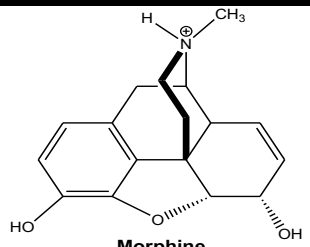
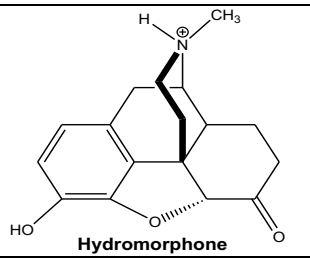
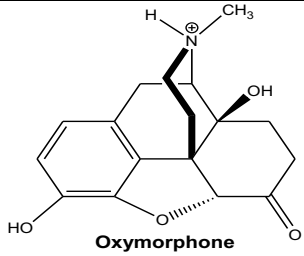
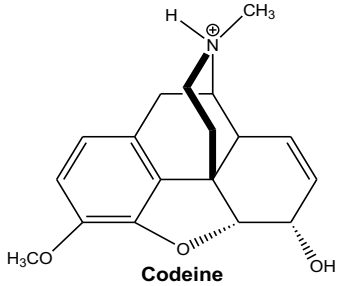
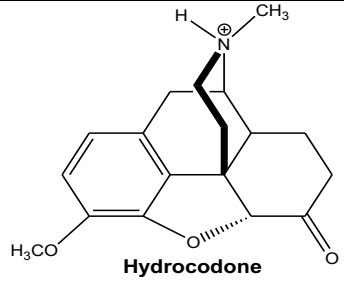
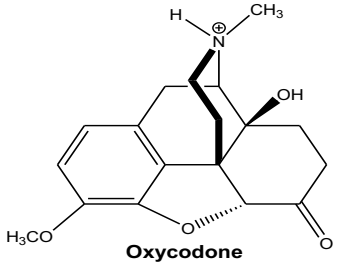
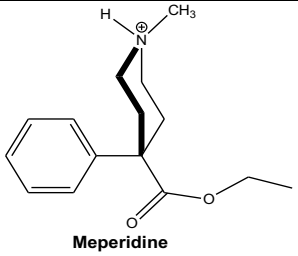
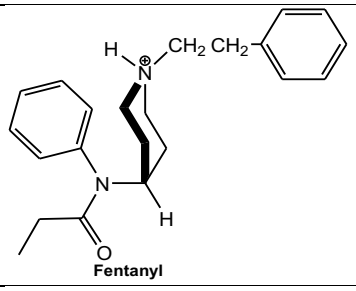
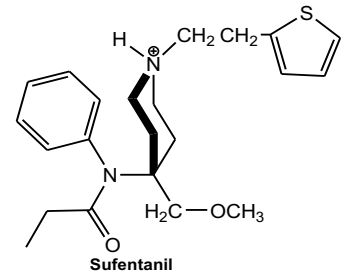
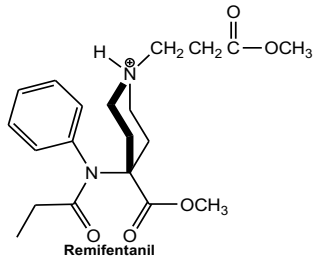
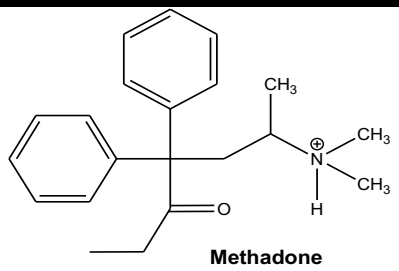
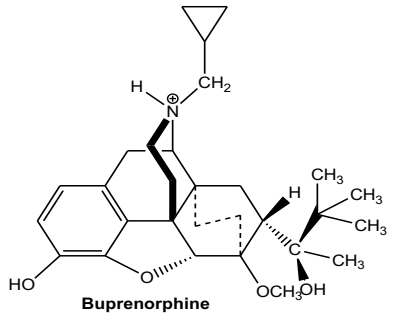
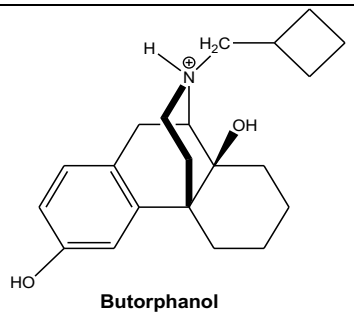
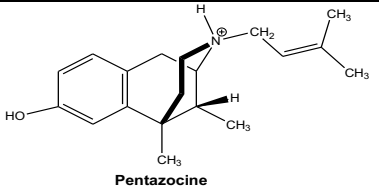
PHARMACOLOGY

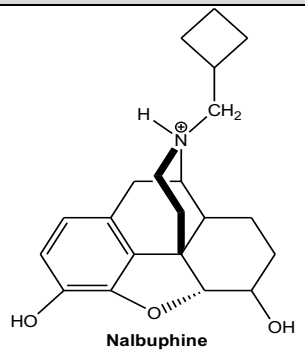
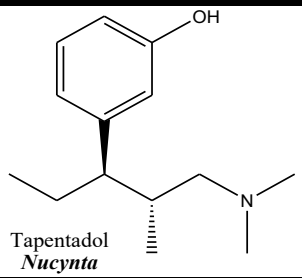
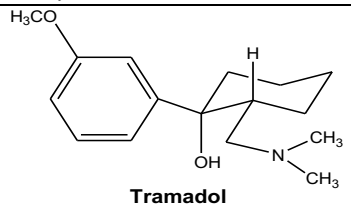
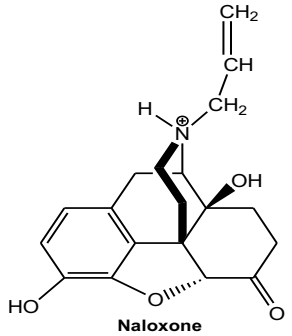
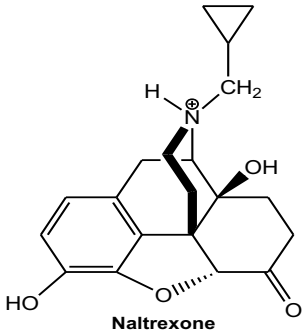
Major opioid receptor types involved in the pharmacology of opioid drugs:[1]

Opioid receptor type	***Agonist Effects***
Mu	Analgesia, Euphoria, Respiratory Depression, Constipation, Emesis, Tolerance, Physical Dependence, Constipation
Kappa	Analgesia, Dysphoria, Sedation, Miosis, Diuresis
Delta	Analgesia, Respiratory Depression, Constipation, Immune Stimulation

Agent	**Mechanism of Action**	**Chemical Structure[1]**	**Chemical Source**
Morphine & Morphine-Like Agonists (Phenanthrenes)			
Morphine	Mu-opioid receptor agonist (selective; pure agonist) Inhibits ascending pain pathways Works in the CNS	 **Morphine** *MS-Contin**	Naturally occurring
Hydromorphone	Mu-opioid receptor agonist (selective; pure agonist) Inhibits ascending pain pathways Also relieves pain through unknown mechanism Works in the CNS	 **Hydromorphone**	Semisynthetic
Oxymorphone	Mu-opioid receptor agonist (relatively selective; pure agonist) Also relieves pain through unknown mechanism Works in the CNS	 **Oxymorphone**	Semisynthetic
Codeine	Mu opioid receptor agonist Converted to morphine in vivo Inhibits ascending pain pathways Produces cough suppression by direct action in the medulla (suppresses cough reflex) Works in the CNS	 **Codeine**	Naturally occurring

Agent	Mechanism of Action	Chemical Structure[1]	Chemical Source
Hydrocodone	Mu opioid receptor agonist (relatively selective; but can bind to other opioid receptor types at higher doses) Works in the CNS	 **Hydrocodone**	Semisynthetic
Oxycodone	Mu opioid receptor agonist (relatively selective; pure agonist) Inhibits ascending pain pathways Works in the CNS	 **Oxycodone**	Semisynthetic
Meperidine and Meperidine-Like Agents (Phenylpiperidines)			
Meperidine	Mu opioid receptor agonist Kappa opioid receptor agonist (higher affinity than morphine) Inhibits ascending pain pathways Works in the CNS	 **Meperidine**	Synthetic
Fentanyl	Mu opioid receptor agonist (strong) Kappa opioid receptor agonist (strong) Inhibits ascending pain pathways Works in the CNS	 **Fentanyl**	Synthetic
Sufentanil	Mu opioid receptor agonist (potent) Kappa opioid receptor agonist (lesser effects) Inhibits ascending pain pathways Dose-related (>8mcg/kg) deep level of anesthesia Dose-related (25-30mcg/kg) inhibition of catecholamine release, esp. NE (this mechanism controls sympathetic response to surgical stress) Works in the CNS	 **Sufentanil**	Synthetic

Agent	Mechanism of Action	Chemical Structure[1]	Chemical Source
Remifentanil	Mu opioid receptor agonist (potent) Kappa opioid receptor agonist Inhibits ascending pain pathways Works in the CNS	 **Remifentanil**	Synthetic
Diphenylheptane			
Methadone	Mu opioid receptor agonist (potent; R-isomer has highest affinity vs S-isomer) Low affinity for kappa and delta opioid receptors 5-HT reuptake inhibitor (weak) Inhibits ascending pain pathways NMDA-Receptor antagonist (weak) Binds to receptors in cough center of medulla (cough suppression at low doses) Works in the CNS Blunted euphoric effect due to its long duration of action (unattractive for abusers)	 **Methadone**	Synthetic
Mixed Agonist-Antagonist Derivatives			
Buprenorphine	Mu opioid receptor partial agonist Kappa opioid receptor antagonist (mixed agonist-antagonist effects) Works in the CNS	 **Buprenorphine**	Synthetic
Butorphanol	Mu opioid receptor partial agonist (partial because it has low intrinsic activity at these receptors) Kappa opioid receptor agonist Inhibits ascending pain pathways Works in the CNS	 **Butorphanol**	Synthetic
Pentazocine	Mu opioid receptor partial agonist Kappa opioid receptor agonist Inhibits ascending pain pathways Weakly inhibits the effects of morphine and meperidine	 **Pentazocine**	Synthetic

Agent	Mechanism of Action	Chemical Structure[1]	Chemical Source
Nalbuphine	Mu opioid receptor partial antagonist Kappa opioid receptor agonist Inhibits ascending pain pathways Works in the CNS	 **Nalbuphine**	Synthetic
Other Centrally-Acting Analgesics			
Tapentadol	Mu opioid receptor agonist (18x LESS potent than morphine) NE reuptake inhibitor (helps modifies ascending pain pathway) Inhibits ascending pain pathways Works in the CNS	 Tapentadol ***Nucynta***	Synthetic
Tramadol	Mu opioid receptor agonist (very weak) NE and 5-HT reuptake inhibitor (these neurotransmitters are involved in the descending inhibitory pain pathway responsible for pain relief) Inhibits ascending pain pathways Works in the CNS	 **Tramadol**	Synthetic
Antagonists			
Naloxone	Mu-, Kappa-, and Delta- opioid antagonist (highest affinity for mu) Pure antagonist Blocks opioid effects through competitive antagonism Works in the CNS	 **Naloxone**	Synthetic
Naltrexone	Mu-, Kappa-, and Delta- opioid antagonist May possess some agonist properties, but these are minor compared to potent antagonist properties Blocks opioid agonist effects through competitive antagonism Can also displace opioid agonists from receptor sites (but at high enough doses, opioid agonists can displace the naltrexone) 2x more potent than Naloxone Only becomes active if tablet is chewed, crushed, or dissolved (discourages abuse / diversion) Works in the CNS	 **Naltrexone**	Synthetic

