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 re-injury. In contrast, chronic pain, often defined as pain persisting for longer than 3 to 6 months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2016*).
  - A 2016 study estimated that approximately 50 million adults in the United States have chronic pain, and approximately 20 million have high-impact chronic pain (ie, pain that limits life or work activities on most days). Each year, chronic pain contributes to an estimated $560 billion in direct medical costs, lost productivity, and disability programs (*Dahlhamer et al 2018*).
- Pain may be classified as nociceptive 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 non-opioid 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 recommended 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 (full and partial agonists), alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate (NMDA) 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, ibuprofen, and naloxone. 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 2019*). Naloxone, when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics (*Pentazocine and naloxone prescribing information 2016*). The presence of naloxone in this dosage form is intended to prevent the effect of pentazocine if the combination agent is misused by injection.
- 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 (ie, tablet or capsule) to reduce the risk of liver damage from too much acetaminophen (*FDA Safety Communication 2011*). All products with dosage forms with acetaminophen exceeding 325 mg have since been removed from the market (*FDA Safety Communication 2014*).
- The Controlled Substances Act (CSA) places substances with accepted medical uses into 1 of 4 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 except for butorphanol, which is Schedule IV (C-IV).
  - 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. Pentazocine/naloxone is a C-IV controlled substance.

- 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*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- This review focuses on short-acting opioid agonists and their use in the treatment of pain. This review does not include injectables, although some medications may be available in this formulation. In addition, immediate-release fentanyl products, tapentadol, and tramadol, are covered in other publications and are not covered in this review.
- The agents included in this review are listed in Table 1 and divided by single entity agents and combination products.
- Medispan Class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
codeine sulfate*	✔
Demerol (meperidine hydrochloride)	✔
Dilaudid (hydromorphone hydrochloride)	✔
morphine sulfate*	✔
Opana (oxymorphone hydrochloride)	✔
Oxaydo†, Roxicodone, RoxyBond (oxycodone hydrochloride)	✔
butorphanol*	✔
Combination Products	
Apadaz (benzhydrocodone/acetaminophen)	✔ ‡
ASCOMP with Codeine, Fiorinal with Codeine #3 (codeine/butalbital/aspirin/caffeine)	✔
Tylenol with Codeine (acetaminophen/codeine)	✔
codeine/carisoprodol/aspirin*	✔
Endocet, Nalocet, Percocet, Primlev (oxycodone hydrochloride/acetaminophen)	✔
Fioricet with Codeine (codeine/butalbital/acetaminophen/caffeine)	✔
Hycet*, Lorcet, Lorcet HD, Lorcet Plus, Lortab, Norco, Verdrocet, Vicodin, Vicodin ES, Vicodin HP, Xodol*, Zamicet (hydrocodone bitartrate/acetaminophen)	✔
Ibudone (hydrocodone hydrochloride/ibuprofen)	✔
oxycodone hydrochloride/aspirin*	✔
oxycodone hydrochloride/ibuprofen*	✔
pentazocine/naloxone*	✔
Dvorah, Trezix (dihydrocodeine bitartrate/acetaminophen/caffeine)	✔

*Branded product no longer commercially available
†A generic for Oxaydo is not anticipated until 2025.
‡An authorized generic is commercially available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

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

Indication	butorphanol	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: butorphanol 2018, codeine 2018, Demerol 2018, Dilaudid 2018, morphine sulfate oral solution 2018, morphine sulfate tablets 2017, Opana 2018, Oxaydo 2018, Roxicodone 2018, RoxyBond 2018)

