Therapeutic Class Overview
Opioids, Short Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology.
- Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing reinjury. In contrast, chronic pain, often defined as pain persisting for longer than three to six months, may be considered a disease in that it serves no useful purpose (Cohen et al, 2016).
    - Chronic pain is estimated to affect 100 million Americans, and the total annual incremental cost of health care in 2010 due to pain ranged from $560 billion to $635 billion in the United States. This includes medical costs and costs related to disability days and lost wages and productivity (American Academy of Pain Medicine [AAPM], 2014).
- Pain may be classified as nociceptive pain or neuropathic pain.
    - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
    - Neuropathic pain results from disease or injury to the peripheral or central nervous systems (CNS). It is often treated with adjuvant drugs such as antidepressants and antiepileptics. Opioids are used as second or third line agents. (Cohen et al, 2016).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional approaches, and surgery. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (Cohen et al, 2016).
    - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (Cohen et al, 2016; The Medical Letter, 2013).
- Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics, alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained-release formulations (Cohen et al, 2016).
    - Short-acting opioid analgesics are available as single entities and in combination with acetaminophen, aspirin, butalbital, caffeine, carisoprodol and ibuprofen. Acetaminophen, aspirin, and ibuprofen are non-opioid analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a CNS stimulant. Carisoprodol is a centrally-acting muscle relaxant (Micromedex 2.0, 2017).
- In January 2011, the Food and Drug Administration (FDA) recommended that manufacturers of combination products limit the amount of acetaminophen to no more than 325 mg in each dosage form (i.e., tablet or capsule) to reduce the risk of liver damage from too much acetaminophen. All products with dosage forms with acetaminophen exceeding 325 mg have since been removed from the market (FDA, 2014).
- The Controlled Substances Act (CSA) places substances with accepted medical uses into one of four schedules, with the substances with the highest potential for harm and abuse in Schedule II, and substances with progressively less potential for harm and abuse in Schedules III through V. Substances that are considered Schedule I do not have an accepted medical use.
    - All single-entity agents within this review are Schedule II (C-II) controlled substances.
    - Oxycodone and hydrocodone combination products are C-II controlled substances. The codeine and dihydrocodeine tablet combination products are Schedule III (C-III) controlled substances and liquid products are Schedule V (C-V) controlled substances.
        - In August 2014, it was announced that all products containing hydrocodone bitartrate were to be rescheduled as C-II controlled substances as of October 6, 2014. Prior to this rescheduling, they were C-III controlled substances (Drug Enforcement Agency [DEA] press release, 2014).

- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the United States (Dowell et al, 2016).
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (Dowell et al, 2016).
- Also in March 2016, the FDA announced enhanced warnings for immediate-release opioid pain medications related to the risks of misuse, abuse, addiction, overdose, and death (FDA, 2016). A summary of the required label updates is provided in this review.
- In August 2016, based on FDA-conducted studies and review of several published studies, the FDA added Boxed Warnings to opioid pain medications regarding combined used with benzodiazepines, alcohol, and other drugs that depress the CNS, resulting in serious side effects including slowed or difficult breathing and death (FDA Drug Safety Communication, 2016).
- This review focuses on short-acting opioid agonists and their use in the treatment of pain. This review does not include injectable formulations, although some medications may be available in an injectable formulation. In addition, immediate-release fentanyl products, butorphanol, tapentadol, pentazocine, and tramadol are covered in other publications and are not covered in this review.
- The agents included in this review are listed alphabetically by brand name in Table 1. Since there are multiple branded agents that contain the same generic component(s), many tables in the review are organized alphabetically by generic name.
- Medispan Class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Single Entity Agents			
codeine sulfate*	Various manufacturers	07/16/2009	✔
DEMEROL® (meperidine hydrochloride)	Various manufacturers	10/10/1942	✔
DILAUDID® (hydromorphone hydrochloride)	Various manufacturers	12/07/1992	✔
morphine sulfate*	Various manufacturers	03/17/2008	✔
OPANA® (oxymorphone hydrochloride)	Various manufacturers	06/22/2006	✔
ROXICODONE®, OXAYDO®† (oxycodone hydrochloride)	Various manufacturers	08/31/2000	✔
Combination Products			
ASCOMP WITH CODEINE®, FIORINAL WITH CODEINE #3® (codeine/butalbital/ aspirin/caffeine)	Various manufacturers	10/26/1990	✔
CAPITAL W/CODEINE®, TYLENOL-CODEINE® (acetaminophen/codeine)	Various manufacturers	08/17/1977	✔
codeine/carisoprodol/aspirin*	Various manufacturers	10/05/1960	✔
ENDOCET®, PERCOCET®, PRIMLEV®, ROXICET® (oxycodone hydrochloride/ acetaminophen)	Various Manufacturers	12/12/1984	✔
ENDODAN®, PERCODAN® (oxycodone hydrochloride/ aspirin)	Various manufacturers	08/05/2005	✔

