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, MORPHABOND, 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). MORPHABOND, 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	Manufacturer	Original FDA Approval Date	Generic Availability
Single Entity Agents			
ARYMO ER, AVINZA®¶, KADIAN®, MS CONTIN® (morphine sulfate)	Various	1/9/2017 (ARYMO ER) 03/20/2002 (AVINZA); 07/03/1996 (KADIAN); 05/29/1987 (MS CONTIN)	✔
BUTRANS® (buprenorphine)	Purdue	06/30/2010	-
DOLOPHINE, METHADOSE (methadone)	Various	08/13/1947	✔
DURAGESIC® (fentanyl)	Janssen	08/07/1990	✔
EXALGO® (hydromorphone)	Mallinckrodt	03/01/2010	✔

Drug	Manufacturer	Original FDA Approval Date	Generic Availability
HYSINGLA ER† ZOHYDRO™ ER§ (hydrocodone bitartrate)	Purdue Pharma Pernix	11/20/2014 (HYSINGLA ER) 10/25/2013 (ZOHYDRO ER)	-
Levorphanol	Roxane	01/08/1953	✔
NUCYNTA® ER (tapentadol)	Depomed Inc	08/25/2011	-
OPANA® ER* (oxymorphone)	Endo	12/09/2011	✔
OXYCONTIN†, XTAMPZA ER (oxycodone)	Purdue	04/25/2010	✔
Combination Products			
EMBEDA† (morphine sulfate/ naltrexone)	Alpharma King/Pfizer	08/13/2009	-
XARTEMIS® XR (oxycodone hydrochloride/ acetaminophen)	Mallinckrodt	03/11/2014	-

*While the manufacturer may have some patent protection of certain formulations, generic products are available based on expired patents, agreements, and/or litigation.
†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. FDA 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												
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 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 otherwise inadequate to provide sufficient management of pain.	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
Limitations of Use: 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; 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, 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; Ahmedzai et al, 1997; Allan et al, 2001; Allan et al, 2005; Bao et al, 2016; Bekkering et al, 2011; Bruera et al, 1998; 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 (NeuPSIG) 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 extended-release (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 (NNH) of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent. Based on the findings, capsaicin 8% patches were recommended for second-line treatment and strong opioids third-line (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 (RCTs) 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 (SAEs) 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).

- In 2015, the FDA approved OXYCONTIN in opioid-tolerant, pediatric patients aged ≥11 years of age for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. Approval was based on a total of eight studies measuring pharmacokinetics, efficacy, and safety in opioid–naïve and –experienced patients from birth to adult age who were administered oxycodone immediate-release and ER formulations. A total of 155 opioid-tolerant pediatric patients aged five to 16 years with moderate to severe chronic pain were administered oxycodone with a mean daily dose of 33 mg (range, 20 to 140 mg/day) for a median duration of 20.7 days (range, 1 to 43 days). During the extension study, 23 patients were treated up to 28 weeks. According to an analysis conducted by the FDA, a number of study flaws were identified; however, efficacy and safety was demonstrated even if assessments were not statistically rigorous. Three pediatric patients experienced serious adverse events (including vomiting, vertigo, dizziness, headache, lethargy, constipation, and falls) in which contributions due to oxycodone cannot be ruled out. The most frequently reported treatment-emergent adverse events occurring in ≥5% of patients were vomiting (22%), nausea (15%), headache (14%), pyrexia (12%), constipation (10%), diarrhea (5%), dizziness (8%), and pruritus (7%). Safety has not been established in patients aged <11 years as there were too few patients in trials (FDA Summary Review: OXYCONTIN, 2015; OXYCONTIN prescribing information, 2015).

- The approval of XTAMPZA ER was based on an enriched enrollment, randomized-withdrawal, double-blind, placebo-controlled trial in 740 patients with persistent, moderate-to-severe chronic lower back pain. The study duration was up to 24 weeks, including a screening phase of up to 4 weeks, a titration phase of up to 6 weeks, a double-blind maintenance phase of 12 weeks, and a follow-up phase of 2 weeks. There was a significant difference in pain reduction (pain intensity NRS), favoring XTAMPZA ER, compared to placebo. The estimated pain score from randomization baseline to week 12 (change in pain from baseline) for the ITT population was higher for placebo patients (mean [± standard error] 1.85 [0.22]) than for XTAMPZA ER patients (0.29 [0.15]); this difference (-1.56 [0.27]; 95% CI, -2.1 to -1.1) was statistically significant (P< 0.0001) (Katz et al, 2015).