AVAILABLE FORMULATIONS & CONTROLLED SUBSTANCE SCHEDULES

Agent (U.S. Brand Names)	**Dosage Forms on Hospital X Formulary (Brand Name)** **(Note: when not currently available on Hospital X Formulary, it is specified as such and all commercially available dosage forms are listed in this case)**	**Schedule**
Morphine Sulfate (Astramorph®, Avinza®, Duramorph®, Infumorph® Kadian®, MS Contin®) Note: Oramorph®, RMS®, and Roxanol® brands discontinued	Oral tablet (generic): 10 mg Oral tablet, SR (generic): 10, 15, 30, 60mg Oral capsule, ER (Kadian®): 20, 30, 50mg Oral soln (generic): 10mg/5mL Oral soln concentrate (generic): 20mg/mL Injection soln (generic): 1mg/mL, 2mg/mL, 4mg/mL, 10mg/mL, 25mg/mL, 50mg/mL Injection soln (Duramorph®): 0.5mg/mL	C-II
Morphine Sulfate (Liposomal) (DepoDur®)	*Discontinued* Epidural suspension (DepoDur®): 10mg/mL, 15mg/1.5mL	C-II
Morphine Sulfate + Naltrexone Hydrochloride (Embeda®)	**Not currently available on Hospital X formulary** mg morphine – mg naltrexone Oral capsule ER (Embeda®): 20-0.8, 30-1.2, 50-2, 60-2.4, 80-3.2, 100-4mg	C-II
Hydromorphone Hydrochloride (Dilaudid®, Dilaudid®-HP, Exalgo®)	Oral tablet (generic): 2, 4mg Oral liquid (Dilaudid®): 1mg/mL Injection soln (generic, Dilaudid®): 1mg/mL, 2mg/mL, 4mg/mL Injection soln (generic, Dilaudid-HP®): 10mg/mL Injection powder for reconstitution (Dilaudid-HP®): 250mg Rectal suppository (generic, Dilaudid®): 3mg	C-II
Oxymorphone Hydrochloride (Opana®)	Oral tablet, ER (generic, Opana-ER®): 5, 7.5, 10, 15, 20, 30, 40mg	C-II
Codeine Sulfate (generic)	Oral tablet (generic): 30mg Injection soln (generic): 15mg/mL	C-II
Codeine + APAP (Tylenol® with Codeine #2, #3, #4)	(mg codeine – mg APAP) Oral tablet (generic, Tylenol #3®): 30mg-300mg Oral soln (generic): 12-120mg/5mL Oral liquid (Tylenol with Codeine®): 2.4-24mg/5mL	C-III (oral solids containing not more than 90mg codeine / dosage unit) C-V (oral liquids or cough preparations containing not more than 200 mg codeine per 100mL)
Codeine + Guaifenesin (Robitussin® AC)	(mg codeine – mg guaifenesin) Oral liquid (Robitussin® AC): 10-100mg/5mL	C-V

Agent (U.S. Brand Names)	Dosage Forms on Hospital X Formulary (Brand Name) (Note: when not currently available on Hospital X Formulary, it is specified as such and all commercially available dosage forms are listed in this case)	Schedule
Codeine + Guaifenesin + Pseudoephedrine (Cheratussin®, Mytussin®)	**Not currently available on Hospital X formulary**	C-V
Codeine + Chlorpheniramine + Pseudoephedrine (Phenylhistine®[OTC], Tricode AR®)	**Not currently available on Hospital X formulary**	C-V
Codeine + APAP + Butalbital + Caffeine (Fioricet® with Codeine)	**Not currently available on Hospital X formulary**	C-III
Hydrocodone Bitartrate (Zohydro®) Note: Zohydro was FDA approved October 2013	**Not currently available on Hospital X formulary** Oral capsule (Zohydro® ER): 10, 15, 20, 30, 40, 50mg	C-II
Hydrocodone Bitartrate + APAP (Hycet®, Lortab®, Norco®, Vicodin®, Xodol®) Note: Lorcet®, Maxidone®, Stagesic®, Zamicet®, Zolvit®, and Zydone® brands have been discontinued	(mg hydrocodone – mg APAP) Oral tablet (generic, Norco®): 5-325mg, 7.5-325mg, 10-325mg Oral soln (generic): 10-300mg/15mL	C-II#
Hydrocodone Polistirex + Chlorpheniramine Polistirex (Tussionex Pennkinetic®)	(Equivalent to mg hydrocodone bitartrate – mg chlorpheniramine maleate) Oral suspension ER (Tussionex Pennkinetic®): 10-8mg/5mL	C-II#
Hydrocodone Bitartrate + Homatropine Methylbromide (Hydromet®, Tussigon®)	**Not currently available on Hospital X formulary** (mg hydrocodone – mg homatropine) Oral tablet (generic, Tussigon®): 5-1.5mg Oral syrup (generic, Hydromet®): 5-1.5mg/5mL	C-II#
Hydrocodone Bitartrate + Ibuprofen (Ibudone®, Reprexain®, Vicoprofen®, Xylon®)	**Not currently available on Hospital X formulary** mg hydrocodone – mg ibuprofen Oral tablet (generic, Ibudone®, Reprexain®, Vicoprofen®, Xylon®): 2.5-200mg, 5-200mg, 7.5-200mg, 10-200mg	C-II#
Hydrocodone Bitartrate + Pseudoephedrine Hydrochloride (Rezira®)	**Not currently available on Hospital X formulary** mg hydrocodone – mg pseudoephedrine Oral soln (Rezira®): 5-60mg/5mL	C-II#
Hydrocodone Bitartrate + Phenylpropanolamine	*Discontinued*	---

Agent (U.S. Brand Names)	Dosage Forms on Hospital X Formulary (Brand Name) (Note: when not currently available on Hospital X Formulary, it is specified as such and all commercially available dosage forms are listed in this case)	Schedule
Hydrocodone Bitartrate + Phenyltoloxamine (Tussionex®)	*Not available in the United States*	---
Hydrocodone Bitartrate + Chlorpheniramine Maleate + Pseudoephedrine Hydrochloride (Zutripro®)	**Not currently available on Hospital X formulary** mg hydrocodone – mg chlorpheniramine – mg pseudoephedrine Oral soln (Zutripro®): 5-4-60mg/5mL	C-II#
Oxycodone Hydrochloride (OxyCONTIN®) Note: Roxicodone® discontinued	Oral tablet (generic): 5mg Oral tablet CR (OxyCONTIN®): 10, 20, 40mg	C-II
Oxycodone Hydrochloride + APAP (Percocet®, Roxicet®, Xartemis®XR) Note: Xartemis® brand approved March 2014	mg hydrocodone – mg APAP Oral tablet (generic): 5-325mg, 10-325mg Oral tablet (Xartemis®XR): 7.5-325mg → **not available on Hospital X Formulary** Oral soln (Roxicet®): 5-325mg/5mL	C-II
Oxycodone Hydrochloride + Aspirin (Endodan®, Percodan®)	**Not currently available on Hospital X formulary** mg oxycodone – mg ASA Oral tablet (generic, Endodan®, Percodan®): 4.84-325mg	C-II
Oxycodone Hydrochloride + Ibuprofen (generic)	**Not currently available on Hospital X formulary** mg oxycodone – mg ibuprofen Oral tablet (generic): 5-400mg	C-II
Oxycodone Hydrochloride + Naloxone Hydrochloride (Targiniq ER®)	*FDA Approved July 2014; Availability date not yet known*	C-II
Meperidine Hydrochloride (Demerol®)	Injection soln (Demerol®): 25mg/mL, 50mg/mL, 100mg/mL	C-II
Meperidine Hydrochloride + Promethazine Hydrochloride (generic)	**Not currently available on Hospital X formulary** mg meperidine – mg promethazine Oral capsule (generic): 50-25mg	C-II
Fentanyl Citrate (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze®, Subsys®)	Oral lozenge (Fentora®): 100, 200, 400mcg Transdermal patch (generic, Duragesic®): 12 (12.5), 25, 50, 75, 100 mcg/hr Injection soln (generic, Sublimaze®): 0.05 mg/mL	C-II

Agent (U.S. Brand Names)	Dosage Forms on Hospital X Formulary (Brand Name) (Note: when not currently available on Hospital X Formulary, it is specified as such and all commercially available dosage forms are listed in this case)	Schedule
	Other dosage forms available that are not currently on Hospital X formulary Buccal film (Onsolis®) Sublingual spray (Subsys®) Oral lozenge, higher strengths than Fentora® (Actiq®) Intranasal soln (Lazanda®) Buccal tablet (Fentora®) Sublingual tablet (Abstral®)	
Fentanyl + Bupivicaine	Injection soln: 2mcg fentanyl – 0.125% bupivacaine	C-II
Sufentanil Citrate (Sufenta®)	Injection soln (generic): 50mcg/mL	C-II
Remifentanil (Ultiva®)	Restricted Use on Hospital X Formulary (neurosurgical procedures) Injection powder for reconstitution: 1, 2, 5 mg	C-II
Methadone Hydrochloride Note: Dolophine® brand discontinued	Oral tablet (generic): 10mg Oral soln (generic): 5mg/5mL Injection soln (generic): 10mg/mL	C-II
Buprenorphine (Buprenex®, Butrans®)	**Not currently available on Hospital X formulary** Sublingual tablet (generic): 2, 8mg Injection soln (generic, Buprenex®): 0.3mg/mL Transdermal patch (Butrans®): 5, 7.5, 10, 15, 20 mcg/mL (weekly)	C-III
Buprenorphine + Naloxone (Suboxone®, Zubsolv®, Bunavail®)	**Not currently available on Hospital X formulary** (mg buprenorphine – mg naloxone) Buccal film (Bunavail®): 2.1-0.3mg, 4.2-0.7mg, 6.3-1mg Sublingual film (Suboxone®): 2-0.5mg, 4-1mg, 8-2mg, 12-3mg Sublingual tablet (generic, Zubsolv®): 1.4-0.36mg, 2-0.5mg, 5.7-1.4mg, 8-2mg	C-III
Butorphanol Tartrate Note: Stadol® brand discontinued	Injection soln (generic): 1mg/mL	C-IV
Pentazocine Lactate (Talwin®)	**Not currently available on Hospital X formulary** Injection soln (Talwin®): 30mg/mL	C-IV
Pentazocine Hydrochloride + APAP	*Discontinued*	C-IV
Pentazocine Hydrochloride + Naloxone Hydrochloride (Talwin NX®)	mg pentazocine – mg naloxone Oral tablet (generic): 50-0.5mg	C-IV
Nalbuphine Hydrochloride (Nubain®)	Injection soln (generic): 10mg/mL	[None]
Tapentadol Hydrochloride (Nucynta®)	Oral tablet (Nucynta®): 50, 75mg	C-II

Agent (U.S. Brand Names)	Dosage Forms on Hospital X Formulary (Brand Name) (Note: when not currently available on Hospital X Formulary, it is specified as such and all commercially available dosage forms are listed in this case)	Schedule
Tramadol Hydrochloride (Ultram®, Ultram® ER) Note: Rybix® ODT, Ryzolt® discontinued	Oral tablet (generic): 50mg	C-IV[$]
Tramadol Hydrochloride + APAP (Ultracet®)	**Not currently available on Hospital X formulary** mg tramadol – mg APAP Oral tablet (generic, Ultracet®): 37.5-325mg	C-IV[$]

[#]Effective October 6, 2014 (previously were C-III)
[$]Effective August 18, 2014