Drug	Manufacturer	FDA Approval Date	Generic Availability
FIORICET WITH CODEINE® (codeine/butalbital/ acetaminophen/caffeine)	Various manufacturers	07/30/1992	✔
HYCET®, LORCET®, NORCO®, VICODIN®, VICODIN ES®, VICODIN HP®, XODOL® (hydrocodone bitartrate/ acetaminophen)	Various manufacturers	07/08/1982	✔
IBUDONE®, REPREXAIN®, VICOPROFEN® (hydrocodone hydrochloride/ibuprofen)	Various manufacturers	09/23/1997	✔
oxycodone hydrochloride/ ibuprofen*	Various manufacturers	11/26/2007	✔
SYNALGOS-DC®‡ (dihydrocodeine bitartrate/aspirin/caffeine)	Caraco Pharmaceuticals	07/07/1958	✔
TREZIX® (dihydrocodeine bitartrate/ acetaminophen/caffeine)	Wraser Pharmaceuticals	11/26/2014	✔

*Branded product no longer commercially available
†A generic for OXAYDO is not anticipated until 2025.
‡Authorized generic.

(Drugs@FDA, 2017; OptumRx, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications for Single Entity Agents

Indication	codeine	hydromorphone	meperidine	morphine	oxycodone	oxymorphone
Management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	✔					
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate		✔	✔	✔	✔	✔

(Prescribing information: codeine, 2016; DEMEROL, 2016; DILAUDID, 2016; morphine sulfate, 2016; OPANA, 2016; OXAYDO, 2016; ROXICODONE, 2016)

Table 3. Food and Drug Administration Approved Indications for Combination Products

Indication	acetaminophen/ codeine	codeine/ butalbital/ acetaminophen/ caffeine	codeine/ butalbital/ aspirin/caffeine	codeine/ carisoprodol/ aspirin	dihydrocodeine/ acetaminophen/ caffeine	dihydrocodeine/a spirin/caffeine	hydrocodone/ acetaminophen	hydrocodone/	oxycodone/ acetaminophen	oxycodone/ aspirin	oxycodone/ ibuprofen
Relief of discomfort associated with acute, painful musculoskeletal conditions in adults				✔							
Relief of mild to moderate pain	✔										
Relief of moderate to moderately severe pain							✔				
Relief of tension or muscle contraction headache		✔	✔								
Short-term (<7 days) management of acute to moderate pain											✔
Short-term (<10 days) management of acute pain								✔			
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate					✔	✔			✔	✔	

(Prescribing information: codeine/carisoprodol/aspirin, 2013; FIORICET WITH CODEINE, 2014; FIORINAL WITH CODEINE, 2014; oxycodone hydrochloride/ibuprofen, 2017; PERCOCET, 2017; PERCODAN, 2016; SYNALGOS-DC, 2016; TREZIX, 2016; TYLENOL WITH CODEINE, 2017; VICODIN, 2014; VICOPROFEN, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain (Furlan et al, 2006; Hartrick et al, 2009).
- Systematic reviews and meta-analyses have demonstrated similar safety and levels of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, neuropathic, rheumatoid arthritis, osteoarthritis, non-cancer, and acute pain (Bekkering et al, 2011; Caraceni et al, 2011; Chaporro et al, 2012; Chaporro et al, 2013; Felden et al, 2011; McNicol et al, 2005; McNicol et al, 2013; Neusch et al, 2009; Pigni et al, 2011; Quigley et al, 2002; Reid et al 2006; Wiffen et al, 2013; Whittle et al, 2011).
- In one double-blind, randomized controlled trial involving patients who underwent total hip or knee replacement surgery, patients were significantly more likely to achieve pain relief of at least 50% following the administration of oxymorphone 10 or 20 mg compared to placebo, but not oxymorphone 30 mg or oxycodone 10 mg. A direct comparison between oxymorphone and oxycodone was not performed (Gimbel et al, 2004).
- Compared to ibuprofen and acetaminophen in children with acute musculoskeletal injury, codeine achieved a level of analgesia that was comparable to acetaminophen but less than that of ibuprofen (Clark et al, 2007).
- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of pain (Litkowski et al, 2005; Marco et al, 2005; Palangio et al, 2000[a]; Palangio et al, 2000[b]; Rodriguez et al, 2007[b]; Wideman et al, 2000; Smith et al, 2004).
- Head-to-head trials involving butalbital-containing products and oxycodone/aspirin are not available.