- ARYMO ER was approved based on bioequivalence to MS CONTIN. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturer of ARYMO ER relied on previous findings of efficacy and safety for MS CONTIN (FDA Summary Review: ARYMO ER, 2017).

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; 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 extended-release/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 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).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for all extended-release 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 eight, that the benefits of reformulated OPANA ER 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. While the FDA will consider the Advisory Committees' vote, the FDA will make the final decision regarding any potential regulatory action (e.g., whether to remove OPANA ER from the market) (Endo Press Release, 2017; FDA Advisory Committee 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	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single Entity Agents				
ARYMO ER, AVINZA†, KADIAN*, MS CONTIN (morphine sulfate)	Extended release capsules: 10 mg 20 mg 30 mg 40 mg[a] 45 mg 50 mg 60 mg 75 mg 80 mg 90 mg 100 mg 200 mg[a] Extended release tablets: 15 mg 30 mg 60 mg 100 mg[b] 200 mg[b] [a] Available only as brand name KADIAN [b] Available only as brand and generic MS CONTIN	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release capsule (AVINZA): initial, 30 mg once daily in opioid-naïve patients; maintenance, titrate conservatively; Extended release tablets (ARYMO ER, MS CONTIN): initial, 15 mg every 8 to 12 hours; Extended release capsule (KADIAN): daily requirements are established using prior analgesic treatment and prior opioid equivalents	Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. Dosage adjustments may be done every one to two days (ARYMO ER, KADIAN, MS CONTIN) or every three to four days in increments of 30 mg (AVINZA). Discontinuation: Use a gradual downward titration of the dose every two to four days to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue.	Swallow whole. Do not cut, crush, dissolve or chew due to the risk of rapid release and absorption of a potentially fatal dose.
BUTRANS (buprenorphine)	Transdermal system: 5 mcg/hour 7.5 mcg/hour 10 mcg/hour 15 mcg/hour 20 mcg/hour	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate:	Titrate based on analgesic requirement and tolerance at a minimum interval of every 72 hours.	Transdermal system: intended to be worn for seven days. After removal of patch, wait 21 days

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		initial, opioid-naïve, 5 mcg/hour patch; previous opioid use <30 mg of oral morphine equivalents per day, 5 mcg/hour patch; previous opioid use 30 to 80 mg of oral morphine equivalents per day, 10 mcg/hour patch; maintenance, titrate based on analgesic requirement and tolerance at a minimum interval of every 72 hours; maximum, 20 mcg/hr transdermally.		before reapplying to the same skin site.
DOLOPHINE, METHADOSE (methadone)	Oral solution concentrate (sugar-free available): 10 mg/mL Oral solution: 5 mg/5 mL 10 mg/5 mL Dispersible tablet: 40 mg Tablet: 5 mg 10 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Tablet, oral solution: for opioid-naïve patients, initial, 2.5 every eight to 12 hours; maintenance, slowly titrate to effect; for opioid-experienced patients, dose is based on total daily opioid equivalents. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs): Concentrate, dispersible tablet, solution, tablet (first day of treatment): initial, single 20 to 30 mg dose to suppress withdrawal symptoms; maintenance, an additional 5 to 10 mg may be provided if withdrawal symptoms have not been suppressed; maximum,	Due to the large variability in half-life (e.g., eight 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. Discontinuation: Use a gradual downward titration of the dose every two to four days.	Do not abruptly discontinue in a physically dependent patient. Monitor closely for any potentially life-threatening adverse reactions. Methadone should be prescribed only by healthcare professionals who have experience with potent opioids. Do not chew or swallow dispersible tablets.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		40 mg/day on first day of treatment Concentrate, dispersible tablet, solution, tablet (short-term detoxification): Titrate total daily dose to 40 mg administered in divided doses; maintenance, stabilization should be continued for two to three days after which the dose should be gradually decreased For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services: Concentrate, dispersible tablet, solution, tablet: maintenance, 80 to 120 mg/day		
DURAGESIC (fentanyl)	Transdermal system: 12 mcg/hour 25 mcg/hour 37.5 mcg/hour 50 mcg/hour 62.5 mcg/hour 75 mcg/hour 87.5 mcg/hour 100 mcg/hour	For the 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 patients: initial, dosage is based upon oral morphine sulfate dose; maintenance, dose may be increased after three days based on the daily dose of supplemental opioid analgesics required by the patients in the second or third day of initial application.	Base dose increments on daily dosage of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12 mcg/hr increase in fentanyl dose. The majority of patients are adequately maintained with administration every 72 hours. Some patients may not achieve adequate analgesia using this dosing interval and may require systems be	Apply to intact, non-irritate skin. Apply immediately upon removal from the sealed package. The patch must not be altered (e.g., cut) in any way. Apply each patch to a different skin site after removal of the previous transdermal system.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			applied at 48 hours. An increase in dose should be evaluated before changing dosing intervals.	
EXALGO (hydromorphone)	Extended release tablets: 8 mg 12 mg 16 mg 32 mg	For the 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 patients: initial, administer a starting dose equivalent to the patient's current opioid use, taken once daily; maintenance, dosing should be individualized. For patients converting from other oral opioids; convert current opioid dose to hydromorphone dose. The recommended starting dose is 50% of the calculated estimate of daily hydromorphone requirement.	Dose may be titrated every three to four days until adequate pain relief. Discontinuation: Dose should be gradually tapered by 25 to 50% every two or three days down to a dose of 8 mg before discontinuation of therapy.	Tablets should be swallowed intact. They are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of hydromorphone.
HYSINGLA ER ZOHYDRO ER (hydrocodone bitartrate)	Extended release tablet (HYSINGLA): 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg Extended release capsule (ZOHYDRO): 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: initial or not opioid tolerant patients, ZOHYDRO 10 mg every 12 hours; HYSINGLA 20 mg once daily; opioid-tolerant patients, dose calculated by adding current opioid use and using conversion factors to determine the appropriate dose.	Titrate ZOHYDRO in increments of 10 mg every 12 hours every three to seven days and HYSINGLA in 10 to 20 mg increments every three to five days, until adequate pain relief and acceptable adverse reactions have been achieved. When discontinuing treatment, use a gradual taper of every two to four days to prevent signs and symptoms of with-	Take whole with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving the drug will result in uncontrolled delivery of hydrocodone and can lead to overdose or death. A single dose >40 mg (ZOHYDRO only), or a total daily dose of ≥80 mg (for ZOHYDRO and HYSINGLA) should