PHARMACODYNAMICS / PHARMACOKINETICS

Agent	***Onset of Action***	***Bioavailability***	***Duration (of Pain Relief or effect)***	***Metabolism***	***Half-Life of Elimination***	***Excretion***
Morphine	Oral (IR): 30min IV: 5-10min	PO: 17-33% Extensive first pass metabolism	IR: 4hr ER: 8-24hr	Hepatic (glucuronidation) Active metabolite: morphine-6-glucuronide (contributes to analgesia) Inactive metabolite: morphine-3-glucuronide (may contribute to side-effects	IR: 2-4 hrs Avinza: 24hrs Kadian: 11-13 hrs	Urine (primarily as inactive metabolite; 2-12% unchanged) Feces (7-10%) Accumulation of active metabolite can occur in renal insufficiency and cause toxicity
Hydromorphone	Oral (IR): 15-30 min Oral (ER): 6hr IV: 5-10min	PO: 62%	Oral (IR): 3-4hr Oral (ER): 13hr IV: 3-4hr	Hepatic (glucuronidation) Inactive metabolites	IR: 2-3hr ER: 11hr (8-15)	Urine (primarily as glucuronide conjugates)
Oxymorphone	IV: 5-10min	PO: 10%	IV: 3-6hr	Hepatic (glucuronidation) Active and inactive metabolites	Oral (IR): 7-9hr Oral (ER): 9-11hr	Urine (<1% unchanged) Feces
Codeine	PO (IR): 0.5-1hr IM: 10-30min	PO: 53%	PO (IR): 4-6hr IM: 4-6hr	Hepatic CYP2D6*, 3A4 UGT2B7, 2B4 (Glucuronidation, N-demethylation, O-demethylation) *Active metabolite: morphine (via 2D6) essential to its analgesic effect → poor metabolizers may not experience efficacy; extensive metabolizers may result in morphine toxicity (respiratory depression and death have occurred in extensive metabolizers (black box warning)	3hr	Urine (90% as metabolites; 10% as unchanged) Feces
Hydrocodone	IR: 10-20min	ER: Cmax increases by 27% with high fat meal	IR: 4-8hr	Hepatic (60%) CYP3A4: N-demethylation to norhydrocodone (major, active	IR: 3.3-4.4hr ER: 8hr	Urine (70% of single oral dose eliminated as parent and metabolites in 24hrs)

Agent	*Onset of Action*	*Bioavailability*	*Duration (of Pain Relief or effect)*	*Metabolism*	*Half-Life of Elimination*	*Excretion*
				metabolite) CYP2D6: O-demethylation to hydromorphone (active metabolite) Fecal, biliary, intestinal, renal metabolic pathways (40%)		(26% of dose eliminated as parent and metabolites in 72hr with 12% being unchanged drug)
Oxycodone	IR: 10-15min CR: unknown (OxyContin® reformulated in 2010 to be abuse deterrent; limited PK info available on reformulated product)	60-87%	IR: 3-6hr CR: ≤12hr	Hepatic CYP3A4: major, active metabolite CYP2D6: minor, active metabolite (oxymorphone) Note: analgesic effect primarily due to parent compound, not as much from metabolites	IR: 2-4hr CR: 5hr	Urine (19% as parent; >64% as metabolites)
Meperidine	PO, SQ: 10-15min IV: 1-5min Epidural: 5-10min	PO: 50-60% Extensive first-pass metabolism	PO, SQ: 2-4hr IV: 2-4hr Epidural: 4-6hr	Hepatic N-demethylation: active metabolite (has ½ analgesic effect and 2-3x the CNS stimulation effects vs parent) Hydrolysis and glucuronidation: inactive metabolite	2.5-4hr Active metabolite: 15-30hr (can accumulate with doses >600mg/day or with decreased renal fx)	Urine (30% as active metabolite; 5% as unchanged) Acidification of urine greatly enhances excretion of parent and metabolites
Fentanyl	IM: 7-8min IV: almost immediate Transdermal (initial placement): 6hr Transmucosal: 5-15min	Buccal film: 71% Buccal tab: 65% Lozenge: 50% SL spray: 76% SL tab: 54%	IM: 1-2hr IV: 0.5-1hr Transdermal: 72-96hr Transmucosal: related to blood level	Hepatic CYP3A4	IV: 2-4hr (prolongs as infusion time increases due to large Vd) Transdermal: 20-27hr Transmucosal: 3-14hr (dose dependent) Nasal spray: 15-25hr	Urine (75%; primarily as metabolites; 7-10% as unchanged drug) Feces (9%)

Agent	*Onset of Action*	*Bioavailability*	*Duration (of Pain Relief or effect)*	*Metabolism*	*Half-Life of Elimination*	*Excretion*
Sufentanil	IV: 1-3min Epidural: 10min Unconsciousness occurs 1-3 min after 4.9-10mcg/kg IV	---	Dose dependent Epidural (10-15mcg + bupivacaine): 1.7hr	Hepatic (CYP3A4, O-demethylation) O-demethylation: active metabolite (10% activity of parent) Small intestine	164 min	Urine (80%; primarily as metabolites; 2% as unchanged drug)
Remifentanil	IV: 1-3min	---	3-10min (DOA of action does NOT increase with prolonged administration)	Blood and tissue esterases (rapid)	10-20min	Urine
Methadone	PO: 0.5-1hr IV: 10-20min	36-100%	PO: 4-8hr (increases to 22-48hr w/ repeated doses)	Hepatic CYP3A4 (main), 2B6, 2C19, 2C9, 2D6 (N-demethylation): inactive metabolites P-glycoprotein	8-59hr (can prolong with alkaline pH) R-methadone: 37.6hr S-methadone: 28.6hr	Feces (major route) Urine (minor route; <10% unchanged; increases with urine pH<6
Buprenorphine	IM: 15min	IM: 70% SL: 29% Patch: 15% Extensive first pass metabolism	IM: ≥6hr	Hepatic CYP3A4: N-dealkylation (major, active metabolite) UGT1A1, 2B7 (minor) UGT1A3 (further metabolism of active metabolite)	IV: 2.2-3hr SL: 37hr (may be due to depot effect) Patch: 26hr	Urine (27-30%) Feces (70%)
Butorphanol	IM, Nasal: ≤15min IV: 1-5min	PO: 5-17% (Extensive first pass metabolism) Nasal: 60-70%	IM, IV: 3-4hr Nasal: 4-5hr	Hepatic (major, inactive metabolite)	2-9hr (parent drug) 18hr (metabolite)	Urine (70-80% as inactive metabolites; 5% unchanged) Feces (15%)
Pentazocine	IM, SQ: 15-20min IV: 2-3min	Extensive first pass metabolism	2-3hr	Hepatic (oxidation, glucuronidation) Undergoes enterohepatic recycling	2-3hr	Urine (60% of dose eliminated in 24hr; very low % as unchanged)

Agent	***Onset of Action***	***Bioavailability***	***Duration (of Pain Relief or effect)***	***Metabolism***	***Half-Life of Elimination***	***Excretion***
Nalbuphine	SQ, IM: <15min IV: 2-3min	Oral is 1/5 as potent as parenteral (must be given parenterally due to extensive first pass metabolism and GI mucosal metabolism)	IM, SQ: 3-6hr	Hepatic	5hr (3-6hr)	Urine Bile Feces
Tapentadol	Within 1hr	PO: 32% Extensive first-pass metabolism Absorption increases with high fat meal	Not available	Hepatic Glucuronidation (UGT): 70% Methylation (CYP2C9, 2C19): 13% Hydroxylation (CYP2D6): 2% Unknown paths: 12% All metabolites inactive	IR: 4hr LA: 5-6hr	Urine (99%; 70% as metabolites, 3% as unchanged drug) Feces (1%)
Tramadol	IR: 1hr	IR: 75% ER: 85-90% relative to IR Undergoes significant first-pass metabolism (may be saturable; IR bioavailability increases to 100% after multiple doses	6-9hr	Hepatic CYP3A4, 2B6 CYP2D6: O-demethylation to active metabolite Glucuronidation Sulfation Active metabolite critical to the analgesic activity of Tramadol	Parent: 6-8hr Active metabolite: 7-9hr	Urine (60% as metabolites; 30% unchanged drug)

FDA LABELED INDICATIONS

Agent	*FDA Labeled Indications*	*Labeled Pediatric Indication?*	*Comments[2]*
Morphine	PO (IR): moderate to severe pain (acute or chronic) PO (ER): severe pain needing around-the-clock dosing when alternatives are inadequate IV: severe pain; pre-anesthesia Epidural/Intrathecal: intractable chronic pain	Yes	1st line agent in severe pain Use IR w/ SR product to control breakthrough pain in cancer patients
Hydromorphone	Moderate to severe pain ER products: severe pain in opioid-tolerant patients needing around-the-clock dosing when alternatives are inadequate	Yes	More potent than morphine; otherwise, no advantages Hydromoprhone may have less pruritus, but research not conclusive
Oxymorphone	Moderate to severe pain (acute) Pain during labor Pre-op med Anesthesia support Relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to heart failure ER products: severe pain in opioid-tolerant patients needing around-the-clock dosing when alternatives are inadequate	No	No advantages over morphine Use IR w/ SR product to control breakthrough pain in cancer patients
Codeine	Mild to moderately severe pain (Anti-tussive use is an unlabeled use)	Yes	Provides only weak analgesia Best when used with NSAIDs, ASA, or APAP
Hydrocodone	Severe pain (chronic): patients requiring daily around-the-clock, long-term treatment and for which alternative treatment options are inadequate	No	Most effective when used with NSAIDs, ASA, or APAP
Hydrocodone + APAP	Moderate to severe pain	Yes	Effective October 6 2014, all hydrocodone-containing products are C-II (changed from C-III)
Oxycodone	Moderate to severe pain CR products: patients requiring daily around-the-clock, long-term treatment and for which alternative treatment options are inadequate	No	Most effective when used with NSAIDs, ASA, or APAP Use IR w/ SR product to control breakthrough pain in cancer patients
Oxycodone + APAP	Moderate to moderately severe pain ER products: acute pain severe	No	

Agent	*FDA Labeled Indications*	*Labeled Pediatric Indication?*	*Comments[2]*
	enough to require opioid treatment and for which alternatives are inadequate		
Meperidine	Moderate to severe pain Adjunct to anesthesia and pre-operative sedation (Unlabeled use: Post-operative shivering; reduce rigors from amphotericin B)	Yes	Oral not recommended Do not use in renal failure May precipitate tremors, myoclonus, seizures MAOIs can induce hyperpyrexia and / or seizures or opioid overdose symptoms Not as potent as morphine and has a shorter analgesic duration Offers no analgesic advantage over morphine, has greater toxicity (due to its metabolite) Use should be limited Avoid in those likely to accumulate the metabolite (which is renally cleared)
Fentanyl	Injection: relief of pain, preoperative medication, adjunct to anesthesia Transdermal patch: chronic pain in opioid-tolerate patients where pain is severe enough to require daily around-the-clock long term pain management where alternatives are inadequate Transmucosal: break-through cancer pain	Yes	Do not use transdermal in acute pain Transmucosal dosage forms only for breakthrough cancer pain in patients already receiving or are tolerant to opioids More potent and faster acting than meperidine
Sufentanil	Epidural analgesia: either alone or in combination with low-dose bupivacaine (12.5mg) during labor and vaginal delivery Surgical analgesia adjunct in patients who are intubated / ventilated Surgical anesthesia: primary agent for induction and maintenance of anesthesia in patients undergoing major surgical procedures; in patients who are intubated / ventilated	Yes	
Remifentanil	Analgesic for use during induction and maintenance of general anesthesia For continued analgesia into the the	Yes	

Agent	*FDA Labeled Indications*	*Labeled Pediatric Indication?*	*Comments[2]*
	immediate post-op period (Unlabeled use: pain in ventilated patients)		
Methadone	Severe pain (chronic): when pain is severe enough to require daily, around-the-clock, long-term treatment where alternatives are inadequate Detoxification of opioid addiction (heroin or other morphine-like drugs)	No	Effective in severe, chronic pain Sedation can be a major problem Titrate no sooner than on a weekly basis Repeated doses accumulate, unpredictable half-life, can cause excessive sedation Conversion from other opioids can be complicated (equianalgesic dose decreases with higher doses of previous opioid)
Buprenorphine	Moderate to severe pain SL: treatment of opioid dependence Transderm Patch: Pain severe enough to require around-the-clock long term dosing when alternatives are inadequate (Unlabeled use: opioid withdrawal in heroin-dependent hospitalized patients)	Yes	2nd line agent for moderate-severe pain May precipitate withdrawal in opioid-dependent patients Lower abuse potential vs morphine due to agonist-antagonist MOA Has a ceiling effect on respiratory depression Ceiling effect on analgesia
Butorphanol	Pain when an opioid is indicated Labor pain Pre-anesthesia medication Supplement to anesthesia	No	2nd line agent for moderate-severe pain May precipitate withdrawal in opioid-dependent patients Lower abuse potential vs morphine due to agonist-antagonist MOA Has a ceiling effect on respiratory depression Ceiling effect on analgesia
Pentazocine	Moderate to severe pain Sedative prior to surgery Supplement to surgical anesthesia	No for analgesia Yes for pre-anesthesia	2nd line agent for moderate-severe pain May precipitate withdrawal in opiate-dependent patients Parenteral doses not recommended Lower abuse potential vs morphine due to agonist-antagonist MOA Has a ceiling effect on respiratory

