Therapeutic Class Overview
Opioids, Long 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 over three to six 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 and 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) and is less responsive to opioids. 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, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2016*).
  - 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*).
  - 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*).
- 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 U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explains the FDA's current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also makes recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance does not address generic opioids. Subsequently in November 2017, the FDA issued a final guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2017*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product's abuse deterrent properties consistent with the FDA's guidance for industry (*Hale et al 2016*).
  - Since the approval of reformulated OxyContin, several other long-acting opioids have been approved with abuse deterrent labeling, including, Arymo ER (morphine), Embeda (morphine and naltrexone), Hysingla ER (hydrocodone), Morphabond (morphine), Targiniq ER (oxycodone and naloxone), Troxyca ER (oxycodone and naltrexone), Vantrela ER (hydrocodone), and Xtampza ER (oxycodone) (*Drugs@FDA 2019, Hale et al 2016*). However, Targiniq ER, Troxyca ER, and Vantrela ER were never launched and were recently discontinued. Branded Arymo ER was also discontinued by the manufacturer, Egalet (*Drugs@FDA 2019*).

- A number of federal agencies have implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The U.S. Office of Disease Prevention and Health Promotion offers an interactive training tool, "Pathways to Safer Opioid Use," which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment. On July 13, 2017, the National Academies of Science, Engineering, and Medicine (NASAM) also released a consensus report, commissioned by the FDA, which outlined the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management (*CMS 2019, Office of Disease Prevention and Health Promotion 2019, NASAM 2017, NIDA 2015*).
- 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*).
- 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*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12) (*Prescribing information: Dolophine 2018, methadone oral solution 2019, Methadose 2018*).
- Included in this review are the long-acting opioids, which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2019*).
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2019*).
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Arymo ER†¶, Avinza¶, Kadian, Morphabond†, MS Contin (morphine sulfate)	✔
Belbuca, Butrans (buprenorphine)	✔
Dolophine, Methadose (methadone)	✔
Duragesic (fentanyl)	✔
Exalgo# (hydromorphone)	✔
Hysingla ER†, Zohydro ER§ (hydrocodone bitartrate)	-
levorphanol	✔
Nucynta ER (tapentadol)	-
Opana ER* (oxymorphone)	✔
OxyContin†‡, Xtampza ER† (oxycodone)	✔

Drug	Generic Availability
Combination Products	
Embeda† (morphine sulfate/naltrexone)	-

*Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
†Approved as an abuse deterrent (AD) formulation, which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*
‡OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.
§In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid.
¶Avinza branded products were discontinued by Pfizer in July 2015. Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
#Brand product discontinued, but generic products are available.
(*Drugs@FDA 2019, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
Pain Management											
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔			✔ *	✔	✔	✔	✔	✔
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †			
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.					✔						
Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		✔ ‡		✔ ‡							
Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate										✔	
Opioid Addiction											
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔					
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔					
Limitations of Use											
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
otherwise inadequate to provide sufficient management of pain.											
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔

*Methadone tablets and oral solution only
†OxyContin only
‡Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

(Prescribing information: Arymo ER 2018, Belbuca 2018, Butrans 2018, Dolophine 2018, Duragesic 2018, Embeda 2018, Exalgo 2018, Hysingla ER 2018, Kadian 2018, levorphanol 2018, methadone oral solution 2019, Methadose 2018, Morphabond 2018, MS Contin 2018, Nucynta ER 2018, OxyContin 2018, oxymorphone extended-release 2018, Xtampza ER 2018, Zohydro ER 2019)

- 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

- As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Aiyer et al 2017, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al [a], 2010, Gordon et al [b], 2010, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Ma et al 2008, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2013, Wild et al 2010*).
- Some systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, other meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N = 39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - 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% 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*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blinded studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only double-blinded, randomized controlled trials for efficacy assessments; open-label and controlled

