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 the Therapeutic Class[4-19]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	Transdermal 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	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		30 mg 60 mg 100 mg§ 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 significantly improved the average pain score over 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 favoring 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 µg/hour or oxycodone immediate-release was compared to treatment with buprenorphine transdermal system 5 µg/hour in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours was greater in the buprenorphine transdermal system 20 µg/hour and oxycodone immediate-release treatment groups compared to the buprenorphine transdermal system 5 µg/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 noninferiority analysis of a hydromorphone extended-release compared to oxycodone extended-release, 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*≤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.[32] 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).[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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Therapeutic Class Review
Long-acting Opioids

Overview/Summary

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.[1]

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.[1] 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.[2]

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.[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.

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.[2,3]

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.[4] Specific Food and Drug Administration (FDA)-approved indications for the individual agents are outlined in Table 2. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

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.[5] 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.[6]

Even though OxyContin® (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[7] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[8] Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) 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.[9] Embeda® (morphine sulfate/naltrexone) is the only combination long-acting opioid currently available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains extended-release morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[10,11] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, Embeda® will be available as soon as possible once the stability issue is resolved.[12] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[13]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine (Butrans®)	Opiate partial agonist	-
Fentanyl (Duragesic®*)	Opioid agonist	✔
Hydromorphone (Exalgo®)	Opioid agonist	-

Generic Name (Trade name)	Medication Class	Generic Availability
Methadone (Dolophine®*, Methadose®*)	Opioid agonist	✔
Morphine sulfate (Avinza®, Kadian®*, MS Contin®*)	Opioid agonist	✔
Oxycodone (OxyContin®*)	Opioid agonist	✔ †
Oxymorphone (Opana® ER)	Opioid agonist	-
Tapentadol (Nucynta ER®)	Opioid agonist	-
Combination Products		
Morphine sulfate/naltrexone (Embeda®)	Opioid agonist/opioid antagonist	-

*Generic is available in at least one dosage form or strength.
†Generic availability is sporadic and does not include all strengths.

Indications

Table 2. Food and Drug Administration Approved Indications[5,9,14-26]

Generic Name	Indications	
Single Entity Agents		
Buprenorphine	The management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	
Fentanyl	The management of persistent, moderate to severe chronic pain in opioid-tolerant patients two years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.	
Hydromorphone	The management of moderate to severe pain in opioid tolerant patients (taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid, for a week or longer) requiring continuous, around-the-clock opioid analgesia for an extended period of time	
Methadone	For the treatment of moderate to severe pain not responsive to non-narcotic analgesics (solution, tablet) For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate, dispersible tablet, solution, tablet) 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)	
Morphine sulfate	Avinza®	The management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
	Kadian®, MS Contin®	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
	Oramorph SR®	For the relief of pain in patients who require opioid analgesics for more than a few days
Oxycodone	For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time	
Oxymorphone	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time	
Tapentadol	For the management of moderate to severe chronic pain in adults, and neuropathic pain associated with diabetic peripheral neuropathy in adults, both when a continuous, around-the-clock opioid analgesic is needed for an extended period of time	

Generic Name	Indications
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

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). Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program. Regulatory exceptions to the general requirement for certification to provide opioid agonist treatment include the following the situations: during inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07[c], to facilitate the treatment of the primary admitting diagnosis), and during an emergency period of no longer than three days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07[b]).[15,19-21]

Pharmacokinetics

Table 3. Pharmacokinetics[28]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Buprenorphine	15	27	Norbuprenorphine	26
Fentanyl	92	75 as metabolites; <7 to 10 as unchanged	None reported	20 to 27
Hydromorphone	24	75; 7 as unchanged	Unknown	11
Methadone	36 to 100	Not specified	None reported	7 to 59
Morphine sulfate	<40	90; 2 to 12 unchanged	Morphine-6-glucuronide	1.5 to 15.0
Oxycodone	60 to 87	19 unchanged; 50 conjugated oxycodone; 14 or less conjugated oxymorphone	Noroxycodone, oxymorphone	4.5 to 8.0
Oxymorphone	10	<1 unchanged; approximately 39 major metabolites	None reported	7.25 to 9.43
Tapentadol	32	99; 70 conjugated; 3 unchanged drug	None reported	4 to 5
Combination Products				
Morphine sulfate/ naltrexone	<40 (morphine sulfate); highly variable (naltrexone)	90; 2 to 12 unchanged (morphine sulfate and metabolites); not reported (naltrexone)	Morphine-6-glucuronide (morphine sulfate); 6-β-naltrexol (naltrexone)	29

Clinical Trials

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 noncancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain is available. Clinical trials demonstrating the effectiveness and safety of the long-acting opioids are outlined in Table 4. 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 adverse event profiles and associated improvements in quality of life or sleep domains.[29-69]

Food and Drug Administration (FDA) approval of buprenorphine transdermal system was based on four unpublished, 12-week double-blind clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. The description of these trials has been obtained from the prescribing information and the manufacturer product dossier. Two of these four trials demonstrated efficacy in patients with chronic low back pain. In one trial (N=1,160), treatment with buprenorphine transdermal system resulted in significant treatment differences in the average pain score over the last 24 hours at week 12 in favor of transdermal buprenorphine 20 µg/hr and oxycodone immediate-release compared to buprenorphine 5 µg/hr (*P*<0.001 for both). In the second trial (N=1,024), treatment with either 10 or 20 µg/hr 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. In the first trial (N=134), treatment with either buprenorphine 5, 10, or 20 µg/hr or a combination of oxycodone and acetaminophen was compared to placebo in patients with low back pain. Differences in the mean change from baseline for "pain on average" and "pain right now", the two primary endpoints, between the buprenorphine transdermal system and the placebo groups were significant for the maintenance period (*P*=0.04 and *P*=0.045, respectively). However, differences between placebo and oxycodone and acetaminophen combination, the active control, were not significant (*P* value not reported). When the trial was evaluated using pain scores at week 12 (an analysis preferred by the FDA), the buprenorphine transdermal system treatment group did not yield a significant difference from placebo (*P* value not reported). In another trial (N=418), treatment with either buprenorphine transdermal system 20 µg/hr or oxycodone immediate-release was compared to buprenorphine transdermal system 5 µg/hr in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours scores from baseline, the primary endpoint, was greater in the buprenorphine transdermal system 20 µg/hr and oxycodone immediate-release treatment groups as compared to the buprenorphine transdermal system 5 µg/hr group, but did not achieve significance (*P* values not reported). Furthermore, none of the results of the sensitivity analyses were significant, supporting the conclusion that this trial lacked assay sensitivity and is a failed trial.[5,70]

Two smaller, double-blind, crossover trials compared buprenorphine transdermal system to placebo in patients with chronic low back pain. In both trials, patients were randomized to receive buprenorphine transdermal system or placebo for four weeks and crossed over to alternate treatments at the end of week 4 for a total of eight weeks. In the first trial (N=79), the treatment difference between buprenorphine 5 to 20 µg/hour and placebo in the average pain score over the last week at the end of each treatment phase, the primary endpoint, was small but statistically significant when reported using a five-point ordinal scale (*P*=0.0226). When the same endpoint was reported using a visual analogue scale, there was no statistically significant difference between the two treatment groups (*P*=0.0919).[29] In the second trial (N=78), the difference in average pain score over the last 24 hours for buprenorphine 10 to 40 µg/hour was significantly lower compared to placebo when reported using both the visual analogue scale and the five-point ordinal scale (*P*=0.005 and *P*=0.016, respectively).[30]

In total, 18 clinical pharmacology trials and 15 chronic pain trials have been completed with buprenorphine transdermal system. Overall, there is a consistent pattern of pain reduction or continuing stable pain control in chronic, non-cancer, non-neuropathic pain models, supporting the analgesic efficacy of buprenorphine transdermal system.[70]

Fentanyl transdermal systems have demonstrated efficacy in the treatment of neuropathic pain, moderate to severe chronic pain due to nonmalignant and malignant disease, and moderate to severe osteoarthritis pain in both open-label and placebo-controlled trials.[33-37] The effectiveness of fentanyl in relieving pain also 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.[38-40]

The available published clinical trial information demonstrating the efficacy and safety of hydromorphone extended-release is currently limited. In a placebo-controlled trial, the medication demonstrated superior efficacy in the treatment of lower back pain with regards to reducing pain intensity (P<0.001) and pain scores (P<0.01). In addition, treatment was well tolerated.[41] In a 2007 noninferiority analysis of a hydromorphone extended-release formulation available only in Europe compared to oxycodone extended-release, it was demonstrated that the two agents provided similar pain relief in the management of osteoarthritic pain.[42]

Methadone has demonstrated "superior" 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.[46,47]

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≤0.05 for both). In addition, both treatments reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each of the treatments statistically improved certain sleep parameters compared to placebo, and when compared head-to-head; Avinza®, administered in the morning, significantly improved overall quality of sleep compared to MS Contin® (P value not reported).[49] In another cross-over trial, morphine sulfate (MS Contin®) was compared to treatment with fentanyl transdermal systems. In this trial, more patients preferred treatment with fentanyl (P<0.001), and reported on average, lower pain intensity scores than during the morphine sulfate phase (P<0.001).[50]

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.[12] Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[53]

Oxycodone controlled-release has demonstrated "superior" efficacy over placebo for the treatment of neuropathic pain and chronic refractory neck pain.[54-56] 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.[57]

Oxymorphone extended-release has established safety and efficacy in the management of cancer pain.[59,60] Specifically, the agent produced comparable mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain. Patients were initially stabilized on morphine sulfate or oxycodone controlled-release and then switched to treatment with oxymorphone extended-release. The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release. No significant changes were observed in mean visual analog pain scores, quality of life domains, or quality of sleep for any of the treatment groups.[60] In another placebo-controlled trial, oxymorphone extended-release demonstrated "superior" efficacy for the treatment of osteoarthritis pain.[61]

The efficacy and safety of tapentadol extended-release was evaluated in three placebo-controlled and active controlled comparator trials along with one 52-week long-term safety trial. Afilalo et al conducted a 12-week randomized, double-blind, multicenter, active- and placebo-controlled trial among adults (N=1,030) with osteoarthritis of the knee who were assigned to receive tapentadol extended-release or oxycodone controlled-release (titrated to response) or placebo. Significant pain relief was achieved with tapentadol extended-release vs placebo, with a least squares mean (LSM) difference of - 0.7 (95% confidence interval [CI], -1.04 to -0.33) at week 12 of the maintenance period compared to placebo. Comparatively, the average pain intensity rating at endpoint compared to baseline with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (LSM difference vs placebo: -0.3), but was not significantly lower at week 12 of the maintenance period (LSM of -0.3; P values not reported). The percentage of patients who achieved ≥30% reduction from

baseline in average pain intensity at week 12 of the maintenance period was not significantly different between tapentadol extended-release and placebo (43.0 vs 35.9%; *P*=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; *P*=0.002). Tapentadol extended-release resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period vs placebo (32.0 vs 24.3%; *P*=0.027) compared to treatment with oxycodone controlled-release which resulted in a reduction vs placebo of 17.3 vs 24.3% (*P*=0.023).[63] Buynak et al evaluated the efficacy of tapentadol extended-release compared to placebo in a prospective, double-blind, placebo controlled, active comparator trial with oxycodone controlled-release in adults (N=981) with moderate to severe lower back pain. Throughout the 12 week maintenance period, average pain intensity scores (primary endpoint) improved in both the tapentadol extended-release and oxycodone controlled-release groups relative to placebo. The mean change in pain intensity from baseline to week 12 was -2.9 for tapentadol extended-release and -2.1 for placebo, resulting in a LSM difference vs placebo of -0.8 (*P*<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for the tapentadol extended-release group and -2.1 for the placebo group, corresponding to a LSM difference vs. placebo of -0.7 (*P*< 0.001).[64] Schwartz et al evaluated the efficacy of tapentadol extended-release in a 12 week, randomized, double-blind, placebo-controlled, maintenance trial among adults (N=395) with at least a six month history of painful diabetic peripheral neuropathy. The LSM change in average pain intensity from the start of double-blind treatment to week 12 (primary endpoint) 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, corresponding to a LSM difference of -1.3 (95% CI, -1.70 to -0.92; *P*<0.001). The mean changes in average pain intensity scores from baseline to week 12 among those receiving tapentadol extended-release were similar regardless of gender, age (<65 years or >65 years), and history of previous opioid use. At least a 30% improvement in pain intensity was observed in 53.6% of tapentadol extended-release -treated patients and 42.2% of placebo-treated patients (*P*=0.017) at week 12; and ≥50% improvement in pain intensity was observed in 37.8% of tapentadol extended-release-treated patients and 27.6% of placebo-treated patients.[62] Wild et al evaluated the long-term safety of tapentadol extended-release in a randomized, active-controlled, open-label, trial compared to oxycodone controlled-release among adults with chronic knee or hip osteoarthritis or low back pain. The proportion of patients who completed treatment in the tapentadol extended-release and oxycodone controlled-release groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1 vs 36.8%). Overall, 85.7% of patients in the tapentadol extended-release group and 90.6% of patients in the oxycodone controlled-release group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), vomiting (7.0 vs 13.5%), and pruritis (5.4 vs 10.3%) were lower in the tapentadol extended-release group than in the oxycodone controlled-release group, respectively. There were no clinically-relevant, treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol extended-release group and 36.8% of patients in the oxycodone controlled-release group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol extended-release group than in the oxycodone controlled-release group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol extended-release and oxycodone controlled-release groups (5.5 vs 4.0%, respectively).[65]