Agent	*FDA Labeled Indications*	*Labeled Pediatric Indication?*	*Comments[2]*
			depression Ceiling effect on analgesia Hallucinations and dysphoria (psychometric effects) limit use
Nalbuphine	Moderate to severe pain Obstetrical analgesia during labor and delivery Pre-operative analgesia Post-operative and surgical anesthesia (Unlabeled use: opioid-induced pruritus)	No	2nd line agent for moderate-severe pain May precipitate withdrawal in opioid-dependent patients Lower abuse potential vs morphine due to agonist-antagonist MOA Has a ceiling effect on respiratory depression Ceiling effect on analgesia
Tapentadol	Moderate to severe acute pain ER products: pain or neuropathic pain associated with diabetic peripheral neuropathy severe enough to require daily, around-the-clock long term analgesia for which alternative treatment options are inadequate	No	
Tramadol	Moderate to moderately severe pain ER products: patients requiring around-the-clock dosing to manage pain for an extended period of time	Yes (for patients aged 17 and older)	Effective August 18 2014, all tramadol-containing products are C-IV Dose reduction needed in renal impairment and elderly
Tramadol + APAP	Acute pain, short term management (</= 5days)	No	Effective August 18 2014, all tramadol-containing products are C-IV
Naloxone	Opioid overdose Diagnosis of suspected or known acute opioid overdose Septic shock: adjunct to increase blood pressure (BUT NO LONGER RECOMMENDED)	Yes	May not be effective in reversing respiratory depression When needing to reverse opioid side effects, titrate to avoid reversing analgesia
Naltrexone	Alcohol dependence Opioid dependence (to block effects of exogenously administered opioids)	No	

DOSING

[$]Opioid Tolerant (defined as: Pts taking at least 60mg PO morphine QD [or morphine equivalent] for at least 1 week

Morphine:

- Acute Pain (moderate-severe), initial doses
  - Opioid Naïve (if not naïve, may require higher initial doses)
    - PO (IR): 10-30mg q4hr PRN
    - IV bolus: 2.5-5mg q3-4hr PRN (2-3mg q5min until pain relief or sedation in immediate post-operative setting or ED)
    - IV bolus (acute MI, unlabeled use): 4-8mg x1; 2-8mg q5-15min PRN
    - IV bolus (critically Ill, unlabeled use): 2-4mg q1-2hr OR 4-8mg q3-4hr PRN
    - PCA:
      - Demand dose: 1mg (0.5-2.5mg)
      - Lockout interval: 5-10min
      - Usual concentration: 1mg/mL
    - Epidural:
      - Single Dose: 30-100mcg/kg x1 (optimal range = 2.5-3.75mg)
      - Continuous Infusion (can be combined w/ bupivacaine): 0.2-0.4mg/hr
    - Intrathecal:
      - Single Dose: 0.1-0.3mg x1
    - Rectal: 10-20mg q3-4hr
  - IV continuous infusion: 0.8-10mg/hr (usual: up to 80mg/hr) → not recommended for Opioid-Naïve
- Chronic Pain (moderate-severe)
  - Opioid Naïve:
    - PO (ER capsules): 30mg QD (90, 100, 120, 130, 150, 200mg are for use in opioid-tolerant[$] only)
    - PO (MSContin tabs): 15mg q8-12hr (100, 200mg are for use in opioid-tolerant only)
    - Max dose of Avinza®: 1600mg QD (due to fumaric acid content)

Hydromorphone:

- Acute Pain (moderate-severe), initial doses
  - Opioid-naïve (if not naïve, may require higher initial doses):
    - PO (IR): 2-4mg q4-6hr PRN (if severe pain, 4-8 mg q4-6hr)
    - IV bolus: 0.2-1mg q2-3hr PRN
    - IV bolus (critically ill, unlabeled use): 0.2-0.6mg q1-2hr PRN OR 0.5mg q3hr PRN
    - IV continuous infusion: 0.5-3mg/hr
    - PCA (unlabeled use):
      - Demand dose: 0.1-0.2mg (0.05-0.4mg)
      - Lockout interval: 5-10min
      - Usual concentration: 0.2mg/mL
      - Basal not recommended if opioid-naïve
    - Epidural PCA (unlabeled use):
      - Bolus: 0.4-1mg
      - Infusion: 0.03-0.3mg/hr
      - Demand: 0.02-0.05mg
      - Lockout interval: 10-15min
      - Usual concentration: 0.01mg/mL
    - Rectal: 3mg q6-8hr PRN
- Chronic Pain (moderate-severe):
  - PO (ER, Exalgo®): For opioid-tolerant patients only; starting dose is highly patient-specific and depends on what opioid patient is currently taking; use standard conversion chart to convert total daily dose of current opioid to hydromorphone equivalent and then start at approx. 50% for q24hr dosing; there is no optimal or maximal dose for hydromorphone for chronic pain; the appropriate dose is one that relieves pain throughout its dosing interval w/o causing unmanageable side effects

Oxymorphone:

- Acute Pain (moderate-severe), initial doses
  - Opioid Naïve (if not naïve, may require higher initial doses)
    - PO (IR): 5-10mg q4-6hr PRN
- Chronic Pain (moderate-severe):
  - Opioid Naïve:

        - PO (ER): 5mg q12hr
- Labor Pain
    - IM: 0.5-1mg q4-6hr PRN

Codeine:
- Pain, initial doses:
    - PO (IR): 15-60mg q4hr PRN (max total daily dose = 360mg/day)
- Anti-tussive (unlabeled use):
    - PO: 7.5-120mg/day as single dose or in divided doses

Codeine + APAP:
- Pain:
    - PO: 30-60mg Codeine q4-6hr (max total daily dose = 4000mgAPAP/day)
- Anti-tussive:
    - PO: 15-30mg Codeine q4-6hr (max total daily dose = 360mg codeine/day)

Codeine + Guaifenesin:
- Anti-tussive:
    - PO (capsule): 9mg-200mg cap: 2 caps q4hr (max: 12caps/day)
    - PO (tablet): 10mg-400mg tab: 1 tab q4-6hr (max: 6tabs/day)
    - PO (liquid): 10mg-100mg/5mL: 10mL q4hr (max: 60mL/day)

Hydrocodone:
- Chronic Pain, initial:
    - Opioid Naïve:
        - PO: 10mg q12hr
    - Opioid Tolerant:
        - Single doses >40mg or total daily dose >80mg are only for patients who are opioid tolerant

Hydrocodone + APAP:
- Pain, initial
    - Opioid Naïve:
        - PO: 5-10mg hydrocodone q4-6hr PRN (limit APAP to 4000mg/day)

Hydrocodone + Chlorpheniramine:
- Anti-tussive/Anti-histamine:
    - PO (suspension, ER): 10-8mg/5mL: 5mL q12h (max: 10mL/day)

Oxycodone:
- Pain, initial
    - Opioid Naïve:
        - PO (IR): 5-15mg q4-6hr PRN
        - PO (ER): 10mg q12hr
    - Opioid Tolerant:
        - PO (ER): 60mg, 80mg strengths, a single dose >40mg, or a total daily dose of >80mg are only for patients who are opioid tolerant

Oxycodone + APAP:
- Pain (moderate to moderately severe), initial
    - PO (IR): 2.5-10mg oxycodone q6hr PRN (max: 4000mg APAP/day)
    - PO (XR): 2 tabs (=15mg oxycodone) q12hr (max: 4000mg APAP/day)

Meperidine:
- Pain:
    - Only use when no other treatment options exist for managing pain; limit use to ≤48hr
    - PO: not recommended
    - IM, SQ: 50-150mg q3-4hr PRN (max 600mg/day)
- Pre-operative analgesic:
    - IM, SQ: 50-150mg given 30-90min before anesthesia

- Post-operative shivering; reduce rigors from amphotericin B (unlabeled use):
    - IV: 25-50mg x1

Fentanyl:

- Surgery Premedication:
    - IM, slow IV: 50-100mcg given 30-60min prior to surgery
- Adjunct to general anesthesia:
    - Slow IV: 1-20mcg/kg x1, then 2-10mcg/kg/hr
- Adjunct to regional anesthesia:
    - IM or slow IV: 50-100mcg over 1-2min
- Postoperative recovery:
    - IM, slow IV: 50-100mcg q1-2hr PRN
- Pain (severe):
    - PCA (unlabeled use):
        - Usual concentration: 10mcg/mL
        - Demand: 10-20mcg
        - Lockout: 4-10min
        - Basal rate: ≤50mcg/hr (best to limit to 10mcg/hr whenever possible)
    - Critically ill (unlabeled use):
        - Slow IV: 0.35-0.5mcg/kg q30-60min PRN
        - Continuous infusion: 0.7-10mcg/kg/hr
    - Intrathecal (unlabeled use):
        - 5-25mcg x1 (may provide relief up to 6 hr)
    - Epidural (unlabeled use):
        - 25-100mcg x1 (may provide relief up to 8hr)
        - Continuous infusion: 25-100mcg/hr (dose can be lower when combined with bupivacaine)
- Break-through pain (Cancer), initial dosing:
    - Oral lozenge: 200mcg consumed over 15min; if pain is not relieved after an additional 15min, give another dose; then must wait another 4hr before re-dosing
    - Buccal film: 200mcg consumed over 15min; if pain is not relieved after an additional 15min, give another dose; then must wait another 2hr before re-dosing
    - Buccal tab: 100mcg consumed over 15min; if pain is not relieved after an additional 15min, give another dose; then must wait another 4hr before re-dosing
    - Nasal spray: 1 spay (=100mcg) in 1 nostril; if no pain relief after 30min, must use another rescue analgesic; must wait at least 2hr before re-dosing
    - Sublingual spray: 100mcg; if no pain relief after 30min, give another dose; then must wait another 4hr before re-dosing
    - SL tab: 100mcg; if no pain relief after 30min, give another dose; then must wait at least 2hr before re-dosing
- Chronic Pain (severe), initial:
    - Transdermal Patch: calculate patient's 24-hr analgesic requirement using standard opioid conversion tables; change patch q72hr

Sufentanil:

- Surgical anesthesia
    - Surgery expected to last 1-2hr:
        - IV: 1-2mcg/kg total dose
    - Surgery expected to last 2-8hr:
        - IV 2-8mcg/kg total dose
- Pain during labor and delivery
    - Epidural: 10-15mcg, given with bupivacaine 0.125% w/ or w/o epinephrine (max: 3 doses in ≥1hr time intervals until delivery)

Remifentanil:

- Induction of anesthesia:
    - IV continuous infusion: 0.5-1mcg/min
- Maintenance of anesthesia:
    - IV: 0.25-1mcg/kg/min
    - Can give supplemental bolus doses of 1mcg/kg q2-5min
- Analgesic in immediate post-op period:
    - IV: 0.1mcg/kg/min (infusion rates >0.2 are associated with respiratory depression)
    - If CABG pt: 1mcg/kg/min

- Critically ill (unlabeled use)
    - IV: 1.5mcg/kg x1, then 0.008-0.25mcg/kg/min

Methadone:

- Chronic Pain, initial
    - Opioid Naïve:
        - PO: 2.5mg q8-12hr
        - IV: 2.5-10mg q8-12hr
- Critically ill (unlabeled use; to slow development of tolerance when escalation with other opioids is required)
    - PO: 10-40mg q6-12hr
    - IV: 2.5-10mg q8-12hr
- Detoxification, initial
    - PO: 20-30mg x1 usually sufficient to suppress symptoms (max=30mg); give additional 5-10mg if symptoms no suppressed or if they reappear after 2-4hrs (max total daily dose: 40mg)
    - Levels will accumulate for the first few days, so do not increase dose until steady state has been achieved (deaths have occurred)

