
Therapeutic Class Overview

Short-acting Opioids

Therapeutic Class

- **Overview/Summary:** Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment, disability, psychological distress and sleep deprivation. Pain can be categorized as being either nociceptive or neuropathic, and the treatments for each are specific. Nociceptive pain is caused by damage to tissues 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.¹ Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. 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.²

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.³⁻²¹ These 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.³ Unlike other analgesic classes, opioids have well-accepted equianalgesic doses, which allows clinicians to convert between agents and between routes of administration. Pure opioid agonists do not have a ceiling effect as other analgesics do; therefore, additional analgesia may be obtained by increasing the opioid dose. Close monitoring after an opioid conversion or dosage change is required to evaluate the need for further dosage adjustments.² Combination therapy has been widely used for the clinical management of acute pain; by combining two agents with different mechanisms of action, the combination therapy provides additive analgesic effects while reducing the risk of adverse effects. Moreover, combination therapies overcome the “ceiling effects” of their individual components. Opioids are found in combination products along with aspirin, acetaminophen, ibuprofen, caffeine and butalbital.³

In patients who experience chronic pain, it is recommended that once a stable short-acting (immediate release) opioid dose is reached, the patient then be converted to a long-acting agent.² The long-acting opioid should be used on a scheduled basis, with as-needed short-acting medications prescribed for breakthrough pain. Patients who routinely require frequent breakthrough doses within a dosing interval may benefit from an increase in their scheduled medication. Due to their known potential for abuse, opioids are classified as controlled substances.³⁻²¹ It is important to recognize that tolerance and physical dependence are potential and common physiologic changes that occur in most patients who receive opioids for a sustained amount of time. Tolerance is defined as the need for increased dosage to produce the same effect, or a reduced effect is observed with a constant dose. Physical dependence occurs when the body becomes accustomed to receiving opioids due to neuroadaptation. Psychological dependence, or addiction, indicates that the patient is using an agent for its psychiatric effects. This occurrence is not a characteristic of the drug class alone, but is a combined effect of biochemical, societal and psychological factors affecting the patient.²²