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

Indication	acetaminophen/ codeine	benzhydrocodone /acetaminophen	codeine/ butalbital/ acetaminophen/ caffeine	codeine/ butalbital/ aspirin/caffeine	codeine/ carisoprodol/ aspirin	dihydrocodeine/ acetaminophen/ caffeine	hydrocodone/ acetaminophen	hydrocodone/ ibuprofen	oxycodone/ acetaminophen	oxycodone/ aspirin	oxycodone/ ibuprofen	pentacozine/ naloxone
Relief of discomfort associated with acute, painful musculoskeletal conditions in adults					✔							
Relief of mild to moderate 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								✔				
Short-term (≤ 14 days) management of acute pain severe enough to require an opioid analgesic 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: Apadaz 2018, codeine/carisoprodol/aspirin 2018, Dvorah 2018, Fioricet with Codeine 2018, Fiorinal with codeine 2018, Ibudone 2017, Nalocet 2018, oxycodone/aspirin 2018, oxycodone/ibuprofen 2017, pentazocine/naloxone 2016, Percocet 2018, Primlev 2018, Trezix 2017, Tylenol with codeine 2018, Vicodin 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, 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*). However, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo (*Busse et al 2018, Stewart et al 2018*).
  - A systematic review and meta-analysis of 96 randomized controlled trials examined the use of opioids in chronic non-cancer pain. Opioid use was associated with reduced pain compared to placebo (weighted mean difference [WMD], -0.69 cm on a 10-cm visual analog scale; 95% confidence interval [CI], -0.82 to -0.56 cm; $p < 0.001$), as well as improved physical functioning as measured by the 36-item Short Form physical component score (SF-36 PCS; WMD, 2.04 points on a 100-point scale; 95% CI, 1.41 to 2.68 points; $p < 0.001$). However, the minimally important difference (pain, 1 cm; SF-36 PCS, 5 points) was not reached for either parameter. Opioids were also associated with increased vomiting vs placebo (5.9% vs 2.3%). When opioids were compared to nonsteroidal anti-inflammatory drugs (NSAIDs), similar improvements in pain and physical functioning were observed (pain WMD for opioids vs NSAIDs, -0.60 cm; 95% CI, -1.54 to 0.34; physical functioning WMD for opioids vs NSAIDs, -0.90 points; 95% CI, -2.69 to 0.89) *(Busse et al 2018).* Similarly, another systematic review and meta-analysis of 29 studies found that opioids and other commonly used classes of pain medication produced similar percent reductions in osteoarthritis pain (opioids, 35.4%; oral NSAIDs, 34.3%; topical NSAIDs, 40.9%; acetaminophen, 32.5%; cyclooxygenase-2 [COX-2] inhibitors, 36.9%) *(Stewart et al 2018).*
- 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, Felden et al 2011, McNicol et al 2005, McNicol et al 2013, 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, Smith et al 2004*).
- Head-to-head trials involving butalbital-containing products and oxycodone/aspirin are not available.
- In April 2017, the FDA approved RoxyBond, a new immediate-release oxycodone formulation. It was approved via the 505(b)(2) pathway with no new clinical efficacy studies. RoxyBond is the first immediate-release opioid analgesic approved with labeling describing its abuse-deterrent properties consistent with the FDA's 2015 Guidance for Industry. The labeling states that there is *in vitro* data demonstrating that RoxyBond has physicochemical properties expected to make abuse via injection difficult. Data from a clinical abuse potential study, along with support from *in vitro* data, also indicate that RoxyBond has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by the intranasal, oral, and intravenous route is still possible (*Roxybond FDA Advisory Committee Briefing Document 2017, RoxyBond Prescribing information 2018).*
  - The manufacturer of Oxaydo (oxycodone) also conducted abuse deterrent studies; however the FDA labeling states that there is no evidence that Oxaydo has reduced abuse liability compared to immediate-release oxycodone (*Oxaydo Prescribing information 2018*).
- In February 2018, the FDA approved Apadaz (benzhydrocodone/acetaminophen) via the 505(b)(2) pathway with no new clinical efficacy studies. Benzhydrocodone is an inactive prodrug of hydrocodone and is converted rapidly to hydrocodone by enzymes in the intestinal tract. While Apadaz may have some theoretical benefit in preventing drug manipulation and deterring opioid abuse, there was insufficient *in vitro* and human abuse potential trial data to support an abuse deterrent claim in the labeling *(Apadaz FDA Advisory Committee Briefing Document 2016, Apadaz Prescribing information 2018).*
- A literature search failed to retrieve a significant amount of clinical trial information regarding the safety and effectiveness of pentazocine/naloxone and butorphanol. Specifically, no clinical trial information was obtained for pentazocine/naloxone.
- Butorphanol nasal solution has demonstrated effectiveness and safety in the management of several etiologies of pain including dental pain, postoperative uvulopalatopharyngoplasty pain, postepisiotomy pain, and anal surgery. Open-label trials have demonstrated that administration of butorphanol nasal solution reduces pain and is well tolerated (*Ladov et al 2000, Madani 2000*). Randomized, placebo-controlled trials demonstrating the effectiveness of butorphanol nasal solution have provided inconsistent results (*Joyce et al 1993, Wermeling et al 2005*). In one study, female patients with moderate to severe postepisiotomy pain achieved superior pain relief with butorphanol nasal solution compared to