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			drawal in the physically-dependent patient. Do not abruptly discontinue.	only be prescribed in opioid-tolerant patients.
Levorphanol	Tablets: 2 mg	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: 2 mg every six to eight hours as needed, dosing may be increased to 3 mg every six to eight hours	In non-opioid tolerant patients, doses of 6 to 12 mg orally daily are not recommended as initial doses.	
NUCYNTA ER (tapentadol)	Extended release tablet: 50 mg 100 mg 150 mg 200 mg 250 mg	For the management of pain, including neuropathic pain, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: initial or not opioid-tolerant, 50 mg twice daily; maintenance, titrate to adequate analgesia.	Dose may be increased by 50 mg no more than twice daily every three days. Discontinuation: use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient.	Swallow tablets whole. Do not cut, crush, dissolve or chew due to the risk of rapid release and absorption of a potentially fatal dose.
OPANA ER (oxymorphone)	Extended release tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: initial or opioid-naïve patients, 5 mg every 12 hours; opioid-experienced patients, initial, dose calculated by adding current opioid use and using conversion factors to determine Opana ER dose.	Titrate at increments of 5 to 10 mg every 12 hours every three to seven days. Discontinuation: use a gradual downward titration of the dose every two to four days to prevent signs and symptoms of withdrawal in the physically-dependent patient.	Swallow tablets whole. Do not cut, crush, dissolve or chew due to the risk of rapid release and absorption of a potentially fatal dose.
OXYCONTIN; XTAMPZA ER (oxycodone)	Extended release tablet: (OXYCONTIN) 10 mg 15 mg§ 20 mg 30 mg§	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Discontinuation: taper the dose gradually to prevent signs and symptoms of withdrawal in the	Swallow whole. Do not cut, crush, dissolve or chew due to the risk of rapid release and absorption of a

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	40 mg 60 mg§ 80 mg Extended release capsule‡ (XTAMPZA ER): 9 mg 15 mg 20 mg 30 mg 40 mg	treatment options are inadequate: *Pediatric (aged ≥11 years) (OXYCONTIN only):* initial doses should be individualized by calculating a patient's 24-hour opioid needs. It is preferred to under-estimate dose and provide rescue medication. *Adult*: initial and not opioid-tolerant, 10 mg every 12 hours. *For adults and pediatric patients:* maintenance, titrate to adequate analgesia every one to two days. For pediatric patients, a total oxycodone dose may be increased by 25% of current daily dose; and for adults total daily dose may be increased by 25% to 50%.	physically-dependent patient. For pediatric patients, opioids should be tolerated for ≥5 days and at an equivalent oxycodone dose of ≥20 mg/day two days preceding dosing.	potentially fatal dose. Discontinue all other around-the-clock opioids when initiated.
Combination Products				
EMBEDA (morphine sulfate/ naltrexone)	Extended release capsule: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: The lowest dose should be used in opioid-naïve patients and for opioid-experienced patients the daily requirements are established using immediate-release morphine sulfate. The 100 mg/4 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established.	Dose adjustment may be done every one to two days. Discontinuation: Use a gradual downward titration of the dose every two to four days to prevent signs and symptoms of withdrawal in the physically-dependent patient.	Swallow capsules intact. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose.
XARTEMIS XR (oxycodone/ acetaminophen)	Extended release tablet: 7.5 mg/325 mg	Management of acute pain severe enough to require opioid treatment	The second dose of two tablets may be administered	Tablets should be swallowed whole. Do not break, chew,