Methadone is the only long-acting narcotic that is FDA-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%).[69]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moderate to Severe Pain				
Gordon et al[29] Buprenorphine transdermal system 5, 10 or 20 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Codeine/ acetaminophen 30/300 mg one or	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	N=79 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last week on a five-point pain intensity scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 mm (no pain) to 100 mm (excruciating pain) Secondary: PDI, Pain and Sleep Questionnaire, level of activity, SF-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Primary: In the ITT analysis, the average pain score reported by patients using the five-point scale at the last week of each treatment phase was 1.8±0.6 for buprenorphine and 2.0±0.7 for placebo (*P*=0.0226). When the pain score was reported using the VAS, the score was 40.2±20.2 for buprenorphine and 44.4±20.2 for placebo (*P*=0.0919). Secondary: In the per-protocol analysis, when buprenorphine was compared to placebo at the last week of each treatment phase, there were no treatment differences with regard to improvement in any of the subscales or the total score of the PDI (results not reported; *P*=0.4860), the Pain and Sleep Questionnaire (172.4±122.8 vs 178.2±112.6; *P* value not reported), the level of activity (43.8±23.0 vs 43.9±23.7; *P*=0.9355) or the SF-36 (results not reported; *P* value not reported). There was no difference between the two treatment groups in patient- and investigator-rated treatment effectiveness at the end of each treatment phase. The patient-rated scores were 1.3±1.1 and 0.9±1.0 for buprenorphine and placebo, respectively (*P*=0.1782), while the investigator-rated scores were 1.2±1.0 and 0.9±1.0, respectively (*P*=0.1221). Forty-three percent of patients preferred the buprenorphine treatment phase, 38% of patients preferred the placebo phase and 19% of patients had no preference (*P*=0.6473). Similarly, 43% of investigators preferred buprenorphine for their patients, 36% of investigators preferred placebo and 21% of investigators had no preference (*P*=0.5371). More patients reported drowsiness with buprenorphine compared to placebo (*P*=0.0066). More patients reported at least one adverse event during treatment with buprenorphine compared to placebo (*P*=0.0143). The most commonly reported adverse events include nausea, somnolence and application site reactions. ES Phase: Forty-two of 51 patients (82%) who completed the DB phase continued to receive OL buprenorphine treatment. The average pain intensity score over the past 24 hours measured by VAS were significantly lower at the end of the ES phase compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
two tablets every 4 to 6 hours as needed was allowed.				DB phase (13.2±20.2 vs 39.5±19.1; *P*=0.0001). There were no differences between the ES and DB phases in the average pain score over the last week and all other study endpoints, with the exception of the standardized physical component of the SF-36, which was significantly lower in the ES phase compared to the DB phase (*P*=0.0226).
Gordon et al[30] Buprenorphine transdermal system 10 to 40 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before randomization and antidepressants or anticonvulsants at a stable dose for 8 weeks before randomization were permitted. Supplemental analgesic medication was	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with moderate to severe chronic low back pain for >3 months, requiring one or more tablet of opioid analgesics daily	N=78 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last 24 hours on a five-point pain intensity scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 (no pain) to 100 mm (excruciating pain) Secondary: Pain and Sleep Questionnaire, PDI, SF-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Primary: In the ITT analysis, buprenorphine was associated with a lower average pain score over the last 24 hours compared to placebo. When reported using VAS, the pain score was 44.6±21.4 for buprenorphine and 52.4±24.0 for placebo (*P*=0.005). The score reported using the five-point scale was 2.0±0.7 and 2.2±0.8 for buprenorphine and placebo, respectively (*P*=0.016). Secondary: The overall score of the Pain and Sleep Questionnaire was significantly lower for buprenorphine compared to placebo (117.6±125.5 vs 232.9±131.9; *P*=0.027). No significant differences were noted between the two treatment groups with regard to the PDI and SF-36 (*P* value not reported for all endpoints). The treatment effectiveness of buprenorphine was rated significantly higher than placebo by patients (1.8±1.1 vs 1.0±1.1; *P*=0.016) and investigators (1.8±1.1 vs 1.0±1.1; *P*=0.013). Sixty-six percent of patients preferred the buprenorphine treatment phase, 24% of patients preferred the placebo phase and 10% of patients had no preference (*P*=0.001). Similarly, 60% of investigators preferred the buprenorphine treatment phase for their patients, 28% of investigators preferred the placebo phase and 12% of investigators had no preference (*P*=0.008). Significantly more patients in the buprenorphine group reported adverse events compared to patients in the placebo group (65.0 vs 64.7%; *P*=0.003). The most commonly reported adverse events with buprenorphine were nausea, dizziness, pruritus, vomiting and somnolence. ES Phase: Forty of 49 patients (81.6%) who completed the ES phase continued to receive OL buprenorphine treatment. The improvements in daily pain intensity, PDI and SF-36 were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
permitted throughout the study. Acetaminophen 325 mg one or two tablets every 4 to 6 hours as needed was allowed.				maintained throughout the ES phase.
Karlsson et al[31] Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two doses Supplemental analgesic medication was permitted throughout the study. Paracetamol* up to 2,000 mg/day was allowed.	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before visit 1	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; *P* value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (*P* value not reported). There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol prolonged-release groups (*P* value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (*P*=0.039 and *P*=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (*P* value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				dizziness (15.9%).
Conaghan et al[32] Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol* 1,000 mg orally four times daily vs codeine/ paracetamol* 8/500 mg or 30/500 mg orally one or two tablets four times daily Supplemental analgesic medication was permitted throughout the study. Ibuprofen up to 1,200 mg/day was allowed.	AC, MC, OL, PG, RCT Patients ≥60 years of age with a clinical diagnosis of OA of the hip and/or knee with severe pain and taking the maximum tolerated dose of paracetamol (four or more 500 mg tablets each day)	N=220 10 weeks of titration period followed by 12 weeks of assessment period	Primary: Average pain score over the last 24 hours on Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, laxative use, sleep parameters on the Medical Outcome Study-Sleep Scale, time to achieve stable pain control, length of time on anti-emetics, discontinuation rate during the titration period and safety	Primary: In the ITT analysis, the treatment difference between buprenorphine plus paracetamol and codeine/paracetamol with regard to the average daily pain score was -0.07 (95% CI, -0.67 to 0.54; *P* value not reported), demonstrating that buprenorphine plus paracetamol was non-inferior to codeine/paracetamol. Secondary: In the per-protocol analysis, patients receiving buprenorphine plus paracetamol required 33% fewer supplemental analgesic medications compared to those receiving codeine/paracetamol. The treatment difference was -0.98 (95% CI, -1.55 to -0.40; *P*=0.002). Fifty percent of patients in each treatment group required laxatives during the study (*P* value not reported). In the per-protocol analysis, the mean sleep disturbance score on the Medical Outcome Study-Sleep Scale decreased from 33.90±22.09 at baseline to 24.30±25.32 at the end of the study in the buprenorphine plus paracetamol group, while the score decreased from 41.8±28.6 to 32.9±26.1 in the codeine/paracetamol group (*P* value not reported). Patients receiving buprenorphine plus paracetamol reported improvement in sleep adequacy, with an increase in score from 50.80±25.35 at baseline to 62.50±28.26 at the end of the study, whereas the score increased from 56.10±25.84 to 59.10±26.41 in patients receiving codeine/paracetamol (*P* value not reported). There was no difference in the number of hours slept between the two groups. The number of patients with optimal sleep slightly increased in the buprenorphine plus paracetamol group and slightly decreased in the codeine/paracetamol group. The snoring score did not change with buprenorphine plus paracetamol and slightly improved with codeine/paracetamol. Neither treatment had any effect on shortness of breath, headache or somnolence (*P* values not reported for all parameters). The mean time to achieve stable pain control during the titration period was 19.5±11.5 days for buprenorphine plus paracetamol and 21.80±13.76 days for codeine/paracetamol (*P* value not reported).

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				The median percentage of days on which anti-emetics were used during the titration period was 18.5% (interquartile range, 0 to 70.6) for buprenorphine plus paracetamol and 0% (interquartile range, 0 to 26.8) for codeine/paracetamol (*P* value not reported). Forty-three of 110 patients in the buprenorphine plus paracetamol group withdrew from the study during the titration period; 34 patients withdrew due to adverse events and five patients withdrew due to lack of therapeutic effect. In the codeine/paracetamol group, 63 of 110 patients withdrew during the titration period; 23 patients withdrew were due to adverse events and 12 patients withdrew due to lack of therapeutic effect. Eighty-six percent and 82% of patients in the buprenorphine plus paracetamol and codeine/paracetamol groups, respectively, reported treatment emergent adverse events. The most commonly reported adverse events in the buprenorphine plus paracetamol group were nausea, application site reaction and constipation.
Agarwal et al[33] Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	OL, PRO Patients >18 years of age with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in pain intensity and daily activity Secondary: Pain relief, cognition, physical function and mood	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in pain intensity. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in pain intensity in the peripheral neuropathy group compared to the CRPS-1 (*P*=0.06) and postamputation (*P*=0.07) groups among the ITT population. Among completers, fentanyl was more effective in reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (*P*<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (*P*<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in pain intensity and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6%, 37.5% and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain.

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				Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (*P* value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (*P* value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (*P* value not significant).
Finkel et al[34] Fentanyl transdermal system 12.5 to 100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment; changes in pain level, PPS, and CHQ and safety Secondary: Not reported	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily pain intensity levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of 11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66

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				patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Mercadante et al[35] Fentanyl transdermal patch 12 µg/hour, doses were titrated according to the clinical response Morphine (5 mg) was allowed for breakthrough pain.	OL, OS Opioid-naïve patient with advanced cancer and moderate pain	N=50 4 weeks	Primary: Pain intensity, opioid-related adverse events, doses, quality of life Secondary: Not reported	Primary: Thirty-one patients completed all four weeks of the trial. Pain control was achieved within 1.7 days after the start of therapy. Pain intensity significantly decreased from baseline through the remaining weekly evaluations (*P*<0.001). Significant differences in doses were observed after two weeks and were almost doubled at four weeks. The mean fentanyl escalation index was 4.04% and 0.012 mg, respectively. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. The pain mechanism did not significantly affect the changes in pain intensity and doses of fentanyl. The mean fentanyl escalation index was similar in patients presenting difference pain mechanisms. There were significant changes in opioid-related symptoms and quality of life between weekly evaluations. Secondary: Not reported
Park et al[36] Fentanyl transdermal patch 12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	OL, PRO Patients ≥19 years of age, with overall good health, and complaining of chronic pain of the spine and limbs that scored >4 points on a numerical	N=65 12 weeks	Primary: Percentage of change in pain intensity from before the administration of the study drug to 12 weeks Secondary: Degree of satisfaction,	Primary: Changes in average pain intensity, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual pain intensity, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; *P*<0.001). The pain intensities evaluated by the patients, at rest and when moving, were decreased from 5.40 to 1.95 (63.9%; *P*<0.0001). Secondary: Within three visits, the sum of patients who answered “very satisfied” or “satisfied” was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of ‘very satisfied’ and “satisfied” measured in week four and the rates on the last visit constituted a significant increase (*P*<0.05). The determinants of the patient’s satisfaction with pain

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	rating scale 72 hours prior to baseline data		patient's function/sleep interference, dose, safety	treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (*P*<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (*P*<0.0001). The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (*P*<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al[37] Fentanyl transdermal system 25 to 100 µg/hour every 72 hours vs placebo	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects of pain relief affecting mobility and quality of life	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; *P*=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (*P*=0.009 and *P*=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (*P*=0.051 and *P*=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; *P*=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; *P*<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed

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				significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all *P*<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (*P*=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; *P*=0.041).
Ahmedzai et al[38] Fentanyl transdermal system replaced every 72 hours for 15 days vs morphine SR (MST-Continus™) every 12 hours for 15 days	MC, OL, RCT, XO Patients 18 to 89 years of age with cancer who required strong opioid analgesia and were receiving a stable dose of morphine for ≥48 hours	N=202 30 days	Primary: Pain control, effect on sedation and sleep, bowel function, treatment preference and adverse events Secondary: Not reported	Primary: No significant differences on any of the pain scales were detected between the fentanyl and morphine phases. During the fentanyl phase, patients used more rescue medications than during the morphine phase. Rescue medication was used for 53.9% of days during treatment with fentanyl, compared to 41.5% of days for morphine (*P*=0.0005) throughout the whole of the phases. A sizeable proportion of patients required upward titration of study medication (47.1% required ≥1 fentanyl dose change and 27.4% required ≥1 morphine dose change). One patient required a downward titration in fentanyl dose. Fentanyl was associated with significantly less daytime drowsiness than morphine (mean percent area under the curve, 34.0; 95% CI, 29.1 to 38.9; vs 43.5; 95% CI, 38.5 to 48.5; respectively, as assessed by VAS in the patient diaries). Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine (mean scores, 32.4; 95% CI, 26.9 to 37.9; vs 22.4; 95% CI, 17.8 to 27.1; for fentanyl and morphine, respectively). The only difference in diary data was that patients reported shorter sleep duration when on fentanyl compared to when on morphine over the whole 15-day treatment period (mean, 8.1; 95% CI, 7.9 to 8.3 hours; vs 8.3; 95% CI, 8.0 to 8.5 for morphine). Fentanyl treatment was associated with significantly less constipation than morphine (*P*<0.001). At the end of the trial, significantly more patients indicated that fentanyl had caused less interruption to their daily activities, and the activities of family and care takers, and had been more convenient to take than the morphine tablets. The percentages expressing preference were as follows: less interruption of daily activities, 55.2% fentanyl; 20.4% morphine; less interruption to care givers, 49.0% fentanyl; 22.3% morphine; and more convenient medication, 58.3% fentanyl; 22.3% morphine. Of the 202 patients who entered the study, 136 felt able to express an opinion about the two treatments. Of these, 14 (10%) had no preference, 73 (54%) preferred fentanyl, and 49 (36%) preferred

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				the morphine tablets (*P*=0.037). The EORTC quality of life questionnaire revealed no other significant differences between the two treatments. When scores for nausea and vomiting were separated, the mean score for nausea was significantly lower in the fentanyl group (1.7; 95% CI, 1.5 to 1.8; vs 1.8; 95% CI, 1.7 to 2.0; *P*=0.04). Although more adverse events were reported during fentanyl treatment, the end of treatment questionnaire indicated that significantly fewer patients considered that fentanyl caused adverse events compared to morphine (40.4 vs 82.5%; *P*<0.001). Secondary: Not reported
Allan et al[39] Fentanyl transdermal system 25 µg/hour replaced every 72 hours; dosage was titrated based on pain levels vs morphine SR 30 mg every 12 hours; dosage was titrated based on pain levels	MC, OL, PG, RCT Adults patients with chronic lower back pain requiring regular strong opioid treatment	N=673 13 months	Primary: Comparison of pain relief achieved with each treatment and incidence of constipation Secondary: SF-36 quality of life, treatment assessment, investigator's overall assessment of disease progression, number of working days lost and adverse events	Primary: Pain relief achieved with both treatments was similar. Mean VAS scores at study endpoint was 56.0±1.5 and 55.8±1.5 for fentanyl and morphine. Based on the 95% CI, the difference between groups established noninferiority (-3.9 to 4.2). After one week of treatment, pain relief was evident with VAS scores being 58.5±1.3 and 59.9±1.4 for fentanyl and morphine. Fentanyl was associated with significantly less constipation than morphine. Baseline levels of constipation were similar, but at endpoint 31% of fentanyl patients (93/299) and 48% of morphine patients (145/298) were constipated (*P*<0.001). Secondary: Mean SF-36 quality of life scores improved to a similar extent in both treatment groups between baseline and endpoint for all domains of overall physical health (*P*<0.001), physical functioning, role-physical, bodily pain, vitality, social functioning and role-emotional. However, the scores for overall mental health did not change significantly from baseline to endpoint in either group (*P*=0.937 for fentanyl and *P*=0.061 for morphine). The mean dose of fentanyl on day one was 25 µg/hour (range 25 to 50 µg/hour) and the mean dose at study end was 57 µg/hour (range 12.5 to 250 µg/hour). The mean dose of morphine on day one was 58 mg (range 6 to 130 mg) and the mean dose at study end was 140 mg (range 6 to 780 mg). The proportion of patients who improved by at least one pain category (e.g., from severe to moderate) during the course of the trial was 50 to

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				70% in both treatment groups. While patients in the fentanyl group improved more than the patients in the morphine group for pain during the day and pain at rest, the groups improved to a similar degree for pain on movement and pain at night. The dose of supplemental medication for breakthrough pain did not differ significantly between the treatment groups. Investigator ratings of disease progression were similar across treatment groups. At endpoint, investigators considered that 49% of fentanyl and 45% of morphine patients had stable disease; 10 and 8%, respectively, had deteriorated and 21 and 23%, respectively, had improved. Based on the number of patients with jobs, loss of working days was applicable to a small population of patients. The proportion of patients reporting >3 weeks off at baseline decreased from 34 and 25% of fentanyl and morphine to 16% for both groups. No differences between treatment groups in patients with lower back pain were observed. Most participants (95%) reported at least one adverse event during the study. The proportion of patients receiving fentanyl and morphine who reported adverse events that were considered to be at least possibly related to the trial medication were 87 and 91%. Adverse events led to discontinuation of trial medication in 37% of the fentanyl group and 31% of the morphine group (*P*=0.098). The most common adverse events leading to discontinuation were nausea (37% of discontinuations in each group), vomiting (24% fentanyl and 20% morphine) and constipation (11% fentanyl and 23% morphine).
Clark et al[40] Fentanyl transdermal system, initially 25 µg/hour every 72 hours, with dosage adjustments to achieve adequate pain control vs	Systematic review (8 trials) Patients ≥18 years of age with defined and documented chronic non-cancer pain (including lower back pain, pain due to rheumatoid	N=2,525 28 days to 13 months	Primary: Pain results and adverse events Secondary: Not reported	Primary: Treatment with fentanyl and morphine was equally effective in improving average pain from baseline to Day 28 (mean changes in scores were -21.8 and -20.6, respectively). In the subgroup analysis, both treatments were similarly effective in improving the average pain scores (-24.5 vs -25.9, respectively in the cancer pain subgroup and -21.0 and -17.7, respectively in the non-cancer pain subgroup). Improvements in pain “right now” scores between baseline and day 28 were significant for both treatment groups, and for both cancer pain patients and non-cancer pain patients (all measures *P*<0.001). The changes in pain “right now” from baseline to day 28 were significantly greater in the fentanyl treatment group compared to the morphine treatment group in the total patient sample (*P*=0.017). The cancer pain subgroup showed a similar trend towards better pain relief from baseline to day 28 with fentanyl treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morphine SR, initially 15 to 30 mg every 12 hours, with dosage adjustments to achieve adequate pain control	arthritis, or OA of the knee or hip) or cancer pain, that had reached a stage requiring treatment with a strong opioid			but this was not statistically significant (*P*=0.171). Overall the type of pain did not influence the incidences of adverse events. However, in the total patient sample, as well as in both pain type subgroups, significantly fewer adverse events occurred in the fentanyl treatment group compared to the morphine treatment group (all measures *P*<0.001). Additionally, serious adverse events were also reported significantly less frequently in the fentanyl treatment group (*P*=0.006). The highest rate of serious adverse events was reported in patients with cancer pain and included 61 deaths. Constipation was the most commonly reported adverse event in the morphine treatment group, and significantly fewer patients reported nausea during the first 28 days of treatment with fentanyl compared to morphine (*P*<0.001). Patients treated with fentanyl also reported less somnolence compared to morphine-treated patients (*P*<0.001). Secondary: Not reported
Hale et al[41] Hydromorphone ER 12 to 64 mg QD vs placebo Patients were enrolled in a 2 to 4 week OL enrichment phase (conversion and titration), followed by a randomized withdrawal phase for opioid-tolerant patients.	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a documented diagnosis of moderate-to-severe chronic lower back pain for ≥3 hours/day and ≥20 days/month for six months and had their pain classified as non-neuropathic or neuropathic	N=268 12 weeks (DB phase only)	Primary: Mean change from baseline to week 12 or final visit in weekly pain intensity based on patient diary numeric rating scale scores Secondary: Mean change from baseline to week 12 in weighted mean pain intensity number rating scale score, mean change from baseline to each	Primary: Hydromorphone significantly reduced pain intensity compared to placebo (*P*<0.001). Secondary: The change from baseline in pain intensity over the entire 12 weeks was statistically significant for hydromorphone compared to placebo (*P*<0.001). A significantly larger increase in mean pain intensity numeric rating scale scores was seen in the placebo group compared to hydromorphone (1.2 vs 0.4; *P*<0.001). Weekly office visit number rating scale scores showed greater improvement following treatment with hydromorphone compared to placebo beginning at visit one and continued throughout the 12 weeks of treatment. The difference between the groups was significant (*P*<0.05) at every office visit except week three. Discontinuations due to treatment failure occurred sooner (*P*<0.001) and more frequently among patients in the placebo group. The difference was apparent by two weeks and the difference in discontinuation rates increased over the entire 12 weeks of treatment. Treatment with hydromorphone significantly improved patient global assessment scores at week 12 or at the final visit (*P*<0.001). A higher proportion of patients rated their