Buprenorphine:

- Long-term use not recommended
- Buprenorphine DOES have an analgesic ceiling
- Acute Pain (moderate-severe), initial doses:
    - Opioid Naïve:
        - IM: 0.3mg q6-8hr PRN (usual range: 0.15-0.6mg q4-8hr PRN)
        - IV bolus: 0.3mg q6-8hr PRN
- Chronic Pain (moderate-severe), initial doses:
    - Opioid Naïve:
        - Transdermal patch: 5mcg/hr q7days
    - Opioid Tolerant:
        - There is a potential for buprenorphine to ppt withdrawal in patients already receiving opioids
        - If receiving <30mg PO morphine equivalents/day:
            - Transdermal patch: 5mcg/hr q7days
        - If receiving 30-80mg PO morphine equivalents/day:
            - Transdermal patch: 10mcg/hr q7days
        - If receiving >80mg PO morphine equivalents/day:
            - Consider alternative analgesic
- Opioid withdrawal in heroin-dependent hospitalized patients (unlabeled use):
    - IV infusion: 0.3-0.9mg over 20-30mins q6-12hr
- Opioid dependence:
    - SL: 8mg day 1, then 16mg subsequent days

Butorphanol:

- Butorphanol DOES have an analgesic ceiling
- Pain:
    - IM: 2mg q3-4hr PRN
    - IV: 1mg q3-4hr PRN
    - Intranasal spray: 1 spray (1mg) in 1 nostril x1, repeat if pain in 60-90min; can repeat again in 3-4hr
- Preoperative medication:
    - IM: 2mg 60-90mins prior to surgery
- Pain during labor:
    - IM, IV: 1-2 mg; may repeat in 4hr

Pentazocine:

- Pain:
    - IM, SQ: 30-60mg q3-4hr (Max: 60mg/dose or 360mg/day)
    - IV: 30mg q3-4hr (Max: 30mg/day or 360mg/day)
- Labor Pain:
    - IM: 30mg x1
    - IV: 20mg q2-3hr PRN (max total dose: 60mg)

Pentazocine + Naloxone:

- Pain:
  - PO: 50mg pentazocine q3-4hr (max: 100mg/day or 600mg/day or 12 tabs/day)

Nalbuphine:

- Pain management:
  - IM, IV, SQ: 10mg/70kg q3-6hr
    - Max single dose: 20mg
    - Max daily dose: 160mg
- Surgical anesthesia supplement:
  - IV:
    - 0.3-3mg/kg over 10min x1
    - 0.25-0.5mg/kg maintenance doses PRN
- Opioid-induced pruritis (unlabeled use):
  - IV: 2.5-5mg; may repeat dose PRN

Trapentadol:

- Acute pain (moderate-severe), initial
  - PO (IR): 50-100mg q4-6hr PRN (max dose on day 1 of tx: 700mg/day; max dose on subsequent days: 600mg/day)
- Chronic pain (moderate-severe), initial
  - Opioid Naïve:
    - 50mg q12hr

Tramadol:

- Pain (moderate-severe)
  - PO (IR): 50-100mg q4-6hr (max: 400mg/day)
  - PO (ER): 100mg QD; titrate q5days (max: 300mg/day) (if already on IR tramadol, calculate total daily dose and round to next lowest 100mg to determine ER dose)

RELATIVE POTENCIES & EQUIANALGESIC DOSES[2,3]

Opioid	***Equianalgesic PO dose (mg)***	***Equianalgesic IV or IM dose (mg)***
Codeine	200	120
Fentanyl	Variable, unknown	0.1-0.2 (injection) 1mcg/hr patch = 2mg PO morphine/day[3] 25mcg/hr patch = 60mg PO morphine/day[3]
Hydrocodone	5-10	---
Hydromorphone	7.5	1.5
Meperidine	300	75
Methadone	Controversial, variable 20 acute 2-4 chronic	Controversial, variable 10 acute 2-4 chronic
Morphine	30	10
Oxycodone	20	---
Oxymorphone	10	1
Tramadol	200	---
Tapentadol	50mg = 5mg oxycodone	---
Pentazocine	200-300	
Butorphanol	---	2 (injection and nasal spray)
Buprenorphine	---	0.3 (0.4 for SL)
Nalbuphine	---	10

DOSE ADJUSTMENTS

Agent	***Geriatric***	***Renal*** ***(CrCl are in units of mL/min)***	***Hepatic***
Morphine	Use with caution; may require reduced dose	CrCl 10-50: 75% of normal dose CrCl<10: 50% of normal dose HD: No adjustment necessary CRRT: 75% of normal dose	None provided in manufacturer's labeling, but half life will be increased in cirrhosis (reduce dose)
Hydromorphone	PO: >70yo: American Pain Society recommends initiating at 25-50% of normal adult starting dose IV: initiate at 0.2mg	PO (IR) or IV: initiate at 25-50% of usual starting dose PO (ER): CrCl 30-60: initiate at 50% of normal starting dose CrCl <30: initiate at 25% of normal starting dose	Moderate Impairment: PO (IR) or IV: initiate at 25-50% of usual starting dose PO (ER): initiate at 25% of usual starting dose Severe impairment: PO (IR) or IV: has not been studied; be even more conservative than moderate impairment; use with caution PO (ER): do not use
Oxymorphone	Initiate at lower end of starting dose range	CrCl<50: reduce initial starting dose	Mild impairment: Initiate at lowest possible dose Moderate to severe impairment: Contraindicated
Codeine	No difference	Initiate at lower doses or longer dosing intervals	No adjustments provided in manufacturer's labeling; initiate a lower doses and longer dosing intervals
Hydrocodone	Initiate at lower end of dosing range	Initiate with a low dose	Mild to moderate impairment: no adjustment necessary Severe impairment: start at 10mg/dose; monitor
Hydrocodone + APAP	2.5-5mg hydrocodone q4-6hr ≤4g APAP/day	No adjustments provided in manufacturer's labeling	Use with caution Avoid chronic use
Oxycodone	No difference	CrCl<60: serum concentrations are increased by 50%; adjust based on clinical situation	IR: reduce initial dose ER: initiate at 25-33% usual starting dose
Oxycodone + APAP	No adjustments provided in manufacturer's labeling; use with caution; consider decreasing initial dose or extending the	IR: No adjustments provided in manufacturer's labeling; use with caution ER: 1 tablet q12hr	

Agent	***Geriatric***	***Renal*** ***(CrCl are in units of mL/min)***	***Hepatic***
	interval		
Meperidine	Avoid use (according to American Pain Society and ISMP)		Use caution in severe impairment; initiate at lower dose; dose reduction more important for PO than IV
Fentanyl	Elderly 2x more sensitive to effects than younger persons	Injection: No adjustments provided in manufacturer's labeling; use with caution Transdermal patch: Mild to moderate impairment: reduce dose by 50% Severe impairment: Do not use	
Sufentanil	Reduce dose	No adjustments provided in manufacturer's labeling; use with caution	
Remifentanil	Reduce dose by 50%	No adjustments necessary	
Methadone	PO, IM: 2.5mg q8-12hr	No adjustments provided in manufacturer's labeling; use with caution	No adjustments provided in manufacturer's labeling; use with caution; methadone undergoes hepatic metabolism and exposure may be increased after repeated dosing
Buprenorphine	Acute Pain: IM, slow IV: 0.15mg q6hr Long-term use not recommended (elderly more likely to suffer from confusion and drowsiness) Chronic Pain: Transdermal Patch: use with caution	No adjustments provided in manufacturer's labeling; use with caution	No adjustments provided in manufacturer's labeling; use with caution because it undergoes extensive hepatic metabolism
Butorphanol	IM, IV: initiate at 50% of usual starting dose Nasal spray: initial dose should not exceed 1mg; a second dose can be given after 90-120 mins if needed		
Pentazocine	Use with caution; initiate at lower doses	No adjustments provided in manufacturer's labeling; use with caution	No adjustments provided in manufacturer's labeling; use with caution
Nalbuphine	Use with caution	Reduce dose; use with caution	Reduce dose; use with caution
Tapentadol	Initiate at lower range of usual starting dose	CrCl ≥30: No adjustment necessary Crl<30: Use not recommended	Mild impairment: no adjustment necessary Moderate impairment: IR: initiate at 50mg q8hr or longer (max: 3 doses/24hr) ER: initiate at 50mg q24hr or longer (max: 100mg q24hr) Severe impairment: Use not recommended

Agent	***Geriatric***	***Renal*** ***(CrCl are in units of mL/min)***	***Hepatic***
Tramadol	<u>>65yo:</u> initiate at lower end of dosing range; use with caution <u>>75yo:</u> IR: Max 300mg/day ER: Use with great caution	<u>CrCl<30:</u> IR: 50-100mg q12hr ER: Do not use	<u>Cirrhosis:</u> IR: 50mg q12hr <u>Severe impairment:</u> ER: Do not use
Naloxone	No difference	No adjustments provided in manufacturer's labeling	No adjustments provided in manufacturer's labeling
Naltrexone	No difference	<u>Mild</u>: no adjustment necessary <u>Moderate to severe</u>: no adjustment provided in manufacturer's labeling; use with caution since it is excreted primarily in urine	<u>Mild to moderate</u>: no adjustment necessary <u>Severe</u>: no adjustment provided in manufacturer's labeling; concentrations do increase 5 to 10 fold in cirrhosis

MONITORING & ADVERSE EFFECTS

Agent	Relative Histamine Release[2]
Morphine	+++
Hydromorphone	+
Oxymorphone	+
Codeine	+++
Hydrocodone	n/a
Oxycodone	+
Meperidine	+++
Fentanyl	+
Methadone	+
Pentazocine	n/a
Butorphanol	n/a
Nalbuphine	n/a
Buprenorphine	n/a
Naloxone	n/a
Naltrexone	n/a
Tramadol	n/a
Tapentadol	n/a

Major Adverse Effects of Opioid Analgesics[2]	Manifestation[2]
Mood Changes	Dysphoria, Euphoria
Somnolence	Sedation, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate
Decreased GI motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention
Histamine release	Urticaria, pruritus Exacerbation of asthma (rare)
Tolerance	Larger doses needed for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
Morphine	Cardiovascular: Bradycardia, hypotension Central nervous system: Drowsiness (9% to 48%; tolerance usually develops to drowsiness with regular dosing for 1-2 weeks), dizziness (6% to 20%), fever (<3% to >10%), confusion, headache (following epidural or intrathecal use) Dermatologic: Pruritus (may be dose related) Gastrointestinal: Xerostomia (78%), constipation (9% to 40%; tolerance develops very slowly if at all), nausea (7% to 28%; tolerance usually develops to nausea and vomiting with chronic use), vomiting Genitourinary: Urinary retention (16%; may be prolonged, up to 20 hours, following epidural or intrathecal use) Hematologic: Anemia (following intrathecal use) Local: Pain at injection site Neuromuscular & skeletal: Weakness	Cardiovascular: Circulatory depression, flushing, shock Central nervous system: Dysphonia, physical and psychological dependence, sedation Endocrine & metabolic: Antidiuretic hormone release, hypogonadism Neuromuscular & skeletal: Bone mineral density decreased