Table 1. Current Medications Available in Therapeutic Class⁴⁻²¹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Codeine	Treatment of mild to moderate pain	Injection (phosphate): 15 mg/mL 30 mg/mL Oral solution (sulfate): 30 mg/5 mL Tablet (sulfate): 15 mg 30 mg 60 mg	✓
Hydromorphone (Dilaudid ^{®*})	Treatment of moderate to severe pain and treatment of postoperative pain	Injection, powder for reconstitution: 250 mg Injection, solution: 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL Oral liquid: 1 mg/mL Suppository: 3 mg Tablet: 2 mg 4 mg 8 mg	✓
Levorphanol (Levo-dromoran ^{®*})	Treatment of moderate to severe pain	Tablet: 2 mg	✓
Meperidine (Demerol ^{®*} , Meperitab ^{®*})	Treatment of moderate to severe pain	Injection: 10 mg/mL 25 mg/mL 50 mg/mL 75 mg/mL 100 mg/mL Oral solution: 50 mg/5 mL Tablet: 50 mg 100 mg	✓
Morphine (MSIR ^{®*} , Roxanol ^{®*})	Treatment of moderate to severe pain	Injection: 0.5 mg/mL 1 mg/mL 2 mg/mL	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL 25 mg/mL 50 mg/mL Oral solution: 10 mg/5 mL 20 mg/5 mL 20 mg/mL Suppository: 5 mg 10 mg 20 mg 30 mg Tablet: 15 mg 30 mg	
Oxycodone (Oxecta [®] , Oxy IR [®] , Oxydose [®] , OxyFast [®] , Roxicodone [®])	Treatment of moderate to severe pain	Capsules: 5 mg Oral solution: 5 mg/5 mL 20 mg/mL Tablets: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg	✓
Oxymorphone (Opana [®])	Treatment of moderate to severe pain	Injection: 1 mg/mL Tablet: 5 mg 10 mg	✓
Tapentadol (Nucynta [®])	Treatment of moderate to severe pain	Tablet: 50 mg 75 mg 100 mg	-
Combination Products			
Codeine/acetaminophen (Capital [®] with Codeine, Cocet [®] ,	Treatment of mild to moderate pain and treatment of moderate to severe pain	Oral solution: 12 mg/120 mg per 5 mL Tablet:	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Tylenol [®] with Codeine*, Vopac [®])		15 mg/300 mg 30 mg/300 mg 60 mg/300 mg 30 mg/650 mg	
Codeine/acetaminophen/caffeine/butalbital (Fioricet [®] with Codeine*)	Treatment of tension headache	Capsule: 30 mg/325 mg/40 mg/50 mg	✓
Codeine/aspirin/caffeine/butalbital (Fiorinal [®] with Codeine*)	Treatment of tension headache	Capsule: 30 mg/325 mg/40 mg/50 mg	✓
Dihydrocodeine/acetaminophen/caffeine (Panlor [®] DC*, Panlor [®] SS*, Trezix [®] , ZerLor [®] *)	Treatment of moderate to severe pain	Capsule: 16 mg/356.4 mg/30 mg	✓
Dihydrocodeine/aspirin/caffeine (Synalgos [®] DC)	Treatment of moderate to severe pain	Capsule: 16 mg/356.4 mg/30 mg Tablet: 32 mg/712.8 mg/60 mg	-
Hydrocodone/acetaminophen (Anexsia [®] *, Bancap-HC [®] *, Co-Gesic [®] *, Hydrocet [®] *, Hydrogesic [®] *, Hycet [®] *, Lorcet [®] *, Lortab [®] *, Margesic [®] *, Maxidone [®] *, Norco [®] *, Polygesic [®] *, Stagesic [®] *, Vanacet [®] *, Vicodin [®] *, Vicodin [®] HP*, Xodol [®] *, Zamiset [®] *, Zolvit [®] , Zydone [®])	Treatment of moderate to severe pain	Capsule: 5 mg/500 mg Oral solution: 10 mg/300 mg per 15 mL 7.5 mg/325 mg per 15 mL 10 mg/325 mg per 15 mL 7.5 mg/500 mg per 15 mL 10 mg/500 mg per 15 mL Tablet: 5 mg/300 mg 7.5 mg/300 mg 10 mg/300 mg 5 mg/325 mg 7.5 mg/325 mg 10 mg/325 mg 5 mg/400 mg 7.5 mg/400 mg 10 mg/400 mg 2.5 mg/500 mg 5 mg/500 mg 7.5 mg/500 mg 10 mg/500 mg 7.5 mg/650 mg 10 mg/650 mg 10 mg/660 mg 7.5 mg/750 mg	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		10 mg/750 mg	
Hydrocodone/ ibuprofen (Ibudone ^{®*} , Reprexain ^{®*} , Vicoprofen ^{®*})	Short-term treatment of acute pain	Tablet: 2.5 mg/200 mg 5 mg/200 mg 7.5 mg/200 mg 10 mg/200 mg	✓
Oxycodone/ acetaminophen (Endocet ^{®*} , Lynox [®] , Magnacet [®] , Percocet ^{®*} , Tylox ^{®*} , Xolox [®])	Treatment of moderate to severe pain	Capsule: 5 mg/500 mg Oral solution: 5 mg/325 mg per 5 mL Tablet: 5 mg/300 mg 7.5 mg/300 mg 10 mg/300 mg 2.5 mg/325 mg 5 mg/325 mg 7.5 mg/325 mg 10 mg/325 mg 5 mg/400 mg 7.5 mg/400 mg 10 mg/400 mg 5 mg/500 mg 7.5 mg/500 mg 10 mg/500 mg 10 mg/650 mg	✓
Oxycodone/aspirin (Endodan ^{®*} , Percodan ^{®*})	Treatment of moderate to severe pain	Tablet: 4.8355 mg/325 mg	✓
Oxycodone/ ibuprofen (Combunox ^{®*})	Treatment of moderate to severe pain and short-term treatment of acute pain	Tablet: 5 mg/400 mg	✓

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Systematic reviews and meta-analyses have demonstrated similar safety and level of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of chronic cancer, chronic non-cancer and acute pain.²³⁻²⁸
- Meperidine appears to have comparable analgesic effect as morphine and oxycodone but may be associated with higher incidence of adverse events.^{25,29}
- In one double-blind, randomized controlled trial involving patients who underwent total hip or knee replacement surgery, patients were significantly more likely to achieve a pain relief of at least 50% following administration of oxymorphone 10 or 20 mg compared to placebo, but not with oxymorphone 30 mg or oxycodone 10 mg. A direct comparison between oxymorphone and oxycodone was not performed.³⁰
- Several placebo- and active-controlled, randomized studies have demonstrated immediate-release tapentadol to be noninferior to oxycodone in the management of postoperative pain and pain associated with degenerative joint disease, low back pain or osteoarthritis.³¹⁻³⁴ Results from these studies also demonstrate that therapy with tapentadol may have a more favorable adverse effect

profile, specifically in terms of the incidence of gastrointestinal adverse events, compared to immediate-release oxycodone.³⁵⁻³⁷

- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of acute pain.³⁸⁻⁴⁰ One randomized controlled trial also showed similar efficacy between codeine/acetaminophen and hydrocodone/acetaminophen in the management of chronic cancer pain.⁴¹ A randomized controlled trial showed that oxycodone/ibuprofen may provide greater total pain relief than hydrocodone/acetaminophen or oxycodone/acetaminophen in pediatric patients who underwent dental procedure.⁴²
- Head-to-head trials involving codeine, levorphanol, butalbital-containing products, dihydrocodeine-containing products or oxycodone/aspirin are not available.
- A meta-analysis of 35 double-blind, randomized controlled trials showed that a single dose of codeine 60 mg produced significantly greater pain relief compared to placebo in patients with postoperative pain.⁴³ When compared to ibuprofen and acetaminophen in children with acute musculoskeletal injury, codeine 1 mg/kg achieved a level of analgesia that was comparable to acetaminophen 15 mg/kg but less than that of ibuprofen 10 mg/kg.⁴⁴
- An observational study demonstrated that levorphanol was shown to be effective in relieving chronic non-cancer pain in patients whose pain was not adequately relieved by other strong opioids.⁴⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The World Health Organization suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine.^{46,47}
 - Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids.^{46,47}
 - Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids.^{46,47}
 - Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids.^{46,47}
 - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with “around-the-clock” extended release or long acting formulation opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain.^{46,47}
 - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.^{46,47}
 - Rescue doses of short-acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals.^{46,47}
 - Clinicians may consider using a written chronic opioid therapy management plan to document patient and clinician responsibilities and expectations and assist in patient education.^{46,47}
- Other Key Facts:
 - Generic products are available for all products with the exception of tapentadol (Nucynta[®]) and dihydrocodeine/aspirin/caffeine (Synalgos[®] DC).³

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Therapeutic Class Overview Long-acting Opioids

Therapeutic Class

- Overview/Summary:** Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment, disability, psychological distress and sleep deprivation. Pain can be categorized as being either nociceptive or neuropathic, and the treatments for each are specific. Nociceptive pain is caused by damage to tissues 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.¹ 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.²

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.³⁻¹⁹ These 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.^{2,20} The long-acting opioids 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.³ Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.³

Oxycontin[®] (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, but oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.²¹ The Food and Drug Administration (FDA) approved a new Oxycontin[®] formulation in April of 2010 that was designed to discourage misuse and abuse. The reformulated Oxycontin[®] is intended to prevent the medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may result in less risk of overdose due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by ingesting larger than recommended doses. The manufacturer is required to conduct a postmarketing study evaluating the extent to which the new formulation reduces abuse and misuse.²² Similarly, a new, crush-resistant formulation of Opana ER[®] (oxymorphone extended-release) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose or addiction.²³

Table 1. Current Medications Available in Therapeutic Class⁴⁻¹⁹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine	The management of moderate to severe	Transdermal	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Butrans [®])	chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	system: 5 µg/hour 10 µg/hour 20 µg/hour	
Fentanyl (Duragesic ^{®*})	The management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids	Transdermal system: [‡] 12 µg/hour 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	✓
Hydromorphone (Exalgo [®])	The management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time	Extended release tablets: [‡] 8 mg 12 mg 16 mg	-
Methadone (Dolophine ^{®*} , Methadose ^{®*})	Treatment of moderate to severe pain not responsive to non-narcotic analgesics, for detoxification treatment of opioid addiction (heroin or other morphine-like drugs) and for maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services	Concentrate (sugar-free available): 10 mg/mL Dispersible tablet: 40 mg Solution: 5 mg/5 mL 10 mg/5 mL Tablet: 5 mg 10 mg	✓
Morphine sulfate (Avinza [®] , Kadian ^{®*} , MS Contin ^{®*} , Oramorph SR [®])	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (Avinza [®]), for the relief of moderate to severe pain requiring continuous, around the clock opioid therapy for an extended period of time (Kadian [®] and MS Contin [®]) and for the relief of pain in patients who require opioid analgesics for more than a few days (Oramorph SR [®])	Extended release capsules: 10 mg [§] 20 mg [§] 30 mg 45 mg [§] 50 mg [§] 60 mg ^{‡,¶} 75 mg 80 mg [§] 90 mg ^{‡,} 100 mg ^{‡,§} 120 mg ^{‡,} 200 mg ^{‡,§} Extended release tablets: 15 mg 30 mg 60 mg 100 mg [§]	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		200 mg [§] Tablet (Oramorph SR [®]) 15 mg 30 mg 60 mg 100 mg	
Oxycodone (Oxycontin ^{®*})	For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time	Extended release tablet: 10 mg 15 mg [#] 20 mg 30 mg [#] 40 mg 60 mg ^{†,#} 80 mg [†]	✓ [†]
Oxymorphone (Opana [®] ER)	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time	Extended release tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	-
Tapentadol (Nucynta ER [®])	For the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time and treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults	Extended release tablet: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/naltrexone	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time	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 [†]	-