observational studies were allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and "current pain in the morning;" however, the "worst pain in the past 24 hours" and "current pain in the evening" were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- A recent pragmatic, 12-month, randomized trial (N = 240) compared opioid vs non-opioid medications on pain-related function, pain intensity, and adverse effects in patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use *(Krebs et al 2018)*.
  - Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen or an NSAID. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.
  - Groups did not significantly differ on pain-related function over 12 months (p = 0.58); mean 12-month Brief Pain Inventory (BPI) interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1; 95% CI, −0.5 to 0.7). Pain intensity was significantly better in the nonopioid group over 12 months (p = 0.03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5; 95% CI, 0.0 to 1.0). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (p = 0.03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9; 95% CI, 0.3 to 1.5).
- Arymo ER and Morphabond were approved based on bioequivalence to MS Contin. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturers relied on previous findings of efficacy and safety for MS Contin (*FDA Summary Review: Arymo ER 2017, Morphabond 2018*).
- The efficacy of buprenorphine buccal films was evaluated in three 12-week, double-blind (DB), placebo-controlled (PC) trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. In the trials, the DB treatment phase was preceded by an OL dose titration period. Patients were eligible for randomization into the 12-week DB treatment phase if they were able to titrate to a tolerable and effective buprenorphine dose. The primary efficacy variable was the patients' pain scores (based on a 0 to 10 numeric rating scale). Two of these studies demonstrated efficacy in patients with low back pain. One trial did not show a statistically significant pain reduction for Belbuca compared to placebo, and the results of this trial are not included in the Prescribing Information (*Belbuca Prescribing Information 2018, Gimbel et al 2016, Rauck et al 2016*).
  - In one study of opioid-naïve patients, pain scores increased more in the placebo group vs. the buprenorphine group during the DB phase; mean (standard deviation [SD]) changes from baseline to week 12 were 0.94 (1.85) and 1.59 (2.04) in the buprenorphine and placebo groups, respectively, with a significant between-group difference (-0.67; 95% CI, -1.07 to -0.26; p = 0.0012). A higher proportion of buprenorphine patients (62%) had at least a 30% reduction in pain score from prior to OL titration to study endpoint when compared to patients who received placebo (47%) (*Rauck et al 2016*).
  - In another study, opioid-experienced patients experienced a higher increase in their pain scores in the placebo vs. buprenorphine group after randomization. The difference between groups in the mean change from baseline to week 12 was -0.98 (95% CI, -1.32 to -0.64; p < 0.001). A significantly larger percentage of patients receiving buprenorphine than placebo had pain reductions ≥ 30% and ≥ 50% (p < 0.001 for both) (*Gimbel et al 2016*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2017, Qaseem 2017, Paice et al 2016, The Medical Letter 2013*). However, opioid rotation is recommended if a patient experiences

adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou 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 ER/long-acting opioids (category A, evidence 4).
  - Clinicians should prescribe opioids at 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 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, 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).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (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).
- The guidelines from the American College of Physicians and the American Society of Interventional Pain Physicians state that buprenorphine has lower quality evidence and is a third-line opioid for the treatment of pain (*Manchikanti et al 2017, Qaseem et al 2017*).
- Guidelines from the Society of Critical Care Medicine do not specifically address the use of long-acting opioids in intensive care unit patients; 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 (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons does not make recommendations on long-acting opioid use in this setting, but 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 (*Overton et al 2018*). A guideline from the Orthopaedic Trauma Association provides recommendations for pharmacologic and nonpharmacologic pain management strategies in acute musculoskeletal injury; this guideline recommends avoiding long-acting opioids in the acute setting (*Hsu et al 2019*).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for ER and long-acting opioids; on September 18, 2018, this 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.

- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine buccal and transdermal systems, which are Schedule III controlled substances.
- Most long-acting opioids are associated with boxed warnings regarding the potential for abuse and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, an interaction with alcohol, and accidental ingestion risks. Dolophine and methadone products have additional boxed warnings regarding life-threatening QT prolongation. Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER also have a Boxed Warning for an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers). An additional Boxed Warning for Duragesic cautions against exposure to heat as it may cause increased fentanyl release.
- Key contraindications across the class include acute or severe bronchial asthma, significant respiratory depression, and known or suspected paralytic ileus.
- There are multiple warnings and precautions with each agent. Key safety concerns associated with the opioid analgesics include respiratory depression, driving and operating machinery, hypotension, interactions with other CNS depressants, neonatal opioid withdrawal syndrome, use in special populations, and use in those with gastrointestinal conditions.
- The frequency of adverse reactions varies to some degree with each agent; however, overall adverse reactions are similar within the class. The most common adverse events in adults include nausea, vomiting, constipation, and somnolence.
- OxyContin is approved in patients aged ≥ 11 years. The most frequent adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.
- In March 2016, the FDA issued a drug safety communication warning about several safety issues with opioids and describing new class-wide labeling requirements. The warnings include the following (*FDA Drug Safety Communication 2016*):
  - Opioids can interact with antidepressants and migraine medications to cause serotonin syndrome.
  - Taking opioids may rarely lead to adrenal insufficiency.
  - Long-term opioid use may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- In August 2016, the FDA announced that it is requiring class-wide changes to drug labeling, including patient information, in order to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines (*FDA Drug Safety Communication 2016*).
  - Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concomitantly. Risks include extreme sleepiness, respiratory depression, coma, and death.
- On March 14, 2017, the FDA Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to 8, that the benefits of reformulated Opana ER (which did not originally gain the labeling describing potential abuse deterrent properties) no longer outweigh its risks. This vote followed an FDA analysis of epidemiological data that indicated that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated (*FDA Advisory Committee 2017*). Following the FDA's official withdrawal request, the manufacturer (Endo) announced the voluntary market withdrawal of reformulated Opana ER (*Endo Press Release 2017*).
- On September 20, 2017, the FDA advised clinicians that opioid addiction medications, such as methadone and buprenorphine, should not be withheld from patients receiving concurrent benzodiazepines or other CNS depressants (*FDA Drug Safety Communication 2017*). Even though combination therapy with these agents increases the risk of serious side effects, the harm caused by untreated opioid addiction can outweigh these risks.
- In April 2019, the FDA issued a drug safety communication regarding the risk of serious harm when opioid medications are suddenly discontinued or doses are rapidly decreased in patients who are physically dependent on opioids. Sudden discontinuation or rapid dose reduction may result in serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. Opioid medications should be tapered gradually according to an individualized schedule if discontinuation or dose reduction is necessary (*FDA Drug Safety Communication 2019*).

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. A detailed description is available within the prescribing information for each agent regarding when a patient is considered opioid-tolerant, and which strengths are appropriate in these patients.
- See prescribing information for detailed conversion recommendations as there are no established conversions from other opioid agents. When converting from one agent to another, it is better to underestimate need and monitor for breakthrough pain.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arymo ER‡, Avinza*, Kadian, Morphabond, MS Contin (morphine sulfate)	ER capsules and tablets	Oral	Arymo ER, Morphabond, MS Contin: Every 8 to 12 hours Avinza: Once daily Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans, Belbuca (buprenorphine)	Transdermal system (Butrans) Buccal film (Belbuca)	Topical Oral	Administration every 7 days Every 12 hours	• Not evaluated in patients with severe hepatic impairment and should be administered with caution (Butrans). • The maximum dose is 900 mcg every 12 hours. Do not exceed this dose due to the potential for QTc interval prolongation. If pain is not adequately managed on a 900 mcg dose, consider an alternate analgesic (Belbuca). • For severe hepatic impairment, reduce the starting and incremental dose by half (Belbuca).
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every 3 to 5 days; however, some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require systems be applied at 48 hours)	• Avoid use in patients with severe renal impairment. • Avoid use in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Exalgo§ (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe hepatic impairment, reduce the Hysingla ER dose to 1/2 the usual initial dose and start Zohydro ER at the lowest dose of 10 mg every 12 hours. • Hysingla ER: In moderate to severe renal impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment. • Not recommended in patients with severe hepatic impairment. • In patients with moderate hepatic impairment, initiate at 50 mg every 24 hours and do not exceed 100 mg/day.
Opana ER (oxymorphone)†	ER tablets	Oral	Every 12 hours	• Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.
Combination Products				
Embeda (morphine sulfate/ naltrexone)	ER capsules	Oral	Once daily	• Renal dose adjustment may be required in severe renal impairment. • Hepatic dose adjustment may be required in severe hepatic impairment.

*All Avinza branded products have been removed from the market.
†Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
‡Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
§Brand product discontinued, but generic products are available.

CONCLUSION

- 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 long-acting opioid agents available, which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen et al 2016*).
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in this class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has been FDA-approved as an option in pediatric patients, aged ≥ 11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥ 20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary: OxyContin 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Embeda (morphine sulfate/naltrexone), Hysingla ER (hydrocodone bitartrate extended release), Morphabond (morphine sulfate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).
- All long-acting opioids are part of the Opioid Analgesic REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
  - Several generic long-acting opioids exist, including hydromorphone; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
- Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*). Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has 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*).

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