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
	Respiratory: Oxygen saturation decreased Miscellaneous: Histamine release	
Hydromorphone		Cardiovascular: Bradycardia, extrasystoles, flushing (facial), hypertension, hypotension, palpitations, peripheral edema, peripheral vasodilation, syncope, tachycardia Central nervous system: Abnormal dreams, abnormal gait, abnormality in thinking, aggressive behavior, agitation, apprehension, ataxia, brain disease, burning sensation of skin (Exalgo), central nervous system depression, chills, cognitive dysfunction, confusion, decreased body temperature (Exalgo), depression, disruption of body temperature regulation (Exalgo), dizziness, drowsiness, drug dependence, dysarthria, dysphoria, equilibrium disturbance, euphoria, fatigue, hallucination, headache, hyperesthesia, hyperreflexia, hypoesthesia, hypothermia, increased intracranial pressure, insomnia, lack of concentration, lethargy, malaise, memory impairment, mood changes, myoclonus, nervousness, painful defecation, panic attack, paranoia, paresthesia, psychomotor agitation, restlessness, sedation, seizure, sleep disorder (Exalgo), suicidal ideation, uncontrolled crying, vertigo Dermatologic: Diaphoresis, erythema (Exalgo), hyperhidrosis, pruritus, skin rash, urticaria Endocrine & metabolic: Antidiuretic effect, decreased amylase, decreased libido, decreased plasma testosterone, dehydration, fluid retention, hyperuricemia, hypokalemia, weight loss Gastrointestinal: Abdominal distention, anal fissure, anorexia, bezoar formation (Exalgo), biliary tract spasm, constipation, decreased appetite, decreased gastrointestinal motility (Exalgo), delayed gastric emptying, diarrhea, diverticulitis, diverticulosis, duodenitis, dysgeusia, dysphagia, eructation, flatulence, gastroenteritis, gastroesophageal reflux disease (aggravated; Exalgo), hematochezia, increased appetite, intestinal perforation (large intestine; Exalgo), nausea, paralytic ileus, stomach cramps, vomiting, xerostomia Genitourinary: Bladder spasm, decreased urine output, difficulty in micturition, dysuria, erectile dysfunction, hypogonadism, sexual disorder, ureteral spasm, urinary frequency, urinary hesitancy, urinary retention Hematologic & oncologic: Oxygen desaturation Hepatic: Increased liver enzymes Hypersensitivity: Histamine release Local: Pain at injection site, post-injection flare

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
		Neuromuscular & skeletal: Arthralgia, dyskinesia, laryngospasm, muscle rigidity, muscle spasm, myalgia, tremor, weakness Ophthalmic: Blurred vision, diplopia, dry eye syndrome, miosis, nystagmus Otic: Tinnitus Respiratory: Apnea, bronchospasm, dyspnea, flu-like symptoms (Exalgo), hyperventilation, hypoxia, respiratory depression, respiratory distress, rhinorrhea Postmarketing and/or case reports: Angioedema, hypersensitivity
Oxymorphone	Incidence usually on higher end with extended release (ER) tablet. Central nervous system: Drowsiness (9% to 19%), dizziness (7% to 18%), headache (7% to 12%) Dermatologic: Pruritus (8% to 15%) Gastrointestinal: Nausea (19% to 33%), constipation (4% to 28%), vomiting (9% to 16%) Miscellaneous: Fever (1% to 14%)	
Codeine		Cardiovascular: Bradycardia, cardiac arrest, circulatory depression, flushing, hypertension, hypotension, palpitations, shock, syncope, tachycardia Central nervous system: Abnormal dreams, agitation, anxiety, apprehension, ataxia, chills, depression, disorientation, dizziness, drowsiness, dysphoria, euphoria, fatigue, hallucination, headache, increased intracranial pressure, insomnia, nervousness, paresthesia, sedation, shakiness, taste disorder, vertigo Dermatologic: Diaphoresis, pruritus, skin rash, urticaria Gastrointestinal: Abdominal cramps, abdominal pain, anorexia, biliary tract spasm, constipation, diarrhea, nausea, pancreatitis, vomiting, xerostomia Genitourinary: Urinary hesitancy, urinary retention Hypersensitivity: Hypersensitivity reaction Neuromuscular & skeletal: Laryngospasm, muscle rigidity, tremor, weakness Ophthalmic: Blurred vision, diplopia, miosis, nystagmus, visual disturbance Respiratory: Bronchospasm, dyspnea, respiratory arrest,

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
		respiratory depression
Hydrocodone	Gastrointestinal: Constipation (8% to 11%)	
Oxycodone	Note: Percentages as reported with OxyContin Central nervous system: Drowsiness (23%), dizziness (13%) Dermatologic: Pruritus (13%) Gastrointestinal: Constipation (23%), nausea (23%), vomiting (12%)	
Meperidine		Cardiovascular: Bradycardia, cardiac arrest, circulatory depression, flushing, hypotension, palpitations, shock, syncope, tachycardia Central nervous system: Agitation, confusion, delirium, depression, disorientation, dizziness, drowsiness, drug dependence (physical dependence), dysphoria, euphoria, fatigue, habituation, hallucination, headache, increased intracranial pressure, malaise, myoclonus, nervousness, paradoxical central nervous system stimulation, restlessness, sedation, seizure (associated with metabolite accumulation), serotonin syndrome Dermatologic: Diaphoresis, pruritus, skin rash, urticaria Gastrointestinal: Abdominal cramps, anorexia, biliary colic, constipation, nausea, paralytic ileus, spasm of sphincter of Oddi, vomiting, xerostomia Genitourinary: Ureteral spasm, urinary retention Hypersensitivity: Anaphylaxis, histamine release, hypersensitivity reaction Local: Injection site reaction (including pain, wheal, and flare) Neuromuscular & skeletal: Muscle twitching, tremor, weakness Ophthalmic: Visual disturbance Respiratory: Dyspnea, respiratory arrest, respiratory depression
Fentanyl	Cardiovascular: Bradycardia, chest wall rigidity (high dose I.V.), edema Central nervous system: Central nervous system depression, confusion, dizziness, drowsiness, fatigue, headache, sedation Dermatologic: Diaphoresis Endocrine & metabolic: Dehydration Gastrointestinal: Constipation, nausea, vomiting, xerostomia	

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
	Local: Application site erythema Neuromuscular & skeletal: Muscle rigidity, weakness Ophthalmic: Miosis Respiratory: Dyspnea, respiratory depression	
Sufantanil	Dermatologic: Pruritus (epidural: 25%)	
Remifentanil	Cardiovascular: Hypotension (2% to 19%), bradycardia (1% to 7%; dose dependent) Central nervous system: Headache (<2% to 18%) Dermatologic: Pruritus (<2% to 18%) Gastrointestinal: Nausea (<36% to 44%), vomiting (<16% to 22%) Neuromuscular & skeletal: Muscle rigidity (<1% to 11%; includes chest wall rigidity)	
Methadone		Frequency not defined. During prolonged administration, adverse effects may decrease over several weeks; however, constipation and sweating may persist. Cardiovascular: Bigeminy, bradycardia, cardiac arrest, cardiac arrhythmia, cardiac failure, cardiomyopathy, ECG changes, edema, extrasystoles, flushing, hypotension, inversion T wave on ECG, orthostatic hypotension, palpitations, peripheral vasodilation, phlebitis, prolonged Q-T interval on ECG, shock, syncope, tachycardia, torsades de pointes, ventricular fibrillation, ventricular tachycardia Central nervous system: Agitation, confusion, disorientation, dizziness, drowsiness, drug dependence (physical dependence), dysphoria, euphoria, habituation, hallucination, headache, insomnia, sedation, seizure Dermatologic: Diaphoresis, hemorrhagic urticaria (can occur locally with intravenous administration [rare]), localized erythema (intravenous/subcutaneous), pruritus, rash at injection site (intravenous), skin rash, urticaria, urticaria at injection site (intravenous) Endocrine & metabolic: Amenorrhea, antidiuretic effect, decreased libido, hypokalemia, hypomagnesemia, weight gain Gastrointestinal: Abdominal pain, anorexia, biliary tract spasm, constipation, glossitis, nausea, stomach cramps, vomiting, xerostomia Genitourinary: Impotence, urinary hesitancy, urinary retention

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
		Hematologic: Thrombocytopenia (reversible, reported in patients with chronic hepatitis) Local: Local pruritus (intravenous), local pain (intravenous/subcutaneous), local swelling (intravenous/subcutaneous) Neuromuscular & skeletal: Weakness Ophthalmic: Miosis, visual disturbance Respiratory: Pulmonary edema, respiratory arrest, respiratory depression
Buprenorphine	Central nervous system: Sedation (≤66%)	
Butorphanol	Central nervous system: Drowsiness (43%), dizziness (19%), insomnia (nasal spray 11%) Gastrointestinal: Nausea and vomiting (13%) Respiratory: Nasal congestion (nasal spray 13%)	
Pentazocine		Cardiovascular: Circulatory depression, facial edema, flushing, hypertension, hypotension, increased peripheral vascular resistance, shock, syncope, tachycardia Central nervous system: Central nervous system depression, chills, confusion, disorientation, dizziness, drowsiness, drug dependence (physical and psychological), euphoria, excitement, hallucination, headache, insomnia, irritability, malaise, nightmares, paresthesia, sedation Dermatologic: Dermatitis, diaphoresis, erythema multiforme, pruritus, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria Gastrointestinal: Abdominal distress, anorexia, constipation, diarrhea, dysgeusia, nausea, vomiting, xerostomia Genitourinary: Urinary retention Hematologic & oncologic: Agranulocytosis (rare), decreased white blood cell count, eosinophilia Hypersensitivity: Anaphylaxis Local: Injection site reaction (tissue damage and irritation) Neuromuscular & skeletal: Tremor, weakness Ophthalmic: Blurred vision, diplopia, miosis, nystagmus

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
		Otic: Tinnitus Respiratory: Dyspnea, respiratory depression (rare) Postmarketing and/or case reports: Hypogonadism
Nalbuphine	Central nervous system: Sedation (36%)	
Tapentadol	Central nervous system: Dizziness (24%), somnolence (15%) Gastrointestinal: Nausea (30%), vomiting (18%)	
Tramadol	Cardiovascular: Flushing (8% to 16%) Central nervous system: Dizziness (10% to 33%), headache (4% to 32%), drowsiness (7% to 25%), central nervous system stimulation (7% to 14%), insomnia (2% to 11%) Dermatologic: Pruritus (3% to 12%) Gastrointestinal: Constipation (9% to 46%), nausea (15% to 40%), vomiting (5% to 17%), xerostomia (3% to 13%), dyspepsia (1% to 13%) Neuromuscular & skeletal: Weakness (4% to 12%)	
Naloxone		Adverse reactions are related to reversing dependency and precipitating withdrawal. Withdrawal symptoms are the result of sympathetic excess. Adverse events occur secondarily to reversal (withdrawal) of opioid analgesia and sedation. Cardiovascular: Cardiac arrest, fever, flushing, hypertension, hypotension, tachycardia, ventricular fibrillation ventricular tachycardia Central nervous system: Agitation, coma, crying (excessive [neonates]), encephalopathy, hallucination, irritability, nervousness, restlessness, seizure (neonates), tremulousness Gastrointestinal: Abdominal cramps, diarrhea, nausea, vomiting Local: Injection site reaction Neuromuscular & skeletal: Ache, hyperreflexia (neonates), paresthesia, piloerection, tremor, weakness Respiratory: Dyspnea, hypoxia, pulmonary edema, respiratory depression, rhinorrhea, sneezing Miscellaneous: Diaphoresis, hot flashes, shivering, yawning
Naltrexone	Cardiovascular: Syncope (13%) Central nervous system: Headache (3% to 25%), insomnia (3%	

Agent	*AE with >10% Frequency*	*AE with undefined frequency*
	to 14%), dizziness (4% to 13%), anxiety (2% to 12%), decreased energy (>10%), nervousness (4% to >10%) Gastrointestinal: Nausea (10% to 33%), vomiting (3% to 14%), appetite decreased (14%), diarrhea (13%), abdominal pain (11%), abdominal cramping Hepatic: ALT increased (13%) Local: Injection site reaction (≤69%; includes bruising, induration, nodules, pain, pruritus, swelling, tenderness) Neuromuscular & skeletal: CPK increased (11% to 39%), arthralgia (12%), myalgia (>10%) Respiratory: Pharyngitis (7% to 11%)	

