# *Therapeutic Class Overview*
# *Long-acting Opioids*

**Therapeutic Class**

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 1.[1-19] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[20] Currently, long-acting opioids are indicated 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. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[20] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[20] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[21]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[21] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[22]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[22]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[22,23]

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. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[24]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[25]

Buprenorphine buccal film is formulated using bioerodible mucoadhesive (BEMA®) technology. BEMA® is a film formulation that consists of a water-soluble polymer that adheres to the buccal mucosa. The film dissolves over approximately 30 minutes into the buccal mucosa, leaving behind no residual film. Delivery into the buccal mucosa enhances the bioavailability of buprenorphine, as it bypasses gastrointestinal absorption and first-pass metabolism.[1]

Hysingla ER® (hydrocodone extended-release [ER]) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some ER properties after tampering. Attempts to dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[5] In addition, the tablets appear to be associated with less “drug liking”

based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of non-dependent recreational opioid users.[26]

There are currently two formulation of oxycodone ER which are considered abuse deterrent, OxyContin® and Xtampza ER®. OxyContin® utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[28-29] Xtampza ER® utilizes DETERx technology, which is designed to provide adequate pain control while maintaining its drug release profile after being subjected to common methods of manipulation, including chewing and crushing.[30,31]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[32] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third ER opioid analgesic to obtain this designation and the first among the morphine ER products.[33] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[18] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[33]

**Table 1. Current Medications Available in the Therapeutic Class**[1-19]

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Single-Entity Agents** | | | |
| Buprenorphine (Belbuca®, Butrans®) | The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. | Buccal Film (Belbuca®):<br>75 µg<br>150 µg<br>300 µg<br>450 µg<br>600 µg<br>750 µg<br>900 µg<br><br>Transdermal patch:<br>5 µg/hour<br>7.5 µg/hour<br>10 µg/hour<br>15 µg/hour<br>20 µg/hour | - |
| Fentanyl (Duragesic®*) | The 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.† | Transdermal system‡:<br>12 µg/hour§<br>25 µg/hour<br>37.5 µg/hour<br>50 µg/hour<br>62.5 µg/hour<br>75 µg/hour<br>87.5 µg/hour<br>100 µg/hour | ✔ |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Hydrocodone (Hysingla ER®, Zohydro ER®) | The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. | Capsule, extended release (Zohydro ER®):<br>10 mg<br>15 mg<br>20 mg<br>30 mg<br>40 mg<br>50 mg‡<br><br>Tablet, extended release (Hysingla ER®):<br>20 mg<br>30 mg<br>40 mg<br>60 mg<br>80 mg‡<br>100 mg‡<br>120 mg‡ | - |
| Hydromorphone (Exalgo®*) | The 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.† | Tablet, extended release:<br>8 mg‡<br>12 mg‡<br>16 mg‡<br>32 mg‡ | ✔ |
| Methadone (Dolophine®*, Methadose®*) | Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet).<br><br>For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet).<br><br>For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet). | Concentrate solution, oral (sugar-free available):<br>10 mg/mL<br><br>Solution, oral:<br>5 mg/5 mL<br>10 mg/5 mL<br><br>Tablet, extended release:<br>5 mg<br>10 mg<br><br>Tablet for oral suspension:<br>40 mg | ✔ |
| Morphine sulfate (Avinza®*, Kadian®*, 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 (biphasic capsule, capsule, tablet). | Capsule, biphasic extended release:<br>30 mg<br>45 mg<br>60 mg<br>75 mg<br>90 mg‡<br>120 mg‡ | ✔ |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | | Capsule, extended release:<br>10 mg<br>20 mg<br>30 mg<br>40 mg<br>50 mg<br>60 mg<br>80 mg<br>100 mg‡<br>200 mg‡<br><br>Tablet, extended release:<br>15 mg<br>30 mg<br>60 mg<br>100 mg‡<br>200 mg‡ | |
| Oxycodone (OxyContin®*, Xtampza ER®) | 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 adults (all formulations) and in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (extended release tablet).¶ | Capsule, extended release (Xtampza ER®):<br>9 mg<br>13.5 mg<br>18 mg<br>27 mg<br>36 mg<br><br>Tablet, extended release (OxyContin®):<br>10 mg<br>15 mg<br>20 mg<br>30 mg<br>40 mg<br>60 mg‡<br>80 mg‡ | ✔ # |
| Oxymorphone (Opana® ER*) | 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. | Tablet extended release:<br>5 mg<br>7.5 mg<br>10 mg<br>15 mg<br>20 mg<br>30 mg<br>40 mg | ✔ |
| Tapentadol (Nucynta ER®) | Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.<br><br>Neuropathic pain associated with diabetic | Tablet, extended release:<br>50 mg<br>100 mg<br>150 mg<br>200 mg | - |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | 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. | 250 mg | |
| **Combination Products** | | | |
| Morphine sulfate/ naltrexone (Embeda®) | Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡ | Capsule, extended release:<br>20 mg/0.8 mg<br>30 mg/1.2 mg<br>50 mg/2 mg<br>60 mg/2.4 mg<br>80 mg/3.2 mg<br>100 mg/4 mg‡ | - |
| Oxycodone/ Acetaminophen (Xartemis XR®) | For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate | Biphasic tablet, extended release:<br>7.5 mg/325 mg | - |