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Hydromorphone IR was allowed as rescue medication during all phases of the study.			visit in pain intensity during the 12 weeks of treatment recorded in the office, time to treatment failure, mean change from baseline in patient global assessment, rescue medication use, mean changes from baseline in RMDQ total scores and the proportion of total study dropouts in each treatment group	treatment as good, very good or excellent compared to placebo at week 12 or final visit (80.5 vs 62.4%). The overall percentage of patients requiring rescue medication at least once over the 12 week course was similar between hydromorphone and placebo groups (96.2 vs 97.0%). The mean number of rescue medication tablets used per day at the week 12 visit also was similar between the groups (*P*=0.49). Weekly RMDQ scores were "superior" in patients treated with hydromorphone compared to placebo. Hydromorphone-treated patients showed a median change from baseline to week 12 or final visit of 0 on this measure; placebo-treated patients showed a median change of 1, indicating that placebo patients' self-reported functional status was significantly worse compared to hydromorphone (*P*<0.005). Significant differences were seen at weeks one, two, three, eight and 12 (or final visit). The difference between treatment groups was not statistically significant at weeks four, six or ten. A significantly higher proportion of patients in the placebo group discontinued the study compared to patients in the hydromorphone group (67.2% [90/134] vs 50.7% [68/134]; *P*<0.01).
Hale et al[42] Hydromorphone ER 8 to 64 mg QD vs oxycodone ER 10 to 80 mg BID	MC, OL, PG Patients ≥18 years of age who met ACR clinical criteria for OA of the knee or hip for ≥3 months before enrollment, with a mean daily pain rating at the affected joint of moderate to severe, despite	N=147 6 weeks	Primary: Mean pain relief score at end point Secondary: Change from baseline to end point in the mean pain relief score; mean pain intensity score at end point; change from baseline to end point in mean pain intensity score; change	Primary: The mean (SD) pain relief score was 2.30 (0.95) in the hydromorphone group and 2.30 (1.00) in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.30 to infinity. Secondary: The mean changes in pain relief from baseline to end point are reported in graphic form; as such the results could not be accurately interpreted. The mean time to the third day of moderate to complete pain relief was 6.20 (4.00) days in the hydromorphone group and 5.50 (2.57) days in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.31 to infinity. The mean (SD) changes in pain intensity from baseline to end point were -0.6 (0.80) points in the hydromorphone ER group and -0.4 (1.15) in the oxycodone ER group; the 1-sided 95% CI for the difference of means was -0.53 to infinity.

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	chronic use of stable doses (≥30 days with no regimen change) of NSAIDs or other nonsteroidal, nonopioid therapies (with or without as-needed opioids)		from baseline to end point in mean total daily dose of study medication; change from baseline to end point in mean daily number of tablets of study medication; and changes from visit one to subsequent visits in the MOS sleep scale, investigator and patient global evaluations and WOMAC	The results of the patient and investigator global evaluations indicated that both treatments were considered clinically effective. Patient global evaluations improved from baseline by a mean (SD) of 1.20 (1.01) points in the hydromorphone group and by 1.00 (1.33) points in the oxycodone group. The magnitude of change was not significantly different between groups. The overall effectiveness of treatment was rated as good, very good or excellent by 67.2% of patients in the hydromorphone group and 66.7% of patients in the oxycodone group. The mean patient global evaluation scores at end point were similar in the two groups (2.90 [1.06] and 2.90 [1.11], respectively). Similarly, investigator global evaluations improved by 1.20 (1.01) and 1.10 (1.16) points, with a median of one point in each group. The effectiveness of treatment was rated as good, very good or excellent by 71.9% of investigators for hydromorphone and by 70.0% for oxycodone. Mean investigator global evaluation scores at end point were similar between groups (3.00 [0.95] and 3.10 [1.08]). At end point, the mean (SD) change in WOMAC total score was -2.00 (1.90) points in the hydromorphone group and -1.80 (2.14) points in the oxycodone group (*P* value not reported). Mean changes in WOMAC pain scale scores were -2.10 (1.96) in the hydromorphone and -2.00 (2.03) in the oxycodone group (*P* value not reported). The mean changes in WOMAC stiffness and physical function scale scores were not significantly different between the two groups (*P* values not reported). At end point, scores on the MOS Sleep Problem Index I indicated significantly less sleep disruption and daytime somnolence in the hydromorphone group compared to the oxycodone group (mean [SD], 25.70 [17.82] and 35.30 [22.56], respectively; *P*<0.012). Both agents were associated with numerical improvements, the change from baseline was significantly greater for hydromorphone (-13.30 [21.10] vs -5.20 [22.09]; *P*<0.045). Changes on the MOS Sleep Problems Index II were comparable in the two groups.
Quigley et al[43] Hydromorphone, long- or short-acting vs	MA (48 RCTs) Patients of any age suffering from any illness with either acute or chronic pain, including cancer	N=3,293 Duration not reported	Primary: Pain relief and safety Secondary: Not reported	Primary: Overall, studies varied in quality and methodology. The review did not demonstrate any clinically significant difference between hydromorphone and other strong opioids. Compared to meperidine, hydromorphone appeared more effective in achieving acute pain relief without an increase in adverse events. For the treatment of chronic pain, two studies showed that hydromorphone CR and

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strong opioids, long- or short-acting or placebo or non-opioids	pain and postoperative pain			morphine CR achieved similar pain relief; however, one of the studies showed that patients taking hydromorphone CR required more doses of rescue medication and were more likely to experience withdrawal compared to morphine. Diarrhea was more commonly seen with hydromorphone. No significant differences were seen in other adverse events. In studies comparing hydromorphone to morphine for the treatment of acute pain, hydromorphone-to morphine equianalgesic ratio was shown to vary from 7:1 to 5:1 for parenteral and spinal administration. Both drugs were associated with nausea, sleepiness and pruritus. Less anger and anxiety but lower cognitive function was associated with hydromorphone compared to morphine. One study comparing patient-controlled hydromorphone, morphine and sufentanil showed that morphine was superior with regard to time to treatment failure and was associated with the lowest incidence of adverse events. No significant differences were seen in chronic pain relief between hydromorphone CR and oxycodone SR. One study showed that transmucosal fentanyl led to greater improvement in pain and anxiety compared to hydromorphone. Studies comparing different formulations and/or routes of administration of hydromorphone found no differences in chronic pain relief between IR vs CR tablets, subcutaneous bolus vs subcutaneous infusion, intravenous vs subcutaneous and oral vs intramuscular. For the treatment of acute pain, epidural hydromorphone was associated with higher incidence of pruritus compared to intravenous or intramuscular hydromorphone. For the treatment of acute pain, hydromorphone IR was associated with greater pain relief compared to placebo, and there were no significant differences in adverse events between hydromorphone and placebo. One study showed that subcutaneous hydromorphone and intravenous indomethacin were equally effective in pain relief, although the duration of nausea and vertigo was longer following hydromorphone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Felden et al[44] Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; *P*=0.006). No differences were observed for the treatment of chronic pain relief (*P*=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (*P*=0.005) and vomiting (*P*=0.001). Secondary: Not reported.
Pigni et al[45] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting	Systematic review (9 RCTs, 4 non-RCTs) Patients ≥18 years of age with chronic cancer pain who had not taken a strong opioid in the past	N=1,208 Duration not specified	Primary: Pain relief and safety Secondary: Not reported	Primary: MA was not performed due to study heterogeneity. Overall, the review supported the use of hydromorphone in the treatment of moderate to severe cancer pain as an alternative to morphine and oxycodone. There was no clinically significant difference between hydromorphone and morphine. The majority of the studies showed similar safety and efficacy in pain relief between hydromorphone and morphine or oxycodone. The following agents of different formulations were found comparable in safety and efficacy: hydromorphone IR vs morphine IR; hydromorphone CR or SR vs morphine CR or SR, hydromorphone IR vs intramuscular morphine and hydromorphone SR vs oxycodone SR. In one non-RCT, hydromorphone SR was shown to have similar analgesia with more vomiting and less constipation compared to transdermal fentanyl and buprenorphine. Two studies comparing hydromorphone IR to SR demonstrated similar pain relief and safety profile between the two formulations. Other studies comparing different routes of administration of hydromorphone also showed similar safety and efficacy between the following routes: intravenous vs subcutaneous, intravenous vs oral and intramuscular vs oral. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Morley et al[46] Methadone 10 to 20 mg/day vs placebo In Phase 1 of the study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total). In Phase 2 of the study, patients were instructed to take methadone 10 mg BID or placebo on odd days and to take no medication on even days (20 days total).	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous drug regimens	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum pain intensity by 16.00 (*P*=0.013) and VAS average pain intensity by 11.85 (*P*=0.020) and increased VAS pain relief by 2.16 (*P*=0.015). Analgesic effects, by lowering VAS maximum pain intensity and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (*P*=0.065 and *P*=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum pain intensity by 12.02 (*P*=0.010), a lowering of VAS average pain intensity by 10.46 (*P*=0.026), and an increase in VAS pain relief by 0.94 (*P*=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who completed the trial. Secondary: Not reported
Bruera et al[47] Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer	N=103 4 weeks	Primary: Difference in pain intensity Secondary: Change in toxicity and patient-reported global	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; *P*=0.50). Secondary:

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breakthrough pain vs slow-release morphine 15 mg BID, in addition to IR morphine 5 mg every 4 hours as needed for breakthrough pain	necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed consent		benefit	The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; *P*=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI, 38 to 68 vs 61%; 95% CI, 47 to 75; *P*=0.41).
Musclow et al (abstract)[48] Morphine long acting 30 mg BID for 3 days vs placebo	DB, PC, RCT Patients undergoing total hip or knee replacement surgery	N=200 3 days	Primary: Decrease in pain scores by 2 points on a 10 point rating scale Secondary: Acute confusion, pain-related interferences in function and sleep, length of stay, patient satisfaction, safety	Primary: Most pain scores did not reach the predetermined improvement for clinical significance. Secondary: There was an increase in opioid usage (*P*<0.0001) and over sedation (*P*=0.08). There were no significant changes in function or sleep. Improved satisfaction with pain management was minimal (*P*=0.052). There was an increase in vomiting (*P*=0.0148).
Caldwell et al[49] Morphine ER (Avinza®) 30 mg in the morning plus placebo in the evening vs placebo in the	DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with both a clinical diagnosis and grade II-IV radiographic evidence of OA	N=295 4 weeks	Primary: Analgesic efficacy of morphine ER QD compared to placebo and safety of morphine ER QD compared to morphine CR BID Secondary:	Primary: Overall, a statistically significant reduction in pain from baseline was demonstrated by morphine ER in the morning (17%; *P*≤0.05) and in the evening (20%; *P*≤0.05), and morphine CR BID (18%; *P*≤0.05), as compared to placebo (4%). Morphine ER in the morning (26%) and in the evening (22%) and morphine CR BID (22%) reduced overall arthritis pain intensity as compared to placebo (14%), but these differences were not statistically significant. Pain intensity (measured on a 100-mm scale) was reduced by approximately 20 to 23 mm in the morphine ER and CR groups compared to 14 mm in the placebo group. Decreases in pain intensity were apparent in all treatment groups by week one and further reductions in pain throughout the four week period were observed as compared to baseline.

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morning plus morphine ER (Avinza®) 30 mg in the evening vs morphine CR (MS Contin®) 15 mg BID vs placebo	of the hip and/or knee; have had prior suboptimal analgesic response to treatment with NSAIDs and acetaminophen or had previously received intermittent opioid analgesic therapy; and have a baseline VAS pain intensity score of ≥40 mm in the index joint		Physical functioning; stiffness; sleep measures; and analgesic efficacy of morphine ER in the morning, morphine ER in the evening and morphine CR	Secondary: Statistically significant differences in physical function were not achieved among the treatment groups. Mean improvements in physical function (total score, 0 to 1,700 mm) at Week four were as follows: morphine ER in the morning (207 mm, 18%) and in the evening (205 mm, 19%), morphine CR (181 mm, 14%) and placebo (97 mm, 8%). Reductions in stiffness were also observed for all treatment groups. The changes were not large enough to achieve statistical significance. Active treatment groups provided greater improvements in all sleep measures compared to placebo. Morphine ER in the morning provided statistically significant improvements compared to placebo for overall quality of sleep, less need for sleep medication, increases hours of sleep and less trouble falling asleep because of pain (*P* values not reported). Morphine ER in the evening provided statistically significant improvements compared to placebo for overall quality of sleep and duration of sleep each night. Relative to placebo, morphine CR provided statistically significant improvements in overall quality of sleep and patients had less trouble falling asleep because of pain (*P* values not reported). Morphine ER in the morning demonstrated a statistically significant improvement in overall quality of sleep compared to morphine CR (*P* value not reported) and no significant differences were observed between morphine ER in the morning and the evening (*P* value not reported). A total of 197 patients (67%) experienced at least one adverse event during this trial, with constipation and nausea reported most frequently. Adverse events were higher in all active treatment groups compared to the placebo group. Among the 33 pair-wise comparisons the only significant differences observed were a higher rate of constipation with morphine ER in the morning (49%) vs morphine CR (29%), a higher rate of vomiting with morphine ER in the evening (16%) vs morphine ER in the morning (6%) and a higher rate of asthenia with morphine CR (9%) vs morphine ER in the morning (1%).
Allan et al[50] Morphine (MS Contin®) 10 to 200 mg for 4 weeks	MC, OL, RCT, XO Patients >18 years of age with chronic	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; *P*<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief.

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vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate pain control with a stable dose of oral opioid for seven days before the trial		assessment, rescue drug use, SF-36 quality of life, and safety	Secondary: Patients treated with fentanyl reported on average lower pain intensity scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; *P*<0.001), irrespective of the order of treatment. More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; *P*=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (*P*<0.001). The corresponding percentages from the patient assessments were 60% for fentanyl and 36% for morphine (*P*<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; *P*<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (*P*<0.001), vitality (*P*<0.001), social functioning (*P*=0.002), and mental health (*P*=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
Wiffen et al[51] Morphine, long- or short-acting vs Opioids or non-	MA (54 RCTs) Adults and children with cancer pain requiring opioid treatment	N=3,749 3 days to 6 weeks	Primary: Pain relief and adverse events Secondary: Not reported	Primary: The review showed that morphine was comparable to other opioids in achieving cancer pain relief, and different formulations of morphine were effective. Limited evidence suggested that transmucosal fentanyl may provide more rapid pain relief for breakthrough pain compared to morphine. Thirteen studies (n=939) compared long-acting morphine to other opioids of either long- or short-acting formulation. There were no significant differences in pain relief and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
opioid analgesics				adverse events between long-acting morphine and long- or short-acting oxycodone, long-acting hydromorphone or tramadol. Pain relief was similar between morphine and transdermal fentanyl, though patients in the transdermal fentanyl group required more rescue medication and reported less sedation and constipation. Compared to methadone, morphine was associated with similar pain relief and fewer adverse events. Six studies (n=973) compared short-acting morphine to other opioids. One study comparing morphine to transmucosal fentanyl for breakthrough pain showed that pain intensity scores were significantly lower with transmucosal fentanyl at all time points compared to morphine. No differences in pain relief were seen between morphine and methadone, short-acting oxycodone or tramadol. Compared to methadone, morphine was associated with more dry mouth and fewer headaches. Morphine was also associated with more nausea than oxycodone. Fifteen studies (n=460) compared long- to short-acting morphine and demonstrated that the two formulations were comparable in pain relief and adverse events. No carry-over effects were observed with long-acting morphine. One study showed long-acting morphine was associated with greater improvement in sleep quality. Twelve studies (n=1,010) compared long-acting morphine of different dosage strengths, dosing intervals or dosage formulations. Results from these studies showed no significant differences in pain relief or adverse events between the following comparisons: 12-hourly vs eight-hourly dosing, 12-hour-release capsule (M-Eslon®†) vs tablet (MS Contin®), 24-hour-release capsule or tablet (Kadian®, Kapenol®†, Morcap®† or MXL®†) vs 12-hour-release tablet (MS Contin®) and long-acting tablet vs long-acting suspension. One study showed that long-acting morphine suppository caused less nausea compared to long-acting morphine oral tablet. Another study showed rectal administration of morphine solution led to faster and greater pain relief compared to oral solution. In one study, oral and epidural morphine achieved similar pain relief. Patients on epidural morphine reported significantly fewer adverse events Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Caraceni et al[52] Morphine, long- or short-acting vs opioids	MA (16 RCTs and 1 MA) Patients ≥18 years of age with chronic cancer pain	N=2,487 Duration not reported	Primary: Pain relief and adverse events Secondary: Not reported.	Primary: No significant differences in pain relief were observed when long- and short-acting morphine was compared to diamorphine†, hydromorphone, methadone, oxycodone or transdermal fentanyl. No clinically significant differences were observed between morphine and other opioids; however, transdermal fentanyl was associated with a lower incidence of constipation, and patients on methadone were more likely to withdraw from the study due to sedation. Secondary: Not reported
Katz et al (abstract)[53] Morphine/ naltrexone vs placebo All patients received morphine/ naltrexone, titrated to 20/160 mg/day, prior to randomization. Patients randomized to placebo were tapered off morphine/ naltrexone over a two week period.	DB, MC, RCT Patients with chronic, moderate to severe, OA (hip or knee) pain	N=547 12 weeks	Primary: Change from baseline in diary average-pain scores to the last seven days of the trial Secondary: Remaining BPI scores, WOMAC OA index, opioid withdrawal symptoms	Primary: Combination therapy maintained pain control better than placebo (mean change from baseline dairy average-pain score: -0.2±1.9 vs ±0.3±2.1; *P*=0.045). Change from baseline for combination therapy pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks two to 12 (*P*<0.05). Secondary: WOMAC composite score change from baseline was superior at most visits. Combination therapy was generally well tolerated, with a typical morphine safety profile. No patient taking combination therapy as directed experienced withdrawal symptoms.