Guidelines

- Clinical guidelines have been published that address back pain, cancer pain, neuropathic pain and osteoarthritis pain. These guidelines make recommendations for the specific place in therapy for opioids as a class but do not make any recommendations for the use of one agent over another (AAOS, 2013; Attal et al, 2010; Bril et al, 2011; Pop-Busui et al, 2017; Dubinsky et al, 2004; Carville et al, 2008; Chou et al, 2007; Chou et al, 2009; Hochberg et al, 2012; The Medical Letter, 2013). Additional guidelines are available on codeine use in patients with various cytochrome P450 (CYP) 2D6 phenotypes (Crews et al, 2014).
- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (Dowell et al, 2016):
    - Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (category A, evidence 3).
    - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
    - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
    - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (category A, evidence 4).
    - When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day (category A, evidence 3).

- Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (category A, evidence 4).
- Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
- Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
- Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
- When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).
- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:
- Category A: Applies to all persons; most patients should receive the recommended course of action.
- Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:
- Type 1: Randomized clinical trials or overwhelming evidence from observational studies.
- Type 2: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
- Type 3: Observational studies or randomized clinical trials with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (Qaseem et al, 2017).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.

- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (Manchikanti et al, 2017):
    - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
    - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
    - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
    - Strong).
    - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
    - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
    - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).

SAFETY SUMMARY

- In general, opioids are contraindicated in patients with a hypersensitivity to any component or the active ingredient. They should not be administered to patients with significant respiratory depression, acute or severe bronchial asthma, or suspected or documented paralytic ileus.
- Short-acting opioids that contain acetaminophen, codeine, dihydrocodeine, and ibuprofen carry boxed warnings.
    - Acetaminophen has been associated with acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury were associated with the use of acetaminophen at doses that exceeded 4,000 mg per day, and often involved more than one acetaminophen-containing product.
    - Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP 2D6 polymorphism. The use of codeine is contraindicated for postoperative pain control in pediatric patients undergoing tonsillectomy or adenoidectomy.
    - Cardiovascular risk may be increased with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
    - Gastrointestinal risk is increased with the use of NSAIDs including serious gastrointestinal adverse events (e.g., bleeding, ulceration, and perforation of the stomach or intestines), which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.
- Adverse events may limit the use of opioid analgesics. The most frequently reported adverse events are light-headedness, dizziness, sedation, nausea, and vomiting (Micromedex 2.0, 2017).
- In March 2016, the FDA announced label changes and enhanced warnings for all opioids (FDA, 2016):
    - Among the changes for immediate-release opioids, the FDA is requiring a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death. The boxed warning includes a precaution that chronic maternal use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome. Updated indications clarify that immediate-release opioids should be reserved for pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated. Updates to the dosing information provide clearer instructions regarding drug administration and patient monitoring, including initial dosage, dosage changes during therapy, and a warning not to abruptly stop treatment in a physically dependent patient. Similar labeling changes were required for ER/LA opioids in 2013.
    - In addition, updated labeling is required for all opioids to include safety information about the risk of adrenal insufficiency; androgen deficiency; and drug interactions with antidepressants and migraine medications that can result in serotonin syndrome. The FDA has issued a drug safety communication describing these risks (FDA Drug Safety Communication, 2016).

- In August 2016, the FDA announced the addition of boxed warnings to opioid-containing products regarding the serious risks including death when used in combination with benzodiazepines or other drugs that depress the CNS, including alcohol (FDA Drug Safety Communication, 2016).
    - The FDA recommends that for patients who require concomitant treatment with opioids and benzodiazepines or other CNS depressants due to inadequate treatment alternatives, the dosage and duration of each drug should be limited to the lowest dose possible required for therapeutic effect.