placebo; however, no difference was observed in another trial evaluating dental pain. Specifically, no significant differences in summed pain intensity difference (SPID) values through 6 hours post-dose and Total Pain Relief values at 6 hours post-dose were observed between butorphanol nasal solution and placebo (*Wermeling et al 2005*). Additionally, when compared to intramuscular meperidine, treatment with butorphanol nasal solution achieved comparable pain relief but had higher incidences of somnolence, dizziness, and nausea (*Mai et al 2009*). Butorphanol nasal spray also provided superior pain relief to the combination of butalbital, caffeine, aspirin, and codeine, after the first 2 hours when given for migraine pain (*Goldstein et al 1998*).

CLINICAL 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 (*American Academy of Orthopaedic Surgeons [AAOS] 2013, Attal et al 2010, Bril et al 2011, Pop-Busui et al 2017, Chou et al 2007, Chou et al 2009, Hochberg et al 2012, MacFarlane et al, 2017, Manchikanti et al 2017, Qaseem 2017, 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*):
  - Non-pharmacologic therapy and non-opioid 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 non-pharmacologic therapy and non-opioid 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 7 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 (ACP) 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 (eg, 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).
  - There is 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).

- Clinical guidelines provide little information about the role of partial opioid agonists in the treatment of pain (*Chou et al 2009, Hegmann 2014, Medical Letter 2013*). Unlike full agonists, the partial agonists have a ceiling on their analgesic effects, and may precipitate withdrawal if given to patients dependent on full opioid agonists (*Medical Letter 2013*).

- The two recently published clinical practice guidelines from the ACP and the ASIPP do not discuss the place in therapy of pentazocine and butorphanol.
- Guidelines from the Society of Critical Care Medicine note that opioids are a mainstay of pain management in most intensive care unit settings: however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control. Opioids used for procedural pain management should be used at the lowest effective dose (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons recommends the maximization of non-opioid analgesia (ie, ibuprofen). It also provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed. The maximum recommended number of tablets for any surgical procedure covered in the guideline is 20 tablets, but in some procedures, it is recommended that no opioids be prescribed upon discharge (*Overton et al 2018*).

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 4000 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 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 2019*).
- In March 2016, the FDA announced label changes and enhanced warnings for all opioids (*FDA Safety Communication 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 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 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.