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Gimbel et al[54] Oxycodone CR (OxyContin®) 10 to 60 mg BID vs placebo	DB, MC, PC, PG, RCT Adult diabetic patients with a history of stable diabetes mellitus and a HbA1c ≤11.0%, painful symmetrical distal polyneuropathy, a history of pain in both feet for more than half the day for ≥3 months prior to enrollment, and at least moderate pain in the absence of any opioid analgesic therapy for three days before receiving the study treatment	N=159 6 weeks	Primary: Average daily pain intensity during the past 24 hours obtained during the study period from days 28 to 42 Secondary: Patient reported scores for average pain intensity from days one to 27, current and worst pain, satisfaction, and sleep quality from days one to 42; total and subscale scores from the 14-item BPI; scores for validated measures of psychological state, physical functioning, and general health status; the proportion of patients who discontinued study medication due to lack of efficacy; and time to mild pain, number of days with mild	Primary: In the ITT cohort, the efficacy analysis of the primary endpoint showed that oxycodone provided "superior" analgesia compared to placebo (*P*=0.002). Least squares mean scores for overall average daily pain intensity from days 28 to 42 were 4.1 and 5.3 for the oxycodone and placebo groups. The primary efficacy results from the per protocol cohort confirmed these results: least squares mean scores for overall average daily pain intensity from days 28 to 42 in this cohort was 4.2 and 2.3 for the oxycodone and placebo groups (*P*=0.009). Secondary: Oxycodone produced significant improvements in overall scores for average pain intensity from days one to 27 (*P*<0.001), pain right now (*P*=0.002), worst pain (*P*=0.001), satisfaction with study medication (*P*<0.001) and sleep quality from days one to 42 (*P*=0.024). Significant improvements in all pain measurements (except worst pain) and in sleep quality were observed within one week of initiation of oxycodone therapy. An improvement from baseline in nine out of 14 items (average pain intensity [*P*=0.004], pain right now [*P*<0.001], worst pain [*P*=0.001], least pain [*P*=0.004], pain relief [*P*<0.001], interference score [*P*=0.015], relations with other people [*P*=0.023], sleep [*P*<0.001] and enjoyment of life [*P*=0.016]) were significant and improved in the oxycodone group compared to placebo. No significant improvements occurred for the five remaining items which included physical function score, general activity, mood, walking ability and normal work. There were no significant differences between treatments in physical functioning, general health and mental health subscales of the SF-36 Health Survey or in the seven subscales of the Rand Mental Health Inventory. A significant difference in ambulation, a subscale of the Sickness Impact Profile, was observed between oxycodone and placebo at the final visit. Of the 12 patients discontinuing study medication due to inadequate pain control, one patient was in the oxycodone group and 11patients were in placebo group (*P*=0.002). The median time to achieve mild pain was shorter for the patients treated with oxycodone (six days) compared to placebo-treated patients (17 days; *P*=0.017). Patient treated with oxycodone had more days with mild pain: mean (SD) of 20.0 (16.6) days vs

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			pain and proportion of days with mild pain	12.5 (16.0) days for the placebo (*P*=0.007). Oxycodone-treated patients reported a higher mean (±SD) percentage of days with mild pain (47%±39%) compared to placebo-treated patients (29%±37%; *P*=0.006).
Ma et al[55] Oxycodone CR 5 to 10 mg or larger dosages every 12 hours vs placebo	DB, PRO, RCT Patients 40 to 70 years of age with a history of chronic refractory neck pain for >6 months, a MRI or computer topography scan suggesting a degenerative disease process, with a frequency of acute pain flares occurring >3 times/day that are VAS >4 for 3 days	N=116 4 weeks	Primary: Frequency of pain flares, pain intensity, quality of life, quality of sleep, adverse events and SF-36 Secondary: Not reported	Primary: Compared to the pretreatment and placebo group, the frequency of acute pain flares (>3 times/day) in the oxycodone group decreased significantly on day three and day seven (*P*<0.05). Only 20.7% of patients (12/58) continued to have acute flare pain (>3 times/day) on day seven, and 21 days later no patient complained of acute flare pain in the oxycodone group (*P*<0.01). Patients treated with oxycodone had a stepwise reduction in pain intensity during the first week compared to their baseline. The VAS decreased from 6.82±1.83 to 3.35±1.57 on day three, and to 3.24±0.92 on day seven (*P*<0.05). Patients in the oxycodone group had lower scores for pain intensity compared to patients in the placebo group (*P*<0.05). The oxycodone group had dramatic improvements in performance status and performance status scale scores after seven days of treatment. Compared to pretreatment levels and the placebo group, performance status decreased from 2.74±1.01 to 1.25±0.42 on day seven, and to 0.28±0.07 on day 28, respectively (*P*<0.05). Similarly, performance status scale increased from 3.21±0.68 to 4.74±0.95 on day seven and to 7.23±1.44 on day 28 (*P*<0.05). Bad quality of sleep was 63.8% before treatment and was decreased to 15.5% on day three, 8.6% on day seven, and 5.6% on day 14 in patients treated with oxycodone. Additionally, there was significant improvement in the quality of sleep, with 13.8% as the baseline for good quality of sleep, rising to 46.6%, 50.0%, and 58.3% on day three, seven and 14 respectively after oxycodone treatment (*P*<0.01). Adverse events, including mild-to-moderate nausea (31.0%) constipation (22.4%), pruritus (18.9%) and dizziness (27.6%) were only seen on day seven of the treatment in oxycodone patients (*P*<0.05). However, events diminished starting from day 14 of the treatment until day 28; only two patients had persistent constipation. Most domains of SF-36 were effective positively in patients treated with oxycodone. The score for physical functioning, pain index, vitality, social functioning, emotional role and mental health index were significantly better in the oxycodone group compared to

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				placebo at the end of the study ($P<0.05$). Secondary: Not reported
Watson et al[56] Oxycodone CR (OxyContin®) 10 to 40 mg BID vs active placebo (Benztropine® 0.25 to 1 mg BID)	DB, RCT, XO Adult diabetic patients in stable glycemic control; with painful symmetrical distal sensory neuropathy; at least moderate pain in the lower extremities; a medical history of moderate daily pain for previous three months; one or more symptoms of diabetic neuropathy; and signs of reduced sensation, strength or tendon reflexes not attributable to any other cause	N=36 8 weeks	Primary: Pain intensity, SF-36 and PDI Secondary: Not reported	Primary: Oxycodone resulted in significantly lower VAS ($P=0.0001$) and ordinal ($P=0.0001$) pain scores and better pain relief ($P=0.0005$) compared to placebo during the last week of treatment assessed in patients' daily diaries. There was no evidence of sequence effect ($P=0.2098$). Steady ($P=0.0001$), brief ($P=0.0001$) and skin pain ($P=0.0001$) were significantly reduced with oxycodone treatment compared to placebo. For the SF-36, results were significantly better during the oxycodone treatment phase compared to active placebo for Physical Functioning ($P=0.0029$), Pain Index ($P=0.0001$), Vitality ($P=0.0005$), Social Functioning ($P=0.0369$) and Mental Health Index ($P=0.0317$) domains. All variables in the PDI were significantly better in the oxycodone treatment phase ($P\leq0.0005$ and $P\leq0.05$) with the exception of sexual behavior, which showed no difference between the two treatments. Secondary: Not reported
Bruera et al[57] Oxycodone CR (OxyContin®) and	DB, DD, PC, RCT, XO Patients ≥18	N=32 2 weeks	Primary: Pain intensity, overall effectiveness, and	Primary: There were no significant differences between treatments in pain-intensity VAS scores when tested by day of treatment, time of day, or overall ($P=0.43$) or between categorical scores pain-intensity scores by day of treatment, time of day, or overall ($P=0.36$).

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placebo every 12 hours for 7 days vs morphine CR (MS Contin®) and placebo every 12 hours for 7 days	years of age who had cancer pain and who were receiving treatment with an oral opioid analgesic during study entry and who gave informed consent		adverse events Secondary: Not reported	For both formulations, there was a significant (*P*=0.02) difference in rescue use with respect to doses taken during the night (2 to 6 AM) as compared to the remainder of the 24-hour day. The rate of rescue use during the night was 55 and 67% of that used during the daytime in the oxycodone and morphine groups, respectively. The average daily number of rescue doses in a 24-hour period was 2.3±2.3 for oxycodone and 1.7±2.1 for morphine (*P*=0.01). There were no significant differences in sedation or nausea between oxycodone CR and morphine. Secondary: Not reported
King et al[58] Oxycodone vs strong opioids	Systematic Review (14 RCTs, 1 MA, 10 OS) Patients ≥18 years of age with moderate to severe cancer pain	N=3,875 3 days to 3 months	Primary: Pain relief and adverse events Secondary: Not reported	Primary: This review found no significant differences in safety and cancer pain relief between oxycodone and hydromorphone, morphine or oxymorphone. The MA included in this review showed no difference in analgesia and safety between oxycodone and morphine or hydromorphone (pooled standardized mean difference, 0.04; 95% CI, -0.29 to 0.36; *P*=0.8). Similarly, results from RCT and PRO OS also showed no difference between oxycodone and hydromorphone, morphine or oxymorphone. Studies that compared short- to long-acting oxycodone showed similar pain relief and safety profile between the two formulations. Studies comparing intravenous vs rectal and intramuscular vs oral oxycodone also demonstrated similar safety and efficacy between different routes of administration. Secondary: Not reported
Slatkin et al[59] (abstract) Oxymorphone ER Patients who had	Post-hoc analysis of 2 ES, OL Patients with cancer	N=80 12 months	Primary: Current, average, worst and least pain scores normalized to a 100-point scale	Primary: Of the 80 patients who were entered into the ES, 26 patients completed 52 weeks, seven patients discontinued owing to loss of effectiveness, and 20 patients discontinued owing to adverse events (most unrelated to the study drug). No significant increase in mean (SD) average pain intensity was observed from baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
been taking oxymorphone ER continued the dose established in a previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of oxymorphone ER.			Secondary: Patients rated global assessment of study medication and adverse events	(30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; *P*=0.37). Secondary: The most common adverse events were concomitant disease progression (28.8%; n=23), nausea (22.5%; n=18), dyspnea (16.3%; n=13), fatigue (16.3%; n=13) and edema of the lower limb (15%; n=12). Patient rated global assessment of study medication was not reported in the abstract.
Sloan et al[60] Oxymorphone ER Patients were stabilized for ≥3 days on morphine CR (MS Contin®) or oxycodone CR (OxyContin®), and then treated for 7 days at their stabilized dose (Period 1). Patients were then crossed over for 7 days of treatment at an estimated equianalgesic dosage of oxymorphone ER (Period 2).	MC, MD, OL, PRO, XO Patients 18 to 80 years of age with a history of chronic cancer pain requiring ≥20 mg of oxycodone or the analgesic equivalent of ≥30 mg of oral morphine per day	N=63 7 days (Period 2)	Primary: Efficacy Secondary: Not reported	Primary: Mean daily pain intensity scores were comparable during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain was achieved with oxymorphone as with oxycodone. The average scheduled daily dose of study medication and the average total daily dose decreased after XO to oxymorphone. There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for the treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kivitz et al[61] Oxymorphone ER 10 mg every 12 hours for 2 weeks vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 40 mg every 12 hours for 1 week vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 50 mg every 12 hours for 1 week vs placebo	DB, DR, MC, PG, RCT Patients ≥18 years of age with OA (defined by the presence of typical knee or hip joint symptoms [pain, stiffness, and disability] and signs [bony crepitus], and radiographic evidence of OA [grade II-IV in the index joint on the Kellgren-Lawrence scale]); who are regularly taking acetaminophen, NSAIDs or opioid analgesics for 90 days before the screening visit with suboptimal analgesic response	N=370 2 weeks	Primary: Mean change in arthritis pain intensity Secondary: Change in pain, stiffness, and physical function subscales of WOMAC OA index and WOMAC composite index; SF-36 quality of life, CPSI and tolerability	Primary: In the ITT population, the least squares mean change in arthritis pain intensity from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for oxymorphone 10, 40 and 50 mg; and placebo, respectively. The least squares mean differences in change from baseline compared to placebo were -4.3 (95% CI, -12.8 to -4.3; *P* value not significant), -11.1 (95% CI, -19.7 to -2.5; *P*=0.012) and -12.2 (95% CI, -20.9 to -3.5; *P*=0.006) for oxymorphone 10, 40 and 50 mg, respectively. Compared to placebo, arthritis pain intensity scores were improved by 62.8% and 70.9% after treatment with oxymorphone 40 or 50 mg every 12 hours, respectively (*P*=0.012 and *P*=0.006). Secondary: Overall, improvements in WOMAC scores were two- to three-fold greater in oxymorphone compared to placebo. From baseline to the final visit, two-fold greater decreases in WOMAC pain subscale scores were found in all three oxymorphone groups compared to the placebo group (*P*≤0.025). Improvements in WOMAC physical function subscale scores also were significantly greater for each of the oxymorphone groups compared to the placebo group (*P*≤0.025). Improvements in the WOMAC stiffness subscale score were significant compared to placebo only for the oxymorphone 40 and 50 mg groups (*P*≤0.001). With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone groups found significantly greater improvements in each oxymorphone group (*P*≤0.025). All patients who received oxymorphone, irrespective of the dose, had significant improvements in the SF-36 quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with oxymorphone 10, 40 and 50 mg; and placebo, respectively (*P*<0.001). Improvements in the CPSI scores for overall sleep quality were two-fold greater in patients who received oxymorphone 40 and 50 mg than in the placebo group (*P*≤0.05). The most frequently reported adverse event in the oxymorphone groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%) and headache (14.7%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Schwartz et al[62] Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3 days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg increments every 3 days (within dose range of 100 to 250 mg BID). Acetaminophen ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.	DB, PC, PG, RCT Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with the following: HbA1c ≤11.0%, ≥3-month history of analgesic use for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average pain intensity score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)	N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (main-tenance phase after a 3-week titration phase)	Primary: The change from baseline in average pain intensity over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in pain intensity of at least 30% and 50% at week 12 (i.e., responder rate), PGIC at weeks two, six, and 12, and safety measures	Primary: The least square mean change in average pain intensity from the start of DB treatment to 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. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; *P*<0.001). Secondary: The mean changes in average pain intensity scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (*P*=0.017). At least a 50% improvement in pain intensity from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (*P*=0.032). Of the patients who achieved ≥ 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period. Of those patients who were randomized to placebo after achieving ≥30%improvement in pain intensity (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in pain intensity during the maintenance phase.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Among patients who achieved ≥50% improvement in pain intensity (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in pain intensity (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (*P*<0.001). The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.
Afilalo et al[63] Tapentadol ER 100 mg BID vs	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis	N=1,030 12 weeks (main-tenance phase after a	Primary: Change in average pain intensity at week-12 of the maintenance	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo vs oxycodone CR 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3	of OA of the knee (per ACR criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current analgesic regimen, and had a baseline pain intensity score ≥5 during the 3 days prior to randomization	3-week titration phase)	period compared to baseline Secondary: Change in average pain intensity over the entire 12-week maintenance period compared to baseline	The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (*P*-values not reported). The average pain intensity rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); *P*-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; *P*=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; *P*=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; *P*=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least a 50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; *P*=0.023). Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; *P*=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; *P*=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; *P*<0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; *P*=0.051). The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; *P*=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; *P*=0.019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
consecutive days) was permitted.				The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; *P*=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; *P*=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al[64] Tapentadol ER 100 mg BID vs oxycodone CR 20 mg BID vs placebo Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100	AC, DB, MC, PC, PRO, RCT Patients ≥18 years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses, if applicable, were equivalent to	N=981 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change from baseline in mean pain intensity at week-12 of the maintenance period Secondary: Change from baseline in mean pain intensity over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in pain intensity at week-12 of maintenance, PGIC score, BPI	Primary: Throughout the 12-week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo. The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; *P*<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; *P*<0.001). Secondary: The mean pain intensity was also reduced for the oxycodone CR group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; *P*<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; *P*<0.001). Reductions in mean pain intensity were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline pain intensity. Significantly greater reductions in mean pain intensity with tapentadol ER compared to placebo were also observed for the overall maintenance

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3 consecutive days) was permitted.	≤160 mg of oral morphine		survey, SF-36 health survey	period in patients with both moderate baseline pain intensity and severe baseline pain intensity. Reductions in mean pain intensity were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline pain intensity at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (*P*=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (*P*=0.090). A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in pain intensity at week-12 compared to baseline (*P*<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo responded with 50% improvement in pain intensity at week-12 compared to baseline (*P*<0.016). The percentage of patients in the oxycodone CR group with ≥30% improvement in pain intensity at week-12 compared to baseline was 30.4% (*P*=0.365) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with ≥50% improvement in pain intensity at week-12 compared to baseline was 23.3% (*P*=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (*P*< 0.001) and oxycodone CR (*P*<0.001) compared to placebo. Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score.