DOSAGE AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single Entity Agents				
codeine sulfate	Solution: 30 mg/5 mL Tablet: 15 mg 30 mg 60 mg	Analgesia: Solution, tablet: 15 to 60 mg every four hours as needed	Not applicable	May be taken with or without food.
DEMEROL, MEPERITAB (meperidine hydrochloride)	Solution: 50 mg/5 mL Tablet: 50 mg 100 mg	Analgesia: Solution, tablet: 50 to 150 mg every three to four hours as needed	The dose should be reduced by 25% to 50% when co-administered with phenothiazines or other tranquilizers.	Not applicable
DILAUDID (hydromorphone hydrochloride)	Solution: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg 8 mg	Analgesia: Oral solution: 2.5 to 10 mg every three to six hours as required Rectal suppository: one suppository inserted every six to eight hours Tablet: 2 to 4 mg every four to six hours as necessary	Not applicable	May be taken with or without food.
morphine sulfate	Oral concentrate: 20 mg/mL Rectal suppository: 5 mg 10 mg 20 mg 30 mg Solution: 10 mg/5 mL 20 mg/5 mL Tablet: 15 mg 30 mg	Analgesia: Tablet: 5 to 30 mg every four hours as needed Solution: 10 to 20 mg every 4 hours as needed for pain Rectal suppository: 10 to 20 mg every four hours	The oral concentrate should be used for opioid-tolerant patients only who have already been titrated to a stable analgesic regimen using lower strengths of morphine and who can benefit from use of a smaller volume of oral solution.	Not applicable

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
OPANA (oxymorphone hydrochloride)	Tablet: 5 mg 10 mg	Analgesia: Tablet: 10 to 20 mg every four to six hours as needed	For patients receiving other central nervous system depressants, the initial dose of oxymorphone should be one-third to one-half the usual dose.	Take on an empty stomach; 1 hour before or 2 hours after a meal.
OXAYDO, ROXICODONE (oxycodone hydrochloride)	Capsule: 5 mg Oral concentrate: 100 mg/5 mL Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 15 mg 20 mg 30 mg Abuse-deterrent tablet: 5 mg 7.5 mg	Analgesia: Capsule, solution, tablet: 5 to 15 mg every four to six hours as needed	The oral concentrate should be used for opioid-tolerant patients only who have already been titrated to a stable analgesic regimen using lower strengths of oxycodone and who can benefit from use of a smaller volume of oral solution.	Swallow whole, do not crush or dissolve. Do not crush for administration in feeding tubes (obstruction of the tube may occur).
Combination Products				
ASCOMP WITH CODEINE, FIORINAL WITH CODEINE #3 (codeine/ butalbital/ aspirin/caffeine)	Capsule: 30 mg/50 mg/ 325 mg/40 mg	Headache: Capsule: one or two capsules every four hours	Not applicable	Not recommended for extended and repeated use.
CAPITAL W/CODEINE, TYLENOL-CODEINE (codeine/ acetaminophen)	Elixir: 12 mg-120 mg/ 5 mL Suspension: 12 mg-120 mg/ 5 mL Tablet: 15 mg/300 mg 30 mg/300 mg 60 mg/300 mg	Analgesia: Elixir, suspension: 15 mL every four hours as needed Tablet: 15 to 60 mg codeine/300 to 1,000 mg acetaminophen every four hours as needed	Not applicable	Not applicable
codeine/ carisoprodol/ aspirin	Tablet: 16 mg/200 mg/325 mg	Acute, painful musculoskeletal conditions: Tablet: one or two tablets four times daily as needed	Not applicable	Maximum duration of use