*Generic is available in at least one dosage form or strength.

†Generic availability is sporadic and does not include all strengths.

‡For use in opioid-tolerant patients only.

§Kadian[®] only.

||Avinza[®] only.

¶Avinza[®] 60 mg extended-release capsules are for use in opioid-tolerant patients only.

#Oxycontin[®] only.

Evidence-based Medicine

- In one trial, treatment with the buprenorphine transdermal system resulted in significant improvement in the average pain score over the last 24 hours at week 12 compared to treatment with buprenorphine 5 µg/hour ($P < 0.001$ for both). In a second trial, treatment with either 10 or 20 µg/hour

of buprenorphine transdermal system resulted in a treatment difference in favor of buprenorphine (95% confidence interval [CI], -1.02 to -0.14; $P=0.01$) compared to placebo. Two other trials failed to show efficacy for buprenorphine transdermal system in patients with low back pain and osteoarthritis, respectively against oxycodone/acetaminophen and oxycodone immediate-release. In another trial, treatment with either buprenorphine transdermal system 20 $\mu\text{g}/\text{hour}$ or oxycodone immediate-release was compared to treatment with buprenorphine transdermal system 5 $\mu\text{g}/\text{hour}$ in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours scores from baseline was greater in the buprenorphine transdermal system 20 $\mu\text{g}/\text{hour}$ and oxycodone immediate-release treatment groups as compared to the buprenorphine transdermal system 5 $\mu\text{g}/\text{hour}$ group, however the difference was not significant (P values not reported).^{4,24}

- 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.²⁵⁻²⁷
- In one trial, hydromorphone extended-release 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.²⁸ In a 2007 noninferiority analysis of a hydromorphone extended-release compared to oxycodone extended-release, it was demonstrated that the two agents provided similar pain relief in the management of osteoarthritic pain.²⁹
- 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.^{30,31}
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza[®] (morphine sulfate extended-release) and MS Contin[®] (morphine sulfate controlled-release) significantly reduced pain from baseline ($P\leq 0.05$ for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each of the treatments significantly improved certain sleep parameters compared to placebo.³² In another cross-over 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 during the morphine sulfate phase ($P<0.001$).³³
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.³⁴
- Oxycodone controlled-release has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.³⁵⁻³⁷ For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release ($P=0.01$), and the incidence of nausea and sedation were similar between treatments.³⁸
- Oxymorphone extended-release has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain.^{39,40} The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release from morphine sulfate or oxycodone controlled-release. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.⁴⁰ In another trial, oxymorphone extended-release demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.⁴¹
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol extended-release 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 controlled-release 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).⁴² 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 extended-release and oxycodone controlled-release relative to placebo ($P<0.001$).⁴³

Schwartz et al evaluated tapentadol extended-release 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 extended-release group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; $P < 0.001$).⁴⁴

- 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%).⁴⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine.^{46,47}
 - Opioid selection, initial dosing, and titration should be individualized according to the patient’s health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.⁴⁷
 - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulation opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain.⁴⁶
 - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.^{46,47}
 - In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.⁴⁶
 - Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.⁴⁶
 - Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.⁴⁶
 - In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.^{46,47}
- Other Key Facts:
 - All of the long-acting opioids are classified as Schedule II controlled substances by the Food and Drug Administration (FDA), with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance.⁴⁻¹⁹ Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven-day transdermal opioid approved by the FDA.⁵
 - On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program will require 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.⁴⁸
 - 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.⁴⁸

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