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				The percentage of patients with "any pain today other than everyday kinds of pain" on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group. The percentage of patients who reported "at least 50% pain relief during the past week" was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared to the placebo group. The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wild et al[65] Tapentadol 100 to 250 mg BID vs oxycodone CR 20 to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Occasional pain	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or low back pain (non-malignant) with a ≥ 3 month history of pain, who were dissatisfied with current analgesic therapy, and had a pain intensity score ≥4 on an 11-point rating scale after therapy washout	N=1,121 51 weeks (main-tenance phase)	Primary: Safety and tolerability Secondary: Change in mean pain intensity score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone CR group, respectively. The incidence of pruritis was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone CR groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean pain intensity scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of “excellent,” “very good,” or

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relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and acetaminophen ≤1,000 mg/day (up to a max of 7 consecutive days and no more that 14 out of 30 days) were permitted.				"good" among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was "much improved" for both the tapentadol ER and oxycodone CR groups (35.7 and 32.8%, respectively). A rating of "very much improved" or "much improved" was reported by 48.1 and 41.2%, respectively.
Bekkering et al (2011)[66] Strong opioids vs placebo or strong opioids	Systematic review (56 RCTs) Patients ≥18 years of age with cancer-related or non-cancer-related chronic pain	N=not reported ≥24 hours	Primary: Change of pain intensity Secondary: Safety	Primary: *Morphine vs another strong opioids* One trial favored other opioids, one trail favored morphine, and the remaining eight trials did not find any difference between the two treatments. In the subgroup of trials with a duration between one week and one month, morphine was more effective than other opioids (eight trials: weighted mean difference, -5.8; 95% CI, -9.5 to -2.1). Other differences were not significant. Network analyses showed that fentanyl (weighted mean difference, 6.3; 95% CI, 1.8 to 10.9) and hydromorphone (weighted mean difference, 5.1; 95% CI, 0.5 to 9.6) were less effective compared to morphine. Also placebo was less effective (weighted mean difference, 10.7; 95% CI, 7.2 to 14.1). No differences with morphine were found for oxycodone (weighted mean difference, 2.9; 95% CI, -0.4 to 6.2), methadone (weighted mean difference, 3.3; 95% CI, -4.6 to 11.3), oxymorphone (weighted mean difference, 0.4; 95% CI, -5.5 to 6.3) and buprenorphine (weighted mean difference, 3.0; 95% CI, -3.0 to 9.0). Differences between morphine and fentanyl and between morphine and hydromorphone were not significant (3.6; 95% CI, -2.0 to 9.3 and 4.8; 95% CI, -0.1 to 9.8). No differences were found when excluding trials examining opioids in neuropathic pain. Secondary: No difference between morphine and other strong opioids were found for risk of treatment discontinuation due to any reasons (ten trials: RR, 1.06; 95% CI, 0.88 to 1.29), treatment discontinuation due to lack of efficacy (nine trials: RR, 0.83; 95% CI, 0.55 to 1.25), or treatment discontinuation due to adverse events (nine trials: RR, 1.05; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.67 to 1.65). Network analyses showed no difference between morphine and any other strong opioid or placebo in treatment discontinuation when all reasons for discontinuation were pooled. Patients using buprenorphine and those using placebo are more likely to discontinue treatment due to lack of efficacy (OR, 2.32; 95% CI, 1.37 to 3.95; OR, 4.12; 95% CI, 2.66 to 6.38). Patients using methadone are more likely to discontinue due to adverse events (OR, 3.09; 95% CI, 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR, 0.29; 95% CI, 0.17 to 0.50), buprenorphine (OR, 0.30; 95% CI, 0.16 to 0.53), and placebo (OR, 0.12; 95% CI, 0.08 to 0.18). After excluding trials with reversed design, oxymorphone showed increased risk for treatment discontinuation for any reason (OR, 2.32; 95% CI, 1.49 to 3.63) whereas this was nonsignificant in the overall analysis (OR, 1.00; 95% CI, 0.70 to 1.44). No differences were found when excluding trials examining opioids in neuropathic pain. Three trials comparing morphine to another strong opioid reported serious adverse events; no differences in risk was found in the pair-wise MA (RR, 1.15; 95% CI, 0.79 to 1.67). The network analysis also found no difference in risk of serious adverse events for patients using morphine compared to those using oxycodone, fentanyl, placebo, buprenorphine, oxymorphone, and hydromorphone. Limitations: Patients with non-cancer pain and cancer pain were included; therefore, differences in patient populations exist among included trials. Some trials included patients with moderate pain which may not require a strong opioid. Use of RCTs is less suitable for evaluating adverse events, and the majority of trials were industry funded. Conclusion: Current evidence is moderate, both in respect to the number of directly comparative trials and in the quality of reporting of these trials. No clear superiority in efficacy and tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Whittle et al[67] Opioids vs placebo, opioids or NSAIDs	MA (11 RCTs) Patients ≥18 years of age with a diagnosis of rheumatoid arthritis	N=672 <24 hours (four studies) 1 to 6 weeks (seven studies)	Primary: Percentage of patients with pain relief ≥30% and number of withdrawals due to adverse events Secondary: Percentage of patients with pain relief ≥50%, changes in function, quality of life, withdrawals due to inadequate analgesia and adverse events	Primary: Data from the four single-dose studies were not included in the MA. A review of these studies showed that single-dose aspirin, acetaminophen, caffeine/phenacetin/ isopropylantipyrine†, codeine, codeine/aspirin, codeine/aspirin/phenacetin†, dextropropoxyphene/acetaminophen†, pentazocine and propoxyphene† were all associated with greater pain relief compared to placebo. No significant differences in efficacy were found between these agents. Five of the remaining seven studies that were at least one week in duration compared codeine/acetaminophen, morphine CR, pentazocine, tilidine/naloxone† and tramadol/ acetaminophen to placebo. One study compared dextropropoxyphene/aspirin† to aspirin, and one study compared codeine/acetaminophen plus diclofenac to diclofenac. None of these studies reported data on percentage of patients with pain relief of ≥30%. The rate of withdrawal due to adverse events was higher with opioids but not significantly different from placebo (RR, 2.67; 95% CI, 0.52 to 13.75). Secondary: One study showed that 60% of patients receiving codeine/acetaminophen achieved ≥50% pain relief compared to 26% with placebo (RR, 2.28; 95% CI, 0.99 to 5.25). Three studies showed that opioids were associated with greater improvement in CGI within the first six weeks compared to placebo (RR, 1.44; 95% CI, 1.03 to 2.03; NNT, 6). There were no significant differences between opioids and placebo with regard to changes in function, as measured by HAQ (weighted mean difference, -0.10; 95% CI, -0.33 to 0.13). One study showed that codeine/acetaminophen led to a greater improvement in self-reported disability scale compared to placebo (*P*=0.04). The number of withdrawals due to inadequate analgesia was similar between opioids and placebo (RR, 0.82; 95% CI, 0.34 to 2.01). The risk of adverse events was higher in patients receiving opioids compared to patients receiving placebo (OR, 3.90; 95% CI, 2.31 to 6.56; NNH, 4). The most commonly reported adverse events were nausea, vomiting, dizziness, lightheadedness and constipation.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When a net efficacy was adjusted for risk, opioids provided no additional benefit compared to placebo (RR, 1.20; 95% CI, 0.89 to 1.61). Moreover, there were no significant differences in efficacy and safety between opioids and NSAIDs.
Eisenberg et al[68] Opioids vs placebo, opioids or non-opioid analgesics	MA (23 RCTs) Patients ≥18 years of age with neuropathic pain	N=727 Short-term: <24 hours (14 RCTs) Intermediate-term: 8 to 70 days (nine RCTs)	Primary: Change in pain intensity Secondary: Safety	Primary: Among the 14 short-term studies (n=267), the following opioids were compared to placebo: morphine, alfentanil, fentanyl, meperidine and codeine. Six trials showed greater pain relief with opioids compared to placebo; five trials showed equivalent efficacy between opioids and placebo; two trials demonstrated mixed efficacy and one trial showed a reduction in the affective but not the sensory component of pain. MA was performed on six trials and showed that opioids were associated with a lower pain intensity score by 16 points on a 100-point VAS compared to placebo (95% CI, -23 to -9; *P*<0.001). When analyzed separately for peripheral and central pain, the differences in pain intensity between opioids and placebo were 15 (95% CI, -23 to -7; *P*<0.001) and 18 points (95% CI, -30 to -5; *P*=0.006), respectively. MA on two trials using percentage of pain reduction showed an additional 26% reduction in pain with opioids vs placebo (95% CI, 17 to 35; *P*<0.00001). Among the nine intermediate-term studies (n=460), the following opioid analgesics were compared to placebo: morphine, oxycodone, methadone and levorphanol. Three of the trials also compared opioids to carbamazepine, nortriptyline, desipramine and gabapentin. Two of the trials compared different dosages of the same opioid, including methadone and levorphanol. MA of seven studies showed pain intensity score was 13 points lower with opioids than placebo (95% CI, -16 to -9; *P*<0.00001). Evoked pain intensity was measured in two studies, which showed that pain intensity was 24 points lower with opioids than placebo (95% CI, -33 to -15). Two studies showed a 6-point reduction in pain intensity with morphine or methadone compared to non-opioid analgesics (95% CI, -12 to 0). A dose-dependent analgesic effect was found with methadone and levorphanol (*P* values not reported). Secondary: When comparing opioids to placebo, there was a higher incidence of nausea (33 vs 9%; NNH, 4.2; 95% CI, 3.2 to 5.6), constipation (33 vs 10%; NNH, 4.2; 95% CI, 3.3 to 5.9), drowsiness (29 vs 12%; NNH, 6.2; 95% CI, 4.3 to 10.0), dizziness (21 vs 6%; NNH, 7.1; 95% CI, 5.0 to 11.1) and vomiting (15 vs 3%; NNH, 8.3; 95% CI, 5.6 to 14.3). In four intermediate-term studies, 11 and 4% of patients in the opioid and placebo groups withdrew due to adverse events (NNH, 16.7; 95% CI, 9.1 to 100.0).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Detoxification				
Madlung-Kratzer et al[69] Morphine slow-release vs methadone Patients continued their previous maintenance treatment for 3 consecutive days and then were randomized to treatment based on previous drug for maintenance treatment and dose level. Dose reduction regimens were started and maintained for 3 consecutive days under DB conditions. Thereafter, detoxification was initiated by tapered dose reductions	DB, MC, PG, RCT Patients ≥18 years of age with a confirmed diagnosis of opioid addiction, who have received maintenance treatment with either morphine slow-release or methadone at constant doses for ≥1 month	N=202 22 days	Primary: Non-inferiority of dose reduction regimens Secondary: Patient-reported outcomes and safety	Primary: Completion rate per treatment group was 51 and 49% in the morphine and methadone groups, resulting in a difference in completion rates between treatment groups of 2% (95% CI, -12 to 16). According to the prior-defined non-inferiority margin of -15%, morphine is non-inferior to methadone for detoxification. Secondary: At study entry, signs and symptoms of withdrawal were mild but deteriorated steadily over time (day 0 vs day 22; *P*<0.001). Craving for opiates varied considerably but was generally rated as moderate. No changes became evident during the detoxification phase and there were no significant differences between treatment groups over time, respectively (morphine: day 0, 35.4±35.1 mm; day 22, 32.0±35.1 mm; *P*=0.442; and methadone: day 0; 38.7±38.6 mm, day 22; 36.8±36.5 mm; *P*=0.813). Cravings for alcohol, cocaine and cannabis were low throughout detoxification without any significant differences between groups or over time (*P* values not reported). The proportion of patients reporting at least one adverse event was 16 and 13% in the morphine and methadone groups (*P*=0.586). The majority of adverse events were gastrointestinal system disorders (nausea, vomiting, and dentalgia), followed by psychiatric disorders (dysphoria, agitation, depression and panic attacks).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
over a period of 16 days in order to reach abstinence for 3 days.				

*Synonym for acetaminophen.
†Agent not available in the United States.
Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, MD=multi-dose, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single-arm, XO=crossover
Miscellaneous abbreviations: ACR=American College of Rheumatology, $AUCMB_{avg}$=average area under the curve of VAS scores overtime between baseline and end of study, BDI=Beck depression inventory, BPI=Brief Pain Inventory, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, CPSI=Chronic Pain Sleep Inventory, CRPS=Complex Regional Pain Syndrome, EORTC=European Organization for Research and Treatment of Cancer, HAQ=Health Assessment Questionnaire, HbA1c=glycosylated hemoglobin, MOS=Medical Outcomes Study, MPI=multidimensional pain inventory, MRI=magnetic resonance imaging, NNH=number needed to harm, NNT=number needed to treat, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, OR=odds ratio, PDI-Pain Disability Index, PGIC=Patient's Global Impression of Change, PPS=Play Performance Scale, SF-36=short form 36 health assessment questionnaire, RMDQ=Roland Morris Disability Questionnaire, RR=relative risk, SD=standard deviation, VAS=visual analog scale, WOMAC index=Western Ontario and McMaster Universities Index

Special Populations

Table 5. Special Populations[5,10,14-27]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	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 severe hepatic dysfunction.	C	Yes (% low); breast-feeding is not advised.
Fentanyl	Use with caution in the elderly. Approved for use in opioid-tolerant children ≥2 years of age.	Insufficient information exists; use with caution.	Insufficient information exists; use with caution.	C	Yes (% not reported); do not use in nursing women.
Hydromorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Renal dose adjustment is required in moderate renal impairment.	Hepatic dose adjustment is required in moderate and severe hepatic impairment.	C	Yes (% not reported); breast-feeding is not advised.
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.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Morphine sulfate	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Renal dose adjustment is required.	Hepatic dose adjustment is required.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
					women.
Oxycodone	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 and dose titration should follow a conservative approach.	Hepatic dose adjustment is required and careful dose titration is warranted.	B	Yes (% not reported); breast-feeding is not advised.
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, starting with lower doses and titrating the dosage slowly.	Caution should be used in patients with mild hepatic impairment; starting with the lowest dose and titrating the dosage slowly. Contra-indicated in moderate and severe hepatic impairment.	C	Unknown; caution should be exercised.
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.	Use with caution in patients with moderate hepatic impairment; not recommended in patients with severe hepatic impairment.	C	Insufficient/ limited information on the excretion of tapentadol in human breast milk; should not be used during breast feeding.
Combination Products					
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 is required in severe renal impairment.	Hepatic dose adjustment is required in severe hepatic impairment.	C	Yes (morphine sulfate; % variable); benefits and risks should be evaluated before use in nursing women.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[5,10,14-27]