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		and for which alternative treatment options are inadequate: two tablets (total, 15 mg oxycodone/650 mg acetaminophen) every 12 hours without regard to food.	as early as eight hours after the initial dose if patients require analgesia at that time. Subsequent doses are to be administered two tablets every 12 hours. The total daily dose of acetaminophen from all drug products should not exceed 4,000 mg.	crush, cut, dissolve, or split the tablets. Swallow with enough water to ensure complete swallowing immediately after placing in the mouth. When a patient who has been taking XARTEMIS XR regularly and may be physically dependent no longer requires therapy with XARTEMIS XR use a gradual downward titration of the dose of 50% every two to four days to prevent signs and symptoms of withdrawal. Do not stop XARTEMIS XR abruptly in patients who may be physically dependent.

*Available only as brand name KADIAN
†All AVINZA branded products have been removed from the market.
§Available only as brand name OXYCONTIN.
‡XTAMPZA ER 9 mg = 10 mg oxycodone HCl; 13.5 mg = 15 mg oxycodone HCl; 18 mg = 20 mg oxycodone HCl; 27 mg = 30 mg oxycodone HCl; 36 mg = 40 mg oxycodone HCl

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Single Entity Agents					
ARYMO ER, AVINZA, KADIAN, MS CONTIN (morphine sulfate)	Use with caution in the elderly.	Safety and efficacy in the pediatric population have not been established.	Renal dose adjustment is required.	Hepatic dose adjustment is required.	Pregnancy Category C* (ARYMO ER not categorized†) Excreted in breast milk; benefits and risks should be evaluated before use.
BUTRANS (buprenorphine)	Use with caution in the elderly.	Safety and efficacy in pediatric	Pharmaco-kinetics are not altered	Not evaluated in patients with severe hepatic	Pregnancy Category C*