CONTRAINDICATIONS

Agent	***CI***
Morphine	Hypersensitivity to morphine sulfate or any component of the formulation; severe respiratory depression, acute or severe asthma (in an unmonitored setting or without resuscitative equipment); known or suspected paralytic ileus Epidural/intrathecal formulation: • Astramorph/PF, Duramorph: Upper airway obstruction • Astramorph/PF, Duramorph, Infumorph: Usual contraindications related to neuraxial analgesia apply (eg, presence of infection at infusion site, concomitant anticoagulant therapy, uncontrolled bleeding diathesis) Extended release formulation: GI obstruction Immediate release tablets/solution formulations: Hypercarbia Injectable formulation: Heart failure due to chronic lung disease, cardiac arrhythmias; increased intracranial pressure, head injuries, brain tumors; acute alcoholism, deliriums tremens; seizure disorders; use during labor when a premature birth is anticipated Suppository formulation: Severe CNS depression; cardiac arrhythmias, heart failure due to chronic lung disease; increased intracranial or cerebrospinal pressure, head injuries, brain tumor; acute alcoholism, delirium tremens; seizure disorder; use after biliary tract surgery, suspected surgical abdomen, surgical anastomosis; concurrent use or within 2 weeks of MAO inhibitors
Hydromorphone	Hypersensitivity to hydromorphone, any component of the formulation; acute or severe asthma, severe respiratory depression (in absence of resuscitative equipment or ventilatory support) Additional product-specific contraindications: Dilaudid liquid and tablets: Obstetrical analgesia Dilaudid injection, Dilaudid-HP injection: Opioid nontolerant patients (Dilaudid-HP injection only); patients with risk of developing GI obstruction, especially paralytic ileus Exalgo: Opioid nontolerant patients, paralytic ileus (known or suspected), pre-existing GI surgery or diseases resulting in narrowing of GI tract, loops in the GI tract or GI obstruction Suppository: Intracranial lesion associated with increased intracranial pressure; whenever ventilatory function is depressed (COPD, cor pulmonale, emphysema, kyphoscoliosis, status asthmaticus)
Oxymorphone	Hypersensitivity to oxymorphone, other morphine analogs (phenanthrene derivatives), or any component of the formulation; paralytic ileus (known or suspected); moderate-to-severe hepatic impairment; severe respiratory depression (unless using immediate release or parenteral formulation in monitored setting with resuscitative equipment); acute/severe bronchial asthma; hypercarbia Note: Parenteral formulation is also contraindicated in the treatment of upper airway obstruction and pulmonary edema due to a chemical respiratory irritant.
Codeine	Hypersensitivity to codeine or any component of the formulation; respiratory depression in the absence of resuscitative equipment; acute or severe bronchial asthma or hypercarbia; presence or suspicion of paralytic ileus; postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy
Hydrocodone	Hypersensitivity (eg, anaphylaxis) to hydrocodone or any component of the formulation; paralytic ileus (known or suspected); significant respiratory depression; acute/severe bronchial asthma (in an unmonitored setting or in without resuscitative equipment).
Oxycodone	Hypersensitivity to oxycodone or any component of the formulation; significant respiratory depression; hypercarbia; acute or severe bronchial asthma; paralytic ileus (known or suspected); GI obstruction
Meperidine	Hypersensitivity to meperidine or any component of the formulation; use with or within 14 days of MAO inhibitors; severe respiratory insufficiency

Fentanyl	Hypersensitivity to fentanyl or any component of the formulation Additional contraindications for transdermal patches (eg, Duragesic): Severe respiratory disease or depression including acute asthma (unless patient is mechanically ventilated); paralytic ileus; patients requiring short-term therapy, management of acute or intermittent pain, postoperative or mild pain, and in patients who are not opioid tolerant Additional contraindications for transmucosal buccal tablets (Fentora), buccal films (Onsolis), lozenges (eg, Actiq), sublingual tablets (Abstral), sublingual spray (Subsys), nasal spray (Lazanda): Contraindicated in the management of acute or postoperative pain (including headache, migraine, or dental pain), and in patients who are not opioid tolerant. Abstral and Onsolis also are contraindicated for acute pain management in the emergency room.
Sufantanil	Hypersensitivity to sufentanil or any component of the formulation, or known intolerance to other opioid agonists Documentation of allergenic cross-reactivity for opioids is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Remifentanil	Not for intrathecal or epidural administration, due to the presence of glycine in the formulation; hypersensitivity to remifentanil, fentanyl, or fentanyl analogs, or any component of the formulation
Methadone	Hypersensitivity to methadone or any component of the formulation; significant respiratory depression (in the absence of resuscitative equipment or in an unmonitored setting); acute or severe bronchial asthma (in the absence of resuscitative equipment or in an unmonitored setting) or hypercarbia; known or suspected paralytic ileus; concurrent use of selegiline (Emsam product labeling) Methadone is not to be used on an as-needed basis; it is not for pain that is mild or not expected to persist; it is not for acute pain or postoperative pain.
Buprenorphine	Hypersensitivity to buprenorphine or any component of the formulation Transdermal patch: Additional contraindications: Significant respiratory depression; acute or severe asthma; known or suspected paralytic ileus Documentation of allergenic cross-reactivity for morphine and related drugs in this class is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Butorphanol	Hypersensitivity to butorphanol or any component of the formulation
Pentazocine	Hypersensitivity to pentazocine or any component of the formulation
Nalbuphine	Hypersensitivity to nalbuphine or any component of the formulation
Tapentadol	Hypersensitivity to tapentadol or any component of the formulation; significant respiratory depression; acute or severe asthma or hypercapnia in unmonitored settings or in absence of resuscitative equipment or ventilatory support; known or suspected paralytic ileus; use with or within 14 days of MAO inhibitors
Tramadol	Hypersensitivity to tramadol, opioids, or any component of the formulation Additional contraindications for Ultram®, Rybix™ ODT, and Ultram® ER: Any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs Additional contraindications for ConZip: Severe/acute bronchial asthma, hypercapnia, or significant respiratory depression in the absence of appropriately monitored setting and/or resuscitative equipment
Naloxone	Hypersensitivity to naloxone or any component of the formulation
Naltrexone	Hypersensitivity to naltrexone or any component of the formulation; opioid dependence or current use of opioid analgesics (including partial opioid agonists); acute opioid withdrawal; failure to pass naloxone challenge or positive urine screen for opioids

HIGH RISK DRUG INTERACTIONS (RISK D OR X)

Opioid	***Interacting Drug***
Morphine Hydromorphone Oxymorphone	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Clopidogrel: Morphine (Systemic) may diminish the antiplatelet effect of Clopidogrel. Morphine (Systemic) may decrease serum concentrations of the active metabolite(s) of Clopidogrel. Management: Consider alternatives to morphine in clopidogrel treated patients, or the use of other P2Y12 receptor antagonists (e.g., prasugrel or ticagrelor) if morphine use is necessary. The risk of alternative opioids is presently unclear. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification MAO Inhibitors: May enhance the adverse/toxic effect of Morphine (Systemic). Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Codeine	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to

Opioid	*Interacting Drug*
	combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Hydrocodone	Alcohol (Ethyl): May enhance the CNS depressant effect of Hydrocodone. Alcohol (Ethyl) may increase the serum concentration of Hydrocodone. Management: Patients using the Zohydro ER brand of extended-release hydrocodone must not consume alcohol or alcohol-containing products due to possibly fatal outcomes. Other hydrocodone products are also expected to interact, but to a less significant degree. Risk X: Avoid combination Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification CNS Depressants: May enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination

Opioid	*Interacting Drug*
	MAO Inhibitors: May enhance the adverse/toxic effect of Hydrocodone. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification St Johns Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
Oxycodone	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification CYP3A4 Inhibitors (Moderate): May enhance the adverse/toxic effect of OxyCODONE. CYP3A4 Inhibitors (Moderate) may increase the serum concentration of OxyCODONE. Serum concentrations of the active metabolite Oxymorphone may also be increased. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May enhance the adverse/toxic effect of OxyCODONE. CYP3A4 Inhibitors (Strong) may increase the serum concentration of OxyCODONE. Serum concentrations of the active metabolite oxymorphone may also be increased. Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination MAO Inhibitors: May enhance the adverse/toxic effect of OxyCODONE. Management: Per Canadian labeling, use of oxycodone is contraindicated in patients who either are receiving MAO inhibitors or have used them within 14 days. Though not contraindicated in U.S. prescribing information, consider alternatives when possible. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may

Opioid	*Interacting Drug*
	need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Voriconazole: May enhance the adverse/toxic effect of OxyCODONE. Voriconazole may increase the serum concentration of OxyCODONE. Management: A reduced oxycodone dose may be necessary with concurrent voriconazole. Increased frequency and duration of monitoring for oxycodone-related adverse effects is recommended. Risk D: Consider therapy modification Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
Meperidine	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Dapoxetine: May enhance the adverse/toxic effect of Serotonin Modulators. Risk X: Avoid combination Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification HydrOXYzine: May enhance the CNS depressant effect of Meperidine. Management: Consider a decrease in meperidine dose, as appropriate, when used together with hydroxyzine. With concurrent use, monitor patients closely for excessive response to the combination. Risk D: Consider therapy modification MAO Inhibitors: May enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Protease Inhibitors: May enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. Risk D: Consider therapy modification Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Exceptions: Tedizolid. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Fentanyl	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Crizotinib: May increase the serum concentration of FentaNYL. Risk X: Avoid combination CYP3A4 Inhibitors (Moderate): May increase the serum concentration of FentaNYL. Management: Monitor patients extra closely for several days following initiation of the combination, and fentanyl dosage reductions should be made as appropriate. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May increase the serum concentration of FentaNYL. Management: Monitor patients extra closely for several days following initiation of the combination, and fentanyl dosage reductions should be made as appropriate. Risk D: Consider therapy modification Dapoxetine: May enhance the adverse/toxic effect of Serotonin Modulators. Risk X: Avoid combination Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Enzalutamide: May decrease the serum concentration of FentaNYL. Risk X: Avoid combination Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination

Opioid	*Interacting Drug*
	Lomitapide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lomitapide. Management: Limit the maximum adult dose of lomitapide to 30 mg daily when used in combination with any weak CYP3A4 inhibitor. Risk D: Consider therapy modification MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of FentaNYL. Management: Avoid fentanyl during and 2 weeks following mifepristone for treatment of hyperglycemia in Cushing's syndrome. The interaction magnitude could be lower with single doses used to terminate pregnancy, but neither effect has been studied clinically. Risk X: Avoid combination Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. Risk X: Avoid combination Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Exceptions: Tedizolid. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination

Opioid	*Interacting Drug*
	Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Sufentanil	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Ceritinib: Bradycardia-Causing Agents may enhance the bradycardic effect of Ceritinib. Management: If this combination cannot be avoided, monitor patients for evidence of symptomatic bradycardia, and closely monitor blood pressure and heart rate during therapy. Risk X: Avoid combination Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Remifentanil	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients

Opioid	*Interacting Drug*
	who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Methadone	Alcohol (Ethyl): May enhance the CNS depressant effect of Methadone. Risk X: Avoid combination Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Benzodiazepines: May enhance the CNS depressant effect of Methadone. Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-

Opioid	*Interacting Drug*
	injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification CarBAMazepine: May increase the metabolism of Methadone. Risk D: Consider therapy modification Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP2B6 Substrates. Management: Seek alternatives to the CYP2B6 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Dapoxetine: May enhance the adverse/toxic effect of Serotonin Modulators. Risk X: Avoid combination Didanosine: Methadone may decrease the serum concentration of Didanosine. Management: If use of methadone with didanosine is necessary, enteric coated didanosine is preferred. Avoid using didanosine powder for solution with methadone. Increased monitoring of clinical response to didanosine (including viral load) is necessary. Risk D: Consider therapy modification DOXOrubicin (Conventional): CYP2D6 Inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to moderate CYP2D6 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fluconazole: May increase the serum concentration of Methadone. Management: Methadone dose reduction may be necessary when used with fluconazole. With any concurrent use, monitor patients closely for evidence of methadone toxicities such as QT-prolongation or respiratory depression. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Highest Risk QTc-Prolonging Agents: Moderate Risk QTc-Prolonging Agents may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Itraconazole: May increase the serum concentration of Methadone. Risk X: Avoid combination Ivabradine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. Risk X: Avoid combination Ketoconazole (Systemic): May increase the serum concentration of Methadone. Risk X: Avoid combination Lomitapide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lomitapide. Management: Limit the