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Central Nervous System									
Abnormal gait	-	✔	-	-	<5	<1	-	-	-
Agitation	-	✔	-	✔	<5	<1	<1	-	-
Anxiety	✔	3 to 10	0 to 4	-	<5 to 6	1 to 5	≥1 to <10	2	2.2
Aphasia	-	<1	-	-	-	-	-	-	-
Ataxia	-	-	-	-	<5	-	-	-	-
Balance disorder	-	-	<2	-	-	-	-	-	-
Central nervous system depression	-	-	-	-	-	-	<1	-	-
Cognitive disorder	-	-	<2	-	-	-	-	-	-
Coma	-	-	-	-	<5	-	-	-	-
Convulsions	-	✔	<2	-	<5	-	-	-	-
Coordination abnormal	-	✔	<2	-	-	-	-	-	<1
Depressed level of consciousness	-	-	<2	-	-	-	<1	-	<1
Depression	✔	3 to 10	3	-	<3 to 10	<1	≥1 to <10	1	≥1 to <10
Difficulty in walking	-	-	<2	-	-	-	-	-	-
Disturbance in attention	-	-	<2	-	-	-	-	1	<1
Dizziness	2 to 16	3 to 10	2 to 11	✔	6	13	4.8 to 17.8	17	1.2 to 7.7
Drowsiness	-	-	-	-	9	-	-	-	-
Dysarthria	-	-	<2	-	-	-	-	-	-
Dysgeusia	-	-	<2	-	-	-	-	-	-
Dyskinesia	-	-	<2	-	-	-	-	-	-
Encephalopathy	-	-	<2	-	-	-	-	-	-
Foot drop	-	-	-	-	<3	-	-	-	-
Headache	5 to 16	3 to 10	5 to 12	✔	<3 to >10	7	2.9 to 12.2	15	2.3 to 6.9
Hostility	-	<1	-	-	-	-	-	-	-
Hyperesthesia	-	-	<2	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	<1	-	-	-
Hyperreflexia	-	-	<2	-	-	-	-	-	-
Hypertonia	-	<1	-	-	-	-	-	-	-
Hypoesthesia	2	-	<2	-	-	<1	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Hypotonia	-	<1	-	-	-	<1	-	-	-
Irritability	-	-	-	-	-	-	-	-	≥1 to <10
Loss of concentration	-	-	-	-	<3	-	-	-	-
Memory impairment	-	-	<2	-	-	-	-	✔	<1
Mental impairment	-	-	-	-	-	-	<1	-	<1
Migraine	✔	-	-	-	-	<1	-	-	-
Myoclonus	-	-	<2	-	<3	-	-	-	-
Paresthesia	2	✔	<2	-	<3 to 10	<1	-	-	<1
Psychomotor hyperactivity	-	-	<2	-	-	-	-	-	-
Sedation	-	-	<2	✔	-	-	5.9	-	≥1 to <10
Seizures	-	-	-	✔	<3	<1	-	-	-
Somnolence	2 to 14	>10	1to 15	-	>10	23	1.9 to 19.1	12	1.2 to 13.9
Stupor	-	<1	-	-	-	<1	-	-	<1
Speech disorder	-	✔	-	-	<3	<1	-	-	-
Tremor	2	✔	<2	-	<5	<1	-	1	≥1 to <10
Vertigo	-	<1	<2	-	<5	<1	-	2	-
Visual disturbances	-	-	-	✔	-	<1	-	1	-
Dermatological									
Application site reaction	2 to 15	✔	-	-	-	-	-	-	-
Clamminess	-	-	-	-	-	-	<1	-	-
Cold sweat	-	-	-	-	-	-	-	-	<1
Decubitus ulcer	-	-	-	-	<3	-	-	-	-
Dermatitis	-	-	-	-	-	-	<1	-	-
Dry skin	-	-	-	-	<5	<1	-	-	-
Edema	-	✔	-	✔	<5	<1	≥1 to <10	-	-
Erythema	-	✔	<2	-	-	-	-	-	-
Exfoliative dermatitis	-	<1	-	-	-	<1	-	-	-
Hemorrhagic urticaria	-	-	-	✔	-	-	-	-	-
Hyperhidrosis	4	-	1 to 6	-	-	-	-	5	3.4
Itching	-	✔	-	-	-	-	-	-	-
Night sweats	-	-	-	-	-	-	-	-	<1
Other skin rashes	-	-	-	✔	-	-	-	-	-
Papules	-	✔	-	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Piloerection	-	-	-	-	-	-	-	-	<1
Pruritus	4	3 to 10	1 to 8	✔	<3	-	0 to 15.2	5	5.6 to 6.2
Pustules	-	<1	-	-	-	-	-	-	-
Rash	2	✔	3	-	<3 to 10	1 to 5	-	1	<1
Skin reaction localized	-	✔	-	-	-	-	-	-	-
Sweating	-	>10	-	✔	5 to 10	5	8.6 to >10.0	-	-
Urticaria	-	-	-	✔	<5	<1	<1	-	-
Gastrointestinal Disorders									
Abdominal distention	-	<1	<2	-	-	-	<1	-	<1
Abdominal pain	-	3 to 10	2 to 5	✔	<3 to 10	1 to 5	≥1 to <10	-	-
Abdominal pain; lower	-	-	-	-	-	-	-	-	<1
Abdominal pain; upper	-	-	-	-	-	-	-	-	1.1 to 2.3
Abdominal tenderness	-	-	-	-	-	-	-	-	<1
Abnormal feces	-	-	<2	-	-	-	-	-	-
Anal fissure	-	-	<2	-	-	-	-	-	-
Anorexia	2	3 to 10	1 to 6	✔	<3 to 10	1 to 5	-	-	≥1 to <10
Bezoar	-	-	<2	-	-	-	-	-	-
Biliary colic	-	-	-	-	<3	-	-	-	-
Biliary pain	-	-	-	-	<5	-	-	-	-
Biliary tract spasm	-	-	-	✔	✔	-	-	-	-
Constipation	3 to 14	>10	7 to 31	✔	9 to >10	23	5.7 to 27.6	17	7.0 to 31.2
Cramps	-	-	-	-	✔	-	-	-	-
Decreased appetite	-	-	-	-	-	-	≥1 to <10	2	≥1 to <10
Delayed gastric emptying	-	-	-	-	<3	-	-	-	-
Diarrhea	3	3 to 10	3 to 8	-	<3 to 10	1 to 5	≥1 to <10	-	1.1 to 7.0
Diverticulum	-	-	<2	-	-	-	-	-	-
Dry mouth	7	>10	1 to 5	✔	<3 to 10	6	≥1 to <10	7	1.8 to 5.7
Duodenitis	-	-	<2	-	-	-	-	-	-
Dyspepsia	3	3 to 10	4	-	<5	1 to 5	≥1 to <10	3	≥1 to <10
Dysphagia	-	-	<2	-	<5	<1	-	-	-
Eructation	-	-	<2	-	-	<1	-	-	-
Fecaloma	-	-	-	-	-	-	-	-	<1

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Flatulence	-	✔	<2	-	-	<1	-	-	≥1 to <10
Gastritis	-	-	-	-	-	1 to 5	-	-	-
Gastroenteritis	-	-	<2	-	<5	-	-	-	-
Gastro-esophageal reflux	-	-	-	-	<3	-	-	-	-
Gastrointestinal motility disorder	-	-	<2	-	-	<1	-	-	-
Glossitis	-	-	-	✔	-	-	-	-	-
Hematochezia	-	-	<2	-	-	-	-	-	-
Hemorrhoids	-	-	<2	-	-	-	-	-	-
Ileus	-	-	<2	-	-	<1	<1	-	-
Impaired gastric emptying	-	-	<2	-	-	-	-	-	-
Increased appetite	-	-	<2	-	-	<1	-	-	-
Intestinal obstruction	-	-	<2	-	-	-	-	-	-
Large intestine perforation	-	-	<2	-	-	-	-	-	-
Nausea	8 to 23	>10	9 to 28	✔	7 to >10	23	2.9 to 33.1	21	11.1 to 22.2
Pancreatitis	-	-	-	-	-	-	-	-	<1
Painful defecation	-	-	<2	-	-	-	-	-	-
Rectal disorder	-	-	-	-	<5	-	-	-	-
Stomach atony disorder	-	-	-	-	<3	-	-	-	-
Stomach discomfort	2	-	-	-	-	-	-	-	≥1 to <10
Stomatitis	-	-	-	-	-	<1	-	-	-
Thirst	-	-	-	-	<5	<1	-	-	-
Vomiting	2 to11	>10	6 to 14	✔	<3 to >10	12	0 to 15.6	8	4.1 to 8.4
Weight gain	-	-	-	✔	-	-	-	-	-
Weight loss	-	✔	1 to 3	-	<5	-	≥1 to <10	✔	-
Laboratory Values									
Abnormal liver function tests	-	-	-	-	<5	-	-	-	-
Alanine aminotransferase increased	-	-	-	-	-	-	-	-	<1
Anemia	-	-	-	-	<5	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	-	-	-	-	<1
Blood amylase increased	-	-	<2	-	-	-	-	-	-
Blood potassium decreased	-	-	<2	-	-	-	-	-	-
Blood testosterone decreased	-	-	<2	-	-	-	-	-	-
Gynecomastia	-	-	-	-	<3	-	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Hepatic enzyme increased	-	-	<2	-	-	-	-	-	-
Hypokalemia	-	-	-	✔	-	-	-	-	-
Hypomagnesemia	-	-	-	✔	-	-	-	-	-
Hyponatremia	-	-	-	-	<3	<1	-	-	-
Leukopenia	-	-	-	-	<3	-	-	-	-
Oxygen saturation decreased	-	-	<2	-	-	-	<1	-	-
Syndrome of inappropriate antidiuretic hormone secretion	-	-	-	-	-	<1	-	-	-
Thrombocytopenia; reversible	-	-	-	✔	<5	-	-	-	-
Psychiatric Disorders									
Abnormal dreams	-	✔	<2	-	<5	1 to 5	-	1	<1
Aggression	-	-	<2	-	-	-	-	-	-
Amnesia	-	✔	-	-	<5	<1	-	-	-
Apathy	-		-	-	<3	-	-	-	-
Confusional state	2	>10	<2	✔	<5	1 to 5	≥1 to <10	-	<1
Crying	-	-	<2	-	-	-	-	-	-
Delirium	-	-	-	-	<5	-	-	-	-
Depersonalization	-	<1	-	-	-	<1	-	-	-
Disorientation	-	-	-	✔	-	-	≥1 to <10	-	<1
Dysphoria	-	-	<2	✔	-	-	<1	-	-
Emotional lability	-	-	-	-	-	<1	-	-	-
Euphoric mood	-	3 to 10	<2	✔	<5	1 to 5	<1	✔	<1
Hallucination	-	3 to 10	<2	✔	<5	<1	<1	-	<1
Insomnia	3	3 to 10	3 to 7	✔	<3 to 10	1 to 5	≥1 to <10	4	1.3 to 2.9
Listless	-	-	<2	-	-	-	-	-	-
Mental status changes	-	-	-	-	-	-	<1	-	<1
Mood altered	-	-	<2	-	-	-	-	-	-
Mood swings	-	-	-	-	-	-	-	-	<1
Nervousness	-	3 to 10	<2	-	<5	1 to 5	≥1 to <10	-	<1
Panic attack	-	-	<2	-	-	-	-	-	-
Paranoid reaction	-	✔	<2	-	-	-	-	-	-
Restlessness	-	-	<2	-	-	-	≥1 to <10	-	≥1 to <10
Suicide ideation	-	-	<2	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Thinking abnormal	-	✔	-	-	<5	1 to 5	-	✔	<1
Other									
Abnormal ejaculation	-	-	-	-	<5	-	-	-	-
Accidental injury	-	✔	-	-	<3 to 10	<1	-	-	-
Allergic reaction	-	✔	-	-	-	-	<1	-	-
Amblyopia	-	<1	-	-	<5	-	-	-	-
Amenorrhea	-	-	-	✔	<3	<1	-	-	-
Anaphylactic reaction	-	-	-	-	-	<1	-	-	-
Anorgasmia	-	✔	-	-	-	-	-	-	-
Apnea	-	3 to 10	-	-	-	-	-	-	-
Arrhythmia	-	✔	-	✔	-	-	-	-	-
Arthralgia	2	-	2 to 6	-	<3	-	-	-	≥1 to <10
Asthenia	-	>10	1 to 11	✔	<3 to 10	6	-	2	<1
Asthma	-	<1	-	-	<3	-	-	-	-
Atelectasis	-	-	-	-	<3	-	-	-	-
Atrial fibrillation	-	-	-	-	<3	-	-	-	-
Back pain	3	3 to 10	3 to 4	-	<3 to 10	-	-	-	-
Bladder pain	-	<1	-	-	-	-	-	-	-
Bone pain	-	-	-	-	<3	-	-	-	-
Bradycardia	-	<1	<2	✔	<5	-	<1	-	-
Bronchitis	-	✔	-	-	-	-	-	-	-
Bronchospasm	-	-	<2	-	-	-	-	-	-
Cardiomyopathy	-	-	-	✔	-	-	-	-	-
Chest discomfort	-	-	2	-	-	-	-	-	-
Chest pain	-	✔	-	-	<3	<1	-	-	-
Chills	-	-	<2	-	<3	1 to 5	-	1	≥1 to <10
Conjunctivitis	-	-	-	-	<3	-	-	-	-
Contusion	-	-	<2	-	-	-	-	-	-
Coughing	-	✔	-	-	-	<1	-	-	-
Decreased libido	-	✔	<2	✔	<5	<1	-	-	-
Dehydration	-	-	<2	-	-	<1	≥1 to <10	-	-
Depressed cough reflex	-	-	-	-	<3	-	-	-	-
Diaphoresis	-	-	-	-	<3	-	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Difficult micturition	-	-	-	-	-	-	<1	-	-
Drug withdrawal syndrome	-	-	2 to 10	-	<5	<1	-	-	<1
Diplopia	-	-	<2	-	<3	-	-	-	-
Dry eye	-	-	<2	-	-	-	-	-	-
Dyspnea	3	3 to 10	3	-	<3 to 10	1 to 5	≥1 to <10	1	<1
Dysuria	-	-	<2	-	<5	<1	-	-	<1
Electrocardiogram abnormalities	-	-	-	✔	-	-	-	-	-
Edema peripheral	7	-	2 to 5	-	<3 to 10	<1	-	-	≥1 to <10
Ejaculatory difficulty	-	✔	-	-	-	-	-	-	-
Erectile dysfunction	-	-	<2	-	-	-	-	1	<1
Extrasystoles	-	-	<2	✔	-	-	-	-	-
Eye pain	-	-	-	-	<5	-	-	-	-
Facial edema	-	-	-	-	-	<1	-	-	-
Facial flushing	-	-	-	-	<3	-	-	-	-
Fall	4	-	2	-	-	-	-	-	-
Fatigue	5	3 to 10	-	-	-	-	≥1 to <10	9	4.1
Feeling abnormal	-	-	<2	-	-	-	-	-	-
Feeling drunk	-	-	<2	-	-	-	-	-	-
Feeling hot and cold	-	-	<2	-	-	-	-	-	-
Feeling jittery	-	-	<2	-	-	-	<1	-	<1
Fever	-	3 to 10	-	-	<3 to 10	1 to 5	-	-	-
Flu syndrome	-	-	-	-	<3 to 10	-	-	-	-
Fluid retention	-	-	<2	-	-	-	-	-	-
Flushing	-	✔	<2	✔	<3	-	≥1 to <10	-	<1.0 to 2.3
Hangover	-	-	<2	-	-	-	-	-	-
Heart failure	-	-	-	✔	-	-	-	-	-
Hematuria	-	-	-	-	-	<1	-	-	-
Hemoptysis	-	✔	-	-	-	-	-	-	-
Hiccups	-	✔	-	-	<5	1 to 5	-	-	-
Hot flashes	-	-	-	-	-	-	<1	-	-
Hot flush	-	-	-	-	-	-	-	2	≥1 to <10
Hypersensitivity	-	-	-	-	-	-	<1	✔	-
Hypertension	✔	✔	<2	-	<5	-	≥1 to <10	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Hyperuricemia	-	-	<2	-	-	-	-	-	-
Hyperventilation	-	-	<2	-	-	-	-	-	-
Hypogonadism	-	-	<2	-	-	-	-	-	-
Hypotension	-	-	<2	✔	<5	-	<1	-	<1
Hypothermia	-	-	<2	-	-	-	-	-	-
Hypoventilation	-	3 to 10	-	-	<5	-	-	-	-
Hypoxia	-	-	<2	-	<3	-	<1	-	-
Impotence	-	-	-	-	<5	<1	-	-	-
Infection	-	-	-	-	5 to 10	-	-	-	-
Influenza-like symptoms	✔	3 to 10	-	-	-	-	-	-	-
Joint swelling	3	-	-	-	-	-	-	-	-
Lightheadedness	-	-	-	✔	✔	-	-	-	-
Lethargy	-	-	-	-	<5	-	≥1 to <10	1	≥1 to <10
Lymphadenopathy	-	-	-	-	-	<1	-	-	-
Malaise	-	-	<2	-	<5	<1	-	-	<1
Micturition disorder	-	-	<2	-	-	-	-	-	-
Miosis	-	-	<2	-	<3	-	<1	-	-
Muscle spasms	-	-	1 to 3	-	-	-	-	-	≥1 to <10
Muscle weakness	-	-	-	-	-	-	-	-	<1
Myalgia	✔	-	<2	-	-	-	-	-	<1
Neck pain	✔	-	-	-	-	<1	-	-	-
Non-cardiogenic pulmonary edema	-	-	-	-	<3	-	-	-	-
Nystagmus	-	-	-	-	<3	-	-	-	-
Oliguria	-	<1	-	-	<5	-	-	-	-
Orthostatic hypotension	-	-	-	-	-	-	-	-	<1
Overdose	-	-	<2	-	-	-	-	-	-
Pain	✔	3 to 10	2	-	<3	<1	-	-	-
Pain in extremity	3	-	3	-	-	-	-	-	-
Pallor	-	-	-	-	<3	-	-	-	-
Palpitations	-	-	<2	✔	<5	-	<1	-	-
Pharyngitis	-	3 to 10	-	-	-	<1	-	-	-
Polyuria	-	-	-	-	-	<1	-	-	-
Postural hypotension	-	-	-	-	-	1 to 5	<1	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Pulmonary edema	-	-	-	✔	-	-	-	-	-
Pyrexia	-	-	2	-	-	-	≥1 to <10	-	-
QT interval prolongation	-	-	-	✔	-	-	-	-	-
Respiratory depression	-	✔	<2	✔	-	-	<1	-	-
Respiratory disorder	-	<1	-	-	-	-	-	-	-
Respiratory distress	-	-	<2	-	-	-	<1	-	-
Respiratory insufficiency	-	-	-	-	<3	-	-	-	-
Respiratory rate decreased	-	-	-	-	-	-	<1	✔	-
Rhinorrhea	-	-	<2	-	-	-	-	-	<1
Rhinitis	-	✔	-	-	<3	-	-	-	-
Rigors	-	✔	-	-	-	-	-	-	-
Sexual dysfunction	-	-	<2	-	-	-	-	✔	-
Sinusitis	-	✔	-	-	-	-	-	-	-
Skeletal muscle rigidity	-	-	-	-	<5	-	-	-	-
Sneezing	-	-	<2	-	-	-	-	-	-
ST depression	-	-	-	-	-	<1	-	-	-
Stertorous breathing	-	<1	-	-	-	-	-	-	-
Syncope	-	✔	<2	✔	<5	<1	<1	-	-
T-wave inversion	-	-	-	✔	-	-	-	-	-
Tachycardia	-	✔	<2	✔	<5	-	<1	-	-
Taste perversion	-	-	-	-	<5	<1	-	-	-
Tinnitus	-	-	<2	-	-	<1	-	-	-
Torsade de pointes	-	-	-	✔	-	-	-	-	-
Twitching	-	-	-	-	-	1 to 5	-	-	-
Upper respiratory tract infection	✔	3 to 10	-	-	-	-	-	-	-
Urinary abnormality	-	-	-	-	<3	-	-	-	-
Urinary frequency	-	<1	<2	-	-	-	-	-	-
Urinary hesitancy	-	-	<2	✔	<3	-	-	✔	-
Urinary retention	-	-	<2	✔	<5	<1	<1	-	<1
Urinary tract infection	3	-	-	-	5 to 10	-	-	-	-
Urination impaired	-	-	-	-	-	<1	-	-	-
Vasodilation	-	-	-	-	<5	<1	-	-	-
Ventricular fibrillation	-	-	-	✔	-	-	-	-	-