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		patients ≤18 years of age have not been established.	during the course of renal failure.	impairment and should be administered with caution.	Excreted in breast milk; breastfeeding not advised.
DOLOPHINE, METHADOSE (methadone)	Use with caution in the elderly.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.	Pregnancy Category C* Excreted in breast milk; benefits and risks should be evaluated before use.
DURAGESIC (fentanyl)	Use with caution in the elderly.	Approved for use in opioid-tolerant children ≥2 years of age.	Insufficient information exists; use with caution. Avoid use in patients with severe renal impairment.	Insufficient information exists; use with caution. Avoid use in patients with severe hepatic impairment.	Pregnancy Category C* Excreted in breast milk; do not use in nursing women.
EXALGO (hydromorphone)	Elderly patients are more sensitive to adverse effects than younger patients. Closely monitor patients for respiratory and CNS depression.	Safety and efficacy in pediatric patients ≤17 years of age have not been established.	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.	Pregnancy Category C* Excreted in breast milk; breastfeeding not advised.
HYSINGLA ER ZOHYDRO ER (hydrocodone bitartrate)	Start at low doses and monitor closely. Evaluate elderly patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. Hydrocodone may cause confusion or over sedation.	Safety and efficacy have not been established. HYSINGLA: Pediatric patients are at increased risk of esophageal obstruction, dysphagia, and choking because HYSINGLA forms a viscous hydrogel and the smaller GI lumen.	ZOHYDRO: Initiate therapy with a low dose and monitor for sedation and respiratory depression. HYSINGLA: In moderate to severe impairment (including end stage renal disease), reduce the	No initial dose adjustment for patients with mild or moderate impairment. For severe impairment, reduce the HYSINGLA dose to 1/2 the usual initial dose and start ZOHYDRO at the lowest dose of 10 mg every 12 hours.	Pregnancy Category C* May precipitate fetal withdrawal; discontinue nursing or drug depending on the importance.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			initial dose to 1/2 the usual initial dose.		
levorphanol	Reduce the usual dose by at least 50% in the infirm elderly.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	No formal studies have been conducted in patients with renal impairment.	No formal studies have been conducted in patients with hepatic impairment. Use with caution due to risk of accumulation.	Pregnancy Category C* Unknown whether excreted in breast milk; discontinue drug or discontinue nursing.
NUCYNTA ER (tapentadol)	Use with caution in the elderly.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Not recommended in patients with severe renal impairment.	Moderate hepatic impairment: start with 50 mg daily; maximum 100 mg daily. Not recommended in patients with severe hepatic impairment.	Pregnancy Category C* Insufficient data whether excreted in breast milk; breastfeeding not advised.
OPANA ER (oxymorphone)	Use with caution in the elderly.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Caution should be used in patients with moderate to severe renal impairment. Start with lower doses and titrate slowly.	Caution should be used in patients with mild hepatic impairment. Start with lower doses and titrate slowly. Contra-indicated in moderate and severe hepatic impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use caution.
OXYCONTIN, XTAMPZA ER (oxycodone)	Use with caution in the elderly. In debilitated and not opioid tolerant patients, initiate dose at 1/3 to 1/2 the recommended initial dose.	OXYCONTIN: Safety and efficacy in patients aged <11 years have not been established. XTAMPZA ER: Safety and effectiveness in pediatric patients aged	In CrCL < 60 mL/min, concentrations are about 50% higher vs normal CrCL. Renal dose adjustment may be required and dose titration should follow a conservative approach.	In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.	Pregnancy Category C* Excreted in breast milk; breastfeeding not advised.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		<18 years have not been established.			
Combination Products					
EMBEDA (morphine sulfate/ naltrexone)	Use with caution in the elderly.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Renal dose adjustment may be required in severe renal impairment.	Hepatic dose adjustment may be required in severe hepatic impairment.	Pregnancy Category C* Excreted in breast milk; benefits and risks should be evaluated before use.
XARTEMIS XR (oxycodone/ acetaminophen)	No unexpected adverse reactions were seen in the elderly patients in clinical trials. Use caution in geriatric patients, since a greater sensitivity may be observed in this population.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	In patients with renal impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression	In patients with hepatic impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression.	Pregnancy Category C* Excreted in breast milk; discontinue drug or discontinue nursing.

Abbrv: CNS=central nervous system; CrCL=creatinine clearance
*Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

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 five 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).

- 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; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate extended-release 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).

Table 5. Advantages and Disadvantages of Long Acting Opioids

Drug	Advantages	Disadvantages
Single Entity Agents		
ARYMO ER (morphine)	• Abuse deterrent mechanism: anti-crush; viscous hydrogel	• No generic available
AVINZA, KADIAN, MS CONTIN (morphine)	• Generic available	
BUTRANS (buprenorphine)	• Once weekly • Transdermal	• No generic available
DOLOPHINE, METHADOSE (methadone)	• Generic available • Duration of action not contingent on formulation	• Cardiac effects
DURAGESIC (fentanyl)	• Generic available; • Administered every 72 hours • Transdermal	
EXALGO (hydromorphone)	• Generic available	
HYSINGLA ER (hydrocodone bitartrate)	• Abuse deterrent mechanism: anti-crush; viscous hydrogel • Once daily dosing vs. twice daily with ZOHYDRO ER	• No generic available • Reported difficulties swallowing (incidence: N= 11/2,476; one required medical intervention)
levorphanol	• Generic available	
NUCYNTA ER (tapentadol)	• Indicated for neuropathic pain	• No generic available
OPANA ER (oxymorphone)	• Generic available	• Both regular and crush resistant formulations are available; not determined abuse deterrent
OXYCONTIN (oxycodone)	• Abuse deterrent mechanism: anti-crush; viscous hydrogel • Indication for pediatric patients	• Twice daily dosing • Reported difficulties swallowing (incidence=not reported)

Drug	Advantages	Disadvantages
XTAMPZA ER (oxycodone)	• Abuse deterrent mechanism: anti-crush; viscous hydrogel	• No generic available • Maximum daily dose of 288 mg (equivalent to 320 mg oxycodone HCl)
ZOHYDRO ER (hydrocodone bitartrate)		• No generic available • Twice daily dosing • Not deemed abuse-deterrent
Combination Products		
EMBEDA (morphine sulfate/naltrexone)	• Abuse deterrent mechanism: If manipulated naltrexone is released • Once or twice daily dosing	• No generic available • No upper dose limit
XARTEMIS XR (oxycodone/acetaminophen)		• No generic available

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