Opioid	*Interacting Drug*
	maximum adult dose of lomitapide to 30 mg daily when used in combination with any weak CYP3A4 inhibitor. Risk D: Consider therapy modification Lopinavir: Methadone may enhance the QTc-prolonging effect of Lopinavir. Lopinavir may decrease the serum concentration of Methadone. More specifically, the combination of Lopinavir and Ritonavir may decrease Methadone serum concentrations. Risk X: Avoid combination MAO Inhibitors: May enhance the adverse/toxic effect of Methadone. Management: Initial safety testing, where small incremental doses of methadone are given with the patient closely monitored (including vitals, etc.), is recommended if methadone is to be used with (or within 14 days of) an MAO inhibitor. Avoid transdermal selegiline. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Metoprolol: CYP2D6 Inhibitors may increase the serum concentration of Metoprolol. Management: Consider an alternative for one of the interacting drugs in order to avoid metoprolol toxicity. If the combination must be used, monitor response to metoprolol closely. Metoprolol dose reductions may be necessary. Risk D: Consider therapy modification Mifepristone: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. Risk X: Avoid combination Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Moderate Risk QTc-Prolonging Agents: May enhance the QTc-prolonging effect of other Moderate Risk QTc-Prolonging Agents. Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. Risk X: Avoid combination Posaconazole: May enhance the QTc-prolonging effect of Methadone. Posaconazole may increase the serum concentration of Methadone. Risk X: Avoid combination Reverse Transcriptase Inhibitors (Non-Nucleoside): May increase the metabolism of Methadone. Management: Methadone dosage adjustments will likely be required with efavirenz and nevirapine, and may be necessary with rilpivirine as well. Exceptions: Delavirdine; Etravirine. Risk D: Consider therapy modification Rifamycin Derivatives: May decrease the serum concentration of Methadone. Management: Seek alternatives when

Opioid	*Interacting Drug*
	possible. If used concomitantly, monitor closely for symptoms of methadone withdrawal upon rifamycin derivative initiation, and for excess sedation upon rifamycin derivative discontinuation. Exceptions: Rifabutin. Risk D: Consider therapy modification Saquinavir: Methadone may enhance the QTc-prolonging effect of Saquinavir. Saquinavir may decrease the serum concentration of Methadone. Management: Use methadone and saquinavir cautiously in combination, seeking alternatives when possible due to the potential for excessive QT interval prolongation and associated arrhythmias. Risk D: Consider therapy modification Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. Risk D: Consider therapy modification Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Exceptions: Tedizolid. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification St Johns Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the metabolic formation of highly potent active metabolites. Management: Consider alternatives with less of an inhibitory effect on CYP2D6 activity when possible. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Thioridazine: CYP2D6 Inhibitors may increase the serum concentration of Thioridazine. Risk X: Avoid combination Voriconazole: May increase the serum concentration of Methadone. Management: Methadone dose reduction may be necessary when used with voriconazole. With any concurrent use, monitor patients closely for evidence of methadone toxicities such as QT-prolongation or respiratory depression. Risk D: Consider therapy modification Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
Buprenorphine	Alcohol (Ethyl): May enhance the CNS depressant effect of Buprenorphine. Management: Advise patients receiving buprenorphine about the increased risk of CNS depression if they consume alcohol. Consider alternatives to buprenorphine for opioid addiction treatment in patients who are dependent on alcohol. Risk D: Consider therapy modification Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Atazanavir: Buprenorphine may decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Buprenorphine. Management: Avoid this combination in patients un-boosted atazanavir due to possible decreased atazanavir concentrations. This combination is not contraindicated in patients also receiving ritonavir, but monitoring for buprenorphine toxicity is recommended. Risk X: Avoid combination Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination CNS Depressants: May enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination MAO Inhibitors: Buprenorphine may enhance the adverse/toxic effect of MAO Inhibitors. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification St Johns Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Butorphanol	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Analgesics (Opioid): Mixed Agonist / Antagonist Opioids may diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider

Opioid	*Interacting Drug*
	reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
Pentazocine	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Analgesics (Opioid): Mixed Agonist / Antagonist Opioids may diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is

Opioid	*Interacting Drug*
	recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Nalbuphine	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Analgesics (Opioid): Mixed Agonist / Antagonist Opioids may diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Tapentadol	Alcohol (Ethyl): May enhance the CNS depressant effect of Tapentadol. Alcohol (Ethyl) may increase the serum concentration of Tapentadol. Specifically, alcohol may increase the maximum serum concentrations when used with extended-release tapentadol. Risk X: Avoid combination Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification CNS Depressants: Tapentadol may enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Dapoxetine: May enhance the adverse/toxic effect of Serotonin Modulators. Risk X: Avoid combination Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification MAO Inhibitors: Tapentadol may enhance the adverse/toxic effect of MAO Inhibitors. Risk X: Avoid combination Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider

Opioid	*Interacting Drug*
	therapy modification Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Exceptions: Tedizolid. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Tramadol	Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. Risk D: Consider therapy modification Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). Risk X: Avoid combination Bosentan: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr when used with other CNS depressants. Monitor closely. Risk D: Consider therapy modification CarBAMazepine: TraMADol may enhance the CNS depressant effect of CarBAMazepine. TraMADol may diminish the therapeutic effect of CarBAMazepine. CarBAMazepine may decrease the serum concentration of TraMADol. Risk X: Avoid combination Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Cyclobenzaprine: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. Cyclobenzaprine may enhance the serotonergic effect of TraMADol. This could result in serotonin syndrome. Management: Seek alternatives. If these agents are given in combination, monitor for seizure activity and signs and symptoms of serotonin toxicity/serotonin syndrome. Risk D: Consider therapy modification CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). Risk D: Consider therapy modification Dapoxetine: May enhance the adverse/toxic effect of Serotonin Modulators. Risk X: Avoid combination

Opioid	*Interacting Drug*
	Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. Risk D: Consider therapy modification Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. Risk D: Consider therapy modification Idelalisib: May increase the serum concentration of CYP3A4 Substrates. Risk X: Avoid combination MAO Inhibitors: TraMADol may enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. TraMADol may enhance the serotonergic effect of MAO Inhibitors. Management: Consider alternatives to combined treatment with tramadol and monoamine oxidase inhibitors due to an increased risk of serotonin syndrome and seizures. Avoid transdermal selegiline. Risk D: Consider therapy modification Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. Risk D: Consider therapy modification Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Risk D: Consider therapy modification Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. Risk D: Consider therapy modification Mixed Agonist / Antagonist Opioids: May diminish the analgesic effect of Analgesics (Opioid). Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. Risk D: Consider therapy modification Naltrexone: May diminish the therapeutic effect of Analgesics (Opioid). Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. Risk D: Consider therapy modification Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. Risk X: Avoid combination Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. Risk D: Consider therapy modification Selective Serotonin Reuptake Inhibitors: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Risk D: Consider therapy modification Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Exceptions: Tedizolid. Risk D: Consider therapy modification Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. Risk D: Consider therapy modification

Opioid	*Interacting Drug*
	St Johns Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. Risk D: Consider therapy modification Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. Risk D: Consider therapy modification Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. Risk D: Consider therapy modification Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. Risk X: Avoid combination Tricyclic Antidepressants: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Tricyclic Antidepressants. This could result in serotonin syndrome. Management: Seek alternatives to the concomitant use of tramadol and tricyclic antidepressants when possible. Monitor patients receiving these combinations closely for evidence serotonin toxicity. The risk of seizure may also be increased. Risk D: Consider therapy modification Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. Risk D: Consider therapy modification
Naloxone	Hypersensitivity to naloxone or any component of the formulation
Naltrexone	Hypersensitivity to naltrexone or any component of the formulation; opioid dependence or current use of opioid analgesics (including partial opioid agonists); acute opioid withdrawal; failure to pass naloxone challenge or positive urine screen for opioids

RECOMMENDATIONS

- The American Pain Society and ISMP do not recommend meperidine's use as an analgesic.[3] It should only be used when no other treatments options exist. Consider placing it on restricted use on the formulary to discourage its use and encourage use of other drugs to treat pain instead.
- With the recent change in hydrocodone's controlled substance schedule from C-III to C-II, this begs the question regarding whether or not both hydrocodone and oxycodone are needed on the Hospital X formulary. Only a few studies have actually compared the analgesic properties of hydrocodone to oxycodone.[11,12,13] Results are not consistent between studies and some not adequately powered. Some studies suggest oxycodone *may be* 1.5x as potent as hydrocodone (when equi-potent doses are compared), but this finding is not conclusive and would need to be verified in future studies. Even if this were found to be true, it is not a substantial difference. Thus, one could argue that there is no need for both opioids on formulary. However, hydrocodone has an FDA-labeled indication for pediatric use whereas oxycodone does not. Thus, it is recommended to leave hydrocodone-containing products on the Hospital X formulary at this time.
- Zohydro® (hydrocodone) was FDA approved approximately one year ago (October 2013). It is currently not on Hospital X formulary. Although it is an extended release product, other extended release products such as oxycodone (OxyContin®) are available on formulary. In one study comparing hydrocodone to oxycodone, hydrocodone was associated with significantly more constipation.[12] No clear advantages over other opioids currently on formulary are seen at this time (other than its extended release formulation). Thus, it is not recommended for addition to formulary at this time.
- Xartemis®XR (extended release oxycodone-APAP) was recently FDA approved in March 2014. No XR form of oxycodone-APAP exists on Hospital X Formulary. However, oxycodone-APAP immediate release products are on formulary and can be used instead.

- Buprenorphine is the only opioid that is currently not represented on the Hospital X Hospital formulary. However, it is a second-line agent for treatment of moderate-severe pain, and there are other agents on formulary that can be used to treat moderate-severe pain. It carries a drug-drug interaction (category X) with Atazanavir, which none of the other opioids carry. It also has an analgesic ceiling, which most of the other opioids do not have.

REFERENCES

1. Adams, Michael L. Opioids. PowerPoint Slides. PHAR 421: Pharmacology and Medicinal Chemistry III. Spring 2013.
2. Baumann TJ, Strickland JM, Herndon CM. Pain Management. In: DiPiro, JT, ed. Pharmacotherapy, 8th Ed. New York, NY: McGraw Hill; 2011:1049-1053.
3. Johnston, Cindy. Pain Management Issues. PowerPoint Slides. PHAR 547: Therapeutics IV. Spring 2013.
4. [Lexi-Drugs]. Lexi-Comp Institutional: Hospital X Formulary. Accessed 22 September 2014. (used for each drug discussed in this document)
5. [Lexi-Drugs]. Lexi-Comp Online. Accessed 23 September 2014. (used for each drug discussed in this document)
6. Micromedex. Accessed 23 September 2014. (used for each drug discussed in this document)
7. Clinical Pharmacology. Accessed 23 September 2014. (used for each drug discussed in this document)
8. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: rescheduling of hydrocodone combination products from schedule III to schedule II. 21 CFR Part 1308. *Federal Register* 2014; 79(63): 49661-82
9. Drug Enforcement Administration, Department of Justice. Controlled Substance Schedules. http://www.deadiversion.usdoj.gov/schedules/index.html. Accessed September 23, 2014.
10. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm accessed September 4, 2014.
11. Zacny JP, Gutierrez S. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. *Drug and Alcohol Dependence*. 2009; 101: 107-114.
12. Marco CA, Plewa MC, Buderer N, et al. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: a double-blind, randomized, controlled trial. *Academic Emergency Medicine.* 2005; 12:282-288.
13. Litowski LJ, Christensen SE, Adamson DN, et al. Analgesic efficacy and tolerability of oxycodone 5mg/ibuprofen 400mg compared with those of oxycodone 5mg/acetaminophen 325mg and hydrocodone 7.5mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. *Clinical Therapeutics*. 2005; 27(4): 418-425.