Adverse Drug Event	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone*	Metha-done*	Morphine Sulfate†	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone*
Ventricular tachycardia	-	-	-	✔	-	-	-	-	-
Vision blurred	-	✔	<2	-	<3	-	≥1 to <10	-	<1
Voice alteration	-	-	-	-	<5	<1	-	-	-
Weakness	-	-	-	-	✔	-	≥1 to <10	-	-

*During dosage titration and maintenance therapy.
†At least one dosage formulation.
✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[5,10,14-27]

Contraindication(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days	-	-	-	-	-	-	-	✔	-
Hypersensitivity to any components or the active ingredient	✔	✔	✔	✔	✔	✔	✔	✔	-
Management of acute pain or in patients who require opioid analgesia for a short period of time	-	✔	-	-	-	-	-	-	-
Management of intermittent pain (e.g., use on an as-needed basis)	-	✔	-	-	-	-	-	-	-
Management of mild pain	-	✔	-	-	-	-	-	-	-
Management of postoperative pain, including use after out-patient or day surgeries	-	✔	-	-	-	-	-	-	-
Moderate and severe hepatic impairment	-	-	-	-	-	-	✔	-	-
Opioid non-tolerant patients	-	✔	✔	-	-	-	-	-	-
Preexisting gastrointestinal surgery or narrowing of gastrointestinal tract	-	-	✔	-	-	-	-	-	-
Respiratory depression, significant	✔	✔	✔	✔	✔	✔	✔	✔	✔

Contraindication(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Acute or severe bronchial asthma	✔	✔	✔	✔	✔	✔	✔	✔	✔
Suspected or documented paralytic ileus	✔	✔	✔	✔	✔	✔	✔	✔	✔

Boxed Warnings

Boxed Warning for Butrans® (buprenorphine)[5]

WARNING

Abuse Potential
Butrans® contains buprenorphine, an opioid agonist and Schedule III controlled substance with an abuse liability similar to other Schedule III opioids, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Butrans®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Butrans® for signs of misuse, abuse, and addiction during treatment.

Life-Threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with use of Butrans®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Butrans® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Butrans® or following a dose increase.

Accidental Exposure
Accidental exposure to Butrans®, especially in children, can result in a fatal overdose of buprenorphine.

Boxed Warning for Duragesic® (Fentanyl)[17]

WARNING

Abuse Potential
Duragesic® contains fentanyl, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. Duragesic® can be abused in a manner similar to other opioid agonists, legal or illicit. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing Duragesic® and then routinely monitor all patients for signs of misuse, abuse and addiction during treatment

Respiratory Depression and Death
Respiratory depression and death may occur with use of Duragesic®, even when Duragesic® has been used as recommended and not misused or abused. Proper dosing and titration are essential and Duragesic® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Duragesic® is contraindicated for use in conditions in which the risk of life-threatening respiratory depression is significantly increased, including use as an

WARNING
as-needed analgesic, use in non-opioid tolerant patients, acute pain, and postoperative pain. Monitor for respiratory depression, especially during the first two applications following initiation of dosing, or following an increase in dosage. Accidental Exposure Death and other serious medical problems have occurred when children and adults were accidentally exposed to Duragesic®. Advise patients about strict adherence to the recommended handling and disposal instructions in order to prevent accidental exposure. Cytochrome P450 3A4 Interaction The concomitant use of Duragesic® with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Monitor patients receiving Duragesic® and any CYP3A4 inhibitor Exposure To Heat The Duragesic® application site and surrounding area must not be exposed to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds. Exposure to heat may increase fentanyl absorption and there have been reports of overdose and death as a result of exposure to heat. Patients wearing Duragesic® systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of Duragesic® to avoid overdose and death.

Boxed Warning for Exalgo® (hydromorphone)[16]

WARNING
Abuse Potential Exalgo® contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Exalgo®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Exalgo® for signs of misuse, abuse, and addiction during treatment. Life-Threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Exalgo®, even when the drug has been used as recommended and not misused or abused. Exalgo® is for use in opioid tolerant patients only. Proper dosing and titration are essential and Exalgo® should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Exalgo® or following a dose increase. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of hydromorphone. Accidental Exposure Accidental ingestion of Exalgo®, especially in children, can result in a fatal overdose of hydromorphone.

Boxed Warning for Dolophine®, Methadose® (methadone)[15,19-21]

WARNING
Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks. Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction Code of Federal Regulations, Title 42, Sec 8 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). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program. Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment: • During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis. • During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

Boxed Warning for morphine sulfate extended-release tablet[22]

WARNING
Abuse potential: Morphine sulfate extended-release tablets contain morphine; an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing morphine sulfate extended-release tablets. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving morphine sulfate extended-release tablets for signs of misuse, abuse, and addiction during treatment. Life-threatening respiratory depression: Respiratory depression, including fatal cases, may occur with use of morphine sulfate extended-release tablets, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and morphine sulfate extended-release tablets should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of morphine sulfate extended-release tablets or following a dose increase. Instruct patients to swallow morphine sulfate extended-release tablets whole. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of morphine.

WARNING
Accidental exposure: Accidental ingestion of morphine sulfate extended-release tablets, especially in children, can result in a fatal overdose of morphine.

Boxed Warning for Avinza® (morphine sulfate extended-release capsules)[14]

WARNING
Abuse Potential Avinza® contains pellets of morphine sulfate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Avinza®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Avinza® for signs of misuse, abuse, and addiction during treatment Life-Threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Avinza®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Avinza® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Avinza® or following a dose increase. Instruct patients to swallow Avinza® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental ingestion of Avinza®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Avinza® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Avinza® therapy.

Boxed Warning for Kadian® (morphine sulfate extended-release capsule)[18]

WARNING
Abuse Potential Kadian® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Kadian®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Kadian® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Kadian®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Kadian® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Kadian® or following a dose increase. Instruct patients to swallow Kadian® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can

WARNING
cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Kadian®, especially in children, can result in a fatal overdose of morphine.

Boxed Warning for MS Contin® (morphine sulfate controlled-release)[23]

WARNING
Abuse Potential MS Contin® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing MS Contin®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving MS Contin® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of MS Contin®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and MS Contin® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of MS Contin® or following a dose increase. Instruct patients to swallow MS Contin® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of MS Contin®, especially in children, can result in a fatal overdose of morphine.

Boxed Warning to OxyContin® (oxycodone controlled-release)[27]

WARNING
Abuse Potential OxyContin® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of OxyContin®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and OxyContin® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OxyContin® or following a dose increase. Instruct patients to swallow OxyContin® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

WARNING
Accidental Exposure Accidental consumption of OxyContin®, especially in children, can result in a fatal overdose of morphine.

Boxed Warning for Opana ER® (oxymorphone extended-release)[25]

WARNING
Abuse Potential Opana ER® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Opana ER®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Opana ER® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Opana ER®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Opana ER® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Opana ER® or following a dose increase. Instruct patients to swallow Opana ER® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Opana ER®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Opana ER® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Opana ER® therapy.

Boxed Warning for Nucynta ER® (tapentadol extended-release)[24]

WARNING
Abuse Potential Nucynta ER® contains tapentadol, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Nucynta ER®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Nucynta ER® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Nucynta ER®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Nucynta ER® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Nucynta ER® or following a dose increase. Instruct patients to swallow

WARNING
Nucynta ER® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Nucynta ER®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Nucynta ER® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Nucynta ER® therapy.

Boxed Warning for Embeda® (morphine sulfate/naltrexone)[10]

WARNING
Abuse Potential Embeda® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Embeda®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Embeda® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Embeda®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Embeda® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Embeda® or following a dose increase. Instruct patients to swallow Embeda® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Embeda®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Embeda® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Embeda® therapy.

Warnings and Precautions

Table 8. Warnings and Precautions[5,10,14-27]

Warning(s)/Precaution(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Accidental exposure; can result in a fatal overdose, especially in children	✔	-	-	-	✔	✔	-	✔	-
Acute abdominal conditions; administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions	-	-	-	✔	-	✔	-	-	-
Ambulatory surgery and postoperative use; not indicated for pre-emptive analgesia and only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time	-	-	-	-	-	-	✔	-	-
Anaphylaxis have been reported	✔	-	-	-	✔	-	-	-	✔
Application of external heat; avoid exposing the application site and surrounding area to direct external heat sources	✔	✔	-	-	-	-	-	-	-
Application site skin reactions	✔	-	-	-	-	-	-	-	-
Cardiac disease; may produce bradycardia	-	✔	-	-	-	-	-	-	-
Central nervous system depression; may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma	✔	-	-	-	-	-	-	✔	-
Coadministration of anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone; dose should be adjusted accordingly	-	-	-	✔	-	-	-	-	-
Cordotomy	-	-	-	-	✔ (Kadian®)	-	-	-	✔
Cytochrome P450 inducers; should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly	-	-	-	✔	-	✔	-	-	-

Warning(s)/Precaution(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Cytochrome P450 inhibitors; may result in an increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression	-	✔	-	✔	-	✔	-	-	-
Difficulty in swallowing and risk for obstruction in patients at risk for a small gastrointestinal lumen; there have been post-marketing reports of difficulty in swallowing the dosage form	-	-	-	-	-	✔	-	-	-
Driving and operating machinery	✔	✔	✔	-	✔	✔	✔	✔	✔
Gastrointestinal obstruction; do not administer to patients with gastrointestinal obstruction, especially paralytic ileus	✔	-	✔	-	✔	✔	✔	✔	✔
Head injury and increased intracranial pressure	✔	✔	✔	✔	✔	-	✔	✔	✔
Hepatic or renal disease; clearance may be reduced in patients with hepatic dysfunction, while the clearance of its metabolites may be decreased in renal dysfunction	-	✔	-	-	✔	✔	✔	✔	-
Hepatotoxicity	✔	-	-	-	-	-	-	-	-
Hypotensive effect; may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs	✔	-	✔	✔	✔	✔	✔	✔	✔
Impaired respiration/respiratory depression	✔	✔	✔	✔	✔	✔	✔	✔	✔
Interactions with alcohol and drugs of abuse; additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression	✔	✔	-	✔	✔	✔	✔	✔	✔
Interactions with mixed agonist/antagonist opioid analgesics; may reduce the analgesic effect and/or may precipitate withdrawal symptoms	-	-	-	✔	✔	✔	-	-	-
Interactions with other central nervous system depressants; may result in respiratory depression, hypotension, and profound sedation or coma	-	✔	✔	✔	✔	✔	✔	-	✔

Warning(s)/Precaution(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Misuse, abuse and diversion	✔	✔	✔	✔	✔	✔	✔	✔	✔
Monoamine oxidase inhibitors; not recommended for use in patients who have received monoamine oxidase inhibitors within 14 days	✔	-	✔	✔	-	-	-	-	-
Pancreatic/biliary tract disease; use with caution in patients with biliary tract disease, including acute Pancreatitis	-	✔	✔	-	✔	✔	✔	✔	✔
Patients with fever; patients should be monitored for opioid adverse events and the dose should be adjusted if necessary	✔	✔	-	-	-	-	-	-	-
Precipitation of withdrawal; mixed agonist/antagonist analgesics should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic	-	-	✔	-	-	-	-	✔	✔
QTc prolongation	✔	-	-	✔	-	-	-	-	-
Seizures	✔	-	-	-	-	✔	-	✔	-
Risk of relapse; abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms	-	-	-	✔	-	-	-	-	-
Serotonin syndrome risk	-	-	-	-	-	-	-	✔	-
Special risk groups; should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients; caution should be exercised in the administration to patients with central nervous system depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure disorders	✔	-	✔	✔	✔	✔	✔	✔	✔
Sulfites; contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes	-	-	✔	-	-	-	-	-	-

Warning(s)/Precaution(s)	Single Entity Agents								Combination Products
	Bupren-orphine	Fentanyl	Hydro-morphone	Metha-done	Morphine Sulfate	Oxy-codone	Oxy-morphone	Tapent-adol	Morphine Sulfate/ Naltrexone
Tolerance and physical dependence may develop	-	✔	-	✔	✔	✔	-	-	✔
Use in addiction treatment; has not been studied and is not approved for use in the management of addictive disorders	✔	-	-	-	-	-	-	-	-
Use in patients with chronic pulmonary disease; monitor patients for respiratory depression, particularly when initiating therapy and titrating therapy	-	-	-	-	✔	✔	-	✔	-

Drug Interactions

Table 9. Drug Interactions[4]

Drug	Interacting Medication	Potential Result
Buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone	Barbiturate anesthetics	The dose of thiopental required to induce anesthesia may be reduced in the presence of narcotic analgesics. Apnea may be more common with this combination. Drug actions may be additive
Buprenorphine, fentanyl, methadone, oxycodone	Azole antifungals	The pharmacologic effects and adverse reactions of certain opioid analgesics may be increased. Possible inhibition of certain opioid analgesic metabolism (CYP3A4) by azole antifungal agents.
Buprenorphine, fentanyl, methadone, oxycodone	Macrolide and related antibiotics	Fentanyl plasma concentrations may be elevated, increasing the pharmacologic effects and toxicity. Inhibition of fentanyl metabolism (CYP3A4) by macrolide and related antibiotics.
Buprenorphine, fentanyl, oxycodone	Protease inhibitors	Opioid analgesic plasma concentrations may be increased and the half-life prolonged, increasing the risk of adverse reactions (e.g., respiratory depression). Possible inhibition of opioid analgesic metabolism (CYP3A4) in the gut wall and liver.
Buprenorphine, methadone	Benzodiazepines	Increased risk of sedation and life-threatening respiratory depression, especially with overdosage; synergistic effects of opioids and benzodiazepines.
Fentanyl, oxycodone	Rifamycins	Oxycodone plasma concentrations may be reduced, decreasing the pharmacologic effects (e.g., pain management). Oral bioavailability of oxycodone is decreased. Increased oxycodone metabolism (CYP3A4) by rifamycins. Oral bioavailability of oxycodone is decreased. Fentanyl plasma concentrations may be reduced, decreasing fentanyl efficacy. Induction of fentanyl metabolism (CYP3A4) by rifamycins is suspected.
Buprenorphine	Methadone	Narcotic agonists/antagonists may decrease or potentiate the pharmacologic effects of methadone. Narcotic agonists/antagonists potentiate or block the effect of methadone by competitively binding with opiate receptors.
Fentanyl	Amiodarone	Profound bradycardia, sinus arrest, and hypotension have occurred.
Fentanyl	Diltiazem	Opioid analgesic plasma concentrations may be elevated, increasing the pharmacologic effects and risk of toxicity (e.g., severe respiratory depression). Inhibition of opioid analgesic metabolism (CYP3A4) by diltiazem.
Methadone	Fluvoxamine	Increased serum methadone concentrations with possible toxicity. Fluvoxamine may inhibit the hepatic metabolism of methadone.
Methadone	Hydantoins	The actions of methadone may be reduced. Patients receiving chronic methadone treatment may experience withdrawal symptoms. Hydantoins appear to increase the metabolic clearance of methadone.
Methadone	Quinolones	Methadone plasma levels may be elevated by ciprofloxacin and

Drug	Interacting Medication	Potential Result
		norfloxacin, increasing pharmacologic effects and adverse reactions. Coadministration of methadone and gatifloxacin, levofloxacin, or moxifloxacin may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes. Inhibition of methadone metabolism (CYP1A2 and 3A4). Possible additive prolongation of the QT interval with methadone and certain quinolones. In addition, methadone inhibits cardiac potassium channels.
Methadone	Rifamycins	The actions of methadone may be reduced. Patients receiving chronic methadone treatment may experience withdrawal symptoms. Rifampin primarily appears to stimulate the hepatic and intestinal metabolism of methadone.
Morphine	Remifentanil	The analgesic effect of morphine may be decreased. Unknown; however, acute opioid tolerance and postanesthetic hyperalgesia have been proposed as a possible cause.
Morphine	Rifamycins	The analgesic effects of morphine may be decreased.
Oxycodone	Serotonin reuptake inhibitors	The risk of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may be increased.

