

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 reinjury. 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 2012*).
 - Chronic pain is estimated to affect 100 million Americans and the total annual incremental cost of health care in 2010 due to pain ranges from \$560 billion to \$635 billion in the United States (U.S.). 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 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 and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics (*Cohen et al 2012*).
- 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 2012*).
 - 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 2012*).
 - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2012, 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 March 2016, the FDA issued draft guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2016*).
 - 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); however, Targiniq ER, Troxyca ER, and Vantrela ER have yet to launch (*Drugs@FDA 2017, Hale et al 2016*).

- A number of federal agencies have recently 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 Drug Enforcement Agency (DEA) issued a nationwide alert regarding fentanyl products laced with heroin, causing significant drug incidents and overdoses nationwide. The U.S. Office of Disease Prevention and Health Promotion announced a new 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 (*CMS 2017, DEA 2016, Office of Disease Prevention and Health Promotion 2015, NIDA 2015*)
- 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 2017, methadone oral solution 2016, METHADOSE 2016*).
- 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 2017*). TARGINIQ ER, TROXYCA ER, and VANTRELA ER are not included in this review as they have not been launched yet.
 - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2017*).
- 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)	✓
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)	-
Xartemis XR (oxycodone hydrochloride/ acetaminophen)	-

*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.
(*Drugs @FDA 2017, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

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	oxycodone/ acetaminophen
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 moderate to severe pain in patients where an opioid analgesic is appropriate.					✓							
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.		✓ ‡		✓ ‡								
For the management of acute pain severe enough to require 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												
<i>Limitations of Use:</i> 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	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.												
<i>Limitations of Use:</i> Not indicated as an as-needed (prn) analgesic.	✓		✓	✓		✓	✓	✓	✓	✓	✓	

*Methadone tablets 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 2017, Butrans 2016, Dolophine 2017, Duragesic 2016, Embeda 2016, Exalgo 2016, Hysingla ER 2016, Kadian 2016, levorphanol 2015, methadone oral solution 2016, Methadose 2016, **Morphabond 2017**, MS Contin 2016, Nucynta ER 2016, Opana ER 2016, OxyContin 2016, Xartemis XR 2014, Xtampza ER 2016, Zohydro ER 2016)

- 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, 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*).
- Recent systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*).
 - 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*).
 - 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*).

- 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 2017*).

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, Brill et al 2011, Dubinsky et al 2004, Chou et al 2009, Hochberg et al 2012, Paice et al 2016*). 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 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 oxycodone) 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).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for all ER and long-acting opioids included in this review, with the exception of levorphanol. This program has been updated to include new formulations and medications. The REMS program is part of the national prescription drug abuse plan announced in 2011 to combat prescription drug misuse and abuse. Program components include prescriber education and training, patient education, and a communication plan for prescribers (*FDA REMS 2017*).

- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance.
- 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, 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 due to increases in 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 central nervous system (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 has recently been 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).**

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. Please see a detailed description 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 to an agent, 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, MS Contin: Every 8 to 12 hours Avinza: Once daily Morphabond: Every 12 hours Kadian: Once daily	<ul style="list-style-type: none"> Renal dose adjustment is required. Hepatic dose adjustment is required.
Butrans (buprenorphine)	Transdermal system	Topical	Administration every 7 days	<ul style="list-style-type: none"> Not evaluated in patients with severe hepatic impairment and should be administered with caution.
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	<ul style="list-style-type: none"> 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 three to five 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)	<ul style="list-style-type: none"> Avoid use in patients with severe renal impairment. Avoid use in patients with severe hepatic impairment.
Exalgo (hydromorphone)	ER tablets	Oral	Once daily	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> For severe impairment, reduce the HYSINGLA dose to 1/2 the usual initial dose and start ZOXYDRO at the lowest dose of 10 mg every 12 hours. HYSINGLA: In moderate to severe 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	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	<ul style="list-style-type: none"> Not recommended in patients with severe renal impairment. Not recommended in patients with severe hepatic impairment.
Opana ER (oxymorphone)‡	ER tablets	Oral		<ul style="list-style-type: none"> Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Renal dose adjustment may be required in severe renal impairment. Hepatic dose adjustment may be required in severe hepatic impairment.
Xartemis XR (oxycodone/acetaminophen)	ER tablets	Oral	Every 12 hours	

*Available only as brand name Kadian

†All Avinza branded products have been removed from the market.

§Available only as brand name OxyContin.

‡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.

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 2012*).
 - Xartemis XR is the only long-acting agent in class indicated for severe acute pain.
 - 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 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 recently 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 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), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).

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- Almost all long-acting opioids are part of the 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, 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; oxycodone; 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. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*). 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 the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Dubinsky et al 2004, 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 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*).

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