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
				is up to two or three weeks.
ENDOCET, PERCOCET, PRIMLEV (oxycodone hydrochloride/ acetaminophen)	Solution: 5 mg-325 mg/ 5 mL Tablet: 2.5 mg/325 mg 5 mg/300 mg 5 mg/325 mg 7.5 mg/300 mg 7.5 mg/325 mg 10 mg/300 mg 10 mg/325 mg	Analgesia: Tablet: one to two tablets of 2.5 mg/325 mg every six hours as needed Solution: 5 to 10 mL every six hours as needed	Not applicable	Not applicable
ENDODAN, PERCODAN (oxycodone hydrochloride/ aspirin)	Tablet: 4.835-325 mg	Analgesia: Tablet: one tablet every six hours as needed	Not applicable	Not applicable
FIORICET WITH CODEINE (codeine/ butalbital/ acetaminophen/ caffeine)	Capsule: 30 mg/50 mg/300 mg/40 mg	Headache: Capsule: one or two capsules every four hours	Not applicable	Not recommended for extended and repeated use.
HYCET, NORCO, LORCET, VICODIN, VICODIN ES, VICODIN HP, XODOL (hydrocodone bitartrate/ acetaminophen)	Solution: 7.5 mg-325 mg/ 15 mL 10 mg-325 mg/15 mL Tablet: 2.5 mg/325 mg 5 mg/300 mg 5 mg/325 mg 7.5 mg/300 mg 7.5 mg/325 mg 10 mg/300 mg 10 mg/325 mg	Analgesia: Tablet: one to two every four to six hours as needed; 7.5-300 and 10-300 mg tablets, one every four to six hours as needed Solution: 15 mL every four to six hours as needed; 10-300 mg/15 mL solution, 11.25 mL every four to six hours as needed	Not applicable	Not applicable
IBUDONE, REPREXAIN, VICOPROFEN (hydrocodone bitartrate/ ibuprofen)	Tablet: 2.5 mg/200 mg 5 mg/200 mg 7.5 mg/200 mg 10 mg/200 mg	Analgesia: Tablet: one tablet every four to six hours as needed	Not applicable	Take with food
oxycodone hydrochloride and ibuprofen	Tablet: 5 mg/400 mg	Analgesia: Tablet: one tablet every 6 hours as needed; frequency should be adjusted based on initial response and adverse effects; a maximum of four tablets in a 24-hour period should not be exceeded	Not applicable	Not applicable

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
SYNALGOS-DC (dihydrocodeine bitartrate/aspirin/ caffeine)	Capsule: 16 mg/356 mg/ 30 mg	Analgesia: Capsule: two capsules every four hours as needed	Not applicable	Not applicable
TREZIX* (dihydrocodeine bitartrate/ acetaminophen/ caffeine)	Capsule: 16 mg/320.5 mg/ 30 mg	Analgesia: Capsule: two capsules every four hours as needed	Not applicable	Not applicable

(Micromedex 2.0, 2017; Facts and Comparisons, 2017)

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Single Entity Agents					
codeine sulfate	Use with caution in the elderly	Safety and efficacy have not been established in patients less than 18 years of age.	Use with caution. Start with lower doses or longer intervals.	No formal studies have been conducted in patients with hepatic impairment. Start with lower doses or longer intervals.	Pregnancy Category C* Secreted in breast milk; use with caution.
DEMEROL, MEPERITAB (meperidine hydrochloride)	Use with caution in the elderly	Safety and efficacy have not been established.	Reduce dose by 75% for moderate impairment and 50% for severe impairment.	Use with caution. Reduce initial dose.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
DILAUDID (hydromorphone hydrochloride)	Use with caution in the elderly.	Safety and efficacy have not been established.	Reduce initial dose for moderate impairment. Use even lower dosing or alternative analgesic in severe impairment.	Reduce initial dose for moderate impairment. Use even lower dosing or alternative analgesic in severe impairment.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
morphine sulfate	Use with caution in the elderly.	Safety and efficacy have not been established in patients less than 18 years of age.	Use with caution. Reduce initial dose and titrate slowly.	Use with caution. Reduce initial dose and titrate slowly.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
OPANA (oxymorphone hydrochloride)	Use with caution in the elderly.	Safety and efficacy in pediatric	Caution should be used in patients with	Caution should be used in patients with	Pregnancy Category C*