Dosage and Administration

When selecting an individualized initial dose for any of the long-acting opioids, taking into account the patient's prior opioid and non-opioid analgesic treatment, consideration should be given to the general condition and medical status of the patient, the daily dose, potency and kind of analgesic(s) the patients has been taking, the reliability of the conversion estimate used to calculate the dose of the new long-acting opioid, the patient's opioid exposure and opioid tolerance (if any), any safety issues associated with the specific long-acting opioid, and the balance between pain control and adverse outcomes.[5,10,14-27]

Fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface such as the chest, back, flank or upper arm. Each system may be worn continuously for 72 hours and then removed and disposed of immediately. The next system should be applied to a different skin site.[17]

Hydromorphone-, oxycodone-, and oxymorphone-containing long-acting opioids should be swallowed whole and should not be broken, crushed, dissolved or chewed before swallowing.[6,15-17] Hydromorphone-containing agents are to be administered once daily, while oxycodone- and oxymorphone-containing agents can be administered twice daily.[16,25-27]

Methadone differs from many of the other long-acting opioids due to pharmacokinetic properties; high interpatient variability in absorption, metabolism, and relative analgesic potency. For these reasons, it is necessary that a cautious and highly individualized approach to prescribing methadone is practiced. When methadone is used for the treatment of opioid addiction in detoxification or maintenance programs, it is only to be dispensed by opioid treatment programs certified by the Substance Abuse and Mental Health Service Administration and approved by the designated state authority. Also, these programs must only dispense oral formulations of methadone according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). The methadone concentrate is for oral administration only and should never be injected.[15,19-21]

All of the morphine sulfate containing long-acting opioid formulations must be swallowed whole and should not be broken, crushed, dissolved, or chewed before swallowing. The contents of the Avinza® and Kadian® capsules may be opened and sprinkled on a small amount of applesauce immediately prior to

ingestion. Avinza® is the only morphine-sulfate containing long-acting opioid that is available for once-daily dosing. Kadian® can be administered once- or twice-daily and the remaining morphine-sulfate containing long-acting opioids can be administered twice- or three-times daily. Avinza® is also the only long-acting opioid with a maximum daily dose (1,600 mg/day).[14,18,22,23]

Embeda® (morphine sulfate/naltrexone) capsules can be administered once or twice daily. Patients should swallow the capsules whole or sprinkle the contents on applesauce.[10]

Table 10. Dosing and Administration[5,10,14-27]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	The management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time: Transdermal system: intended to be worn for seven days; in opioid-naïve patients, the initial dose is 5 µg/hour; for patients already receiving opioids, conversion instructions should be consulted; dose should not be increased until the patient has been exposed continually to the previous dose for 72 hours; the intent of the titration period is to establish a patient-specific weekly dose that will maintain adequate analgesia with tolerable adverse events for as long as pain management is necessary	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Transdermal system: 5 µg/hour 10 µg/hour 20 µg/hour
Fentanyl	The management of persistent, moderate to severe chronic pain in opioid-tolerant patients two years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids: Transdermal system: 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	Approved for use in opioid-tolerant children ≥2 years of age. The management of persistent, moderate to severe chronic pain in opioid-tolerant patients two years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by	Transdermal system:* 12 µg/hour 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour

Generic Name	Adult Dose	Pediatric Dose	Availability
		other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids: Transdermal system: 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	
Hydromorphone	The management of moderate to severe pain in opioid tolerant patients (taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid, for a week or longer) requiring continuous, around-the-clock opioid analgesia for an extended period of time: Extended release tablets: initial, starting dose should be equivalent to the patient's total daily oral hydromorphone dose taken once daily; maintenance, dose may be titrated every three to four days until adequate pain relief with tolerable adverse events have been achieved; 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	Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Extended release tablets:* 8 mg 12 mg 16 mg 32 mg
Methadone	For the treatment of moderate to severe pain not responsive to non-narcotic analgesics:	Safety and efficacy in pediatric	Concentrate (sugar-free available): 10 mg/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	Solution, tablet: for opioid-naïve patients, initial, 2.5 to 10 mg every eight to 12 hours; maintenance, slowly titrate to effect; for opioid-experienced patients, dose is based on total daily morphine sulfate dose; optimal methadone initiation and dose titration strategies for the treatment of pain have not been determined 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, 40 mg/day 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	patients ≤18 years of age have not been established.	Dispersible tablet: 40 mg Solution: 5 mg/5 mL 10 mg/5 mL Tablet: 5 mg 10 mg
Morphine sulfate	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 (Kadian®, MS Contin®), extended release tablet: daily requirements are established using immediate-release morphine sulfate For the relief of moderate to severe pain requiring continuous, around the clock opioid therapy for an extended period of time: Extended release capsule (Avinza®): initial, 30 mg once daily in opioid-naïve patients; maintenance, titrate conservatively; maximum, 1,600 mg/day For the relief of pain in patients who	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	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

Generic Name	Adult Dose	Pediatric Dose	Availability
	require opioid analgesics for more than a few days: Tablet (Oramorph SR®: daily requirements are established using immediate release morphine sulfate		60 mg 100 mg† 200 mg† Tablet (Oramorph SR®) 15 mg 30 mg 60 mg 100 mg
Oxycodone	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: initial, 10 mg every 12 hours; maintenance, titrate to adequate analgesia	Safety and efficacy in the pediatric population have not been established.	Extended release tablet: 10 mg 15 mg‖ 20 mg 30 mg‖ 40 mg 60 mg*,‖ 80 mg*
Oxymorphone	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: opioid-naïve patients, initial, 5 mg every 12 hours; maintenance, titrate at increments of 5 to 10 mg every 12 hours every three to seven days; opioid-experienced patients, initial, half of the calculated total daily dose of oxymorphone extended-release	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Extended release tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg
Tapentadol	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: Extended release tablet: initial, 50 mg twice daily; maintenance, titrate to adequate analgesia	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	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: once or twice a day; 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	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	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 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.

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. In terms of specific etiologies of pain, opioids are recognized as a possible treatment option for the treatment of noncancer pain, osteoarthritis pain, lower back pain, gout pain and neuropathic pain. Only weak opioids are recommended for the treatment of pain associated with fibromyalgia; strong opioids are not recommended in these patients.

Specific to the long-acting opioids, proposed benefits of these agents when administered around-the-clock include more consistent control of pain, improved adherence, and lower risk of abuse or addiction; however, to date, no well-conducted clinical trials have clearly proven these benefits.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network: **Adult Cancer Pain (2013)**[71]	• Pain is one of the most common symptoms associated with cancer. • The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which 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. • This guideline is unique it that it contains the following components: o In order to maximize patient outcomes, pain is an essential component of oncology management. o Analgesic therapy must be administered in conjunction with management of multiple symptoms or symptom clusters and complex pharmacologic therapies that patients with cancer are generally prescribed. o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect. o Persistent cancer pain often requires treatment with regularly scheduled analgesics with supplemental doses of analgesics provided as needed to manage breakthrough pain. o Psychosocial support must be available. o Specific educational material must be provided to the patient. • The pain management algorithm distinguishes three levels of pain intensity, based on a zero to 10 numerical rating scale: severe pain (seven to 10), moderate pain (four to six) and mild pain (one to three). • Pain associated with oncology emergency should be addressed while treating the underlying condition. • Patients considered to be opioid tolerant are those who are taking >60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer. Patients not meeting this definition are considered opioid naïve. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as

Clinical Guideline	Recommendations
	patient and family education. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. • 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. • Opioid-naïve patients experiencing mild pain intensity should receive nonopioids analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids. • 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. Opioids with rapid onset and short duration as preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice at an initial oral dose of 5 to 15 mg. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (fentanyl, morphine, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. • Due to the ease of titration, opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid. • Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. Methadone use should be initiated by physicians with experience and expertise in its use. • At a maximum dose of 400 mg/day, tramadol is less potent than other opioids and is approximately 1/10 as potent as morphine. • 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. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients

Clinical Guideline	Recommendations
	who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. • The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” • “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. 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. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. • For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate, 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended. • Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. • If the pain decreases to 4 to 6, the same dose of opioid is repeated and reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered “as needed” over the initial 24 hours before proceeding to subsequent management strategies. • No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse events, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new “rescue dose” must be increased by 10 to 20%. • Subsequent treatment is based upon the patient’s continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families.

Clinical Guideline	Recommendations
	• Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. • Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attention should also be focused on psychosocial support and providing education to patients and families.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[72]	• Comprehensive assessment and documentation is recommended prior to initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. • Screening for opioid use is recommended, despite limited evidence for reliability and accuracy, as it will identify opioid abusers and reduce opioid abuse. • Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. • Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

Clinical Guideline	Recommendations
	• Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. Use caution in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. • Patients should be stratified as low, medium, or high risk. • A pain management consult may assist non-pain physicians, if high-dose opioid therapy is utilized. • Establish medical necessity prior to initiation or maintenance of opioid therapy. • Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. • Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain not amenable to short-acting or moderate doses of long-acting opioids, as there is no difference between long-acting and short-acting opioids for their effectiveness or adverse events. • An agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. • Opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid adverse events. • Up to 40 mg of morphine equivalent is considered as low dose, 41 to 90 mg of morphine equivalent as a moderate dose and greater than 91 mg of morphine equivalence as high dose. • In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. • Methadone is recommended for use after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. • Monitoring recommendation for methadone include electrocardiogram prior to initiation, at 30 days and yearly thereafter. • In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT and prescription drug monitoring programs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. • Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. • Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse events.
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[73]	• Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. • Clinicians may consider a trial of chronic opioid therapy as an option for chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. • A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during chronic opioid therapy. • When starting chronic opioid therapy, informed consent should be

Clinical Guideline	Recommendations
	obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy. • Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education. • Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate. • 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. • Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics, and should be initiated and titrated cautiously, by clinicians familiar with its use and risks. • Clinicians should reassess patients on chronic opioid therapy periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies. • In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • In patients on chronic opioid therapy not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultations with a mental health or addiction specialist. • Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management, or discontinuation of chronic opioid therapy. • When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and reassess benefits relative to harms. • 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. • Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse events or inadequate benefit despite dose increases. • Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic

Clinical Guideline	Recommendations
	goals, or experience intolerable adverse events. • Clinicians should anticipate, identify, and treat common opioid-associated adverse events. • As chronic non-cancer pain is often a complex biopsychosocial condition, clinicians who prescribe chronic opioid therapy should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies. • Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment. • Patients on chronic opioid therapy should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe chronic opioid therapy, but should coordinate consultation and communication among all clinicians involved in the patient's care. • Clinicians should pursue consultation, including interdisciplinary pain management, when patients with chronic non-cancer pain may benefit from additional skills or resources that they cannot provide. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk. • Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of chronic opioid therapy during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn. • Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of chronic opioid therapy for chronic non-cancer pain.
Treatment Guidelines from The Medical Letter: **Drugs for Pain (2013)**[7]	• Nociceptive pain can be treated with nonopioid analgesics or opioids. • Neuropathic pain is less responsive to opioids and is often treated with adjuvant drugs such as antidepressants and antiepileptics. • Combining different types of analgesics may provide an additive analgesic effect without increasing adverse events. • Nonopioid analgesics such as aspirin, acetaminophen and NSAIDs are preferred for initial treatment of mild to moderate pain. • For moderate acute pain, most NSAIDs are more effective than aspirin or acetaminophen and some have shown equal or greater analgesic effect than an oral opioid combined with acetaminophen, or even injected opioids. The selective cyclooxygenase-2 inhibitor celecoxib appears to cause less severe gastrointestinal toxicity compared to non-selective NSAIDs. • Moderate pain that does not respond to nonopioids can be treated with a combination of opioid and nonopioid analgesics. • For treatment of most types of severe pain, full opioid agonists are the drugs of choice. Unlike NSAIDs, morphine and the other full agonists generally have no dose ceiling for their analgesic effectiveness except that imposed by adverse events. • Patients who do not respond to one opioid may respond to another. Meperidine use should be discouraged because of the high rate of central

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>nervous system (CNS) toxicity and the availability of less toxic, longer-acting alternatives.
• Tolerance to most of the adverse events of opioids, including respiratory and CNS depression, develops at least as rapidly as tolerance to the analgesic effect; tolerance can usually be surmounted and adequate analgesia restored by increasing the dose.
• When frequent dosing becomes impractical, long-acting opioids may be helpful.</td></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: Diagnosis and Treatment of Low Back Pain (2007)[74]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.
• The potential interventions for low back pain are outlined below:
<table>
<tr><th colspan="4">Interventions for the Management of Low Back Pain</th></tr>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td rowspan="3">Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Book, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="6">Pharmacologic Therapy</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="8">Non-pharmacologic Therapy</td><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

• Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
• In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first-line options.
• Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
• Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution.</td></tr>
</table>

Clinical Guideline	Recommendations
	• Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance. • Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution.
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[75]	<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u> • It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> • It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have

Clinical Guideline	Recommendations
	medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following:

Clinical Guideline	Recommendations
	o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. Pharmacologic recommendations for the initial management of hip osteoarthritis • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
American Academy of Orthopedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[76]	Nonpharmacological/surgical therapy • Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. • Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. • Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. • Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. • It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. • Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. Pharmacological therapy • Glucosamine and/or chondroitin sulfate should not be prescribed for

Clinical Guideline	Recommendations
	patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol. • There is a lack of compelling evidence to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. • There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[77]	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. PHN • Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies. Trigeminal neuralgia • Recommended first-line treatments include carbamazepine and oxcarbazepine. • Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable adverse events may be prescribed lamotrigine but should also be considered for a surgical intervention. Central pain • Recommended first-line treatments include amitriptyline, gabapentin or pregabalin. • Tramadol may be considered second-line. • Strong opioids are recommended as second- or third-line if chronic treatment is not an issue.

Clinical Guideline	Recommendations
	• Lamotrigine may be considered in central post-stroke pain or spinal cord injury pain with incomplete cord lesion and brush-induced allodynia and cannabinoids in multiple sclerosis only if all other treatments fail.
American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[78]	Anticonvulsants • If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options • Capsaicin and isosorbide dinitrate spray should be considered for treatment. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options • Percutaneous electrical nerve stimulation should be considered for treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[79]	Neuropathy • All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. • Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. • Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. • Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is

Clinical Guideline	Recommendations
	lack of sensation or mechanical foot changes. • Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. • When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. • Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. • Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. • Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[80]	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[81]	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.
European League Against Rheumatism: **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[82]	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. • Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. • Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.

Conclusions

Opioids have been the mainstay of pain treatment for a number of years and there is well documented evidence of their effectiveness. Oral morphine sulfate is the standard for comparison for all other opioid agents currently available. There are several long-acting opioid agents available which are Food and Drug Administration (FDA)-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia.[3] Methadone is the only long-acting opioid to also be FDA-approved for the treatment of opioid addiction (maintenance or detoxification treatment).[15,19-21]

The current formulations of OxyContin® (oxycodone extended-release), Opana® ER (oxymorphone extended-release), and Embeda® (morphine sulfate/naltrexone) were developed to deter abuse; however, there is no well-documented clinical evidence to demonstrate these formulations prevent abuse.[8-11,13]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which is a Schedule III controlled substance. On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy for all long-acting opioids which includes the availability of training regarding proper prescribing practices by manufacturers, as well as the distribution of educational materials on the safe use of these agents.[6]

In general, all of the long-acting opioids are similar in terms of associated effectiveness, adverse events, warnings, and contraindications.[4] Head-to-head trials demonstrate similar efficacy among the agents in the class, and 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.[7,71-82] Main differences among the individual agents and formulations are due to dosing requirements and generic availability.[4] Several generic long-acting opioids exist, including fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate extended-release tablets, and oxycodone extended-release tablets. Of note, generic availability of oxycodone extended-release is sporadic and available only for certain dosage strengths. Unlike other non-opioid analgesics, full opioid agonists generally have no ceiling for their analgesic effectiveness, except that imposed by adverse events.[3,4] Even though no true ceiling dose exists, dosing intervals are important with these agents; mainly due to their associated adverse events and risks.[3,4] For the agents in the class that are available in a tablet or capsule form, hydromorphone extended-release and Avinza® are available for once-daily dosing, and Kadian® (morphine sulfate extended-release) and morphine sulfate/naltrexone are available for once or twice daily dosing. Methadone and morphine sulfate (MS Contin®, Oramorph SR®) may be dosed every eight to 12 hours. Fentanyl transdermal systems can be worn continuously for 72 hours, and buprenorphine transdermal systems can be worn for seven days.[4]

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