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® or Xtampza ER® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

**Evidence-based Medicine**

- Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone ER 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[5,36]
- The efficacy and safety of buprenorphine buccal film was evaluated in three phase III clinical trials. However one of the clinical trials, which is currently not published, did not show a significant difference between buprenorphine and placebo.[1] The other two studies evaluated patients who had a diagnosis of chronic low back pain in a randomized withdrawal design. The first study evaluated opioid-naïve patients while the second study evaluated opioid-experienced patients. The double-blind treatment phase for both studies was 12 weeks.[1,38,39] In the first study, the increase in mean (standard deviation [SD]) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film (0.94 [1.85]) was significantly lower than that of patients who received placebo (1.59 [2.04]; P=0.0012).[38] The increase in mean (SD) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film was significantly less than that of placebo (0.88 [1.79] versus 1.92 [1.87], respectively; P<0.00001).[39]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[49-51]
- A trial comparing hydrocodone ER capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone ER had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly

higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (P<0.0001).[52]

- In one trial, hydromorphone ER demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[53] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[54]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[58,59]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[61] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[62]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[32]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[65]
- Oxycodone ER (OxyContin®) has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[66-68] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[69]
- The FDA-approval of oxycodone ER (Xtampza ER®) was based upon an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). Following the titration phase, 389 subjects met the study randomization criteria of adequate analgesia and acceptable tolerability and entered the randomized, double-blind maintenance phase. Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of oxycodone ER (Xtampza ER® or matching placebo. There was a significant difference in pain reduction as assessed by average pain intensity favoring the oxycodone ER group when compared to placebo from randomization baseline to week 12 (0.29 vs. 1.85 ;P<0.0001).[71]
- Oxymorphone ER has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain. [72,73] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER from morphine sulfate or oxycodone ER. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[72] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[74]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol ER compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[76] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol ER and oxycodone ER relative to placebo (P<0.001).[77] Schwartz et al evaluated tapentadol ER among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12

was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[75]

- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; P<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (P=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (P<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (P<0.0001).[83]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[84]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
    - The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole.[86-98]
    - Guidelines published by Centers for Disease Control and Prevention's (CDC) opioid use in the management of chronic pain recommend physicians start with immediate-release (IR) opioids and reserve ER formulations for severe, continuous pain that IR opioids cannot treat.[86]
    - Physicians should prescribe the lowest effective dose and carefully reassess benefits and risks when considering a dose of ≥50 morphine milligram equivalents (MME) while avoiding increasing opioid doses to ≥90 MME unless justified.[86]
    - Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness. ER products are generally similar and selection should be based on clinical or patient-specific factors.[87]

- Other Key Facts:[1-19]
    - Products currently available as a generic include fentanyl patches, hydromorphone ER tablets, methadone (all formulations), morphine ER (all formulations), oxycodone ER tablets and oxymorphone ER tablets.
    - There are currently several abuse deterrent ER opioids approved by the FDA. These include buprenorphine sublingual film (Belbuca®), oxycodone ER (OxyContin®, Xtampza ER®) and hydrocodone ER (Zohydro ER®, Hysingla ER®) as well as morphine sulfate/naltrexone (Embeda®).
    - Oxymorphone ER (Opana ER®) and hydromorphone ER (Exalgo®) have also been formulated with abuse deterrent properties, however they are classified as abuse deterrent by the FDA.
    - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
    - Only fentanyl transdermal system (age 2 to 17 years) and oxycodone ER tablets (age 11 and older) are approved for use in children
    - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
    - Oxymorphone is contraindicated in severe hepatic disease.

- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Frequency of dosing varies by agent:
  - Buprenorphine patch: once every seven days
  - Fentanyl transdermal system: once every 72 hours
  - Hydromorphone ER (Exalgo®), hydrocodone ER (Hysingla ER®) and morphine ER (Avinza®): once daily
  - Morphine ER (Kadian®) and morphine/naltrexone (Embeda®): once or twice daily
  - Morphine ER (MS Contin®) and all methadone formulations: twice or three times daily
  - All remaining long-acting agents: twice daily
- Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose.
  - Avinza® (morphine): max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]
  - Xartemis XR (oxycodone/acetaminophen): max dose is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day[19]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18]
  - Morphine ER capsules (Avinza®, Kadian®), morphine/naltrexone capsules (Embeda®) and oxycodone ER capsules (Xtampza ER®) can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,15,18]
  - Kadian® pellets can also be placed in water and used through a gastrostomy tube.
  - Xtampza® may be opened and administered through a gastrostomy or nasogastric tube.
  - Avinza®, Kadian®, and Embeda® pellets should not be used thorough a nasogastric tube.

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