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		patients ≤18 years of age have not been established.	moderate to severe renal impairment, starting with lower doses and titrating the dosage slowly.	mild hepatic impairment; starting with the lowest dose and titrating the dosage slowly. Contra-indicated in moderate and severe hepatic impairment.	Unknown whether excreted in breast milk; use with caution.
OXAYDO, ROXICODONE (oxycodone hydrochloride)	Use with caution in the elderly; start with lower doses.	Safety and efficacy have not been established.	Dose adjustment may be required with slow titration.	Dose adjustment may be required and titrate slowly.	Pregnancy Category B* Secreted in breast milk; do not breastfeed.
Combination Products					
ASCOMP WITH CODEINE, FIORINAL WITH CODEINE #3 (codeine/butalbital/ aspirin/caffeine)	Use with caution in the elderly.	Safety and efficacy have not been established.	Use with caution.	Use with caution.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
CAPITAL W/CODEINE, TYLENOL-CODEINE (codeine/ acetaminophen)	Use with caution in the elderly.	Safety not established in children <3 years old.	Use with caution in severe renal impairment.	Use with caution.	Pregnancy Category C* Secreted in breast milk; use with caution.
codeine/ carisoprodol/aspirin	Use with caution in the elderly.	Safety and efficacy in pediatric patients below the age of 16 years have not been established.	Use with caution.	Use with caution.	Pregnancy Category D* Secreted in breast milk; do not breastfeed.
ENDOCET, PERCOCET, PRIMLEV (oxycodone hydrochloride/ acetaminophen)	Use with caution in the elderly.	Safety and efficacy have not been established.	Use with caution.	Use with caution.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
ENDODAN, PERCODAN (oxycodone hydrochloride/	Use with caution in the elderly.	Should not be administered to pediatric patients.	Use with caution.	Use with caution.	Pregnancy Category D*

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
aspirin)			Avoid use with severe renal impairment.	Avoid use with severe hepatic impairment.	Secreted in breast milk; do not breastfeed.
FIORICET WITH CODEINE (codeine/ butalbital/ acetaminophen/ caffeine)	Use with caution in the elderly.	Safety and efficacy have not been established.	Use with caution.	Use with caution.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
HYCET, NORCO, LORCET, VICODIN, VICODIN ES, VICODIN HP, XODOL (hydrocodone bitartrate/ acetaminophen)	Use with caution in the elderly.	Safety and efficacy in pediatric patients <2 years old have not been established.	Use with caution.	Use with caution.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.
IBUDONE, REPREXAIN, VICOPROFEN (hydrocodone bitartrate/ ibuprofen)	Use with caution in the elderly.	Safety and efficacy in pediatric patients <16 years old have not been established.	Information not available.	Information not available.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
oxycodone hydrochloride and ibuprofen	Use with caution in the elderly.	Safety and efficacy in pediatric patients <14 years old have not been established.	Information not available.	Information not available.	Pregnancy Category C* Pregnancy Category D* at 30 weeks gestation Unknown whether oxycodone and ibuprofen excreted in breast milk; however, oxycodone alone is excreted in breast milk; do not breastfeed
SYNALGOS-DC (dihydrocodeine bitartrate/aspirin/ caffeine)	Use with caution in the elderly.	Safety and efficacy in have not been established. Not recommended for pediatric	Information not available.	Information not available.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		patients <12 years old.			
TREZIX (dihydrocodeine bitartrate/ acetaminophen/ caffeine)	Use with caution in the elderly.	Safety and efficacy have not been established	Use with caution at a reduced dosage.	Use with caution.	Pregnancy Category C* Secreted in breast milk; do not breastfeed.

*Pregnancy Category B=No evidence or risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D=Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.

(Micromedex 2.0, 2017)

CONCLUSION

- Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment and disability, psychological distress, and sleep deprivation (AAPM, 2014; Cohen et al, 2016).
- Opioids have been the mainstay of pain treatment for a number of years, and there is well documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several short-acting opioids that are available as single entity agents and combination products for the treatment of pain (Cohen et al, 2016).
- As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opioid receptors and effectively relieve pain without producing loss of consciousness. These agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the CNS (Cohen et al, 2016; Micromedex 2.0, 2017).
- Short-acting opioid analgesics are available as single entities and in combination with acetaminophen, aspirin, butalbital, caffeine and ibuprofen. Acetaminophen, aspirin and ibuprofen are non-opioid analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a CNS stimulant. Carisoprodol is a centrally-acting muscle relaxant (Micromedex 2.0, 2017).
- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and functional outcomes in patients with nociceptive, neuropathic pain, or fibromyalgia (Furlan et al, 2006).
- Systematic reviews and meta-analyses have demonstrated similar safety and level of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, neuropathic, rheumatoid arthritis, osteoarthritis, non-cancer, and acute pain (Bekkering et al, 2011; Caraceni et al, 2011; Chaporro et al, 2012; Chaporro et al, 2013; Felden et al, 2011; McNicol et al, 2005; McNicol et al, 2013; Neusch et al, 2009; Pigni et al, 2011; Quigley et al, 2002; Reid et al 2006; Wiffen et al, 2013; Whittle et al, 2011).
- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, and oxycodone/acetaminophen in the management of pain (Litkowski et al, 2005; Marco et al, 2005; Palangio et al, 2000[a]; Palangio et al, 2000[b]; Rodriguez et al, 2007[b]; Smith et al, 2004).
- As a rule, opioids are contraindicated in patients with a hypersensitivity to the active ingredient or any component, respiratory depression, acute or severe bronchial asthma or suspected or documented paralytic ileus. Opioids have an associated abuse potential and can cause cardiovascular effects, respiratory depression and significant CNS depression, especially when used with other CNS depressants. The most frequently reported adverse events are light-headedness, dizziness, sedation, nausea, and vomiting (Micromedex 2.0, 2017).