- In September 2017, the FDA notified manufacturers of immediate-release opioid analgesics intended for use in the outpatient setting that these medications will be subject to more stringent requirements under a Risk Evaluation and Mitigation Strategy (REMS), similar to the requirements already in place for extended-release/long-acting opioid analgesics (*Gottlieb 2017*). On September 18, 2018, the long-acting opioid REMS was modified to include all immediate-release opioids as well. This program, now known as the Opioid Analgesic REMS program, strongly encourages healthcare providers to complete an approved training program on opioid analgesics. The goal of the REMS is to ensure that benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse *(FDA REMS 2018)*.
- The administration of pentazocine and butorphanol is not recommended in patients who are dependent on opioids.
- Naloxone when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics. The presence of naloxone in this dosage form is intended to prevent the effect of pentazocine if the combination agent is misused by injection.
- Other warnings are similar to other opioids and include risk of abuse, misuse, diversion, respiratory depression, and adverse events in patients with acute head injury.
- Pentazocine and butorphanol should not be used with other substances that may cause CNS depression such as alcohol and sedatives.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
codeine sulfate	Tablets	Oral	Every 4 hours as needed	
Demerol, (meperidine hydrochloride)	Solution, tablets	Oral	Every 3 to 4 hours as needed	
Dilaudid (hydromorphone hydrochloride)	Solution, tablets	Oral	Solution: Every 3 to 6 hours as required Tablet: Every 4 to 6 hours as needed	
morphine sulfate	Solution, tablet	Oral	Every 4 hours as needed for pain	
Opana (oxymorphone hydrochloride)	Tablets	Oral	Every 4 to 6 hours as needed	• Contraindicated in moderate and severe hepatic impairment
Oxaydo, Roxicodone, RoxyBond (oxycodone hydrochloride)	Capsules, oral concentrate, solution, tablets, abuse-deterrent tablets	Oral	Every 4 to 6 hours as needed	
Butorphanol	Nasal solution	Intranasal	1 mg administered as 1 spray in 1 nostril; if adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given; the initial dose sequence may be repeated in 3 to 4 hours as required	
Combination Products				
Apadaz (benzhydrocodone/ acetaminophen)	Tablets	Oral	Every 4 to 6 hours as needed	
ASCOMP with codeine, Fiorinal with codeine #3	Capsules	Oral	Every 4 hours	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
(codeine/ butalbital/ aspirin/caffeine)				
Tylenol-codeine (codeine/ acetaminophen)	Solution, tablets	Oral	Every 4 hours as needed	
codeine/ carisoprodol/ aspirin	Tablets	Oral	Four times daily as needed	• Maximum duration of use is up to 2 or 3 weeks.
Endocet, Nalocet, Percocet, Primlev (oxycodone hydrochloride/ acetaminophen)	Solution, tablets	Oral	Every 6 hours as needed	
Fioricet with codeine (codeine/ butalbital/ acetaminophen/ caffeine)	Capsules	Oral	Every 4 hours as needed	
Hycet*, Lorcet, Lorcet HD, Lorcet Plus, Lortab, Norco, Verdrocet, Vicodin, Vicodin ES, Vicodin HP, Xodol*, Zamicet (hydrocodone bitartrate/acetaminophen)	Solution, tablets	Oral	Every 4 to 6 hours as needed	
Ibudone (hydrocodone hydrochloride/ibuprofen)	Tablets	Oral	Every 4 to 6 hours as needed	
oxycodone hydrochloride and aspirin	Tablets	Oral	Every 6 hours as needed	• Avoid use with severe renal impairment. • Avoid use with severe hepatic impairment.
oxycodone hydrochloride and ibuprofen	Tablets	Oral	Every 6 hours as needed	
pentazocine/naloxone	Tablet	Oral	Every 3 to 4 hours	
Dvorah, Trezix (dihydrocodeine bitartrate/ acetaminophen/ caffeine)	Capsules, tablets	Oral	Every 4 hours as needed	

(*Micromedex 2.0 2019*)

*Branded product no longer commercially available.

See the current prescribing information for full details

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 (*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 full and partial agonist actions at mu receptors, which are found in large numbers within the CNS (*Cohen et al 2016, Micromedex 2.0 2019*).

- Short-acting opioid analgesics are available as single entities and in combination with acetaminophen, aspirin, butalbital, caffeine, naloxone, 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 2019*). Naloxone, when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics (*Pentazocine and naloxone prescribing information 2016*).
- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and functional outcomes in patients with nociceptive pain, neuropathic pain, or fibromyalgia (*Furlan et al 2006*). However, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo (*Busse et al 2018, Stewart et al 2018*).
- 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, Felden et al 2011, McNicol et al 2005, McNicol et al 2013, 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, 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 2019*).
- 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, Chou et al 2007, Chou et al 2009, Hochberg et al 2012, MacFarlane et al, 2017, Manchikanti, 2017, Qaseem 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 non-pharmacologic and non-opioid 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*). Guidelines from the Society of Critical Care Medicine note that opioids are a mainstay of pain management in most intensive care settings: however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control. Opioids used for procedural pain management should be used at the lowest effective dose (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons recommends the maximization of non-opioid analgesia (ie, ibuprofen), and provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed (*Overton et al 2018*).
- Limited clinical information regarding the safety and effectiveness of opioid partial agonists within this review is available within the literature, and data are particularly lacking for pentazocine/naloxone. Some clinical trial data are available to demonstrate the effectiveness and safety of butorphanol nasal solution. Clinical guidelines provide little information about the role these agents play in the treatment of pain (*Chou et al 2009, Dowell et al 2016, Hegmann et al 2014, Manchikanti et al 2017, Medical Letter 2013, Qaseem et al 2017*). Unlike full agonists, the partial agonists have a ceiling on their analgesic effects, and may precipitate withdrawal if given to patients dependent on full opioid agonists (*Medical Letter 2013*).

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