactions

It is important to consider pharmacogenomic factors in patients prescribed opioids metabolized by cytochrome P450 enzymes most notably, CYP2D6 and CYP3A4. Patients with CYP2D6 polymorphisms can be poor metabolizers and have a lower clearance of CYP2D6 substrates, leading to a buildup of the parent drug. On the other end of the spectrum, ultrarapid metabolizers, may lead to a rapid conversion of the parent drug to its metabolites. Both types of polymorphisms can increase the risk of drug interactions that may not carry any clinical relevance in another patient. Caucasians are the most common race associated with these polymorphisms, with the most common phenotype being the extensive metabolizer. Opioid analgesics metabolized by CYP2D6 include the prodrugs codeine, hydrocodone, and tramadol. Poor metabolizers can experience down to 14-fold lower concentrations of the active metabolite, leading to significant decrease in their analgesic effects [34]. Codeine is the most studied opioid analgesic as it relates to pharmacogenetics. It is inactive and is metabolized by CYP3A4 into norcodeine, which does not possess analgesic properties and by CYP2D6 into morphine, which is active and will undergo glucuronidation into additional active metabolites. Studies have shown higher concentrations of morphine in CYP2D6 rapid metabolizers compared to poor metabolizers, along with more frequent associated adverse events, such as

constipation, sedation, and respiratory depression [35]. There have been reports of patient deaths associated with normal codeine administration in an ultra-rapid metabolizer due to respiratory depression [36].

Tramadol has minor serotonergic effects due to the (+) enantiomer. Various genetic polymorphisms of CYP2D6 may increase the concentration of the (+) enantiomer, leading to an increased risk of serotonin syndrome when combined with additional CYP2D6 inhibitors or serotonergic medications [28]. The variation in genetics can affect serotonin metabolism regardless of concomitant drug therapy because serotonin metabolism is also modulated by CYP2D6 and CYP3A4.

Hydrocodone is metabolized by CYP2D6 into a more active opioid, hydromorphone. Hydromorphone has up to a 33-fold greater affinity to the mu opioid receptor than hydrocodone. Although CYP2D6 polymorphisms alter the hydromorphone concentrations in patients taking hydrocodone, there are insufficient data to extrapolate to meaningful clinical effects [35].

Oxycodone is also an opioid partially metabolized by CYP2D6 into an even more active metabolite, oxymorphone. Due to pharmacogenomic differences, there may be a delayed analgesic effect in poor metabolizers, or the patient may experience a heightened response in rapid metabolizers. Similar to hydrocodone, patient reports on the effect of fluctuations in oxymorphone concentrations due to metabolizer status on oxycodone did not demonstrate significant clinical changes [35]. One study evaluated the variability of enzyme function in the metabolism of oxycodone due to genetic polymorphisms involving various types of CYP2D6 metabolizers and volunteers without genetic polymorphisms [8]. The enzyme inhibitors quinidine and ketoconazole were used to inhibit CYP2D6 and CYP3A4, respectively. The study found that when one enzyme was inhibited, there appeared to be a shunt of metabolism to the other enzymatic pathway. These findings were especially pronounced in those who had a different CYP2D6 genotypes.

Enzyme polymorphisms in patients taking opioid medications are well studied and reported to cause harm. However, routine pharmacogenetic testing is not routinely performed prior to prescribing them. Literature on the effect of drug interactions in patients with genetic polymorphisms is also scarce. It is important to recognize the need for pharmacogenetic screening in patients who experience inadequate analgesia, or exaggerated responses after taking opioids in normal doses. When genetic polymorphisms are suspected, alternative opioids not metabolized by CYP2D6, such as fentanyl, hydromorphone, morphine, and non-opioid agents are preferred.

Opioid Interactions with Drugs of Abuse

Increasing consumption of non-medical use (or misuse) of novel synthetic opioids (NSO) has risen over the last two decades in the United States and Canada [37]. To date little information is known about the exact metabolic pathway of NSOs; therefore, the frequency (predictability) and severity of drug interactions associated with these agents are largely unknown. Yet, given their increased potency, prolonged

effects, and propensity to be used in combination with other substances, NSOs are particularly at risk for clinically relevant drug interactions and toxicity. Alcohol, barbiturates, benzodiazepines, or heroin combined with NROs may lead to increase in respiratory depression. Additionally, unexpected adverse effects may be observed when patients combine NSOs with stimulants such as cocaine or amphetamines. Furthermore, combining amphetamines with certain NSOs may lead to an increase in serotonin syndrome [38]. Co-ingestion of heroin and ethanol will lead to increases in morphine (heroin metabolite) as a result of ethanol induced inhibition of heroin metabolism [39]. In the setting of NSO misuse, clinicians should anticipate effects to be similar to fentanyl and morphine and anticipate untoward drug interactions with co-stimulant use.

Coronavirus Disease 2019 (COVID-19) and Opioid Interactions

Drugs used for the treatment of patients with COVID-19 such as remdesivir, dexamethasone, and tocilizumab do not have any known drug interactions with opioids. However, as patients with COVID-19 are enrolled in clinical trials using investigational drugs, clinicians should be vigilant in monitoring for potential drug interactions with opioids.

Critically ill patients with COVID-19 receiving mechanical ventilation may require continuous infusions of an opioid and sedative to treat pain and agitation. Shortages of intravenous fentanyl and hydromorphone during the pandemic have forced clinicians to use alternate intravenous or oral opioids with prolonged durations of action, active metabolites, and a potential for increased drug interactions.

Conclusion

Opioid analgesics are frequently administered in the ICU setting, and many of these drugs are metabolized or transported by enzymes prone to drug interactions, including CYP450 and P-gp. Opioids are also responsible for many undesired clinical effects which are often subject to several pharmacodynamic interactions discrete from the opioid receptor. Knowledge of these interactions of the most common opioids and non-opioids that are likely to interact can improve their appropriate use, facilitating effective patient analgesia while minimizing the risk of opioid toxicity and harm. As newer opioids are developed, it is important to study their metabolic pathway and potential for clinically relevant drug interactions.

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