- Clinical guidelines have been published that address back pain, cancer pain, neuropathic pain, and osteoarthritis pain. These guidelines make recommendations for the specific place in therapy for opioids as a class but do not make any recommendations for the use of one agent over another (AAOS, 2013; Attal et al, 2010; Bril et al, 2011; Pop-Busui et al, 2017; Dubinsky et al, 2004; Carville et al, 2008; Chou et al, 2007; Chou et al, 2009; Hochberg et al, 2012; Manchikanti, 2017; The Medical Letter, 2013). Additional guidelines are available on codeine use in patients with various CYP 2D6 phenotypes (Crews et al, 2014). A guideline from the CDC has recently been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (Dowell et al, 2016).

Table 16. Advantages and Disadvantages of Short-Acting Opioids

Drug	Advantages	Disadvantages
Single Entity Agents		
codeine sulfate		Limited manufacturers; concerns in patients with CYP 2D6 ultra-rapid or poor metabolism; C-II substance
DEMEROL, MEPERITAB (meperidine hydrochloride)		Accumulation of metabolite in some patients leading to increased adverse events; C-II substance
DILAUDID (hydromorphone hydrochloride)	Has corresponding long-acting agent for comprehensive pain treatment	C-II substance
morphine sulfate	Has corresponding long-acting agent for comprehensive pain treatment	C-II substance
OPANA (oxymorphone hydrochloride)	Has corresponding long-acting agent for comprehensive pain treatment	C-II substance
OXAYDO, ROXICODONE (oxycodone hydrochloride)	Has corresponding long-acting agent for comprehensive pain treatment	C-II substance
Combination Products		
ASCOMP WITH CODEINE, FIORINAL WITH CODEINE #3 (codeine/butalbital/ aspirin/caffeine)	C-III substance	Aspirin component may be problematic in some patients
CAPITAL W/CODEINE, TYLENOL-CODEINE (codeine/acetaminophen)	C-III substance	Dose limited by acetaminophen content; acetaminophen component may be problematic in some patients
codeine/carisoprodol/aspirin	C-III substance	Aspirin component may be problematic in some patients
ENDOCET, PERCOCET, PRIMLEV (oxycodone hydrochloride/ acetaminophen)	Variety of strengths/strength combinations available	C-II substance; dose limited by acetaminophen content; acetaminophen component may be problematic in some patients
ENDODAN, PERCODAN (oxycodone hydrochloride/ aspirin)		C-II substance; aspirin component may be problematic in some patients

Drug	Advantages	Disadvantages
FIORICET WITH CODEINE (codeine/butalbital/ acetaminophen/caffeine)	C-III substance	Dose limited by acetaminophen content; acetaminophen component may be problematic in some patients
HYCET, NORCO, LORCET. VICODIN, VICODIN ES, VICODIN HP, XODOL (hydrocodone bitartrate/acetaminophen)	Variety of strengths/strength combinations available	C-II substance; dose limited by acetaminophen content; acetaminophen component may be problematic in some patients
IBUDONE, REPREXAIN, VICOPROFEN (hydrocodone bitartrate/ ibuprofen)		C-II substance; ibuprofen component may be problematic in some patients
oxycodone hydrochloride and ibuprofen		C-II substance; ibuprofen component may be problematic in some patients
SYNALGOS-DC (dihydrocodeine bitartrate/aspirin/caffeine)	C-III substance	Limited manufacturers; aspirin component may be problematic in some patients
TREZIX (dihydrocodeine bitartrate/ acetaminophen/caffeine)	C-III substance	Dose limited by acetaminophen content; acetaminophen component may be problematic in some patients

CYP= cytochrome P450

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